

SLOW INVERSION
at
NITROGEN
and its
CONSEQUENCE
for some
AZABICYCLIC SYSTEMS

A thesis presented for the degree of Doctor of
Philosophy in the Faculty of Science of the
University of Leicester

by

M.L.Durrant

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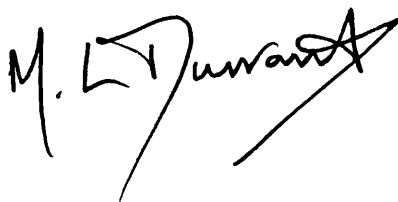


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STATEMENT

The experimental work in this thesis has been carried out by the author in the Department of Chemistry of the Leicester between October 1978 and October 1981. This work has not been, and is not currently being, presented for any other degree.

A handwritten signature in black ink, appearing to read 'M. L. Durrant', with a large, sweeping flourish extending from the end of the name.

University of Leicester

September 1982.

A large, handwritten mark in black ink, resembling a left-facing curly bracket or a large parenthesis, located below the date.

Acknowledgments

There are many people without whose help this thesis would not have been possible and to whom I shall always be grateful.

- I should like to thank Dr. J.R.Malpess, my supervisor, for his enthusiasm, ideas and patience. His advice, both chemical and otherwise, has always been invaluable.

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- Pat, Jonty and Ben for such happy times.

- last, but not least, Yvonne for her love, help and patience in so many ways.

To Yvonne and my Family

The intolerable wrestle
With words and meanings.

T.S. Eliot

All good writing is swimming under water and holding your breath.

F. Scott Fitzgerald

I know why there are so many people who love chopping wood. In
this activity one immediately sees the results.

Albert Einstein

A child of five would understand this. Send somebody to fetch
a child of five.

Groucho Marx

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Author's Note

The final page of this thesis folds out to provide a constant record of key structures as the text is read.

PART 1

CHAPTER 1

INTRODUCTION

I. Pyramidal Inversion at Nitrogen

The ground state, outer valence electrons of a nitrogen atom are sp^3 hybridised. Three of the four sp^3 orbitals are occupied by a single unpaired electron, all available for bonding, and the fourth by an unshared pair of electrons known as the lone pair.

All primary, secondary and tertiary amines exist in an approximately sp^3 hybridised condition in the ground state and, as with carbon, a chiral centre is created if the three ligands attached to nitrogen are different, for the lone pair may be considered as a fourth group in this context. Indeed, this lone pair may be involved in bond formation, as in quaternary salts and N-oxides. A chiral nitrogen atom will impart optical activity to the molecule and a pair of enantiomers will exist, should nitrogen be the only chiral centre.

However, for the vast majority of chiral amines bearing an unshared lone pair, resolution of the enantiomers is rendered impossible by the rapid interconversion of the two forms (1) and (3) by pyramidal inversion^{1,2,3,4}, shown in figure 1.1.

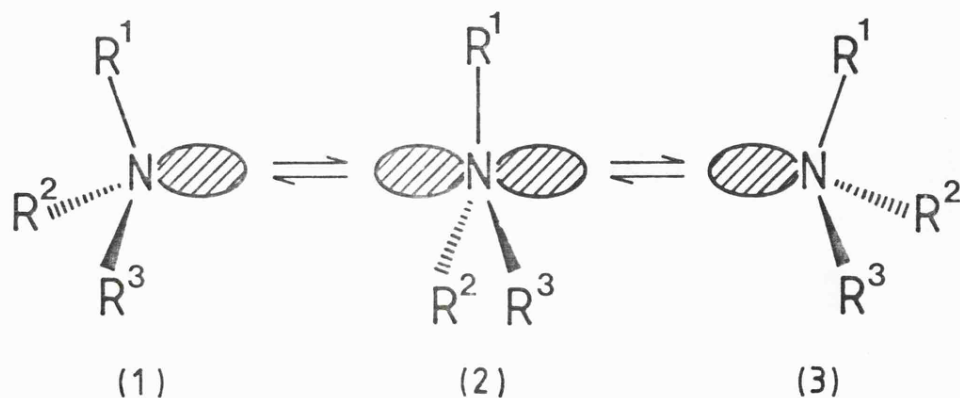
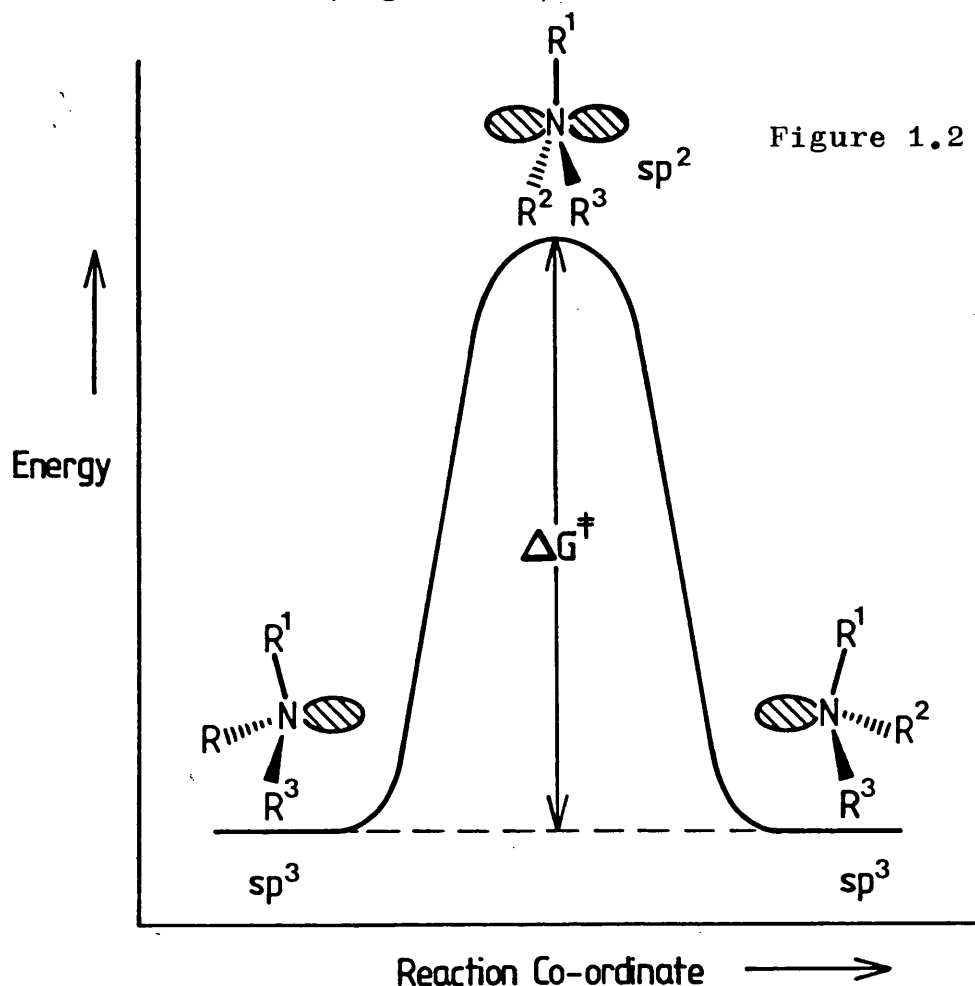


Figure 1.1

The mirror images (1) and (3) are known as invertomers. The conversion of (1) to (3) in nearly all simple amines is believed to involve a rehybridisation from a tetrahedral, sp^3 geometry to a coplanar, or nearly coplanar sp^2 , hybridised state (2), where the three substituents lie roughly in a plane passing through nitrogen. The R-N-R bond angle has changed from about 109° to 120° and the lone pair assumes virtually pure p-orbital character. (The transition state is only strictly planar when the invertomers are mirror images and although this will not be mentioned each time, it should be tacitly understood).

This arrangement of lone pair and substituents is at the maximum of an energy barrier connecting (1) and (3). The energy required to effect this rehybridisation is called the inversion barrier (Figure 1.2).



$\Delta G^\ddagger$ = free energy of activation for inversion.

Several alternative mechanisms for inversion have been proposed² but only one other is believed to be of importance for simple amines, that of quantum mechanical tunnelling. This mode of converting one invertomer into its antipode is operative in ammonia itself and those amines where at least one of the ligands is hydrogen or deuterium, or where the barrier to inversion is very low.

The two invertomers need not be mirror images. The equilibrating forms (1) and (3) may also be diastereoisomers. In carbon chemistry, diastereoisomers frequently have differences in properties which allow their physical separation. This principle is the basis of the most commonly used method of separating enantiomers⁵. The dynamic process occurring at nitrogen similarly makes separation of diastereoisomeric invertomers impossible in the large majority of cases. Such separation has been achieved in a handful of instances, however, and obviously these compounds are of considerable interest for two main reasons. It is important to ascertain exactly which structural features raise the barrier to inversion in order to increase our understanding of nitrogen inversion generally. Secondly, these diastereoisomers may offer the opportunity to study, separately, the chemistry of two isomers related by an extremely subtle process. If the mean lifetime of each isomer is of the order of a few hours or more, rate constants for the inversion of ca. 10^{-4} s^{-1} or less are implied or $\Delta G^\ddagger$ values of greater than 96 kJmol^{-1} at 25°C ⁴. A variety of structural ingredients, which influence either the energy of the ground state or transition

state (and hence the barrier to conformational inversion) have emerged. The effects of such structural features fall broadly into steric and electronic categories.

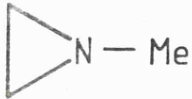
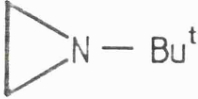
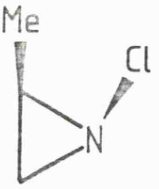
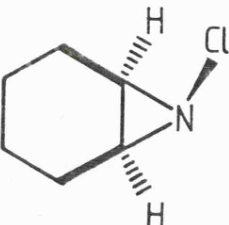
1. Steric Effects

a. Non-bonded Interactions

As the size of the groups attached to nitrogen increases, the congestion in pyramidal ground states (1) and (3) also increases. These non-bonded interactions will tend to flatten the nitrogen pyramid thus making rehybridisation a relatively more easy task. The widening of the R-N-R bond angle to 120° in the transition state (2) is a further incentive to inversion as the strain in the transition state will be relieved relative to the ground state where the R-N-R bond angle is close to 109° . The effect is illustrated in table 1.1.

Table 1.1

Inversion Barrier ($\Delta G^\ddagger/\text{kJmol}^{-1}$)^{1,2}

	81.1
	71.1
	111.7
	99.0

Whilst the substitution of bulky groups on nitrogen destabilises the ground state and leads generally to a lowering of the inversion barrier, many examples exist where non-bonded, steric repulsions are greater in the transition state. In such compounds, it is now the energy of the transition state which increases and serves only to raise the barrier. The temperature-dependent conformational process observed in the ^1H nuclear magnetic resonance (nmr) spectra of a range of 1,3,4 - oxadiazolidines could be identified as slow nitrogen inversion because of the dependence of the barrier upon the size of the substituents at each nitrogen⁶. A similar effect is seen in 1,2 - dialkyl diaziridines⁷. Nitrogen inversion occurs via a transition state in which the substituents are eclipsed and congestion is therefore greater than in the sp^3 hybridised state (Table 1.2).

[Inversion Barriers ($\Delta G^\ddagger$) in kJmol^{-1}]^{6,7}

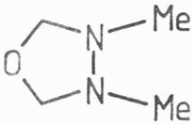
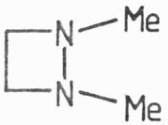
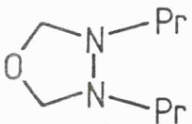
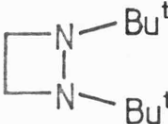
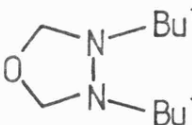
	44.3		68.5
	81.1		91.3
	> 87.8		

Table 1.2

b. Ring Strain

The geometry of the sp^2 hybridised transition state (2) requires an R-N-R bond angle of 120° . The amount of energy needed to dilate the ground state R-N-R angle as it approaches the transition state for inversion increases as this angle is reduced from 109° to smaller R-N-R bond angles as in azetidines (ca. 96°) and aziridines (ca. 60°). The very high barriers in aziridine derivatives were predicted⁸ long before the first two invertomers of an aziridine were separated⁹.

The contents of table 1.3 show the gradation of the inversion barrier as the C-N-C bond angle changes. In aziridines the lone pair is exocyclic and has more s-orbital character than a tetrahedral lone pair. This is a ground state stabilisation which therefore increases the barrier to inversion since the lone pair must assume pure p-character in the transition state.

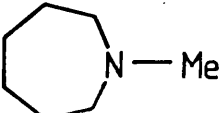
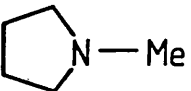
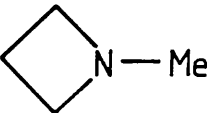
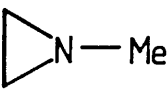
<u>Inversion Barrier ($\Delta G^\ddagger/kJmol^{-1}$)^{1,2}</u>	
	28.4
	33.9
	42.6
	81.1

Table 1.3

c. The Bicyclic Effect¹

A further positive increment to the inversion barrier is incurred if an azamonocycle is bridged by one or more carbon atoms (Table 1.4.).

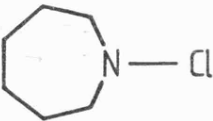
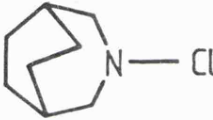
<u>Inversion Barrier ($\Delta G^\ddagger/\text{kJmol}^{-1}$)</u> ²	
	38.5
	42.2

Table 1.4

This bicyclic effect appears to be explicable for the 2-azabicycles of table 1.5 in terms of the degree of flexibility of the all-carbon bridges and hence of each molecule as a whole¹⁰. The substitution of a double bond, a one-carbon bridge or both for a two-carbon bridge increases the rigidity of the bicyclic skeleton and raises the amount of angle strain at nitrogen. The s-character of the lone pair rises and these effects combine to raise the energy of the transition state.

[Inversion Barriers ($\Delta G^\ddagger$) in kJmol^{-1}]¹⁰

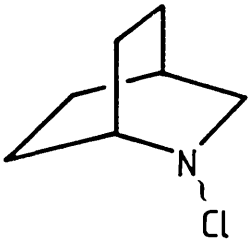
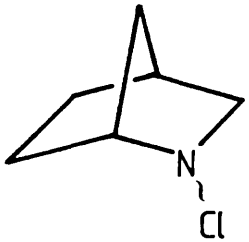
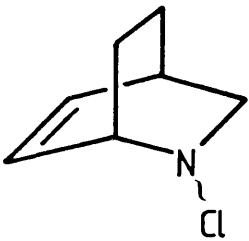
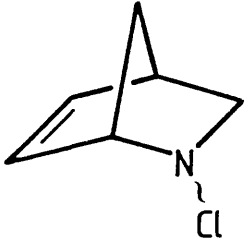
	44.3		51.0
	48.5		64.0 ¹¹

Table 1.5

In the 7-azabicyclo(2.2.1)heptane, -hept-2-ene and -hepta-2,5-diene group of compounds, free energies of inversion are observed which are second only to those recorded for aziridines. The C-N-C bond angle in these azabicycles is ca. 96° ¹², similar to that in azetidines but inversion barriers are considerably larger (Table 1.6).

The extraordinary effect on the barrier to inversion at nitrogen in this 7-position remains unexplained. Lehn¹ and Sutherland¹⁴ have made tentative suggestions which will be explored in particular in the next chapter.

[Inversion Barriers ($\Delta G^\ddagger$) in kJmol^{-1}]

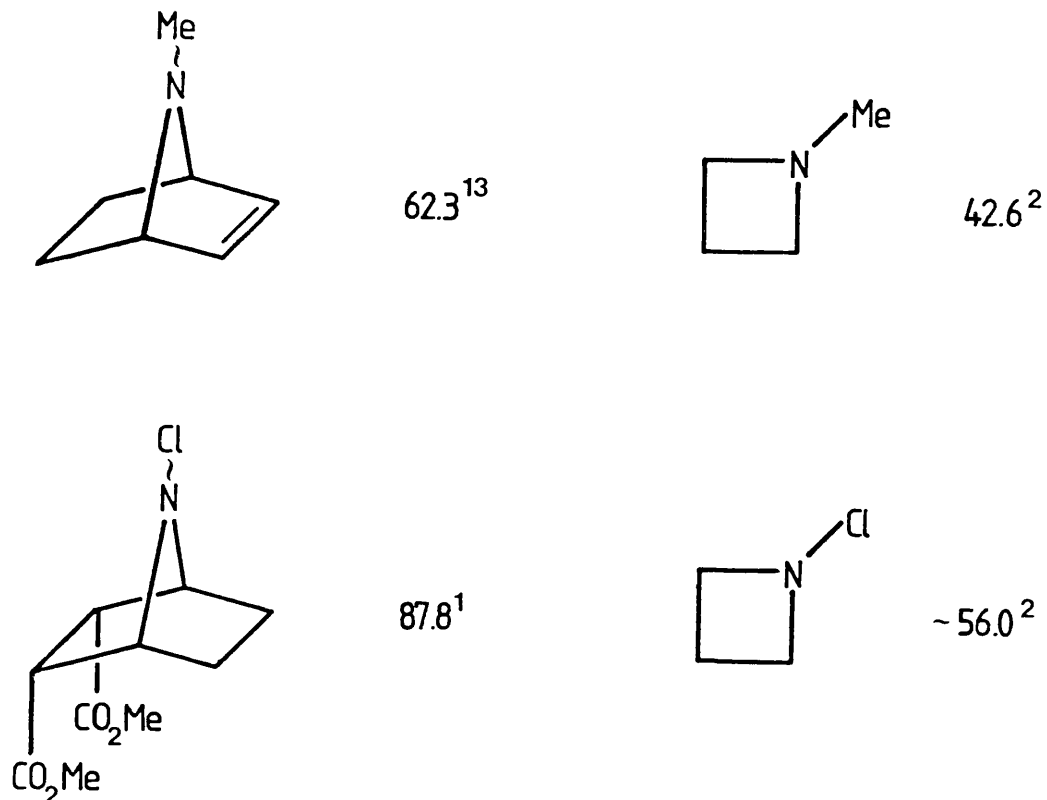


Table 1.6

2. Electronic Effects

a. Conjugating Substituents

i) (p-p) π

If a substituent bonded to nitrogen possesses p-orbitals which are available for conjugation, then the stabilisation of the lone pair will be greatest at the transition state in which these electrons also occupy a p-orbital. Overlap and subsequent delocalisation lowers the energy of the transition state and increases the rate of inversion. The presence of a

conjugating substituent on nitrogen tends also to flatten the nitrogen pyramid. This geometric influence may be offset by incorporating the nitrogen atom into a three-membered ring and it is this class of compounds which vividly charts the effect of (p-p) π overlap in the transition state (Table 1.7).

[Inversion Barriers ($\Delta G^\ddagger$) in kJmol^{-1}]¹

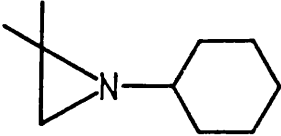
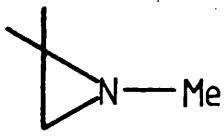
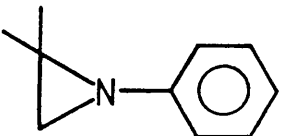
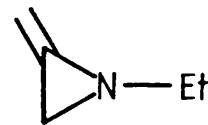
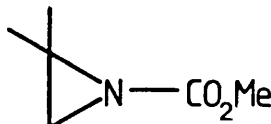
	73.2		78.2
	46.8		43.1
			< 29.3

Table 1.7

ii) (p-d) and σ - π Conjugation

The effect of d-orbitals adjacent to nitrogen upon the inversion barrier should, in principle, be the same as that for p-orbitals but evidence for such stabilisation has been more difficult to garner. Certainly, aziridines bearing substituents on nitrogen containing Si, P, S or As show low inversion barriers. In the case of N-silylamines, however, the nitrogen

atom is planar in the ground state.¹⁵ The inversion barrier in a range of sulphenyl aziridines (4) appears insensitive to the nature of X and Y which were varied from electron-donating ($X=OCH_3$, $Y=H$) to electron-withdrawing substituents ($X=Y=NO_2$)¹⁶. If the $(p-d)\pi$ overlap between S and N were important in the transition state, a decrease in the barrier would be seen on crossing this series. The observed insensitivity suggests that any $(p-d)\pi$ overlap in the transition state is much the same as it is in the ground state. $(\sigma-\pi)$ Hyperconjugation¹⁷ was invoked to explain the substantially lower barriers in this system compared to N-alkyl aziridines (Figure 1.3).

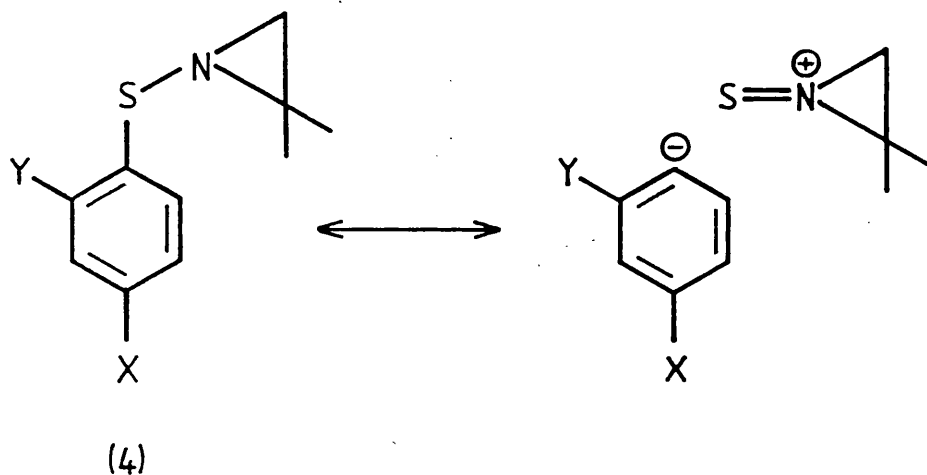


Figure 1.3

$(\sigma-\pi)$ Hyperconjugation has been invoked to explain anomalously low barriers in other aziridines,^{18,19} e.g. (5) and (6) (Figure 1.4).

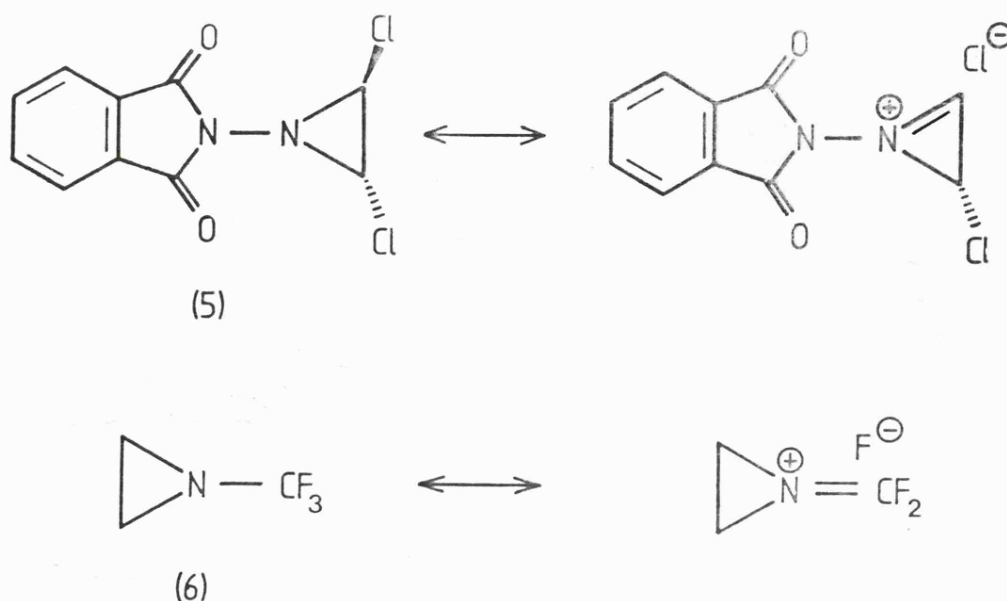


Figure 1.4

b. Heteroatom Effects

If the inverting centre bears a more electronegative atom such as a halogen (F, Cl, Br) or oxygen, the displacement of electron density of the N-O or N-halogen bond away from nitrogen increases the pull of the nitrogen nucleus on the lone pair i.e. it increases the s-character of the lone pair. This is a ground state stabilisation and hence increases the barrier relative to, say, the N-alkyl analogue (Table 1.8).

This reasoning cannot explain the heteroatom effect in cyclic hydrazines and diaziridines. A further general effect associated with a heteroatom is the interaction of the nitrogen lone pair with the lone pair(s) on that heteroatom.

[Inversion Barriers ($\Delta G^\ddagger$) in kJmol^{-1}]

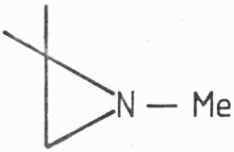
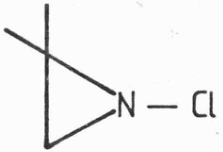
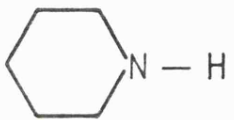
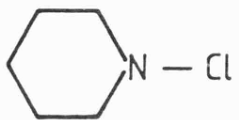
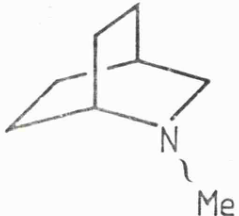
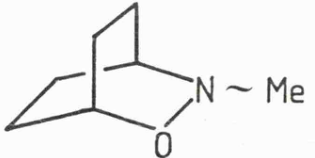
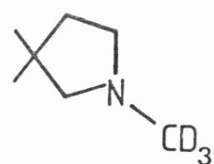
	78.2 ¹		>98.2 ¹
	25.5 ²⁰		42.6 ²¹
	27.6 ²²		62.3 ²³

Table 1.8

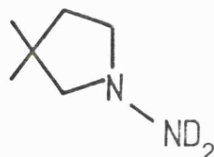
Dewar and Jennings²⁴ note that the inversion barrier in (8), where the N-N bond is exocyclic, is only ca. 5kJmol^{-1} higher than in the corresponding N-alkyl compound (7) (Table 1.9).

Inversion Barrier ($\Delta G^\ddagger/\text{kJmol}^{-1}$)²⁵



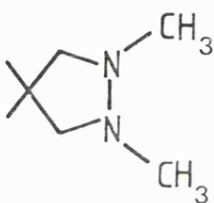
(7)

30.9



(8)

35.5



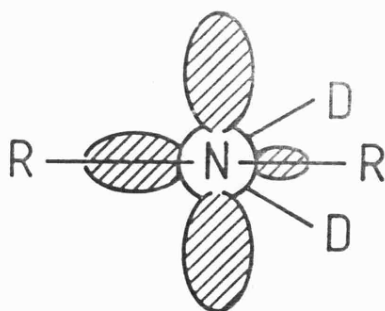
(9)

46.4

Table 1.9

There is a small increase in the barrier to inversion due to the adjacent lone pair on the exocyclic nitrogen of (8), although the interaction is at a minimum when the inversion at the endocyclic nitrogen occurs by the conformation shown in figure 1.5.

Figure 1.5



When the N-N bond is endocyclic, however, the conformation of (9) means that the lone pairs are almost eclipsed when the inversion occurs at either nitrogen atom. This would explain the further increase to the inversion barrier of (9) compared to the barrier of (8), and thus provides good evidence for lone pair - lone pair repulsions as part of the heteroatom effect.

II. The Determination of Inversion Barriers and Invertomer Ratios

1. Inversion Barriers

a. Methods

Inversion barriers in amines have been measured using several methods, each of which covers a different range of energies. Studies based on the calculation and best fit of theoretical and observed microwave and, to a lesser extent, infra red spectra have furnished the barriers to inversion of low molecular weight amines such as ammonia and methylamine. These methods are most commonly used when inversion barriers are in the range 0-20 kJmol⁻¹.

Very low rates of inversion ($\leq 10^{-4} \text{ s}^{-1}$), corresponding to free energies of activation of 85 kJmol⁻¹ and above, may be determined by using classical kinetic techniques. Most commonly, the equilibration of a pure invertomer is followed by some spectroscopic means:- nmr, ultraviolet or infra red absorbance or decay of optical rotation if the invertomer is chiral^{26,27}.

The most rapid and amenable technique is that of dynamic nmr spectroscopy, which can measure barriers in the range 20-100 kJmol⁻¹. It requires inversion to be slow on the nmr time scale⁴ and that the inversion exchanges two magnetically non-equivalent sites. They must be non-equivalent. Temperature dependent coalescence cannot be followed unless the signals due to a particular group in each diastereoisomer are sufficiently separated. Even then, the two signals are distinct only under conditions of slow inversion. As the temperature is raised and the rate of inversion increases, the two peaks

broaden and merge until inversion is sufficiently rapid to ensure that a single, sharp, time-averaged signal is observed. The temperature at which the two signals just become incoherent is known as the coalescence temperature, T_c . The rate constant for inversion at T_c may be simply found from equation (1.1):

$$k_c = \frac{\pi \Delta \nu}{\sqrt{2}} \quad [1.1]$$

where $\Delta \nu$ is the frequency separation at slow exchange. Most reviews discuss the calculation of $\Delta G_c^\ddagger$ (the free energy of inversion at coalescence) with respect to equally populated exchanging sites. Since 1970, however, equations for the treatment of unequally populated sites (the more general case mathematically) have been available²⁸.

The coalescence method provides no measure of the free enthalpy ($\Delta H^\ddagger$) and entropy ($\Delta S^\ddagger$) for inversion. It allows only the calculation of $\Delta G^\ddagger$ at the coalescence temperature, but does so very accurately. Computer-based line shape analysis is most frequently employed nowadays. Not only is its accuracy much greater than any other nmr based technique but it can furnish all the activation parameters for inversion.

b. Problems and Solutions

The decrease in inversion barrier in a series of azamonocycles as the ring size increases from $n=0,1,2$ and 4 (Figure 1.6) may be rationalised in terms of angle strain.

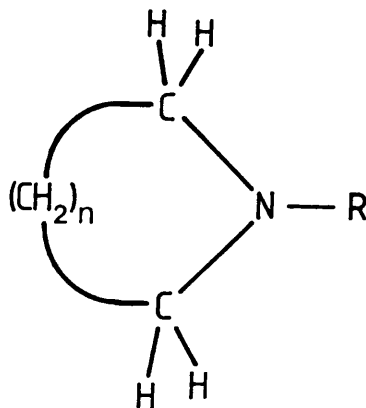


Figure 1.6

Indeed, these cyclic amines were chosen for study to eliminate the chance of confusing N-inversion and hindered bond rotation in their acyclic counterparts. Ring puckering does occur in these molecules but is a very low energy process²⁹ ($< 20 \text{ kJ mol}^{-1}$) and any temperature dependent phenomena can be confidently ascribed to pyramidal inversion.

More care must be exercised in ascertaining the origin of temperature dependent phenomena in the nmr of acyclic amines. In sulphenamides³⁰, hydroxylamines³¹, hydrazines³² and even simple amines³³, nitrogen inversion and hindered rotation about bonds from nitrogen must be distinguished.

Another conformational process must be considered when the nitrogen atom is part of a six-membered ring ($n=3$ in figure 1.6). Ring flipping is competitive with nitrogen inversion in N-substituted piperidines.

When such a dichotomy exists (inversion-ring flipping or inversion-rotation), only the observation of two separate

temperature-dependent processes will allow rigorous assignment of the two dynamic effects. If only one process is apparent, it may be possible to distinguish nitrogen inversion by application of any one of the structural effects mentioned earlier. For example, if the substitution of larger alkyl groups on nitrogen depresses the barrier, then nitrogen inversion is the process observed. This exercise may be academic if the conformational process is held to be a synthesis of, say, inversion and rotation³⁴.

All the foregoing discussion assumes that coalescence phenomena may be readily observed by nmr. This need not be so. Invertomers need not be isoenergetic because, for a variety of steric³⁵ and electronic^{36,37} reasons, one invertomer may be preferred over the other. If the ground state invertomer ratio is 100:0, the calculation of the inversion barrier by dynamic nmr spectroscopy is rendered impossible. The problem of coincidence of the signals of the exchanging site may be overcome by the use of paramagnetic shift reagents but this approach neglects any effect of the shift reagent on the invertomer ratio. The method has found extensive use in the determination of lone pair preferences but only in as far as delineating the preferred invertomer by a consideration of the contact shifts of relevant protons³⁷.

The use of a different solvent may also remove the coincidence of shifts but the solvent effect upon the inversion barrier must be borne in mind when comparisons are being made.

In the mono- and bicyclic amines particularly, signals which are used to monitor slow rates of inversion may overlap with, or be hidden under, the absorptions due to the aliphatic

residue. The simplification of such spectra is possible by specific deuteration but this can often entail laborious synthesis. In the past ten years, therefore, with the advent of spectrometers that are routinely capable of detecting other nuclei, ^{13}C , ^{15}N and, where applicable, ^{19}F , nmr studies have become increasingly important in the investigation of inversion at nitrogen. The ^{13}C nucleus particularly has been used to solve some of the thornier problems remaining from the late 1960's. The inversion barriers of piperidine and N-chloropiperidine were measured using this nucleus^{20,21,40} and other examples exist (see for instance:- ^{13}C : reference 41; ^{15}N : reference 42).

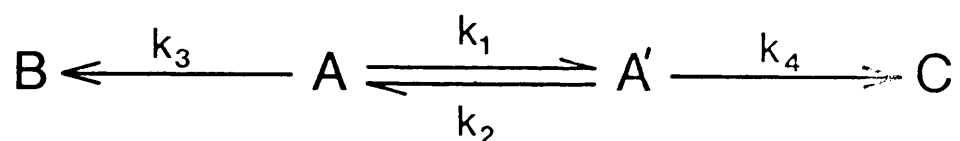
^{13}C Spectra have the advantages of a wider range of chemical shifts and a lack of coupling which allows simplification of spectra. They also show larger values of $\Delta\nu$ which increases accuracy in the coalescence method. To its discredit, the slow relaxation of ^{13}C nuclei increases the errors upon integration of absorptions.

2. Invertomer Ratios

When the inversion barrier in an amine is investigated using dynamic nmr spectroscopy, it is a simple matter to obtain the invertomer ratio. The integration of the signals due to the group exchanged by slow inversion below the coalescence temperature will furnish the relative invertomer populations. The accuracy of this ratio is, like T_c , a function

of the separation of the signals, although the cutting- and - weighing* of absorptions or the use of a planimeter can, to some extent, overcome the problems of overlapping peaks and sloping base lines in nmr spectra.

A second technique relies on fixing the configuration at nitrogen by quaternisation. For the method to succeed, the rate of quaternisation must be very fast relative to the rate of inversion. The ratio of quaternary salts then directly reflects the ratio of the two invertomers at equilibrium⁵. This idea is shown in figure 1.7 with reference to the two amine invertomers, A and A'.



$$[A]:[A'] = x:y$$

then $[B]:[C] = x:y$ only if

$$k_3, k_4 \gg k_1, k_2$$

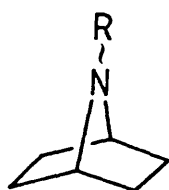
Figure 1.7

* This refers to the method of cutting out the desired signals and weighing them in order to provide a measure of their relative areas.

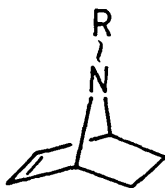
The most common technique involves addition of the amine to a large excess of strong acid (usually a mineral acid). This effects rapid, irreversible protonation of the amine conformers and the ratio of the protonated amine salts reflects the thermodynamic population of each invertomer. The integration of suitable absorptions in the ^1H or ^{13}C nmr spectrum⁴³ provides the ratio. The experimental conditions of such "kinetically controlled protonations" are very strict⁴⁴. Much controversy has raged with regard to the results obtained in the protonations of substituted piperidines, the general implications of which will be discussed more fully in Chapter 2. Fortunately, the simplification of studying inversion afforded by ^{13}C nmr spectroscopy allows direct determination of invertomer ratios, even in piperidine itself^{20,45}. Increasingly, therefore, conformational analysis based on fast chemical reactions will be used only to support direct spectroscopic measurement.

III. Inversion in 7-Azabicyclo(2.2.1) heptane, -hept-2-ene and -hepta-2,5-diene derivatives.

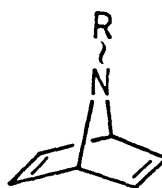
The bicyclic frameworks of the title compounds are (10), (11) and (12) respectively (Figure 1.8). The sole reported measurement of an inversion barrier for a simple derivative is that of 62.3 kJmol^{-1} for 7-methyl-7-azabicyclo(2.2.1) hept-2-ene¹³ (13). All other recorded inversion barriers for this class of amines have been for elaborated systems such as (14), (15) and (16).



(10)

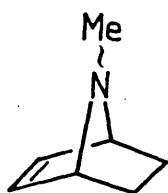


(11)



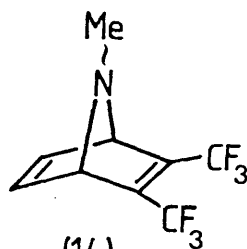
(12)

[Inversion Barriers ($\Delta G^\ddagger$) in kJmol^{-1}]

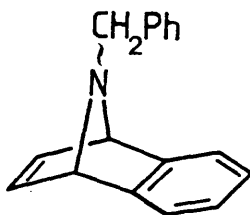


(13)

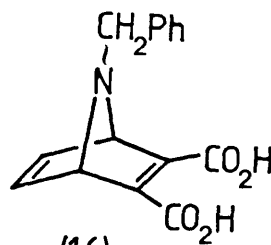
62.3



(14)

62.3⁴⁶

(15)

52.7⁴⁷

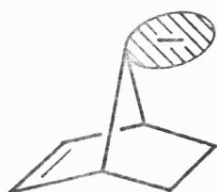
(16)

59.8⁴⁷

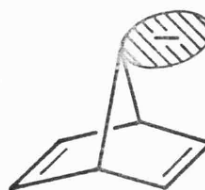
Figure 1.8

Tertiary amines containing these three basic skeleta have inversion barriers at least twice as high as simple, acyclic tertiary amines. They are striking examples of the bicyclic effect, in which the placement of nitrogen as the single bridging atom raises the inversion barrier considerably. Thus there is little difference between the measured inversion barriers for (16) and 2-chloro-2-azabicyclo(2.2.1)hept-5-ene (Table 1.5, 64.0kJmol^{-1}). In each case the nitrogen is contained in a five-membered ring; for the N-methyl amine, the bicyclic effect is sufficient to compensate for the lack of the barrier-raising influence of the heteroatom in the N-chloroamine. This effect has already been illustrated in table 1.8.

7-Azabicyclo(2.2.1)hept-2-ene and -hepta-2,5-diene derivatives are of interest in view of the continuing controversy^{56-59,48-51} over the importance of homoconjugative $n-\pi$ interactions. These bicyclic amines are isoelectronic with the norbornen-7-yl and norbornadien-7-yl carbanions (17) and (18) (Figure 1.9).



anti-(17)



(18)

Figure 1.9

The study of these carbanions has been hampered by ambiguous experimental results⁵² and further investigations have been confined to theoretical calculations⁵³. The nitrogen

analogues (11) and (12) are uncharged species, many derivatives of which are stable at room temperature. Their ease of synthesis and high inversion barrier make study of lone pair preferences by dynamic nmr spectroscopy a straightforward task. These amines can therefore aid the study of homoaromaticity (an area of intense current interest⁵⁴) and the investigation of stereoselective reactions at or from nitrogen. For example, it has been argued that a stereoselectivity would be anticipated in reactions involving the intermediacy of the nitroxide radicals (19) and (20) which are the preferred orientations of the N-O bonds in the two systems⁵⁵ (Figure 1.10).

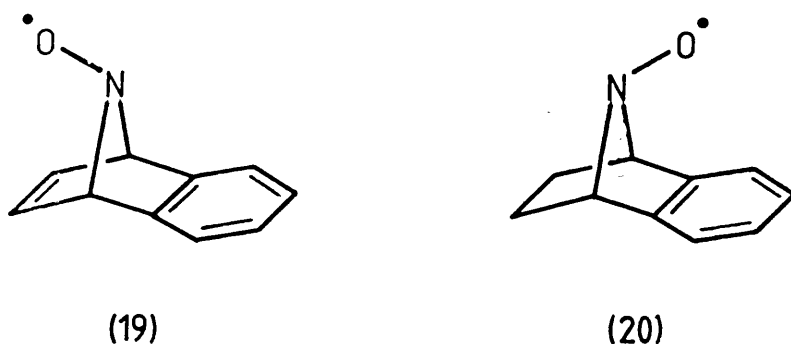
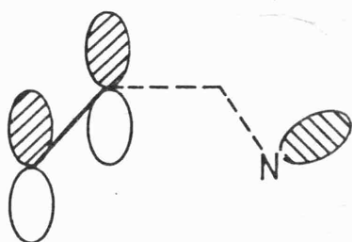


Figure 1.10

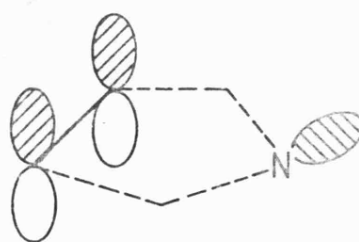
The reasons as to why one invertomer is preferred over the other in such amines remain unclear. Morishima has attempted to construct a model upon which it is possible to predict the preferred orientation of the lone pair based on the nickel (II) acetylacetonate-induced contact shifts^{37,38} photoelectron⁴⁸ and ultraviolet⁴⁹ spectra of a range of amines (both mono- and bicyclic). Two limiting forms have been defined. In the first of these, a lone pair of electrons

on nitrogen overlaps formally with one of the p-orbitals of a π -bond in a monohomoconjugative fashion. It is termed a homoallylic interaction since orthodox allylic conjugation is not possible due to an intervening sp^3 hybridised carbon atom but the geometry of the molecule sustains the overlap of the lone pair and p-orbitals (A in figure 1.11). A homoallylic system is stabilised by this overlap and this should therefore determine the lone pair preference.

The second limiting form is the symmetrical bishomoallylic interaction, B in figure 1.11, where two sp^3 hybridised carbon atoms interrupt normal allylic interaction. This type of overlap is considered a repulsive one and this work predicts that, when possible, the lone pair will prefer that orientation which avoids such an overlap.



A. Homoallylic Interaction.



B. Bishomoallylic Interaction.

Figure 1.11

In Morishima's view, the lone pair, when faced with interaction with two double bonds as in 1,4-dihydronaphthalen-1,4-imine derivatives, will prefer to interact with the less electron rich of the two.

It has been noted by Grutzner⁵⁰ and Underwood⁵¹ that Morishima's own results imply that homoconjugative interactions of this kind cannot be of great energetic consequence. Morishima states that there is no preference for one invertomer over the other in either (21) or (27b) (Figure 1.12), two compounds which typify homo- and bishomoallylic interactions respectively. The preferences anticipated on the basis of figure 1.12 are shown by the dashed continuation of the arrows.

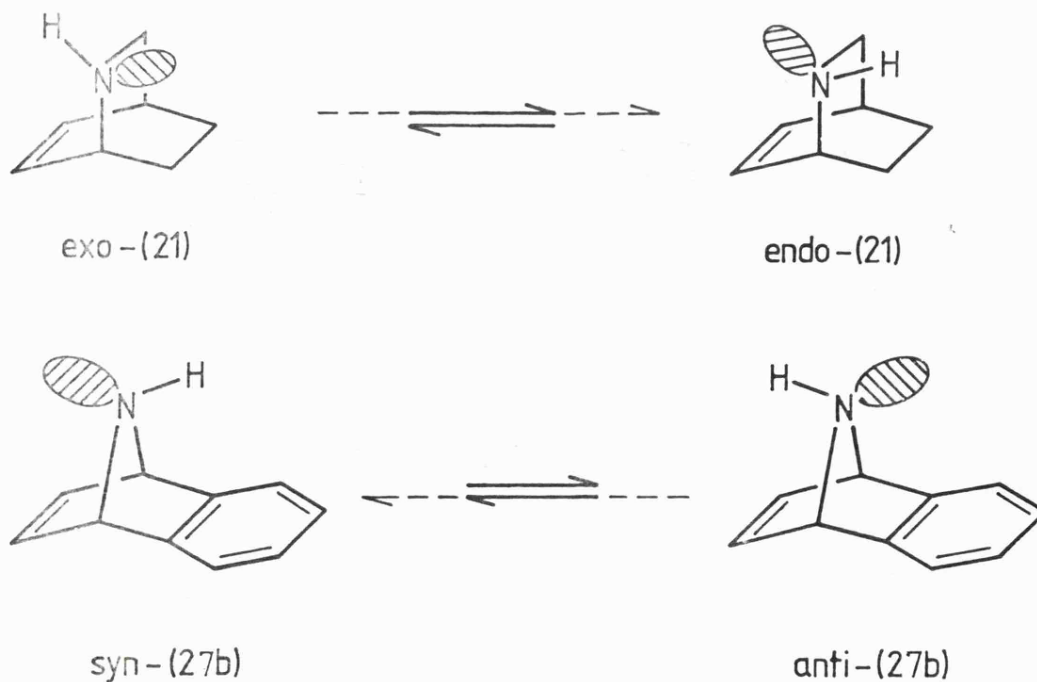


Figure 1.12

It is clear also that with substituents larger than hydrogen on nitrogen, the congestion of neighbouring parts of the molecule and the inverting group (for example, a methyl group) will dominate the invertomer preference and swamp any homoallylic stabilisation. This is the case in 2-methyl-2-azabicyclo(2.2.2) oct-5-ene(23), where the major invertomer is $\text{exo-}^{22,38}$ (Figure 1.13). The observed preference is thought to be due to the diminished steric congestion between the methyl group and the exo-H_x of the saturated two-carbon bridge, an interaction unavoidable in $\text{endo-}(23)$.

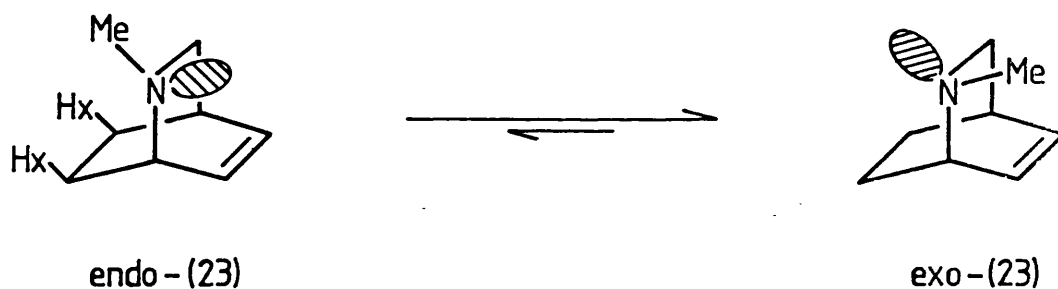


Figure 1.13

That such a minor substitutional change causes a preponderance of one invertomer, compared to the 50:50 ratio suggested for (21), implies that the stabilisation of endo-(23) by homoallylic overlap cannot be very great. It must certainly be less than 5kJmol^{-1} , the energy required to convert a 50:50 ratio to 90:10.*

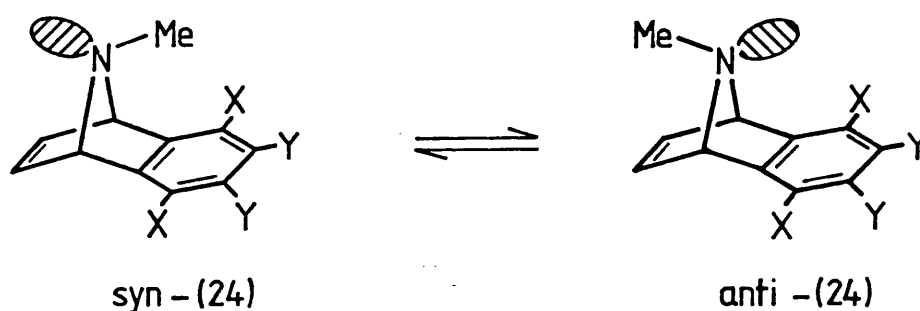
The opposing view, propounded essentially by Grutzner^{50,54c} and Underwood^{39,51}, but suggested initially about ten years ago by Breslow⁵⁶, offers no rationale for deciding invertomer preferences but refutes any significant interaction of a lone pair and $4n\pi$ electrons. The imino bridge of the 7-azabicyclo(2.2.1)hept-2-enes and -hepta-2,5-dienes would have to distort to undergo any overlap but is unlikely to do so if this will increase the level of repulsion⁵⁷.

However, there are few measured invertomer ratios to support one or other of the two viewpoints. This is not unreasonable when the substituent at nitrogen is hydrogen because the barrier to inversion is much lower in these molecules. Underwood and Morishima both conclude that the preferred invertomer in 9-methyl naphthalen-1,4-imines is that with methyl group syn- to the aromatic ring but have taken little advantage of the fact that much higher barriers have been found when a methyl group is bonded to nitrogen in these compounds.

*The energy required to transform an invertomer ratio of 90:10 to one of 10:90 is just 10.8kJmol^{-1} at room temperature. This figure is calculated using the equation:

$$\Delta G^\circ = -RT \ln K$$

Gribble has measured the invertomer ratios and inversion barriers for (24d) and (24e)³⁶ (Figure 1.14). The inversion barriers are ca.58.5kJmol⁻¹ and the syn- and anti-invertomers are readily observed at low temperature in the proton nmr spectrum.



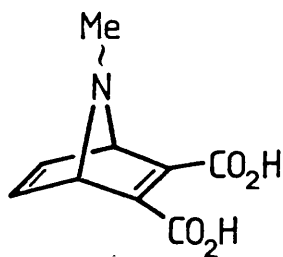
Invertomer Ratio*

	<u>syn</u> : <u>anti</u>
(24d) : X=Y = Cl	25 : 75
(24e) : X=Y = F	17 : 83

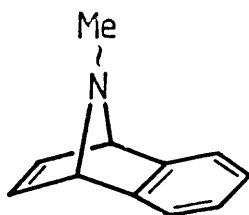
Figure 1.14

* Evidence presented in the next chapter contests both the invertomer ratios observed for (24d) and (24e) and the proposed preference of the lone pair.

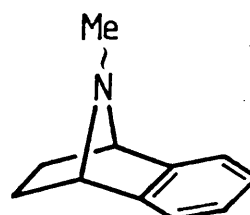
Morishima offers some measured ratios to support his conclusions but only for three compounds (24b), (26b) and (25) (Table 1.10).



(25)



(24b)



(26b)

	<u>Solvent (pD)</u>	<u>Invertomer Ratio</u> <u>syn^a : anti^a</u>
(25)	Me ₂ SO	24 : 76
	D ₂ O (1.4)	58 : 42
	(11.0)	80 : 20
(24b) ^b	CDCl ₃	80 : 20
(26b) ^b	CDCl ₃	94 : 6

Table 1.10

a. For (25), the syn- position is defined as that with the methyl group on the same side as the carboxylic acid groups; for (24b) and (26b), the accepted notation is that syn- refers to the invertomer with the methyl group on the same side as the aromatic ring.

b. The ratios for (24b) and (26b) are not clearly reported in reference 11c. Morishima's discussion concludes that the dominant isomer of (24b) is 80% syn- whilst table 1 reports that it is 94% syn-. Table 1.10 has been compiled on the basis of the results reported in the next chapter which conclude that the major invertomer in (24b) is 71% syn-.

The results for (25) in solutions of varying acidity are crucial in support of bishomoallylic destabilisation. The carboxylic groups ionise as the acidity of the solvent falls ($\text{DMSO} \rightarrow \text{D}_2\text{O}$ (pD 11)) and increase the electron density of the 2,3 π -bond relative to that when the acid groups are not ionised. The proportion of the anti-invertomer decreases on changing the solvent from DMSO to D_2O (pD 11) as the repulsive interaction between the lone pair and the increasingly electron-rich 2,3- double bond increases. However, even here, the lack of dramatic differences in invertomer ratio points to the small effect of any homoallylic interaction between a lone pair and π -bond.

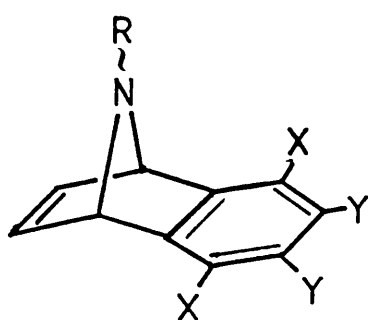
It was clear that there had been much theoretical discussion on the basis of little unambiguous experimental work, with very few invertomer ratios having actually been measured. We felt that an alternative approach to the evaluation of homoconjugative interactions lay in a comparison of the invertomer ratios of a wider range of naphthalen-1,4-imines. A considerable range of compounds was available whose inversion barriers were high and invertomer ratios measured easily. These ratios, in conjunction with further evidence for the assignment of major and minor invertomers, would provide a firmer basis on which to draw conclusions.

CHAPTER 2

INVERSION IN 7-AZABICYCLO(2.2.1)HEPTYL DERIVATIVES

Inversion in 7-Azabicyclo(2.2.1)heptyl Systems

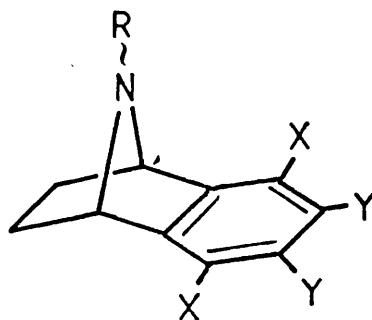
A range of 1,4-dihydronaphthalen-1,4-imines (Figure 2.1) was available from a straight forward synthesis which is outlined in Section I. The advantage of this synthesis was that a number of bicyclic secondary amines with the general structure (27) could be prepared in which the pattern of substitution in (and hence electronic nature of) the benzene ring could be varied considerably.



(27) R = H

(24) R = Me

(29) R = Cl



(28) R = H

(26) R = Me

(30) R = Cl

Figure 2.1

A simple hydrogenation generated a second series of related amines (28) and both series were the starting point for the corresponding N-methyl derivatives (24) and (26) and N-chloro derivatives (29) and (30). Earlier work had suggested that both invertomers of N-methyl-^{36,37} and N-chloro-^{58,59} derivatives of (27) and (28) should be sufficiently long-lived to be observed using ¹H nmr spectroscopy. Thus, it was believed that uncertainty over

the energetic significance of homoconjugative interactions could be directly answered by measuring a wide number of invertomer ratios and looking at their variation as a function of structural and electronic changes.

I. Synthesis

1. Parent Systems (27)

The Diels-Alder addition of an appropriately substituted benzyne⁶⁰ and an N-substituted pyrrole gave the 1,4-dihydronaphthalen-1,4-imine system directly (Figure 2.2). The substituent on the pyrrole nitrogen was the trimethylsilyl group, chosen because of its ability to disrupt the aromaticity of the pyrrole ring (and thus favour the cycloaddition) and because of its simple removal from the cycloadduct⁶¹. For the synthesis of the parent system (27b), better yields were obtained by a two-step process which involved basic hydrolysis of the cycloadduct of N-ethoxycarbonyl pyrrole and benzyne^{51,62} (Figure 2.3).

Figure 2.2

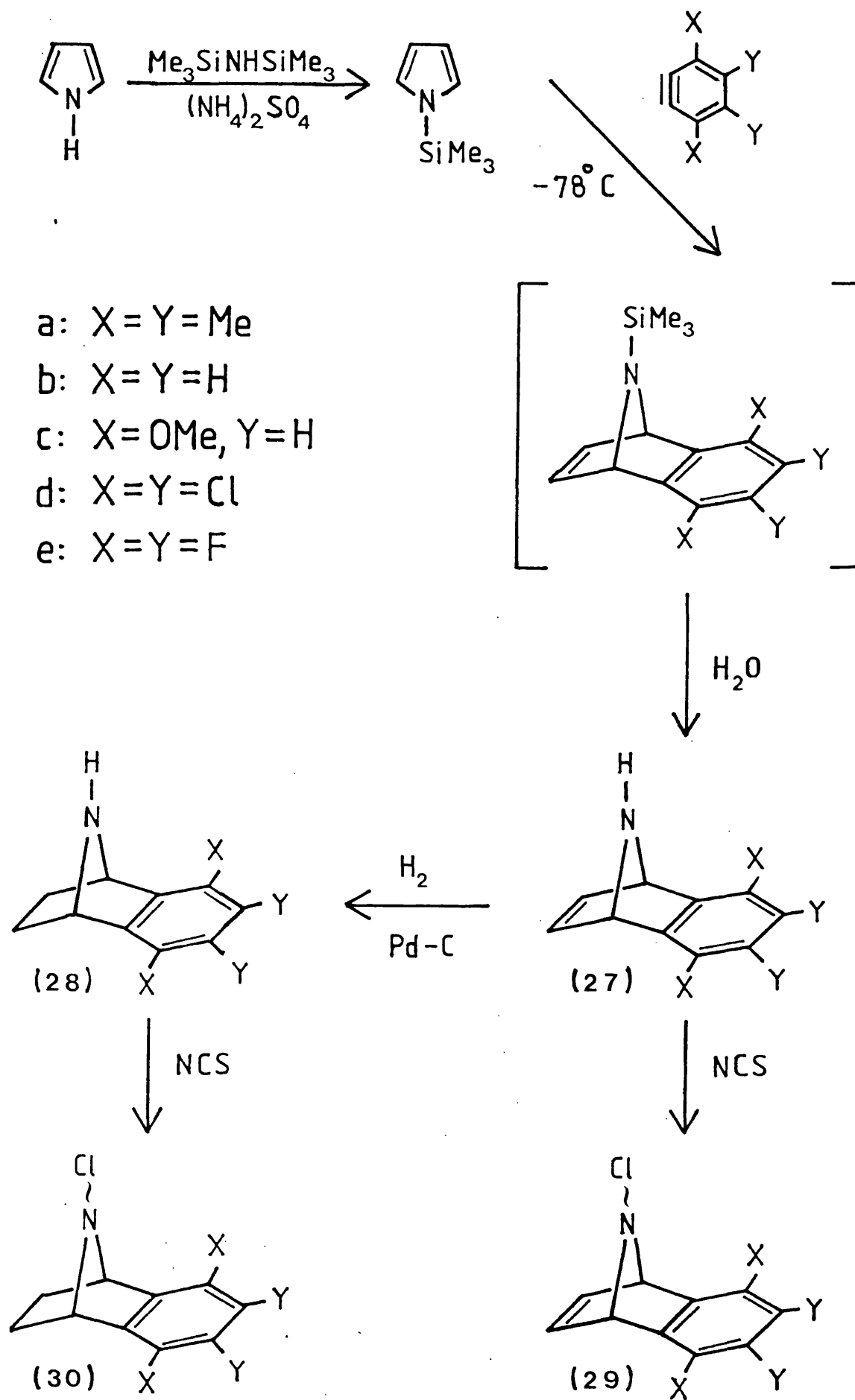
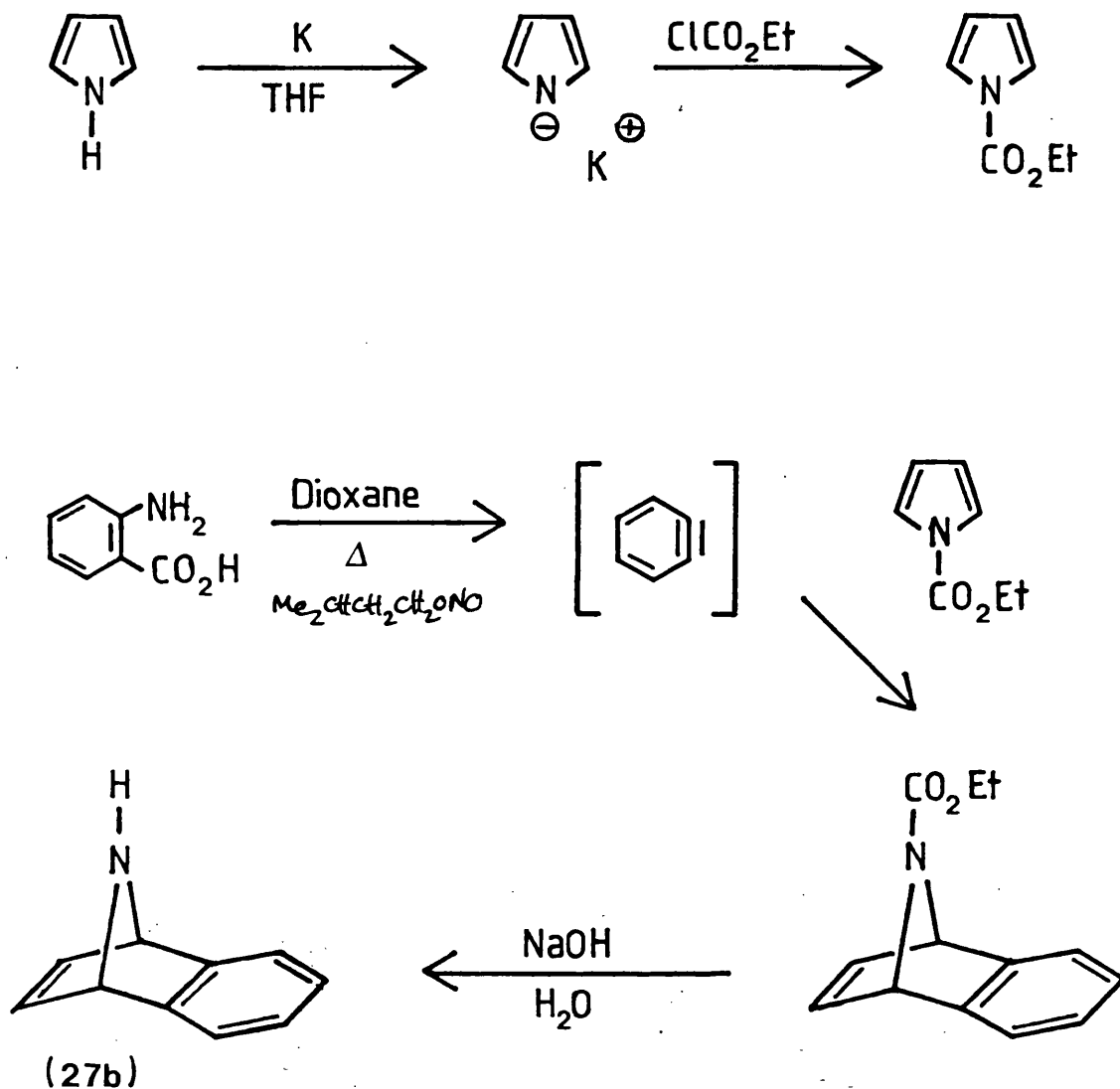
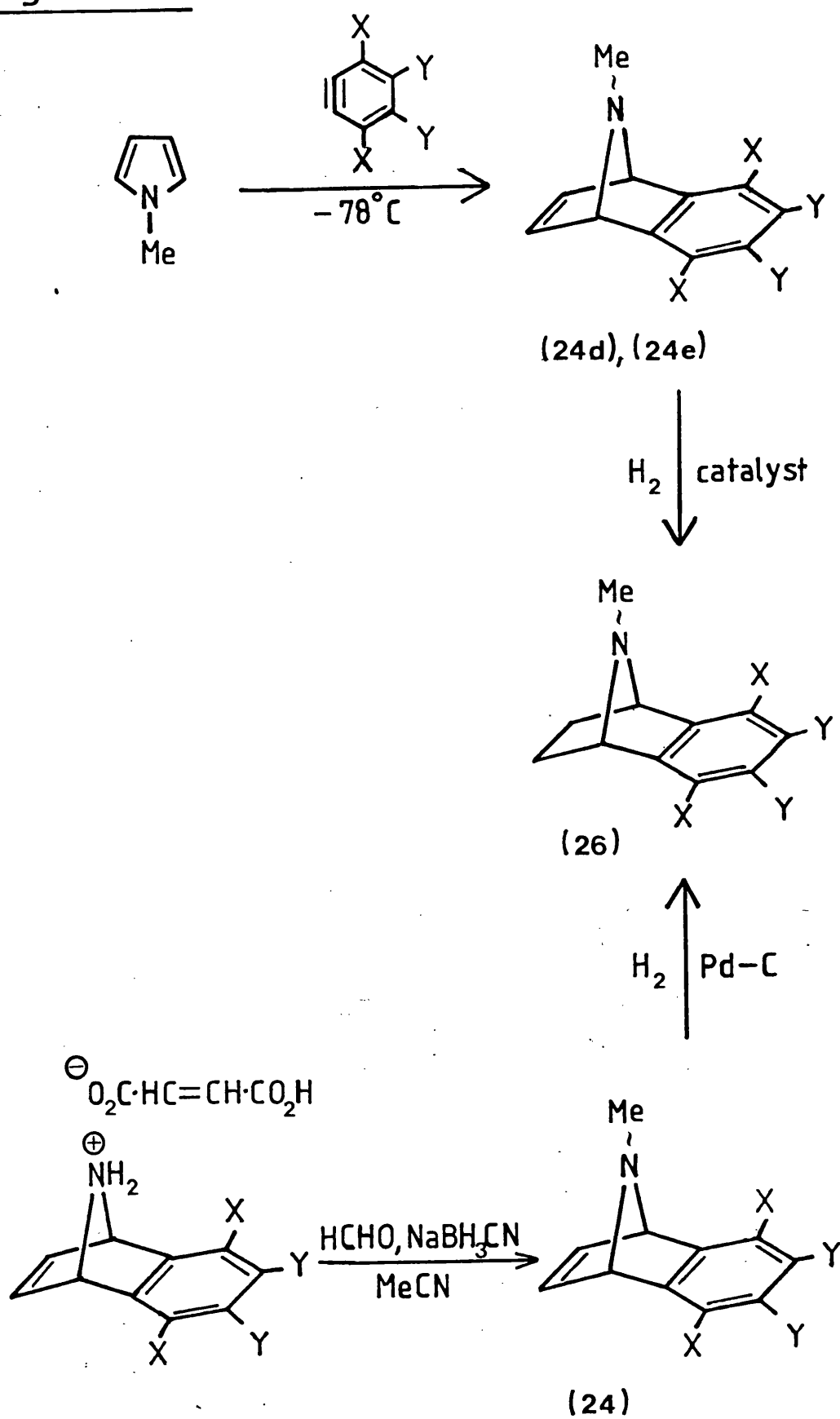


Figure 2.32. N-Methyl Derivatives (24) and (26)

The N-methyl derivatives (24d) and (24e) were the only substrates that could be prepared by the direct cycloaddition of tetrahalobenzyne and N-methylpyrrole^{63,64} (Figure 2.4).

Figure 2.4



The Eschweiler-Clarke methylation⁶⁵ of (27b), using 40% aqueous HCHO and HCO₂H, was unsuccessful as were modern methods such as NaH-MeI in dimethyl formamide⁶⁶ and 40% aqueous HCHO and NaBH₄⁶⁷. However, N-methylation was accomplished using the method of Borch and Hassid wherein the fumarate salts⁶¹ of (27a) - (27c) were treated with 40% aqueous HCHO and NaBH₃CN⁶⁸.

All amines were hydrogenated over 10% Pd/C at 20psi pressure of gas except (24d) where a facile hydrogenolysis of the aromatic C-Cl bonds occurred⁶⁹; (26d) was prepared by hydrogenation of (24d) over PtO₂ as catalyst with 10psi of hydrogen for 10 minutes.

3. N-Chloro Derivatives (29) and (30)

The amines (27) and (28) were chlorinated using N-chlorosuccinimide (NCS) in deuteriochloroform⁵⁹ (CDCl₃). The reactions were performed in nmr tubes and the ratio of invertomers obtained by direct integration. The invertomer ratio obtained in this way was dependent on the temperature at which the reaction was performed⁵⁹.

All preparations are more fully described in Chapter 6.

II. Invertomer Preferences

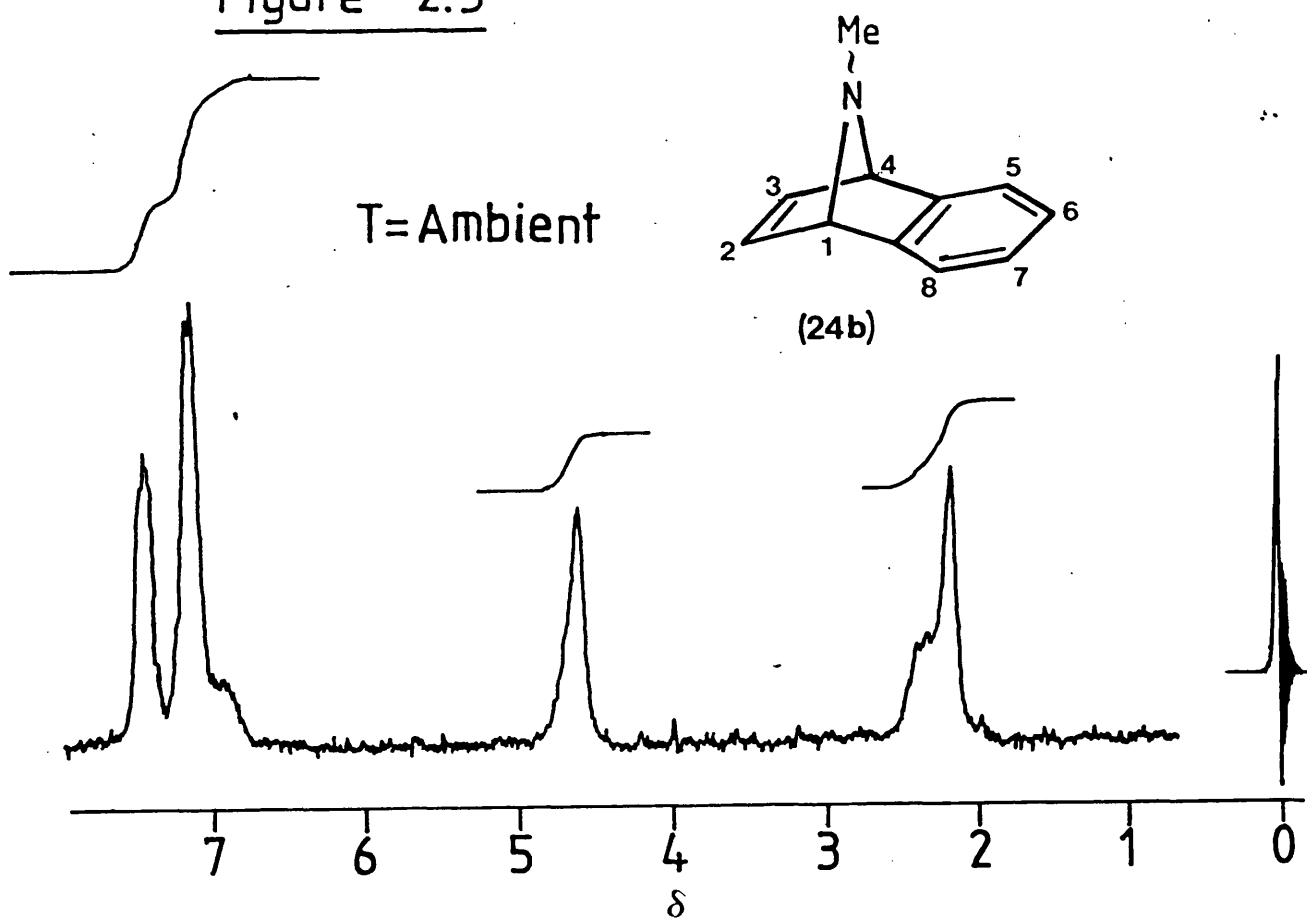
1. N-Methyl Derivatives

a. The Amines (24a) - (24e)

At room temperature in CDCl_3 solution, the signals due to the vinylic (H_2, H_3), bridgehead (H_1, H_4) and N-methyl protons in the ^1H nmr spectra of (24a) - (24e) were broadened by slow inversion on the nmr time scale. On cooling the solution to -50°C , however, the signals were split into minor and major absorptions (Figure 2.5)

For each amine, the ratio of the two invertomers was determined by direct integration of either the vinylic or N-methyl protons. The invertomer ratios of (24a) - (24e) are shown in table 2.1 with the chemical shift (δ ppm) of the N-methyl signal of each invertomer in parentheses, along with the same ratios measured by low temperature ^{13}C nmr spectroscopy. In each amine studied, the major invertomer was assigned the syn-configuration where the syn-configuration is defined as that with the N-substituent syn-to the aromatic ring. This assignment will be justified later.

In passing, the invertomer ratios reported for (24b), (24d) and (24e) in this work conflict with the ratios reported previously for these amines. Morishima has found that, for (24b), the major invertomer constituted 80% of the mixture of the two configurations^{37,70}. In the present study, the ratio of 71:29 in favour of the syn-configuration was confirmed by the 100MHz ^{13}C nmr spectrum of (24b) at -55°C (Figure 2.6). The average ratio of the six pairs of major and minor carbon resonances was 69:31 which was in excellent agreement with the ratio obtained from ^1H nmr spectroscopy, particularly in view of the greater errors associated with the integration of ^{13}C

Figure 2.5

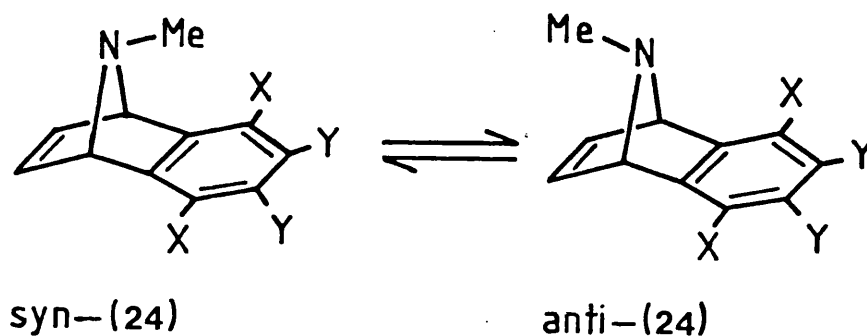
T=-50°C

N-Me

H-2,3+Ar

H-1,4

Table 2.1

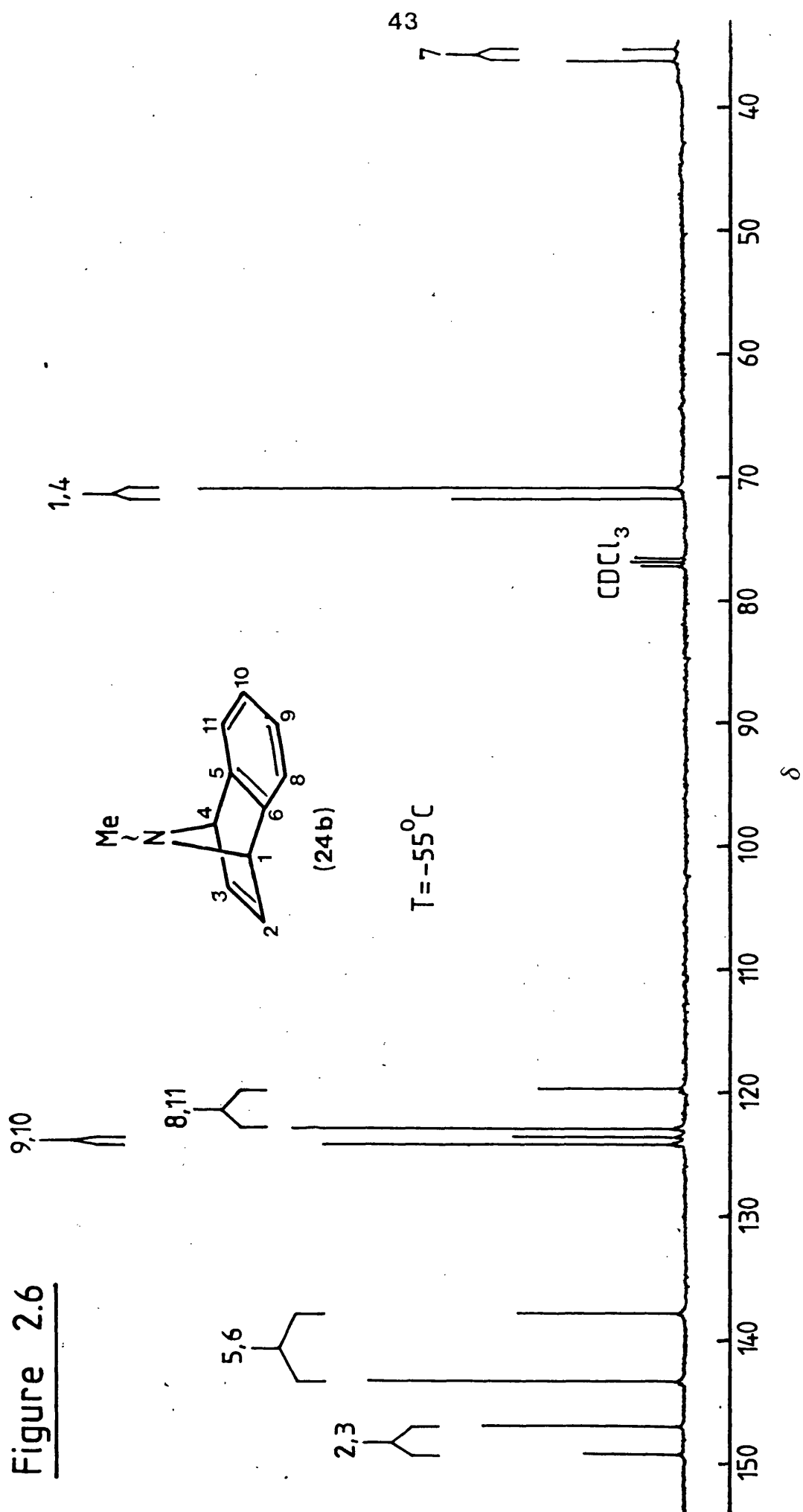


<u>Compound</u>	<u>Invertomer Ratio^a</u>	
	<u>by ¹H nmr</u>	
	<u>syn-Me : anti-Me</u>	
	<u>Invertomer Ratio</u>	
	<u>by ¹³C nmr</u>	
	<u>syn-Me : anti-Me</u>	
(24a) ^b	70 : 30	
(24b)	71(2.10) : 29(2.36)	69 : 31
(24c)	80(2.18) : 20(2.36)	80 : 20
(24d)	82(2.22) : 18(2.36)	77 : 23
(24e)	88(2.18) : 18(2.36)	84 : 16

a. $\pm 2\%$.

b. The ¹H chemical shifts of the N-methyl signals could not be measured accurately at 100MHz due to overlap with the aromatic methyl signals.

Figure 2.6



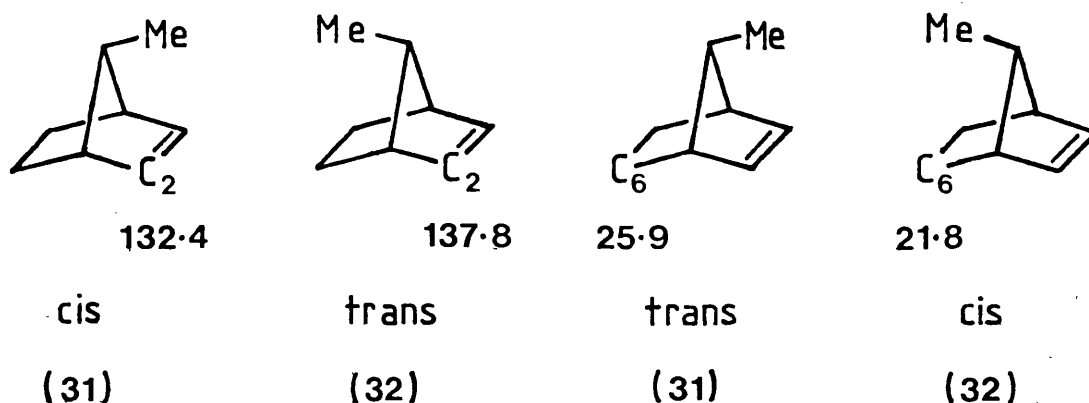
nmr spectra⁷¹. The standard deviation of the ratio over the six pairs was $\pm 1\%$.

Gribble has reported invertomer ratios for (24d) and (24e)³⁶ (Figure 1.14) but these differ by 7% and 5% respectively from those found in this study by ¹H nmr spectroscopy. Freshly purified materials were used in repeat experiments but similar ratios were measured thus eliminating the presence of impurities as reasons for such discrepancies. ¹³C nmr spectroscopy was less helpful in these cases because the average invertomer ratio measured for (24d) varied widely over the six pairs of resonances with a standard deviation of $\pm 6\%$ and the ratio for (24e) could only be measured on just two sets of major and minor absorptions. Extensive ¹³C-¹⁹F coupling in the ¹³C spectrum of (24e) broadened and reduced the intensity of the aromatic carbon signals making analysis impossible. Even so, despite the lack of corroborating evidence for the invertomer ratios of these two amines measured in this study, the differences with the earlier report are not energetically significant. It is noteworthy in this respect that the invertomer ratios of such amines are sensitive to the polarity of the solvent. When (24b) and (24e) were each dissolved in d₄-methanol (CD₃OD) and cooled to -20°C and -55°C respectively, the ratios were 61:39 and 82:18. As before, the syn-configuration was assigned to the major invertomer.

The syn-configuration was assigned to the structure of the major invertomer in the amines studied here on the basis of two substantial pieces of evidence:-

i) Low Temperature ^{13}C Nmr Spectroscopy

The configurations of the minor and major invertomers of (24b) had been assigned previously³⁷ by using a sensitive stereochemical probe known as the " γ -effect of methyl substitution"⁷¹ in analysing the low temperature ^{13}C nmr spectrum of this amine. The γ -effect is illustrated by the ^{13}C chemical shifts of C-2 and C-6 of syn- and anti-7-methylbicyclo(2.2.1)hept-2-ene, (31) and (32) (Figure 2.7). When a carbon atom is eclipsed by a methyl group (or carbon atom) in the γ -position to it, the ^{13}C chemical shift of that carbon atom occurs at higher field than the chemical shift of the same carbon atom when the γ -substituent is trans to it. Thus, the vinylic carbon atom C-2 in (31) was observed to resonate at 132.4ppm, 5.4ppm upfield to the same carbon atom in (32). Similarly, C-6 in (32) was observed to resonate upfield of its counterpart in (31) because of the compression shift induced by the eclipsing γ -methyl group.



^{13}C Chemical shifts in δppm from tetramethylsilane (TMS)

Figure 2.7

The same analysis was obviously applicable to (24a)-(24e) and was particularly helpful in these cases since both syn- and anti- configurations could be observed by ^{13}C nmr spectroscopy simply by lowering the temperature. A typical spectrum is shown in figure 2.6. The problem was then reduced to one of being able to assign the pairs of resonances to the appropriate carbon atoms.

The major and minor absorptions of (24a) and (24c)-(24e) were assigned to their respective carbon atoms by calculating the total increment to be added to the chemical shifts of C-5, 6, C-8, 11 and C-9, 10 of (24b) due to the various substituents on the aromatic ring (Table 2.2) and then comparing these predicted shifts to those observed.

Table 2.2

<u>Compound</u>	<u>C-5,6</u>	<u>C-8,11</u>	<u>C-9,10</u>
(24a)	-2.4	+6.6	+10.2
(24c)	-13.4	+23.7	-13.4
(24d)	+1.1	+6.0	+8.3
(24e)	-14.6	+18.8	+10.4

The calculations were based on the increment (δ ppm) reported in reference 71b.

In many instances, the predicted values correlated very closely with those measured from the spectra. This will be apparent from table 2.3 which contains the ^{13}C chemical shifts of C-2, 3, C-5, 6, C-8, 11 and C-9, 10 of (24a)-(24e) with the predicted values in parentheses.

Compound		C-2,3	C-5,6	C-8,11	C-9,10
(24a)	Major	143.63	145.58(144.55)	131.55(129.59)	133.11(134.44)
	Minor	140.00	146.48(146.85)	127.91(126.26)	132.20(133.85)
	$\Delta\delta$	3.63	-0.09 (-2.30)	3.64 (3.33)	0.91 (0.59)
(24b)		143.32	146.95	122.99	124.24
		137.88	149.25	119.66	123.65
		5.44	-2.30	3.33	0.59
(24c)		143.76	135.07(133.55)	150.18(146.69)	109.70(110.84)
		138.21	135.07(135.85)	146.64(143.36)	109.23(110.25)
		5.55	0 (-2.30)	3.43 (3.33)	0.47 (0.59)
(24d)		143.37	147.12(148.05)	127.77(128.99)	128.81(132.54)
		138.78	148.91(150.35)	126.93(125.66)	128.21(131.95)
		4.59	-1.79 (-2.30)	0.84 (3.33)	0.60 (0.59)
(24e)		143.15	^a (132.35)	^a (141.79)	^a (134.64)
		138.16	^a (134.65)	^a (138.46)	^a (134.05)
		4.99			

a. The signals due to the aromatic carbons of (5e) were not visible due to extensive ^{13}C - ^{19}F coupling.

In each case, the chemical shift of C-5, 6 carbons in the major invertomer was upfield of the shift of the minor. Thus, in the major invertomer, the N-methyl group eclipsed C-5, 6 leading to the conclusion that the major invertomer had the N-methyl group syn- to the aromatic ring. This was confirmed by the observation that the major C-2, 3 resonance (where the N-methyl group does not eclipse C-2, 3) was downfield of the minor in each amine.

ii) ^1H Chemical Shift Correlations

The major resonance of the two N-methyl signals in the ^1H nmr spectra of each of (24b)-(24e) at -55°C was at higher field than the minor. Furthermore, the chemical shift of the minor N-methyl signal remained unchanged at δ 2.36 in these amines, despite the changing electronic character of the aromatic ring, whilst greater variation was observed in the value of the chemical shift of the major N-methyl signal. This observation can be explained if it is assumed that the magnetic environment of the methyl group in the syn- invertomer is more sensitive to the electronic character of the aromatic π - cloud, much more so than when the same methyl group is in the anti-configuration. The downfield signal was thus assigned to the N-methyl group of the anti-invertomer.

Support for the assumption that the chemical shift of a syn-methyl group will be more sensitive to the electron density of the adjacent aromatic ring was provided by the ^1H chemical shifts of the syn- and anti- N-methyl groups of the quaternary salts generated by reaction of (24) and (26)

with deuterated alkylating agents such as trideuteriomethyl iodide (CD_3I), hexadeuteriodimethyl sulphate ($(\text{CD}_3)_2\text{SO}_4$) and trideuteriomethyl fluorosulphonate (CD_3FSO_3) (See Ch. 4). The general forms of the two salts generated by this reaction are shown in figure 2.8 for the amines (24).

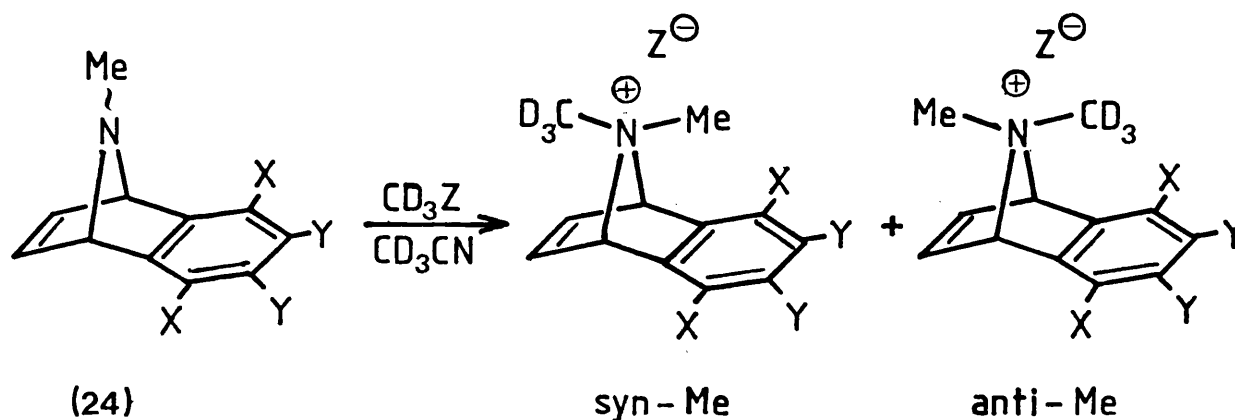


Figure 2.8

The chemical shifts of the N-methyl groups of such diastereoisomeric salts were separated by 0.25-0.45ppm and tabulation of the shifts of the N-methyl groups in all the quaternary salts made revealed a pattern similar to that in table 2.1 : the chemical shift of the N-methyl signal at lower field was relatively insensitive to the substituents on the aromatic ring whilst that at higher field showed greater variation with substituent (Table 2.4).

Further proof that the syn-N-methyl group resonated at higher field than the anti- was provided by the methiodide (35) (Figure 2.9).

Compound	CD_3I^a		$(\text{CD}_3)_2\text{SO}_4^a$		$\text{CD}_3\text{FSO}_3^a$	
	<u>syn-Me:anti-Me</u>		<u>syn-Me:anti-Me</u>		<u>syn-Me:anti-Me</u>	
(24a)	3.40	2.98				
(24b)	3.33	2.88	3.33	2.88	3.30	2.86
(24c)	3.33	2.96	3.33	2.96	3.25	2.90
(24d)	3.42	3.16	3.39	3.11	3.36	3.10
(24e)	3.43	3.16	3.36	3.08	3.32	3.05
^b $\Delta\delta_{\text{max}}$	0.13	0.28	0.06	0.23	0.11	0.24
(26a)	3.18	2.82				
(26b)	3.13	2.73	3.15	2.73	3.12	2.72
(26c)	3.14	2.81	3.13	2.80	3.10	2.77
(26d)	3.18	2.95	3.14	2.91	3.20	2.93
(26e)	3.26	2.98	3.23	2.96	3.18	2.91
^b $\Delta\delta_{\text{max}}$	0.13	0.18	0.10	0.23	0.10	0.21

a. Chemical shifts in δ ppm from TMS.

b. $\Delta\delta_{\text{max}}$ is the largest chemical shift difference in any two of N-methyl signals.

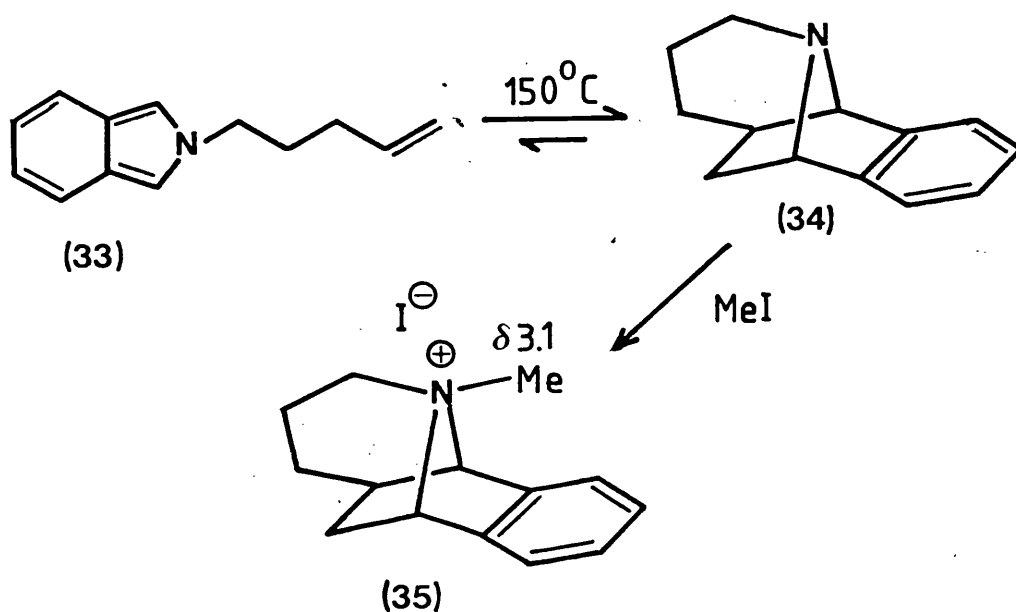


Figure 2.9

Recently, the rigid amine (34) was prepared by distillation of the isoindole (33)⁷². The amine (34) cannot undergo inversion without severe distortion and therefore quaternisation can only take place syn- to the benzene ring. The methiodide (35) is structurally very similar to one of the trideuteriomethiodides formed on quaternisation of (26b) with CD_3I (Figure 2.10).

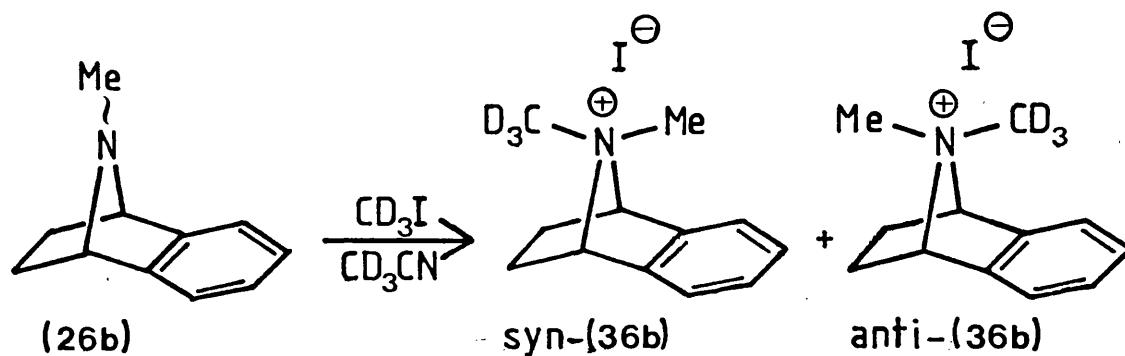


Figure 2.10

When the mixture of syn- and anti- (36b) was dissolved in CDCl_3 , the upfield resonance of the two N-methyl signals occurred at δ 3.10, in exact coincidence with chemical shift of the N-methyl group of (35). The protons of a syn-N-methyl group in these amines and their derived quaternary salts clearly experience the shielding effect of the aromatic ring.

The conclusion that the major invertomer in each of the amines (24a)-(24e) has the syn-configuration is in agreement with the conclusions of Morishima³⁷ and Underwood⁵¹ in their work with (24b) and (24e). This preference was not confined to the amines (24a)-(24e). The amines (37) and (38e) (Table 2.5) were synthesised and the invertomer ratios measured by ^1H nmr spectroscopy in the normal way.

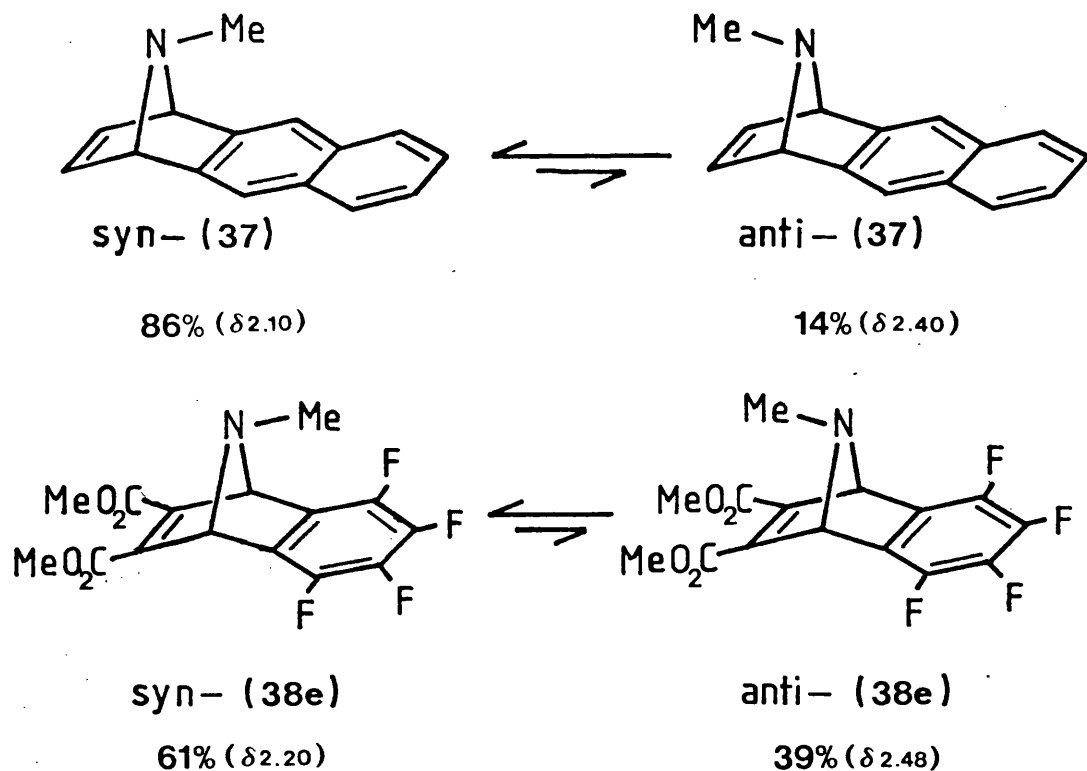


Table 2.5

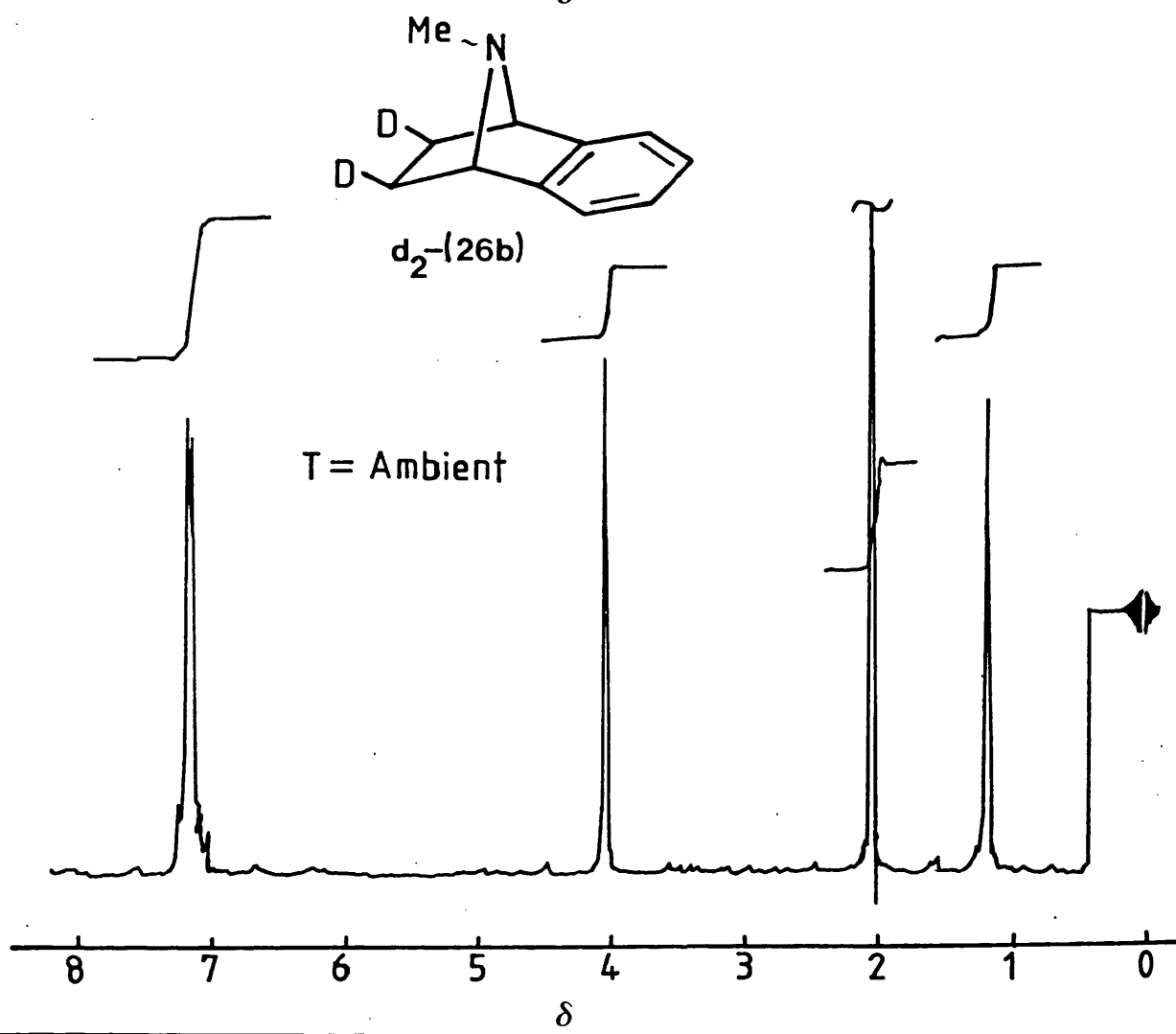
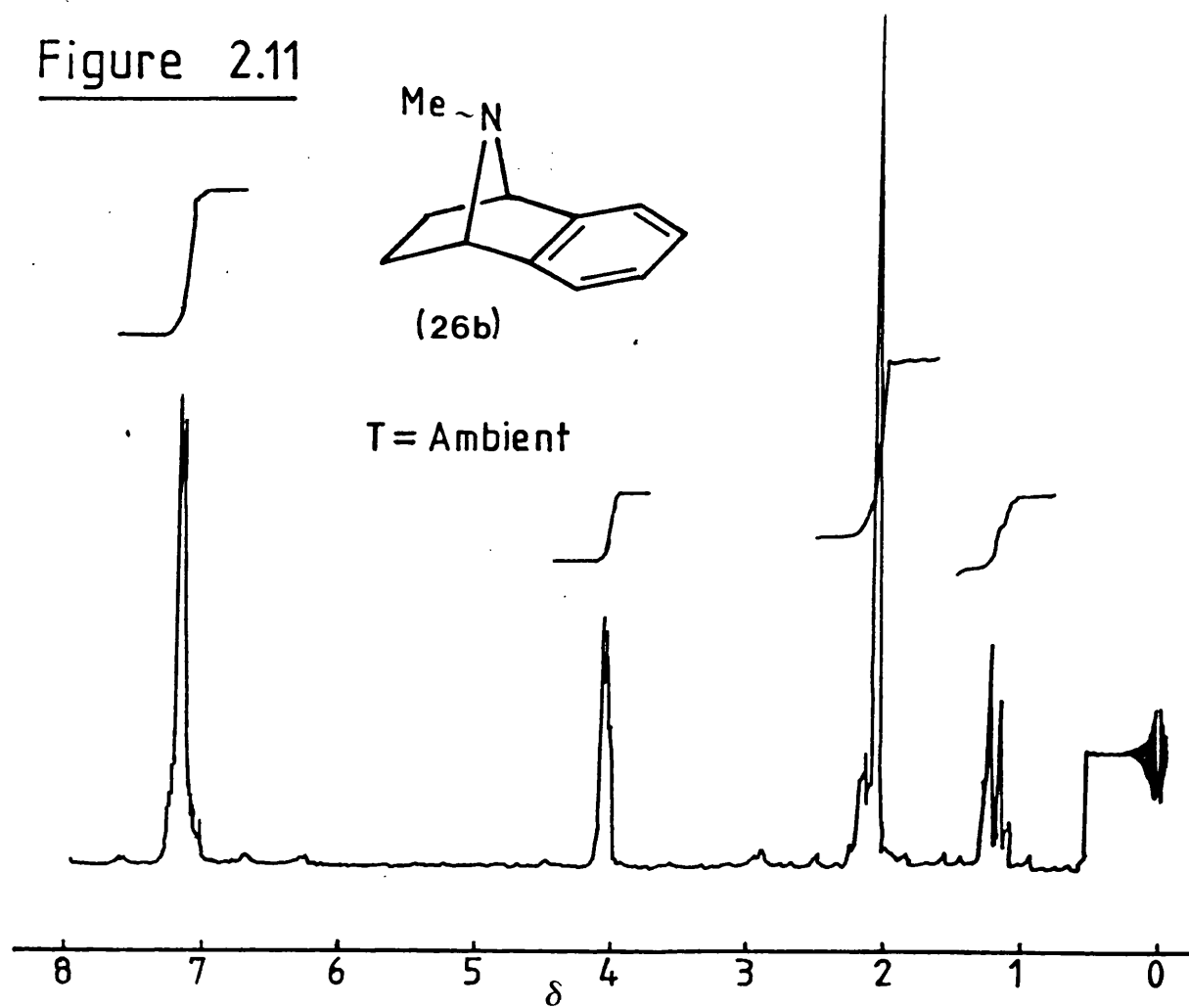
The major invertomer in each amine was assigned the syn-configuration on the basis of the close chemical shift correlations with the syn-N-methyl group of (24b) and (24e), the obvious analogues of (37) and (38e) respectively.

The advantage of this study is that direct measurement of real invertomer ratios has been made, rather than basing conclusions as to the preferred configuration of the lone pair in such amines on the invertomer ratio of a solitary example, the more general lone pair preferences implied indirectly by contact shift studies or from photoelectron spectroscopic data. Moreover, it is clear here and in the following sections that consistent results emerge from a family of related compounds, reinforcing the validity of the approach.

b. The Amines (26b)-(26e)

None of the signals in the 100MHz ^1H nmr spectra of (26b), (26c) or (26e) were separated into minor and major resonances when CDCl_3 solutions of these amines were cooled to -65°C . The most sensitive probe for the inversion process should have been the N-methyl signals at ca. δ 2.1 but this signal was coincident with the broad, complex absorption of the exo-2,3 protons in each amine (Figure 2.11). Thus, it was not possible to judge whether or not there was any splitting of the N-methyl signal as the rate of inversion was reduced, despite the report by Morishima³⁷ that the N-methyl signals of (26b) had been used to calculate the invertomer ratio of 94:6. In our hands, these signals were not resolved even at 220MHz operating frequency.

The substitution of deuterium atoms in place of the exo-2,3 protons of (26b)⁷³ had, however, allowed the invertomer

Figure 2.11

ratio of d_2 -(26b) to be measured by ^1H nmr spectroscopy ¹³ because the two N-methyl resonances at low temperature could be observed and accurately integrated, unencumbered by the exo-2,3 proton signal. The anticipated^{74,75} exo-, syn- addition of deuterium to (24b)-(24e) over Pd/C was confirmed by the singlet resonances of the 1,4-bridgehead and endo-2,3 proton signals (dihedral angle ca. 90° , therefore $J=0\text{Hz}$, Figure 2.11). Therefore, in view of their straightforward synthesis, the d_2 -analogues of (26b)-(26e) were used to measure the invertomer ratios. In all but one case, however, the attempts made to measure those invertomer ratios by ^1H nmr spectroscopy were frustrated by the very small amounts of the minor invertomer present ($\leq 2\%$) which could not be accurately integrated. The technique was only successful for d_2 -(26b) for which a heavily weighted ratio of 94:6 was measured, in agreement with Marchand's study. This result was confirmed by the invertomer ratio measured for d_2 -(26b) from its ^{13}C nmr spectrum at -55°C (Figure 2.12). Fortunately, the small amounts of the minor invertomer in each amine were more clearly visible by ^{13}C nmr spectroscopy and the invertomer ratios of (26c)-(26e) were measured by this technique. A further advantage was that the configurational assignments of the major and minor invertomers could be made using the γ -effect of methyl substitution as before. The invertomer ratios of (26b)-(26e) are recorded in table 2.6 and the predicted and measured ^{13}C chemical shifts in δppm in table 2.7.

Figure 2.12

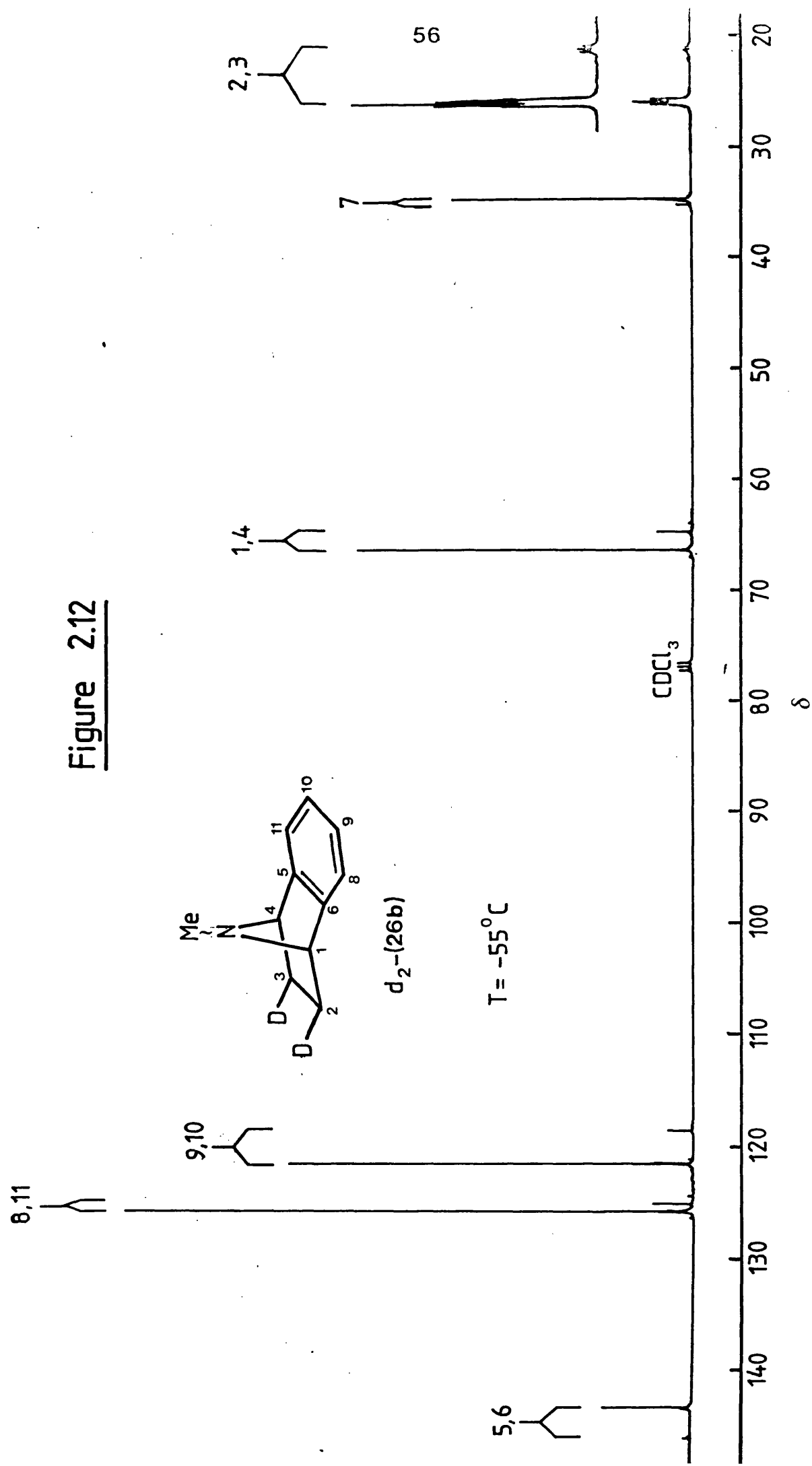


Table 2.6

<u>Compound</u>	<u>Invertomer Ratio</u> <u>syn-Me : anti-Me</u>
(26b)	94 : 6 ^a
(26c)	97 : 3 ^b
(26d)	97 : 3 ^c
(26e)	98 : 2 ^d

a. Ratio measured by ^1H nmr spectroscopy.

b. Average ratio of five; $\sigma = \pm 2\%$.

c. Average ratio of two; $\sigma = \pm 2\%$.

d. Maximum value of a single pair of resonances.

Incidentally, the same ratio (97:3) was measured from the ^{13}C nmr spectra of (26c) and d_2 -(26c) thus eliminating the possibility that the deuterium atoms had had a barrier-raising effect which had allowed the observation of two N-methyl proton signals in the ^1H nmr spectrum of d_2 -(26c) (although they could not be accurately integrated) but not in that of (26c).

In view of the excellent agreement between the invertomer ratios measured for d_2 -(26b) by both ^1H and ^{13}C nmr spectroscopy, the ratios of table 2.6 show that each amine exists almost totally as the syn-invertomer.

2. N-Chloro Derivatives

The thermodynamic invertomer ratios of the derived series of N-chloroamines (29) and (30) had been measured in previous

Table 2.7

Compound	C-2,3	C-5,6	C-8,11	C-9,10
Major	26.23	143.52	125.73	121.47
Minor	21.33	146.15	125.11	118.58
$\Delta\delta$	4.90	-2.63	0.62	2.89
(26c)	26.25	131.93(130.12)	148.80(149.43)	109.03(108.07)
	21.40	135.24(132.75)	145.70 ^b (148.81)	108.50(105.10)
	4.85	-3.31(-2.63)	3.1 (0.62)	0.53(2.97)
(26d)	25.52	(144.62)	(131.73)	(129.77)
	20.88	142.46 ^c (147.25)	129.99 ^c (131.11)	126.77 ^c (126.88)
	4.64	(-2.63)	(0.62)	(2.89)
(26e)	25.94	- ^d (128.92)	- ^d (144.53)	- ^d (131.87)
	21.54	- ^d (131.55)	- ^d (143.91)	- ^d (128.98)
	4.40	- ^d (-2.62)	(0.62)	(2.89)

a. The difference between the chemical shifts of the same carbon atoms in d₂-(26c) and (26c) was less than 0.1ppm and hence the shifts of d₂-(26b) may be substituted for (26b).

b. This shift was measured directly from the spectrum.

c. Only single resonances were observed for these carbons.

d. These signals were not clearly resolved due to extensive ¹³C-¹⁹F coupling.

work in these laboratories⁵⁹. The addition of NCS to each of the amines (27) and (28) gave rise to the syn- and anti-N-chloroamines (29) and (30) respectively (Figure 2.13), the ratios of which were dependent on the temperature at which the chlorination was performed.

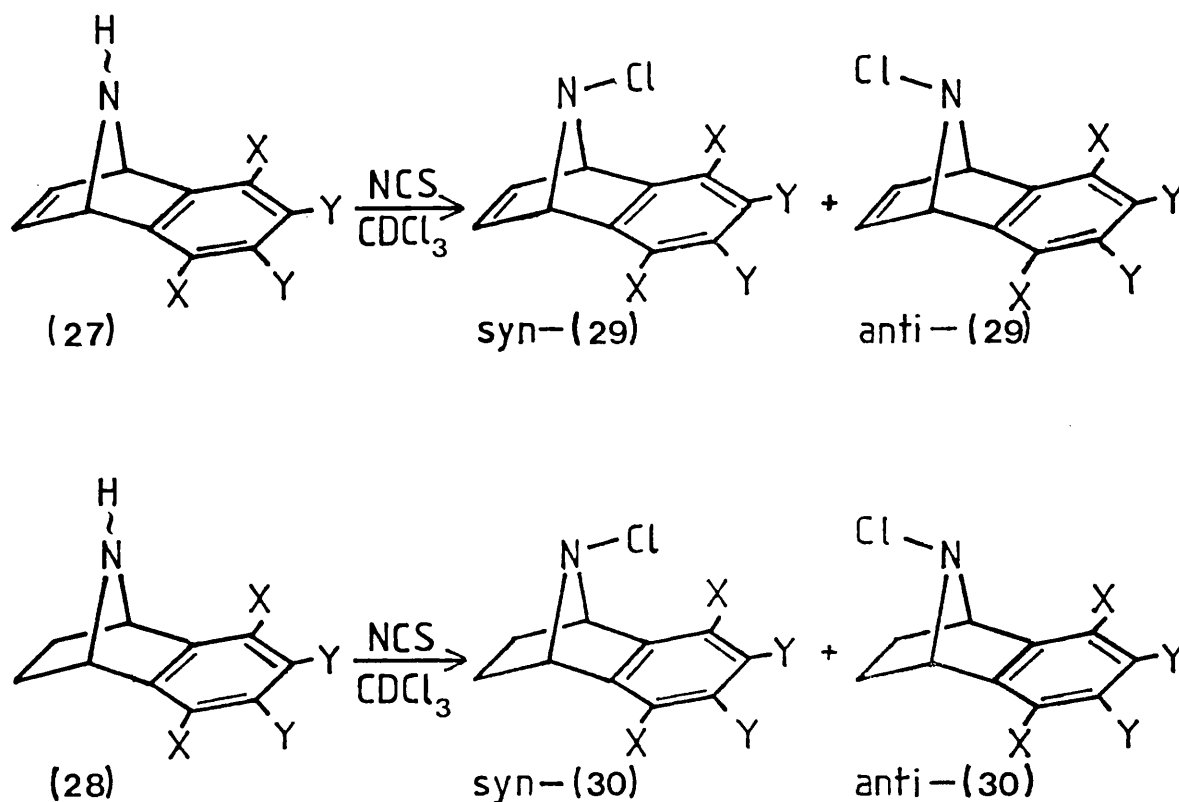


Figure 2.13

These reactions will be discussed in detail in the next chapter but, in summary, the ratios recorded at -50°C , where the product N-chloroamines could not invert (conditions of kinetic control), were found not to be stable at room temperature. Within two hours of warming to 25°C , thermodynamic equilibrium was established and the syn-/anti-

ratios then reflected the relative free energies of the two product configurations in each case. The invertomer ratios after equilibration of (29) and (30) are collected in table 2.8 and include the ratio for (29a) which was measured as part of the present work.

Table 2.8

<u>Compound</u>	<u>Invertomer Ratio^a</u>	
	<u>syn-Cl</u>	: <u>anti-Cl</u>
(29a)	63	37
(29b)	60	40
(29c)	67	33
(29d)	82	18
(29e)	84	16
(30b)	53	47
(30c)	54	46
(30d)	71	29
(30e)	80	20

a. $\pm 2\%$. The ratios are taken from reference 59, apart from that for (29a).

The thermodynamic (and kinetic) ratio of syn- and anti-(29a) were measured in the belief that the tetramethyl substituted aromatic ring would provide a truly electron rich π -system but both ratios were very similar to those measured for (29b) indicating that the methyl groups exerted no dramatic influence (Table 2.9). Consequently, the chlorination of (28a) was not studied.

Table 2.9

<u>Compound</u>	<u>Invertomer Ratio</u>	
	<u>syn-Cl</u>	<u>: anti-Cl</u>
	<u>Kinetic Ratio</u>	<u>Thermodynamic Ratio</u>
(29a)	31 : 69	63 : 37
(29b)	28 : 72	60 : 40

As with the N-methyl derivatives (24) and (26), the general thermodynamic preference in both (29) and (30) is for the syn-chloro configuration. Again, this preference was not confined to simple benzo-bridged systems.

11-Chloro-1,4-dihydroanthracen-1,4-imine (40) (Figure 2.14) was similarly observed to exist mainly as the syn-chloro invertomer.

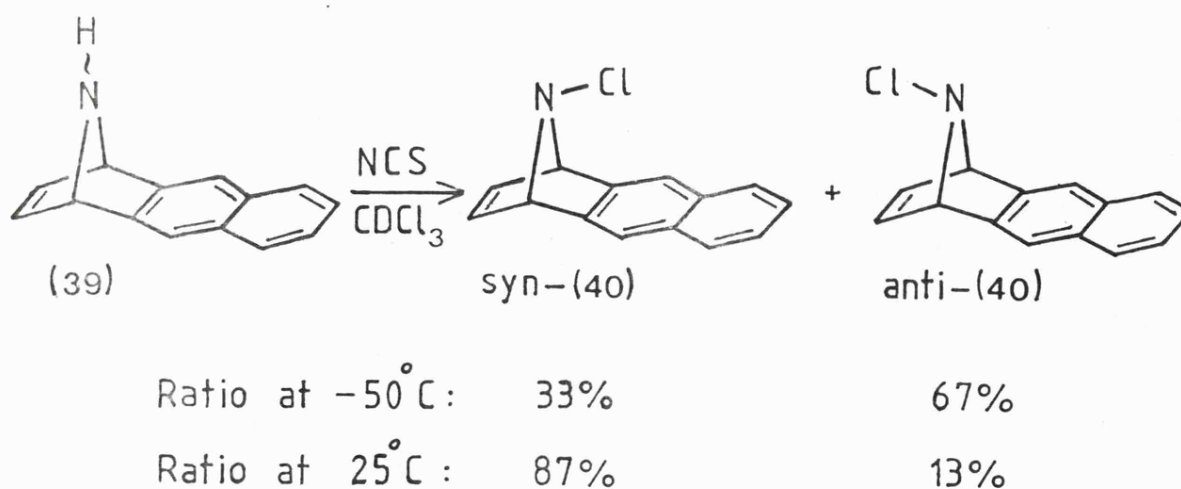


Figure 2.14

This assignment, like that for (29a), was based on the very similar ^1H chemical shift differences of the 1,4- and 2,3- protons of (40) and (29b) where for the latter compound the assignment of syn- and anti-N-chloroamines had been made independently⁵⁸(Table 2.10). Furthermore, the assignment of syn- and anti- configurations in (40) was made straightforward by the facile physical separation of one of the invertomers which, when stirred in dry methanolic silver perchlorate (AgClO_4), gave a product which could arise only from the solvolysis of the anti-chloro invertomer⁵⁸. This observation is discussed in Chapter 5.

Table 2.10

<u>Compound</u>	<u>$\text{H}_{1,4}^{\text{a}}$</u>	<u>$\text{H}_{2,3}^{\text{a}}$</u>
(29b) syn-	6.75	4.67
anti-	6.65	4.87
$\Delta\delta$	-0.10	0.20
(29a) syn-	6.97	5.06
anti-	6.84	5.24
$\Delta\delta$	-0.13	0.18
(40) syn-	6.84	4.98
anti-	6.78	5.20
$\Delta\delta$	-0.06	0.22

a. Chemical shifts in δ ppm from TMS.

3. Discussion

The ground state, thermodynamic invertomer ratios of the N-methyl- and N-chloro- derivatives (24), (26), (29) and (30) are collected together in table 2.11 along with the free energy differences between the major and minor invertomers at 298K.

a. 1,4-Dihydro- Systems (24) and (29)

There are two important conclusions to be drawn from these invertomer ratios.

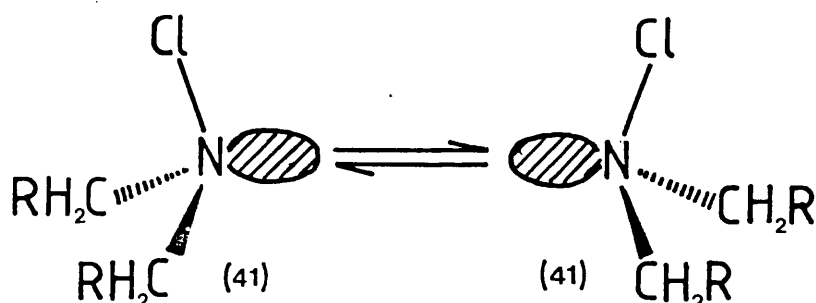
- i) There is a clear preference for the syn- configuration in both the N-methyl and N-chloro series and the predominance of the syn-invertomer increases with increasing electronegativity of the substituents on the aromatic ring.
- ii) There seems to be little dependence of the invertomer ratio on whether the substituent at nitrogen is a methyl or a chlorine group in 1,4-dihydronaphthalen-1,4-imines with the same substituents in the benzene ring. A further, striking similarity of invertomer ratio is observed between the amines (37)(86:14) and (40)(87:13) showing the very small effect of the substitution of halogen for the methyl group.

Both of these observations are contrary to predictions based on Morishima's model that the bishomoallylic interaction of the nitrogen lone pair is a destabilising one and that, when faced with overlap with two π -orbitals, the lone pair will overlap with the less electron-rich of the two. Firstly, if lone pair - π -orbital interactions determine the preferred stereochemistry at nitrogen in these azabicyclic systems, then the extent of such overlap will also be an important factor.

Table 2.11

N-Methyl Derivatives	Invertomer Ratio		$\Delta G_{298}^{\ominus}$ (kJmol ⁻¹)	N-Chloro Derivatives		Invertomer Ratio	$\Delta G_{298}^{\ominus}$ (kJmol ⁻¹)
	syn-Me	anti-Me		syn-Cl	anti-Cl		
(24a)	70 : 30		2.10	(29a)	63 : 37		1.32
(24b)	71 : 29		2.22	(29b)	60 : 40		1.07
(24c)	80 : 20		3.43	(29c)	67 : 33		1.76
(24d)	82 : 18		4.30	(29d)	82 : 18		3.76
(24e)	88 : 12		4.94	(29e)	84 : 16		4.11
(26b)	94 : 6		6.82	(30b)	53 : 47		0.30
(26c)	97 : 3		8.61	(30c)	54 : 46		0.40 $\frac{\text{O}}{\text{N}}$
(26d)	97 : 3		8.61	(30d)	71 : 29		2.22
(26e)	98 : 2		9.64	(30e)	80 : 20		3.44

The lone pair of an N-chloroamine will be much less diffuse than the lone pair of a tertiary N-alkyl amine because of the increase in s-orbital character induced by the electronegative chlorine. An example of this effect has been observed by Jennings who found that the inversion barriers of the N-chloroamines (41) were insensitive to the polarity of the solvent used⁷⁶ (Figure 2.15).



	<u>Solvent</u>	<u>$\Delta G^\ddagger$ (kJ mol⁻¹)</u>
R = Pr ⁱ	CHCl ₂ F	39.71
	CD ₃ OD	39.71

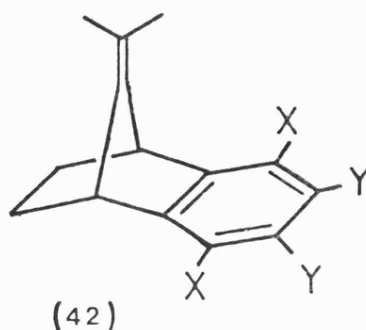
Figure 2.15

Thus, the substitution of chlorine for methyl would be expected to lead to an increase in the amount of the minor invertomer based on Morishima's model, since the degree of destabilisation would be lessened by the reduced n- π interactions. Only slight increases in the amounts of anti-invertomer are observed for (29a)-(29c) compared to (24a)-(24c) and these increases are very small in energy

terms ($\Delta G_{298}^{\ominus} = \text{ca. } 1 \text{ kJmol}^{-1}$). Furthermore, there are as many ratios - for (29d), (29e) and (40) - which do not differ from those observed for their N-methyl analogues (24d), (24e) and (37). This points to the minor role of the lone pair in determining the preferred configuration at nitrogen.⁵⁰

Secondly, the observation that the proportion of the syn- invertomers of (24) and (29) increases as the electronegativity of the aromatic substituent increases is also contrary to the expectation of Morishima's hypothesis. In Morishima's view, the lone pair of (24b) prefers the anti-configuration because the energy of the highest occupied molecular orbital (HOMO) of the benzene ring is greater than the energy of the 5,6- double bond i.e. the "double bond" of the benzo-bridge is the more "electron-rich" of the two. It would be anticipated that the energy of the HOMO of the tetrafluoro- substituted ring in (24e) (and (29e)) would be less than that of (24b) because the powerful -I effect of the fluorine atoms will denude the aromatic carbon nuclei, increasing the attraction of the nuclei for the electrons of the π -cloud and make the π -cloud less diffuse.⁷⁷ n- π Interactions will be reduced and consequently, the proportion of the anti-invertomer (syn- lone pair) in (24e) should be greater than in (24b).

The stabilisation of the HOMO of a tetrafluoro substituted aromatic ring is illustrated by the gradation of the vertical ionisation potentials of a range of 1,4-dihydro-1,4-isopropylidenenaphthalenes(42)⁷⁸(Figure 2.16).



Vertical Ionisation Potential (eV)

	<u>a'(π)</u>	<u>a''(π)</u>	<u>a'(π)</u>
X=Y=H	8.20	8.70	8.85
X=OMe, Y=H	8.20	7.70	8.70
X=Y=F	9.03	8.75	9.03

Figure 2.16

In view of the structural similarity between (42) and the amines (24) and (29), it seems reasonable to anticipate a corresponding deepening of the energy of the HOMO of the aromatic rings in (24e) and (29e) compared to (24b) and (29b). A reduction in the level of n- π interactions in the fluorinated amines runs counter to the observed preference for the syn- invertomer (anti- lone pair) in these amines using Morishima's model.

Finally, the fact that the free energy difference at 298K between the two most extreme ratios in each of the series (24a)-(24c) and (29b)-(29e) are only 2.84 and 3.10 kJmol⁻¹

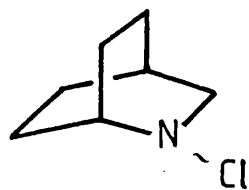
and, indeed, that these amines exist as mixtures of invertomers at all, suggests that homoconjugative interactions are of minor energetic consequence⁵⁰.

b. 1,2,3,4-Tetrahydro- Systems (26) and (30)

In the N-methyl amines (26), the syn-configuration is preferred to the virtual exclusion of the anti-. This is undoubtedly due to the increase in steric congestion of the N-methyl group with the exo-2,3-protons in the anti-configuration. The syn-configuration of the amines (24a)-(24e) is, by comparison, relatively unhindered. The fact that the greatest variation in invertomer ratio amongst (26b)-(26e) is only 4%, compared to much larger maximum variations in (24a)-(24e)(28%), (29a)-(29e)(21%) and (30b)-(30e)(27%), points to a common factor such as this dictating the stereochemical preference.

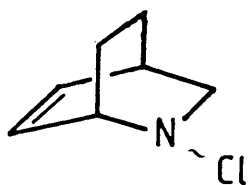
Examples in which steric congestion raises the energy of one amine invertomer relative to its diastereoisomer are widespread. In N-methyl piperidine, the inverting methyl group has been shown to exist predominantly in the equatorial position position⁷⁹. As in cyclohexane chemistry, 1,3- diaxial interactions dominate the stereochemistry at nitrogen. It has also been reported that the major invertomers of the azabicyclic systems (43)-(46)(Table 2.12) correlate on the basis that the preferred configuration is the least sterically hindered¹⁰ and other examples exist⁸⁰.

Invertomer Ratio
exo-Cl: endo-Cl (%)



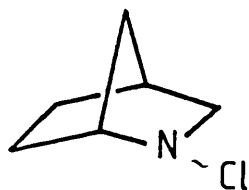
(43)

50:50



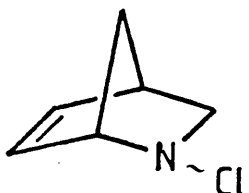
(44)

9:91



(45)

75:25



(46)

12:88

Table 2.12

The preference for the syn-invertomer in series (26b)-(26e) might be interpreted as evidence for a destabilising, bishomoallylic interaction of the lone pair with the remaining π -orbital. However, in view of the apparently minor role of the lone pair in the determination of the preferred configuration in the 1,4-dihydro-systems (24) and (29), there are no obvious reasons why the lone pair should be any more important in the 1,2,3,4-tetrahydro-systems.

Certainly, Morishima himself has noted the subordinate role of the lone pair in determining the preferred stereochemistry of N-methyl-2-azabicyclo(2.2.2)oct-5-ene (23) (Figure 1.13), instead highlighting the influence of steric factors.

In the series of N-chloroamines (30b)-(30e), the overall preference for the syn-invertomer remains, although slightly greater amounts (4-11%) of the anti-invertomer are observed. This might be explained by the reduced destabilisation of the anti-configuration by the absence of the olefinic π -bond/ $\overset{\delta^+}{\text{N}}\text{-}\overset{\delta^-}{\text{Cl}}$ dipole repulsion present in (29a)-(29e)¹¹.

Steric congestion of the chlorine atom with the exo-2,3 protons will replace the former electrostatic repulsion but the level of congestion will be lower than that in the N-methyl compounds (26) because of the obvious difference in size of the nitrogen substituents.

These results lead us to the conclusion that homoconjugative $n\text{-}\pi$ interactions are of minor consequence in determining the invertomer ratios in the bicyclic amines studied here. There appears to be no great preference in any of these amines for one configuration except for the series (26b)-(26e) where the preference for the syn-configuration can be explained by obvious steric factors. These results form an adjunct to recent reports that:

- i) homoconjugative interactions between neutral, closed shell systems are destabilising^{54b} and that
- ii) systems undergoing such an interaction will distort to minimise the repulsive effects^{50,54b}.

The evidence for such conclusions arises from observations such as the crystal structure of the hydrocarbon C_{16} -hexaquinacene (47) (Figure 2.17) which revealed an outward puckering of the cyclopentene-like rings⁸¹. These distortions are in the opposite direction to that anticipated if the π -electrons of the three double bonds had overlapped homoconjugatively. Even when ideally positioned for overlap, the repulsive interaction dominates.

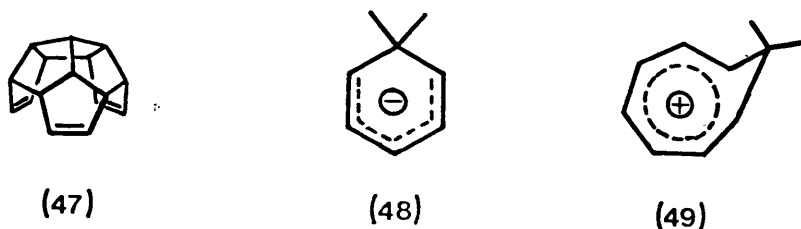


Figure 2.17

Olah et al. has found that, on the basis of detailed 1H and ^{13}C nmr spectroscopic studies, the cyclohexadienyl anion (48) (Figure 2.17) was a planar, non-homoaromatic system despite the presence of 6π electrons^{54a}. Unlike the isoelectronic homotropylium cation⁸²(49), the anion (48) does not undergo a distortion to allow contiguous overlap of p-orbitals and hence acquire aromatic stability.

The question of whether the overlap of closed shell n and/or π -electrons can imbue some degree of aromatic character was raised by Goldstein who extended the idea of homoaromaticity to include small, bicyclic carbon systems which contained a total of $4n$ or $(4n+2)\pi$ -electrons in unsaturated bridges⁸³. Despite the elegance of the mathematical construction, there was very little hard experimental observation to support it⁸⁴. The enhanced acidity

of (50) relative to (51) was claimed to be due to homoaromaticity of the 6π electrons in (52), a stabilisation not available in (53) (Figure 2.18) but calculations performed independently by both Grutzner^{54c} and Mayr^{54d} have since suggested that the electronegative inductive effect of the unsaturated σ -framework in (50) could account for the relative acidities.

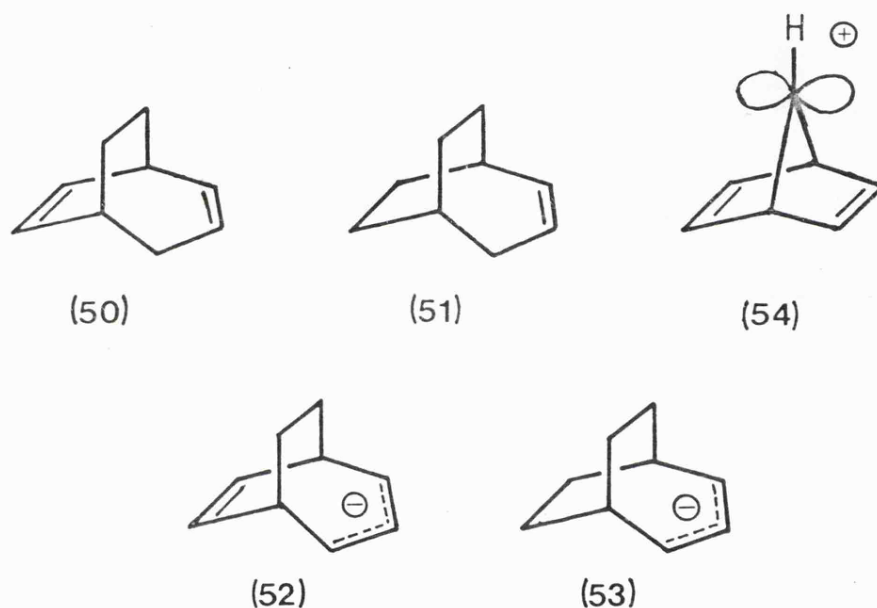


Figure 2.18

These molecular orbital analyses both suggest that the energy difference of the π -orbitals of the two- and three-carbon bridges is too great to allow mixing. This contrasts with the unusual stability of the cation (54) (Figure 2.18) which is due to the overlap of 2π electrons with an empty p-orbital of similar energy⁸⁵. Some authors have suggested that homoaromaticity may be restricted to cationic systems which can undergo distortion to maximise overlap^{54a,54d}. In neutral and anionic $(4n+2)\pi$ systems, the presence of aromatic

stability arising from homoconjugative interaction is crucially dependent on the proximity of the interacting π -systems (and therefore the geometry of the molecule) and on the energy levels of the relevant orbitals⁸⁶.

This study emphasises the part to be played by bicyclic amines in the investigation of homoaromaticity in their carbocyclic analogues. The amines (24) and (55) are isoelectronic with the bicyclic anions (56) and (57) but with the advantage that they are easily prepared and amenable to extensive spectroscopic investigation (Figure 2.19).

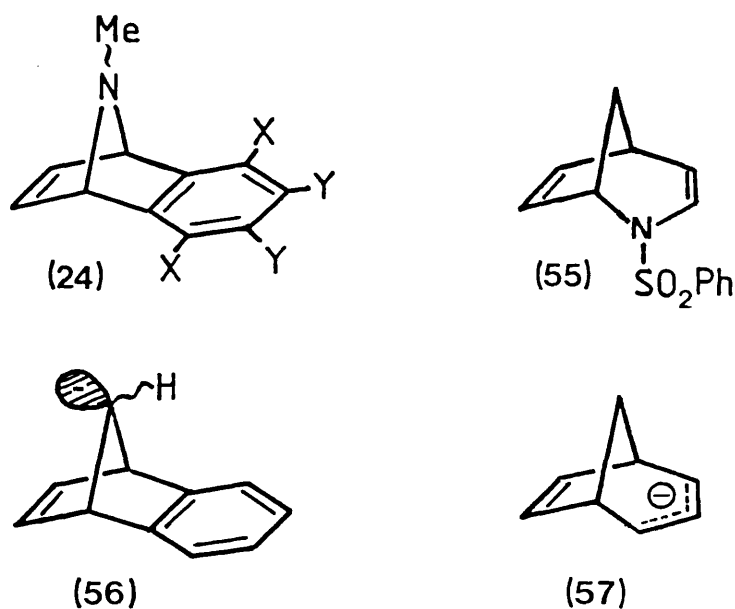


Figure 2.19

By contrast, (56)^{52b} and (57)⁸⁷ may only be studied by the results of deuteron capture of an intermediate anion or at 0°C or below. Young's recent investigation⁸⁸ of the amine (55) revealed that there was no special contribution from $(4n+2)\pi$ neutral bishomoaromatic character.

Despite the weight of evidence against any energetic significance arising from homoconjugative $n-\pi$ interactions,

including the work described here, contrary reports continue to appear. Anastassiou has suggested that the bridged amine (58) (Figure 2.20) shows a photoelectron spectrum consistent with a strong, conjugative interaction of the π -ribbons and lone pair⁸⁹. It must be noted, however, that this was the only bicyclic system of the closely related compounds (59)-(61) to produce any evidence of bicycloconjugation⁹⁰. The upfield shift of the ^1H chemical shift of the bridging methylene group in the anion (62) (Figure 2.20) compared to the parent hydrocarbon has been presented as evidence of homoconjugative overlap of the 10π electrons present in (62)⁹¹. The geometry of the bicyclic system permits satisfactory overlap of p-orbitals. Other examples exist where n- π interactions are thought to play a significant part^{92,93}.

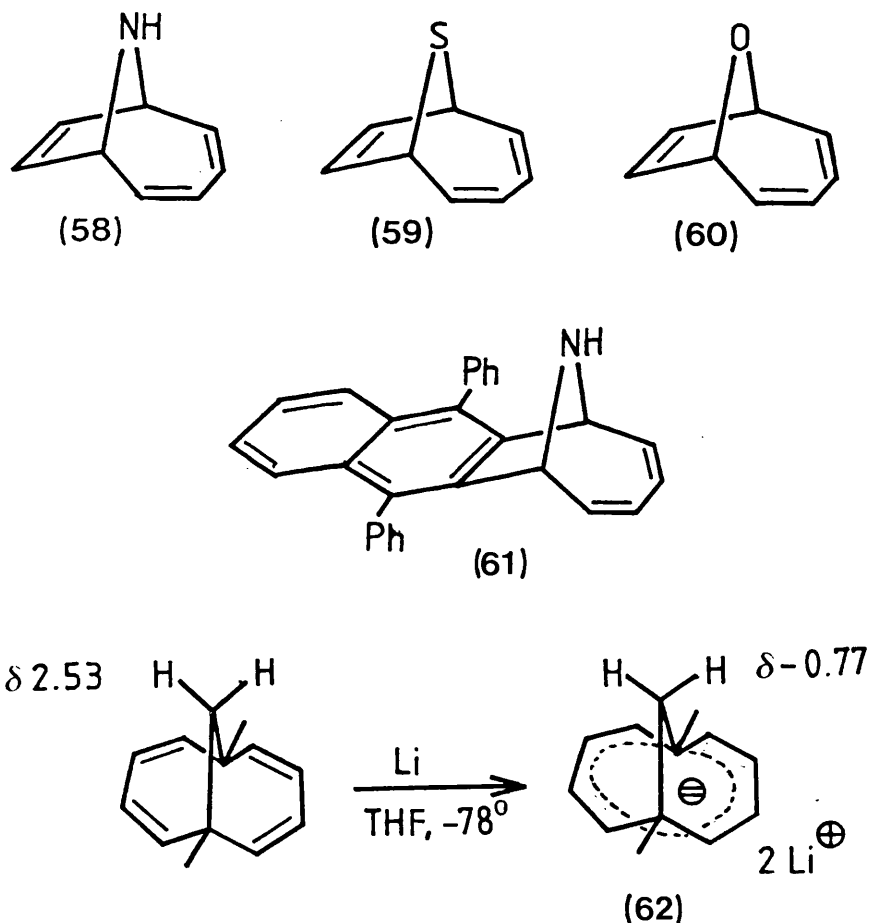


Figure 2.20

There are, however, few easily identifiable reasons to explain the preference for the syn-invertomer in (24), (29) and (30). In the N-chloroamines (29), the preference has been explained tentatively by the diminishing repulsion between the $\delta^+ \delta^-$ N-Cl dipole and the aromatic ring as the ring becomes electron deficient¹¹. This explanation fits the data but the very close similarity of the ratios of (24d), (24e) and (37) to those of the N-chloro analogues (29d), (29e) and (40) militates against such a mechanism because of the very different nitrogen substituents. If anything, the dipole moment of the N-CH₃ bond is likely to be in the opposite sense.

At first sight, a most attractive idea is that of a generalised anomeric effect⁹⁴, used by Anet to explain the unusual *amount* of the axial, equatorial conformation of N,N-dichloropiperazine (63)⁹⁵ (Figure 2.21).

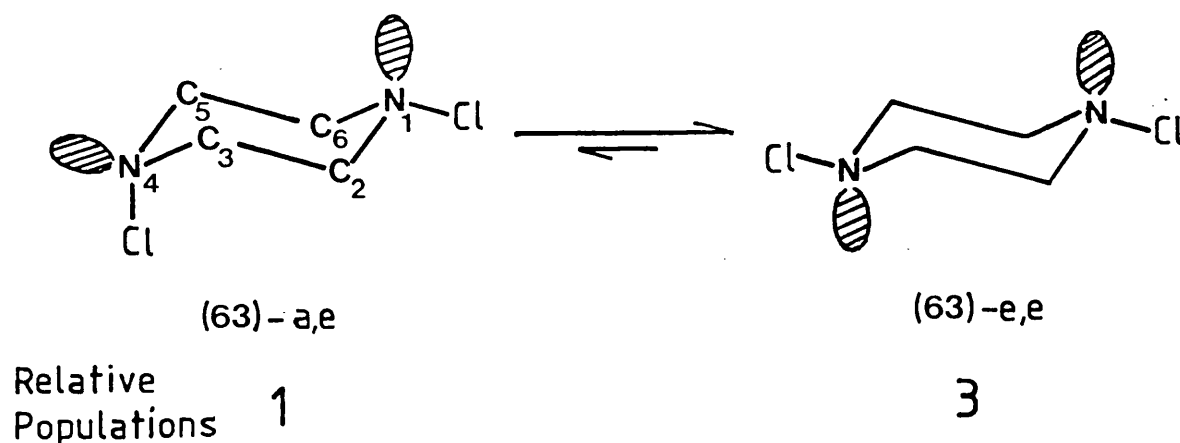


Figure 2.21

This unexpectedly²⁰ significant amount of the axial, equatorial conformation was explained by the anti-periplanar arrangement possible between the N₄-lone pair and the C₂-C₃

and C_5-C_6 bonds. Polarization in these bonds is induced by the $C_2-N_1Cl-C_6$ group. An anti-periplanar arrangement is unavoidable in the 7-azabicyclo(2.2.1)heptane skeleton (Figure 2.22).

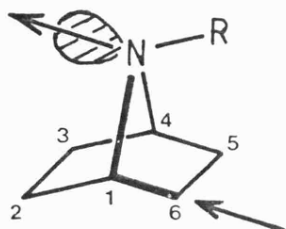


Figure 2.22

The tetrahalogenated aromatic rings of (24d) and (24e) would be expected to polarise the C_1-C_6 and C_4-C_5 bonds and, in an analogous fashion, stabilise the syn-methyl configuration where the lone pair is anti-periplanar with these bonds. However, this mechanism cannot account for the preference for the syn-configuration shown by the lone pair in the amines (27) and (28). If the anomeric effect were significant, the anti-lone pair configuration should be preferred irrespective of the substituent on nitrogen. Additionally, the similarity between the invertomer ratios of (37), (40) and (24d), (24e), (29d), (29e) also casts quite reasonable doubt over the importance of the anomeric effect in view of the undoubtedly very different electron-withdrawing abilities of the naphthalene ring and halogenated benzo groups.

In summary, it seems that a clear understanding of the precise factors which govern the observed invertomer ratios has yet to emerge but the advantage of the broad-based comparisons made here is that existing hypotheses may be evaluated in the light of a wide range of directly observed

invertomer ratios with confidence in the results.

III. Kinetic Protonation of some Naphthalen-1,4-imines

An alternative approach to the investigation of invertomer ratios at rapidly inverting nitrogen centres is to perform a very fast chemical reaction, such as protonation, at the nitrogen atom and thus achieve irreversible conversion of the two amine invertomers into a mixture of stereoisomeric ions. The rate of protonation by strong acids is diffusion- controlled⁹⁶ which is considerably faster than the rate of amine inversion and therefore the ratio of salts produced should reflect directly the thermodynamic amine invertomer ratio^{43,44}. This technique has been employed extensively in the conformational analysis of piperidines and piperazines^{43,45,79,97}, amines which possess much lower inversion barriers than those studied here.

In view of the fact that the minor invertomers of the amines (26) were present to the extent of only a few percent of the mixture, corroboration of these ratios by a second method was thought necessary. Kinetic protonation of d₂-(26b) had previously met with success¹³ so the technique was extended to other saturated amines of the series ((26b)-(26e)). It was also used in the hope that the ratios of protonated (24a)-(24e) would corroborate the ratios observed for these amines by ¹H and ¹³C nmr spectroscopy.

1. Results and Discussion

a) The Amines (24b)-(24e)

The protonations were performed by slow addition of a CDCl₃ solution of the amine to an excess of rapidly stirred 1:4 trifluoroacetic acid (TFA):CDCl₃ solution at ambient temperature¹³. The crude reaction mixtures were transferred

to an nmr tube. As a result of protonation, the N-methyl singlets of (24b)-(24e) at ca. δ 2.1 moved downfield by, on average, 0.5-0.8 ppm, became considerably sharper (since the products (64) are stable) and appeared as major and minor doublets (coupled to the NH proton) separated by ca. 0.2-0.4ppm allowing easy integration (Figure 2.23).

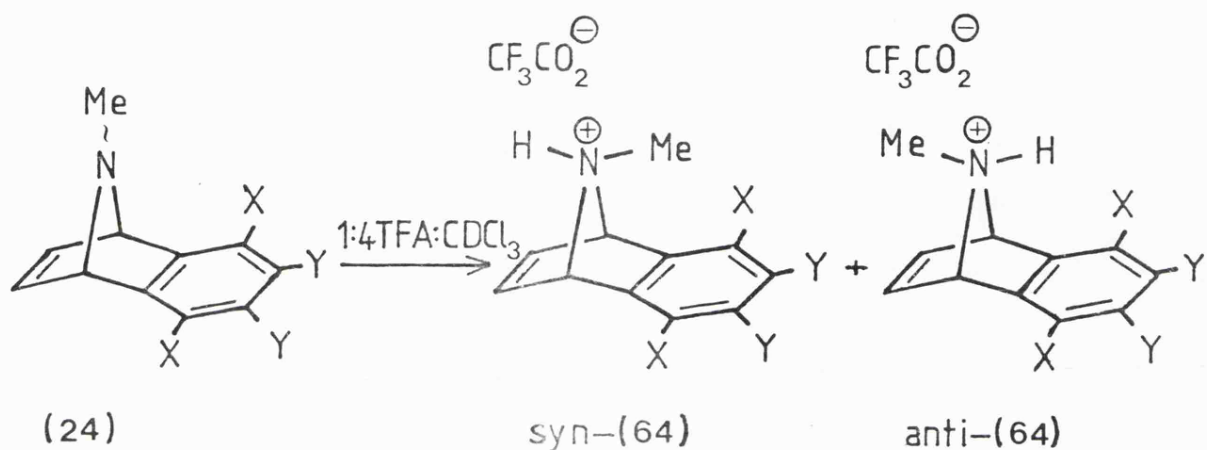


Figure 2.23

The ratios of the diastereoisomeric ions (64b)-(64e) are presented in table 2.13 along with the ground state free amine invertomer ratios from low temperature ¹H nmr spectroscopy. The protonated amine solutions were allowed to stand at room temperature for a week after which time no change in the initially formed ratios was observed i.e. no equilibration had occurred. The assignment of the major and minor diastereoisomeric ions was once more made on the basis that the upfield N-methyl signal was that of the syn-configuration where the methyl group experiences the shielding effect of the aromatic ring.

It will be noted that the protonated amine salt ratios of

Table 2.13

<u>Compound</u>	<u>Thermodynamic</u>	<u>Initial Protonation</u>	<u>Ratio^a after Evaporation</u>	<u>Ratio^a after Addition of</u>
	<u>Invertomer Ratio^a</u>	<u>Ratio^a</u>	<u>and Redissolution</u>	<u>Excess of Amine</u>
	<u>syn-Me : anti-Me</u>	<u>syn-(64) : anti-(64)</u>	<u>syn-(64) : anti-(64)</u>	<u>syn-(64) : anti-(64)</u>
(24b)	71 : 29	71 : 29	79 : 21	77 : 23
(24c)	80 : 20	74 : 26	75 : 25	86 : 14
(24d)	82 : 18	72 : 28	71 : 29	73 : 27
(24e)	88 : 12	76 : 24	68 : 32	73 : 27

a. $\pm$ 3%

(24d) and (24e) do not mirror the respective thermodynamic amine invertomer ratios and similar significant differences were found between the quaternary salt and invertomer ratios of (24e) when the protonation procedure was varied. When CDCl_3 solutions of (24e) were added slowly in drops to neat, rapidly stirred, TFA or trifluoromethane sulphonic acid ($\text{CF}_3\text{SO}_3\text{H}$), the salt ratios were 74:26 and 28:72 respectively. The reason for the observation of equilibrated or partly equilibrated protonated amine salt ratios for (24d) and (24e) seems to lie with the technique of protonation itself. Considerable argument has raged in the literature as to the effectiveness of the mixing process when protonation is performed by the addition of amine solution to acid. Robinson⁴³ and McKenna⁴⁴ have each stated that the primary condition of a truly kinetic protonation is the isolated reaction of a single amine molecule with a vast excess of acid, into which the quaternary ammonium salt is then rapidly dispersed. Partial equilibration may occur, however, in a region where amine, protonated amine and acid briefly meet. Booth has reasoned that such a process upon deuteration of $(n\text{-Bu})_2\text{NH}$ would give rise to $>\text{NH}_2^+$, $>\text{NHD}^+$ and $>\text{ND}_2^+$ species but did not observe the quintet required for the protons H_a (Figure 2.24) in the ^1H nmr spectrum of the solution^{98b} and thus took this as justification for the use of amine solutions in kinetic protonation. However, Robinson observed Me_2NH_2^+ upon deuteration of dimethylamine (Me_2NH) when the protonation was performed in solution but, significantly, did not when dimethylamine vapour was allowed to slowly dissolve in rapidly stirred acid. Subsequently, the same author rigorously

established the validity of kinetic protonation^{43,79} as an aid to conformational analysis and noted the rather stringent conditions for its successful application, conditions which Booth now concedes are necessary⁹⁹.

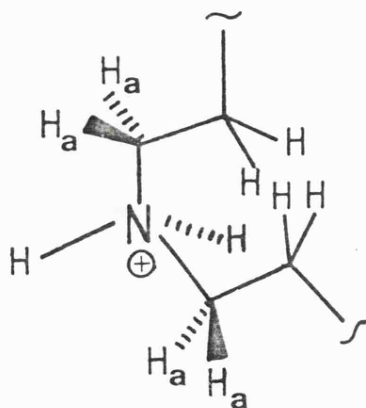


Figure 2.24

In order to gather further evidence that the mixing process could be responsible for the difference in ratio between protonated amine and free amine in the cases of (24d) and (24e), two different approaches were taken. Firstly, each mixture of protonated amine salts was encouraged to equilibrate further to establish that the initially observed ratio was indeed a kinetic or partly equilibrated ratio and not the thermodynamic ratio of amine salts. The thermodynamic ratio reflects the position of equilibrium of $\text{syn-(64)} \rightleftharpoons \text{anti-(64)}$ rather than the position of equilibrium of the free base.

To this end, each mixture of salts was evaporated to dryness, redissolved in CDCl_3 and the ratio monitored for change. An excess of the respective amine was then added to encourage deprotonation and equilibration; the final column of table 2.15 contains the ratio of quaternary salts

observed under equilibrating conditions. It can be seen that in the cases of (24d) and (24e), these ratios are almost the same as those on initial protonation of each amine, suggesting that rapid equilibration occurs during the mixing process to produce a thermodynamic rather than kinetic ratio. Furthermore, the ratios of syn- and anti- (64c), (64d) and (64e) did not match the respective amine invertomer ratios under any of the conditions used. Only the protonation of (24b) seemed to give a ratio of quaternary salts which directly reflected the ground state amine invertomer ratio but the success of the technique in this one instance cannot outweigh its overall failure when used on the remaining substrates.

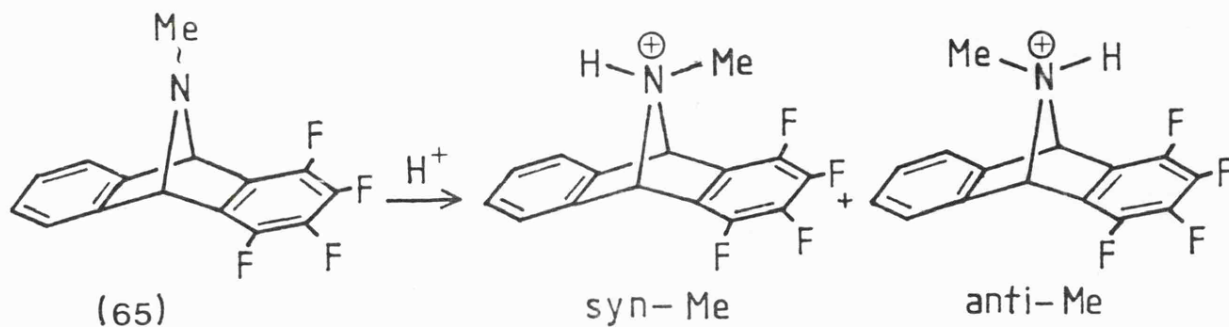
The second approach was to encourage the solution protonations to be as truly "kinetic" as possible. Because the protonation of (24d) and (24e) had given rise to the most anomalous results, each amine (ca.70mg) was dissolved in 20ml of the volatile solvent, Arcton 11(CFCl_3) and dripped slowly from a burette over 2-3 hours into a large excess of neat, rapidly stirred TFA(2ml). Dry nitrogen was gently bubbled through the acid-solvent mixture to remove CFCl_3 . After the addition was complete, the ^1H nmr spectra of the protonated amines were recorded. The ratios obtained for protonated (24d) and (24e) were respectively (syn-methyl:anti-methyl) 72:28 and 76:24. These ratios remained unchanged for a month after the experiments. Once again, the thermodynamic amine invertomer ratios were not mirrored in the ratios of syn- and anti- (64d) and (64e); indeed, the latter ratios were identical to those observed using the original protonation method, showing that high

dilution and slow addition had failed to circumvent equilibration. As a further example, the anthracen-9,10-imine, (65) in table 2.14 also gave ratios which did not match the thermodynamic invertomer population upon protonation. A variety of different procedures and acids were used and these are summarised in table 2.14. The protonation of this amine gave the widest variation of quaternary salt ratio and was also the only salt to equilibrate on standing for one week (Entry 3 in table 2.14). Thus the results in this section appear to support previous fears as to the reliability of protonation by the mixing of amine and acid solutions. Therefore, as a quick and simple technique¹³, it should be used with great caution when investigating invertomer ratios in such systems; and clearly only to support measurements made by a much more reliable technique such as dynamic nmr spectroscopy.

b) The Amines (26b)-(26e)

Protonations using 1:4 TFA:CDCl₃ were performed on selected examples from this series, mainly (26c) and (26e). The major N-methyl signals of protonated (26c) and (26e) were partially obscured by the complex signal due to the exo-2,3-protons which also moved downfield on quaternisation of the nitrogen atom. By analogy with an earlier study, this overlap was removed by using the deuterated analogues d₂-(26c) and d₂-(26e). Marchand had used d₂-(26b) in place of (26b)¹³ to study the lone pair preferences in a range of azabicycles. The protonation of the amine d₂-(26e) was of particular interest to observe whether the equilibration accompanying the protonation of 1,4-dihydronaphthalen-1,4-imines

Table 2.14



Invertomer Ratio = 71:29^a

Protonations

Method

Ratio
syn-Me : anti-Me

1) Amine in $CDCl_3$ (0.2ml) was dripped slowly into neat, rapidly stirred TFA (0.3ml) at ambient temperature.

58 : 42

2) Amine in $CDCl_3$ (0.2ml) was dripped slowly into neat, unstirred CF_3SO_3H (0.2ml) at ambient temperature.

36 : 64

3) i. Amine in $CDCl_3$ (0.2ml) was dripped slowly into stirred 1:4 TFA: $CDCl_3$ (0.2ml) at ambient temperature.

50 : 50

ii. Mixture allowed to stand at ambient temperature for one week.

43 : 57

iii. Mixture was evaporated to dryness and redissolved in $CDCl_3$.

37 : 63

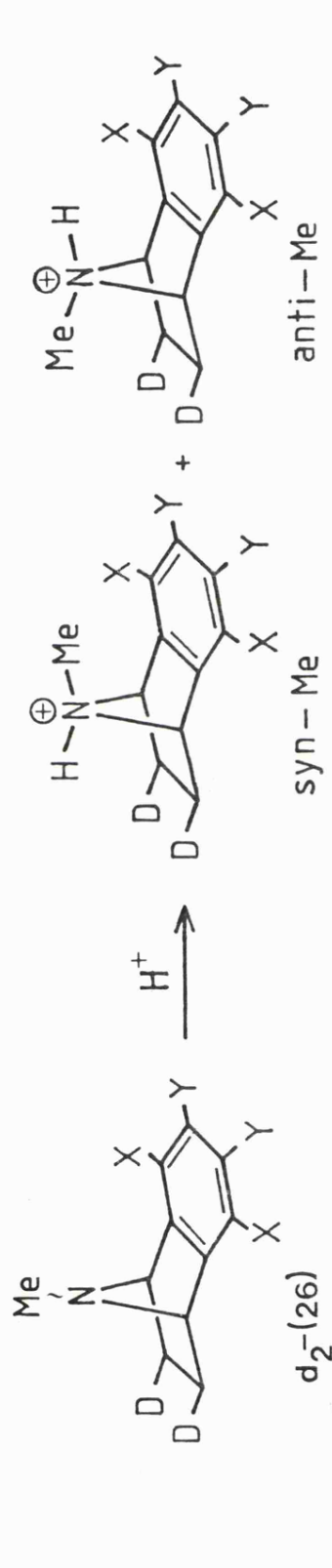
a. Syn- refers to the configuration with the methyl group syn- to the tetrafluorinated ring.

bearing halogen substituents in the aromatic ring would be repeated in the saturated analogue.

Each amine, dissolved in 0.2ml of CDCl_3 , was dripped slowly into 0.3ml of rapidly stirred 1:4 TFA: CDCl_3 . Each whole mixture was transferred to an nmr tube and the ratios calculated by integration of the N-methyl doublets in the ^1H nmr spectra. The ratios, which remained unchanged after one month, are recorded in table 2.15.

Again, every effort was made to ensure that protonated salts were able to equilibrate by measuring the ratios in the presence of an excess of starting amine (column 4, table 2.15). There appears reasonable agreement between the initially observed protonation ratios and the free amine invertomer ratios, although the larger errors associated with the integration of ^{13}C nmr spectra must not be forgotten. There is also sufficient difference between the quaternary salt ratios in excess of acid and in excess of base to suggest that the initially observed protonation ratios are not thermodynamic. At face value, these results would seem therefore to support Marchand's use of the technique, but the results of the previous section allow a not unreasonable degree of scepticism regarding the technique in general.

Table 2.15



Compound	Thermodynamic Invertomer Ratio ^a	Initial Protonation Ratio ^b	Ratio ^b after Evaporation and Redissolution		Ratio ^b after Addition of Excess of Amine	
			syn-Me : anti-Me	syn-Me : anti-Me	syn-Me : anti-Me	syn-Me : anti-Me
d ₂ -(26c)	98 : 2	95 : 5	95 : 5	91 : 9		
d ₂ -(26e)	98 : 2	93 : 7	89 : 11	87 : 13		

a. Ratios calculated from ¹³C nmr spectroscopy.

b. ± 2%

IV. Inversion Barriers

The inversion barriers of the amines (24a)-(24e) were studied for several reasons, apart from the fact that their investigation arose quite naturally from the study of their invertomer ratios. Firstly, comparatively few inversion barriers are known for 7-azabicyclo(2.2.1)heptyl systems and their derivatives amongst the extensive literature of amine inversion barriers^{1,2}. Only Gribble's report³⁶ of the inversion barriers for (24d), (24e) and (65) and Sutherland's⁴⁷ for (66), (67), (68) (Figure 2.25) can be said to constitute studies of the barriers of structurally similar 7-azabicyclo(2.2.1) heptyl derivatives. Secondly, the tabulation of such information for the amines (24a)-(24e) offered the opportunity of observing the effect of varying electron density of the aromatic ring upon the inversion barrier.

Inversion Barriers ($\Delta G^\ddagger$) in kJmol^{-1}

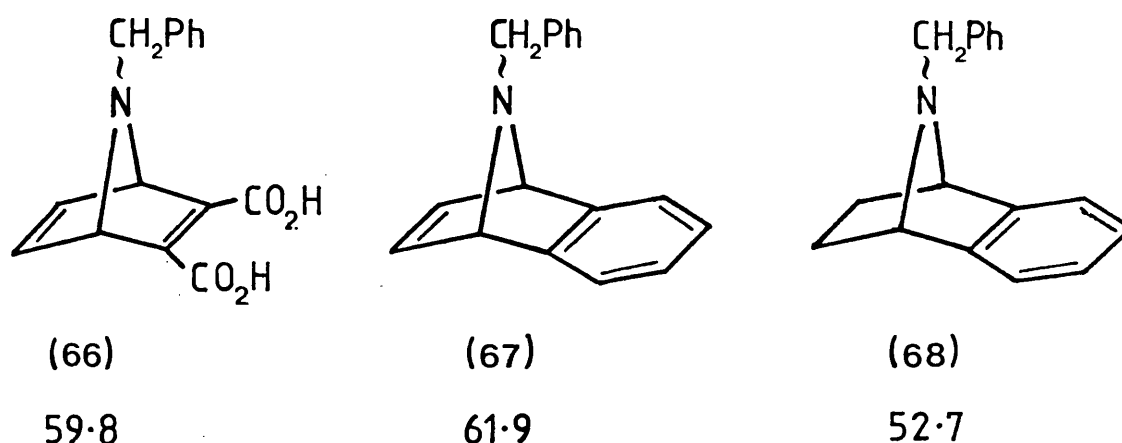


Figure 2.25

The inversion barriers in the N-chloroamines (29) had changed as the substituents in the aromatic ring were varied¹¹. The trend was that the barrier to inversion decreased as the aromatic ring became electron-deficient and it was of interest to see whether such a trend was repeated in the N-methyl compounds (24a)-(24e). The reasons for the high inversion barriers in these systems have not, to date, been identified but Lehn has suggested that repulsion between the nitrogen lone pair and the flanking π -bonds at the transition state may play an important role in raising the energy of the transition state (Figure 2.26). Therefore, a comparative study of the inversion barriers in systems where the electron-density of these π -bonds may be altered in a predictable fashion is vital in assessing this point.

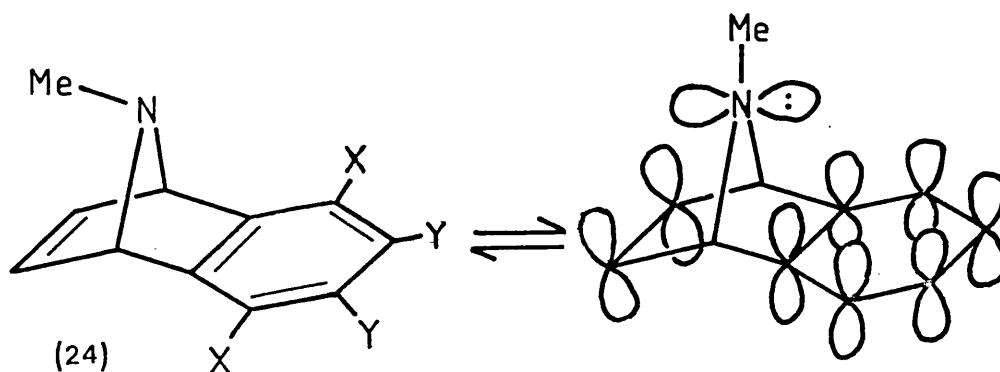


Figure 2.26

In a different sphere, the inversion barrier of (24b) was of interest since its value had been predicted earlier¹⁰⁰, but no subsequent report of the experimentally derived barrier had yet appeared at the inception of this project (October 1978). An inversion barrier of approximately 76.9 kJ mol^{-1} was calculated from the empirically derived relation

$$\frac{\Delta G_{Cl}^{\ddagger}}{\Delta G_{Me}^{\ddagger}} \approx 1.28$$

where $\Delta G_{Cl}^{\ddagger}$ is the inversion barrier of an N-chloroamine and $\Delta G_{Me}^{\ddagger}$ is the inversion barrier of the N-methyl analogue under the same conditions. Anet noted the excellent agreement between the observed inversion barrier of N-chloropiperidine (42.6 kJ mol^{-1})²¹ and the barrier predicted for this amine using such semi-quantitative relationships^{100b} (42.2 kJ mol^{-1}). The investigation of the inversion barrier of (24b) therefore warranted attention in the hope of a similar correlation between theory and experiment.

1. Results

Two N-methyl signals in the ^1H nmr spectra of (24b)-(24e) at -50°C in CDCl_3 indicated that two diastereoisomeric invertomers were present. Careful integration of these resonances (or the major and minor 2,3-vinylic proton resonances) yielded the equilibrium constant. The frequency difference separating the signals ($\Delta\nu$) and the coalescence temperature were determined in each case. The coalescence of the N-methyl signals of (24b) are shown in figure 2.27.

The inversion barriers were calculated using the Gutowsky-Holm approximation and these are summarised in table 2.16. The anticipated increase in the inversion barrier upon using a more polar solvent (CD_3OD) was observed for (24b) and (24e) due to the more effective stabilisation by solvation of the sp^3 ground state compared to the sp^2 transition state in which the electrons are in a more diffuse orbital.

Attempts were made to record the variable temperature ^1H nmr spectroscopic behaviour of d_2 -(26c) and d_2 -(26e) but the very small amount of the minor invertomer in each case made accurate integration of major and minor resonances

Table 2.16

Compound	Invertomer Ratio ^a	T _c (°C) ^c	Δν(Hz) ^d	ΔG [‡] anti→syn (kJmol ⁻¹) ^e	ΔG [‡] syn→anti (kJmol ⁻¹) ^e
	syn-Me : anti-Me				
(24a)	70 : 30	44 ^b	32 ^b	65.7 ^b	67.9 ^b
(24b)	71 : 29	34	31	63.6(68.8) ^f	65.9(70.0) ^f
(24c)	80 : 20	32	18	64.3	67.8
(24d)	82 : 18	5	16	58.6	62.1
(24e)	88 : 12	6	20	58.1(59.8) ^f	62.7(63.4) ^f

a. ± 2%.

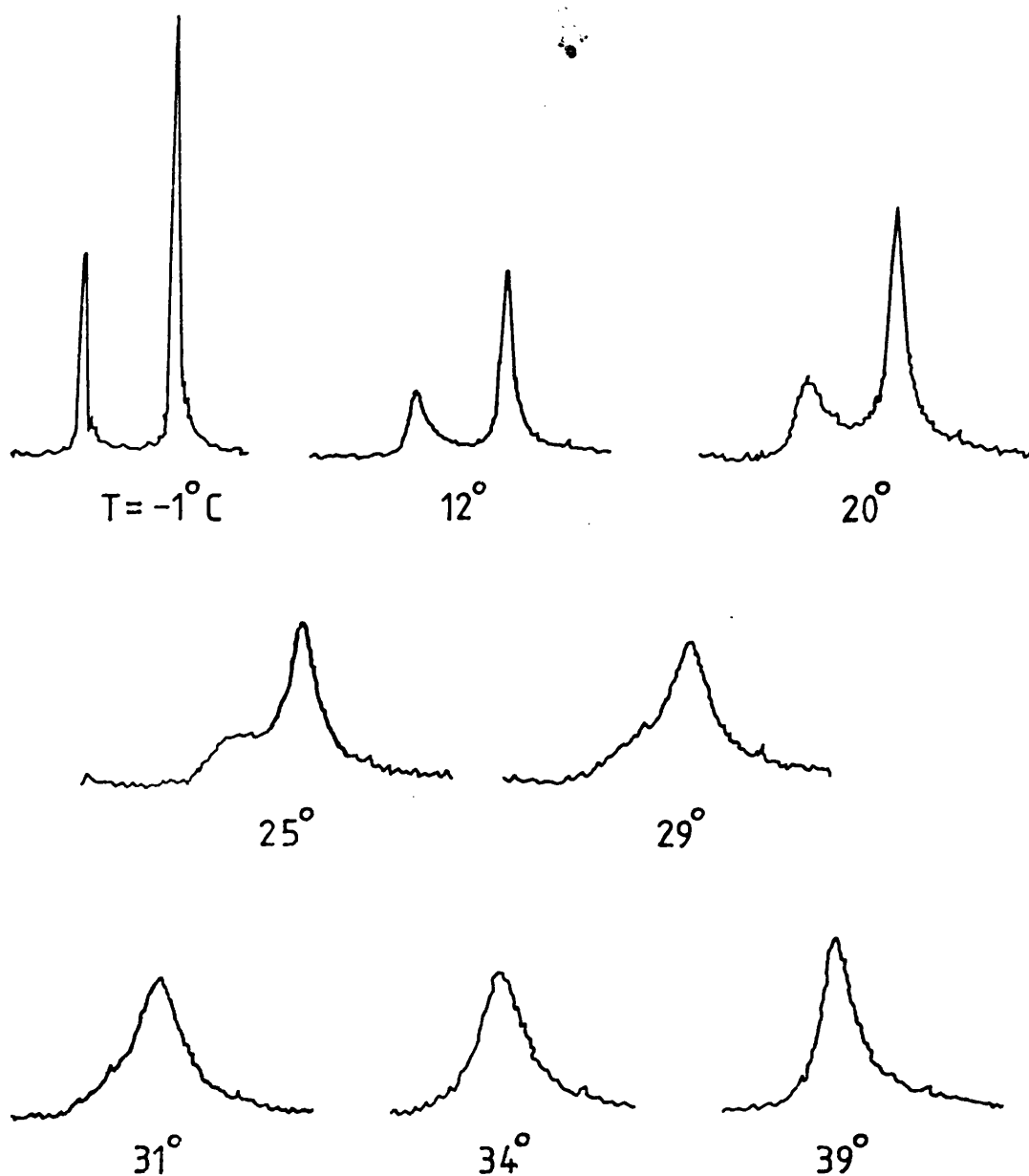
b. All these data are with reference to the vinyl signals of (24a) because the N-methyl signals were obscured by the aromatic methyl resonances.

c. ± 2°C. The figures refer to the coalescence of the N-methyl signals in each case.

d. ± 2Hz.

e. ± 0.43kJmol⁻¹. The largest source of error is attributed to T_c.

f. Inversion barrier when measured in CD₃OD.



Coalescence of the N-methyl signals of (24b)

Figure 2.27

difficult and further, the point of coalescence was impossible to determine. Only the coalescence of d_2 -(26b) could be observed with any confidence and even here the errors on T_c were necessarily greater. The inversion barrier of d_2 -(26b) is recorded in table 2.17, along with those for the amines (37), (38e) and (65).

The configurations of the major and minor invertomers

Table 2.17

Compound	Invertomer Ratio ^a	T _c (°C) ^c	$\frac{\Delta\nu(\text{Hz})}{\text{e}}$	$\Delta G^\ddagger_{\text{anti} \rightarrow \text{syn}}$ (kJmol ⁻¹) ^f	$\Delta G^\ddagger_{\text{syn} \rightarrow \text{anti}}$ (kJmol ⁻¹) ^f
	<u>syn-Me : anti-Me</u>				
d ₂ -(26b)	94 : 6	-5 ^d	24	55.2 ^g	61.3 ^g
(37)	86 : 14	29	30	62.1	66.7
(38)	61 : 39	-3	28	56.2	57.2
(65)	71 : 29 ^b	-6	8	58.0	60.0

a. $\pm$ 2%.

b. The favoured invertomer is tentatively assigned as that with the methyl group syn- to the tetrafluorinated aromatic ring (see text).

c. $\pm$ 2° C. The figures refer to the coalescence temperature of the N-methyl signals in each case.

d. $\pm$ 4° C.

e. $\pm$ 2Hz.

f. $\pm$ 0.43kJmol⁻¹.

g. $\pm$ 1kJmol⁻¹.

of the anthracen-9,10-imine (65) could not be assigned on the basis of the anticipated chemical shifts of an N-methyl group positioned over a tetrafluorinated ($\delta 2.18$) or unsubstituted ($\delta 2.10$) aromatic ring because the two N-methyl absorptions resonated at $\delta 2.38$ (major) and $\delta 2.30$ (minor). The major invertomer was tentatively assigned to the configuration with the methyl group syn- to the fluorinated aromatic ring because the chemical shift difference ($\Delta\delta$) between the syn- N-methyl groups of (24e) and (24b) ($\Delta\delta = 2.18 - 2.10 = 0.08$) was the same as that between the absorptions of the methyl group in (65) ($\Delta\delta = 2.38 - 2.30 = 0.08$). Thus it would be anticipated that the N-methyl resonance at lower field in the nmr spectrum of (65) is that syn- to the tetrafluorinated ring. Intuitively, the fluorine substituents would be expected to reduce the ring current and hence the shielding effect of the aromatic ring, causing the methyl group over it to be deshielded relative to the invertomer where the methyl group is syn- to the unsubstituted ring.

2. Discussion

The values of the inversion barriers over the range of amines investigated in this study are similar to the barriers of other N-alkyl derivatives of the 7-azabicyclo(2.2.1)heptyl system (Figure 1.8 and 2.25) and therefore offer further evidence of the unusual ability of this skeleton to raise the barrier beyond that anticipated by angle strain alone. Indeed, the inversion barriers of (24a), (24b) and (24c) are among the highest recorded for N-alkyl derivatives of this skeleton. In passing, it would appear that the application of Kessler's approximation to (24b) has been less successful

since 13kJmol^{-1} separates the observed (63.6kJmol^{-1}) and predicted (76.9kJmol^{-1}) inversion barriers.

Among the inversion barriers of the series of amines (24a)-(24e), (37), (38e) and (65), one major division can be made. The amines (24d), (24e), (38e) and (65) all possess a tetrahalogenated benzene ring as one of the two-carbon bridges and the inversion barriers are in the range $56\text{--}58\text{kJmol}^{-1}$ (considering the lower energy process, anti- syn). The remaining amines have widely differing aromatic groups yet possess inversion barriers of ca. $62\text{--}65\text{kJmol}^{-1}$. The overall trend in these observations is that the inversion barrier decreases as the aromatic ring becomes more electron-deficient. The inductive effect of a tetrahalogenated benzene ring can be discounted as the reason for such a trend. In the first instance, there is evidence to suggest that the inductive effect of unsaturated bridges via the σ -skeleton in such systems is negligible⁵⁶. Secondly, the withdrawal of electron density by halogenated benzene rings would increase the s-character of the lone pair and raise the barrier to inversion and this is quite contrary to the observed trend.

The trend is in accord with an extension of Lehn's hypothesis in which the height of the inversion barrier would be expected to vary with the electron density of the adjacent π -bonds ie. as the electron density in the aromatic ring decreases, the level of repulsion with the lone pair will also wane thus lowering the energy of the transition state.

The small decrease in inversion barrier accompanying the deuterogenation of (24b) ($63.6 \rightarrow 55.2\text{kJmol}^{-1}$) would also

fit with Lehn's idea since the removal of one π -bond should reduce the amount of repulsion in the transition state. The small decrease in the inversion barrier of (24e) upon substitution of two electron-withdrawing ester groups on the 2,3-double bond (58.1 kJmol^{-1} in (24e) $\rightarrow$ 56.2 kJmol^{-1} in (38e)) appeared to offer further support although the generality of this observation could not be probed further since attempts to prepare analogous adducts eg. (38a) and (38b) (Figure 2.28) were thwarted by the formation of 1:2 adducts between the appropriate isoindole and dimethylacetylene dicarboxylate⁷⁴.

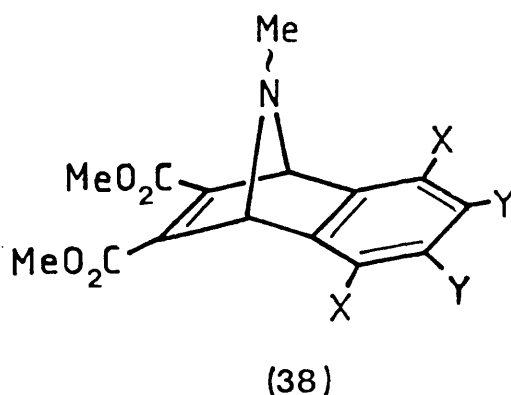


Figure 2.28

At first sight, the substantially lower inversion barriers associated with those azabicyclic systems bridged by a tetrahalogenated ring appears to confirm Lehn's hypothesis. However, there remain other important, contradicting reasons why this hypothesis is not wholly satisfactory. Not least of these is that it seems incongruous to ascribe the barrier-raising effect to the interaction of the lone pair and π -bonds in the transition state when the conclusion from the work described earlier in this chapter is that n - π -interactions are minimal

because of the destabilising influence such an overlap would entail! Admittedly, the lone pair occupying a p-orbital at the transition state will be closer to the adjacent π -orbitals than the lone pair in the sp^3 ground state and perhaps more likely to undergo repulsive interaction. Accepting even this, however, Lehn's idea cannot account for the high barrier observed for (69) where each two-carbon bridge is a σ -bond (Table 2.18).

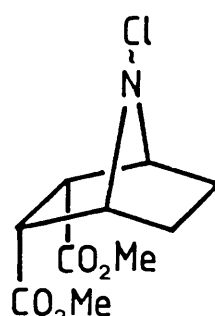
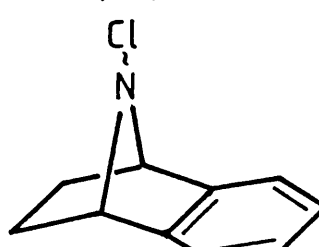
<u>Inversion Barrier ($\Delta G^\ddagger / \text{kJmol}^{-1}$)</u>	
 (69)	87.8 ¹
 (30b)	~94.0 ¹¹

Table 2.18

Clearly, there must be other, equally significant factors operating in (69) for the inversion barrier to be comparable to those observed in related 7-azabicyclo(2.2.1)hepta-2,5-dienyl systems. However, the exact nature of such factors, remain obscure. Sutherland's view that such high barriers are related

to the "known difficulty of forming a planar carbanion at the 7-position in norbornyl derivatives"¹⁴ is general and unspecific but may take account of a combination of plausible factors. Most obviously, the C_1-N-C_4 bond angle must open to ca. 120° in the transition state but is constrained to ca. 96° ¹⁰¹ by analogy with the $C_1-C_7-C_4$ angle in norbornane¹² and norbornadiene¹⁰². The barrier-raising effect of the double bonds (See Table 2.12) may be associated with increases in the rigidity, and therefore the strain, of the bicyclic skeleton. This will increase the s-character of the lone pair and hence raise the inversion barrier.

The origins of the trend of a decrease in the inversion barrier as the aromatic ring becomes more electron deficient in (24a) to (24e) are as equally obscure. Only tentative suggestions can be made but it is conceivable that the change in inversion barriers among these amines could be a function of the changes in the C_1-N-C_4 bond angle and the degree of s-character of the lone pair induced by distortions in the varying aromatic rings. The molecular geometry of aromatic rings can be altered by substituents¹⁰³, but just how much these distortions may affect the bridge angle could only be answered by recourse to crystal structure determinations and these lay beyond the scope of this project.

It is possible that changes in the C_1-N-C_4 bond angle alone cannot account for the difference in inversion barrier between, say, (24b) and (24e). The approximate relation¹⁰⁴

$$E \approx 0.0418(\theta)^2 \text{ kJmol}^{-1} \text{ degree}^2$$

relates the change in angle, θ , to the increase or decrease in angle strain, E. This would mean, however, that

a substantial and unreasonable deformation of 11.5° in the C_4-N-C_4 bond angle of (24b) would be required for the inversion barrier to increase by 5.5kJmol^{-1} over that for (24e). Further insight into reasons for the high barriers and their gradation in this range of amines may lay with the increasingly refined calculations of Jennings¹⁰⁵ and others.

To summarise then, the inversion barriers in the structurally related amines (24a)-(24e) and in other azabicyclic systems studied here have been measured and their values confirm the previous observation that this skeleton leads to unusually high barriers. At first sight, the gradation in inversion barrier with the substituent on the aromatic ring appeared to offer some support for Lehn's hypothesis as to the origin of high barriers in 7-azabicyclo(2.2.1)heptyl systems. However, closer inspection revealed that only an halogenated aromatic ring caused any reduction in the value of the inversion barrier which, significantly, remained almost constant amongst other amines such as (24a), (24b), (24c) and (37) where the substituents on the aromatic ring, even the aromatic group itself in (37), changed widely. Although the reasons for high barriers in such amines cannot be considered fully elucidated, the lack of a uniform variation in barrier with substituent in the aromatic ring amongst the amines studied here suggests that $n-\pi$ interactions in the transition state play a minor role in determining the size of the inversion barrier. The value of the tabulation of inversion barriers in this way to assess such points is emphasised.

PART 2

CHAPTER 3

INTRODUCTION-

REACTIONS AT AN INVERTING NITROGEN ATOM

1. Reactions at an Inverting Nitrogen Atom

The norbornyl compounds *exo*- and *endo*- (70) (Figure 3.1) typify one system that has been used extensively in carbon chemistry to study the dependence of reactivity upon configuration¹⁰⁶.



Figure 3.1

The interconversion of *exo*- and *endo*-(70) is impossible (except for bond-breaking) and a comparative study would require the separation or separate preparation of the two structural isomers. By contrast, the aza-analogue (71) (Figure 3.2) undergoes inversion about the 2-position and thus interconverts the two configurations.

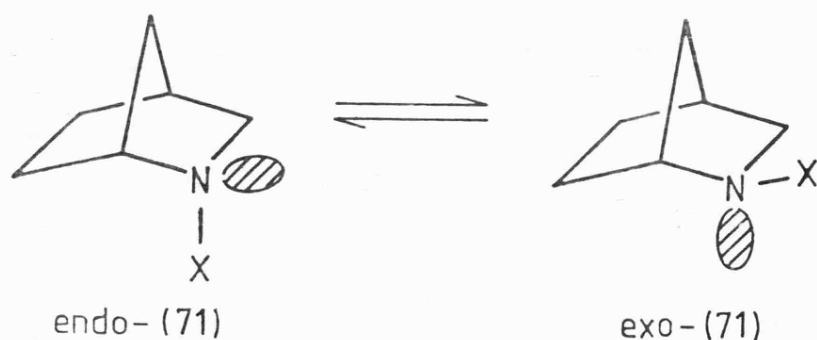


Figure 3.2

If nitrogen were substituted with a suitable leaving group and the solvolysis conducted under conditions of negligible

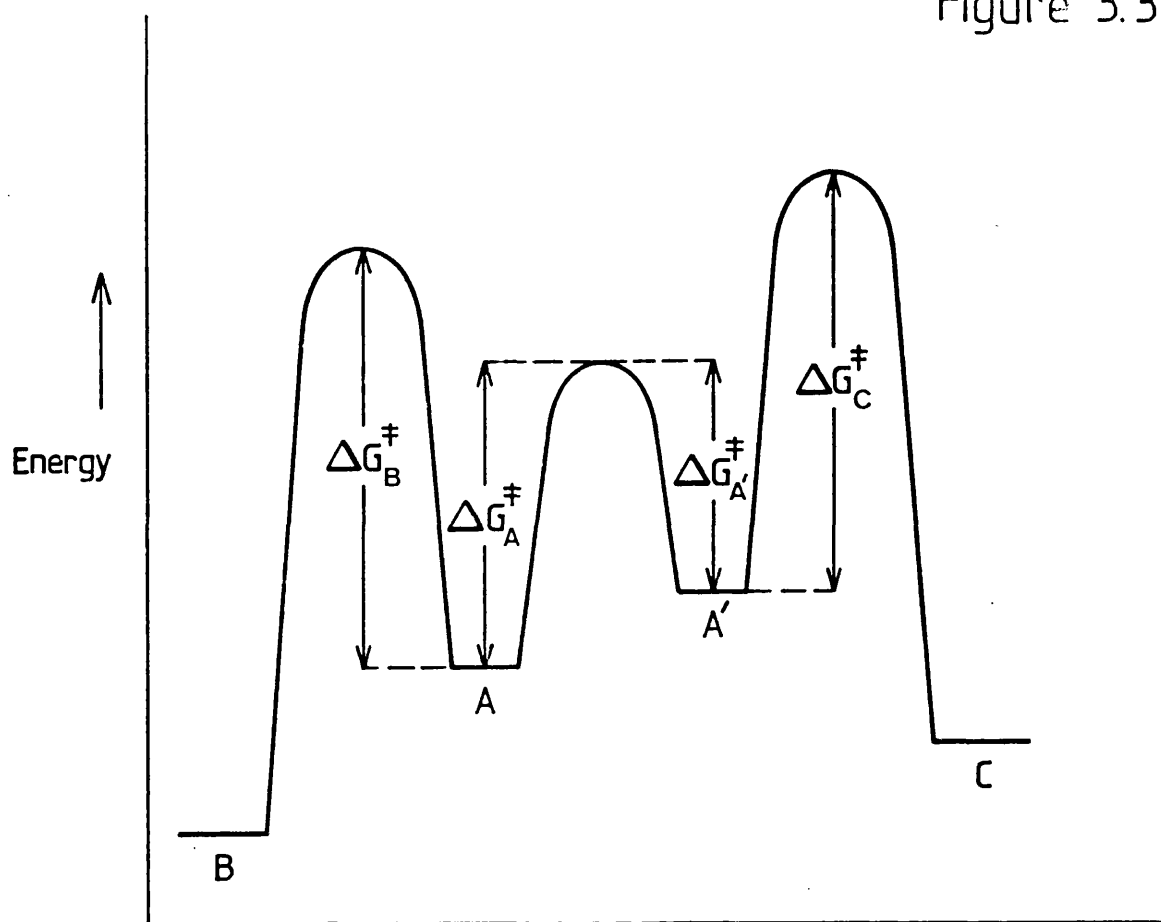
inversion, then the fate of both configurations could be determined from the solvolysis of a single reaction mixture. Potentially, this offers an elegant advantage over the two separate experiments required to study exo- and endo- (70).

The stereochemical consequence of a reaction at nitrogen (whether loss of a group X, or quaternisation of the lone pair) can be studied if the rate of inversion is slow relative to the rate of the chosen reaction. Alternatively, if reaction from one diastereoisomeric invertomer has a much lower free energy of activation than reaction from the other, then the reaction may be funnelled off via the more reactive invertomer. Two limiting situations have been derived¹⁰⁷ (and observed). They are illustrated on free energy diagrams in figure 3.3, with reference to the symbols of figure 1.7.

Case 1 describes the behaviour of two rapidly interconverting, diastereoisomeric invertomers undergoing a reaction whose activation energy ($\Delta G_B^\ddagger$ or $\Delta G_C^\ddagger$) is much greater than the energy barrier separating A and A'. The amounts of B and C, the products, are determined by the relative free energies of transition states preceding them. The product ratio B:C is not determined by the ratio A:A' since the starting material may undergo several thousand inversions for every effective collision. This is the type of behaviour defined by the Curtin-Hammett principle¹⁰⁸.

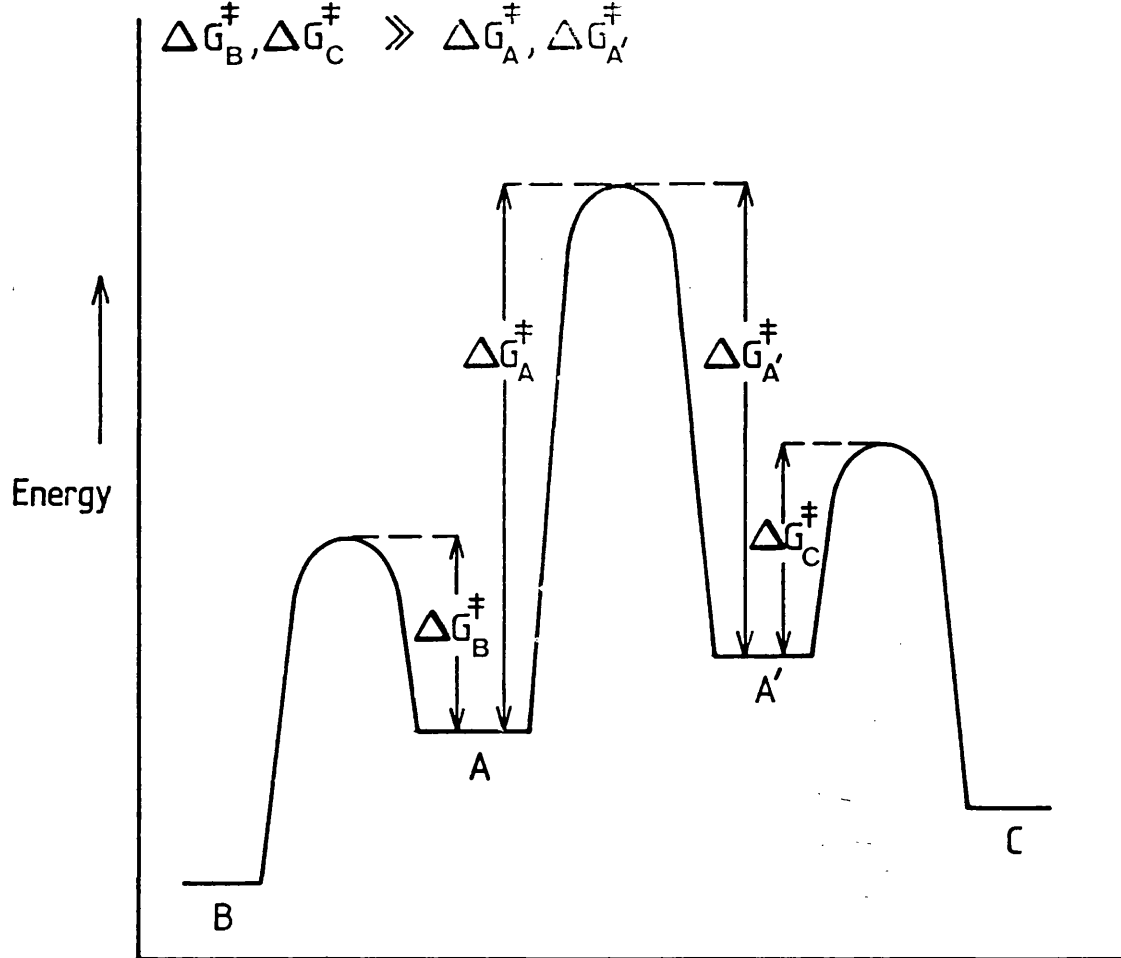
The free energy diagram for Case 2 describes a reaction for which the energy barrier between the invertomers ($\Delta G_A^\ddagger$, $\Delta G_A'^\ddagger$) is very much greater than the barriers to reaction from each of them ($\Delta G_B^\ddagger$ and $\Delta G_C^\ddagger$). Such behaviour is most easily investigated if the amine in question has a slow rate of inversion (ca. 10^{-4} s^{-1}) at or around room temperature. Quite

Figure 3.3

CASE 2

← Reaction Co-ordinate →

$$\Delta G_B^\ddagger, \Delta G_C^\ddagger \gg \Delta G_A^\ddagger, \Delta G_{A'}^\ddagger$$



← Reaction Co-ordinate →

$$\Delta G_A^\ddagger, \Delta G_{A'}^\ddagger \gg \Delta G_B^\ddagger, \Delta G_C^\ddagger$$

possibly, a reduction of the temperature would prevent inversion for some amines but at the expense of a prohibitively slow rate of reaction. It is also preferable to conduct such reactions above 0°C for manipulative ease. One other way of satisfying the criterion would be to make use of an extremely rapid reaction which would allow the study of amines showing much lower inversion barriers. A "rapid" reaction in this sense is one where the reaction rate constant is greater than the conformer-inversion rate constant⁴⁴. Kinetic protonation is such a reaction but as the results and discussion of the previous chapter illustrate, its use is beset with pitfalls.

These two types of behaviour form the basis of the chemistry described in Chapters 4 and 5; this chapter will briefly introduce the common thread running through the following chapters, that of stereoselectivity in the reactions of 7-azabicyclo(2.2.1)heptyl systems.

A. Stereoselectivity in the Quaternisation of Naphthalen-1,4-imines

The creation of a positively charged, ~~ter~~travalently bonded nitrogen atom during a quaternisation reaction has offered considerable advantage in the study of stereoselective reactions at nitrogen. For the majority of amines, the rate of inversion is greater than the rate of quaternisation and, therefore, the structure of the product(s) reflects directly the stereochemical course of the reaction. Quaternary salts are normally stable at room temperature, whose structures can be analysed by nmr spectroscopy¹⁰⁹. The N-chlorination of the 1,4-dihydronaphthalen-1,4-imines (27) (Figure 3.4) with N-chlorosuccinimide is an interesting development of the quaternisation process⁵⁹. In this instance, the stereochemistry of the N-Cl bond is retained during its progression from quaternary salt to N-chloroamine because, at -50°C , the two possible N-chloroamine products (syn-(29) and anti-(29) in figure 3.4) do not interconvert. Thus, although a tervalently bonded nitrogen centre is produced, the relative amounts of syn- and anti-N-chloroamine directly reflect the corresponding amounts of the transition states (72) and (73) (Figure 3.4).

Fortunately, signals due to each invertomer are well separated in the nmr spectra of (29) and it is possible to assign absorptions to syn- and anti- invertomers on spectroscopic grounds as well as on the basis of their preferred reactivity with silver salts in methanol⁵⁸. The ratio of syn- and anti-N-chloroamines (29) depends on the temperature at which the reaction is carried out (Table 3.1). At -50°C , under conditions of kinetic control (the products are not free to invert), the ratio reflects the preference by the chlorinating

agent for one of the two possible modes of attack. It may be seen that approach of NCS anti- to the benzene ring is the lower energy pathway. This is not simply a reflection of the preferred lone pair configuration in the secondary amine (27) since the lone pair has been shown to lie almost exclusively syn- to the benzene ring in the ground state of (27b) and

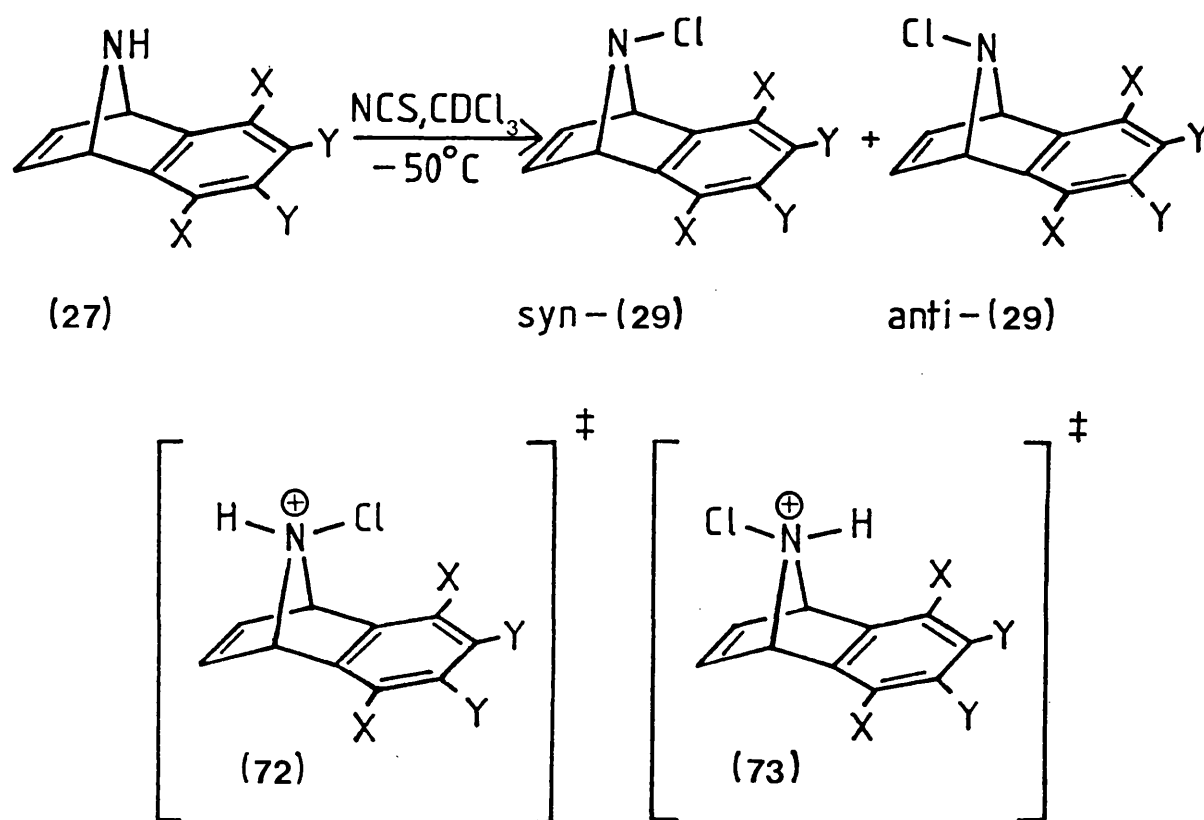


Figure 3.4

(27e)^{50,51}. Furthermore, inversion is still very rapid in the N-H compound even at -50°C . Thus the Curtin-Hammett principle applies. However, this ratio remains constant only at low temperature; upon warming it changes, and under conditions of thermodynamic control, it comes to reflect the ground state preferences of the product N-chloroamines.

syn-Cl:anti-Cl ratios

	<u>Kinetic</u> (-50°C)	<u>Thermodynamic</u> (25°C)
(29a)	31 : 69	63 : 37
(29b)	28 : 72	60 : 40
(29c)	34 : 66	67 : 33
(29d)	41 : 59	82 : 18
(29e)	68 : 32	84 : 16

Table 3.1

The stereoselectivity

observed upon N-chlorination under conditions of kinetic control was explained on the basis of the changing π -electron density of the aromatic rings in (29a)-(29e), in view of the minimal steric differences between the members of the series. The results could be rationalised by considering a transition state in which the interaction between the aromatic ring and the trailing succinimide moiety leads to increasing stabilisation of syn- attack as the ring becomes electron deficient (Figure 3.5).

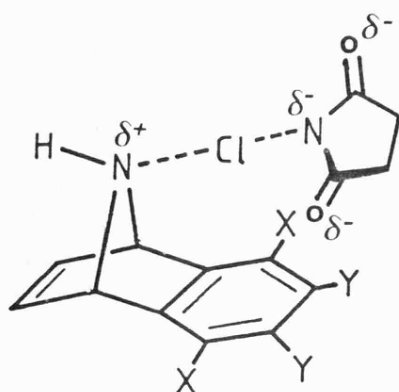


Figure 3.5

Clearly, it became of interest to see if such electronic control of reactivity was operating in the quaternisation of N-alkyl derivatives of the naphthalen-1,4-imine system because of the considerable advantages involved. These were twofold: alkylation of the tertiary amines (24) and (26) with deuterated quaternising agents would give rise to configurationally stable, crystalline, quaternary compounds as salts, not mere transition states such as (72) and (73). Only one N-methyl group in each diastereoisomeric quaternary salt would be visible by ^1H nmr spectroscopy and would thus provide a convenient means of monitoring the amounts of, for example syn- and anti-(36b) (Figure 2.10). Furthermore, the rate of inversion is still very much greater than the rate of quaternisation and hence the product ratio should reflect preferences at each transition state. The resulting quaternary salts may be expected to be configurationally stable at room temperature.

Finally, the investigation of any stereoselectivity in the quaternisation of these amines becomes even more intriguing in view of the overwhelming part that steric factors have played in the rationalisation of other stereoselective amine quaternisations¹⁰⁹. It does not seem unreasonable to expect the electronic influence of the benzene ring in (24) and (26) to dominate the course of quaternisation as it had done in the analogous chlorination of (27).

B. Stereoelectronic Control in the Solvolysis of N-Chloro-Naphthalen-1,4-imines.

The solvolysis of the N-chloroamine (46) (Figure 3.6) provides the obvious comparison to similar work on norbornenyl

systems in carbon chemistry, although the inversion barrier (64kJmol^{-1}) is still too low to allow N-Cl heterolysis under conditions of negligible inversion. The reaction mixture would have to be cooled to -67°C^* to ensure solvolysis of each invertomer uncomplicated by inversion. In fact, chloroamine (46) did not react in methanolic silver salt even at -5°C^{11} . Even so, this did not prevent the study of stereoelectronic control because, when the solvolysis was performed at 40°C , the structure of the products demonstrated that the preferred pathway involved the exo-configuration and that, under these conditions, endo-(46) "reacted" only via prior inversion to the exo- invertomer.

* This figure was calculated from the Eyring equation, assuming that the rate constant at the point of no inversion is 10^{-4}s^{-1} .

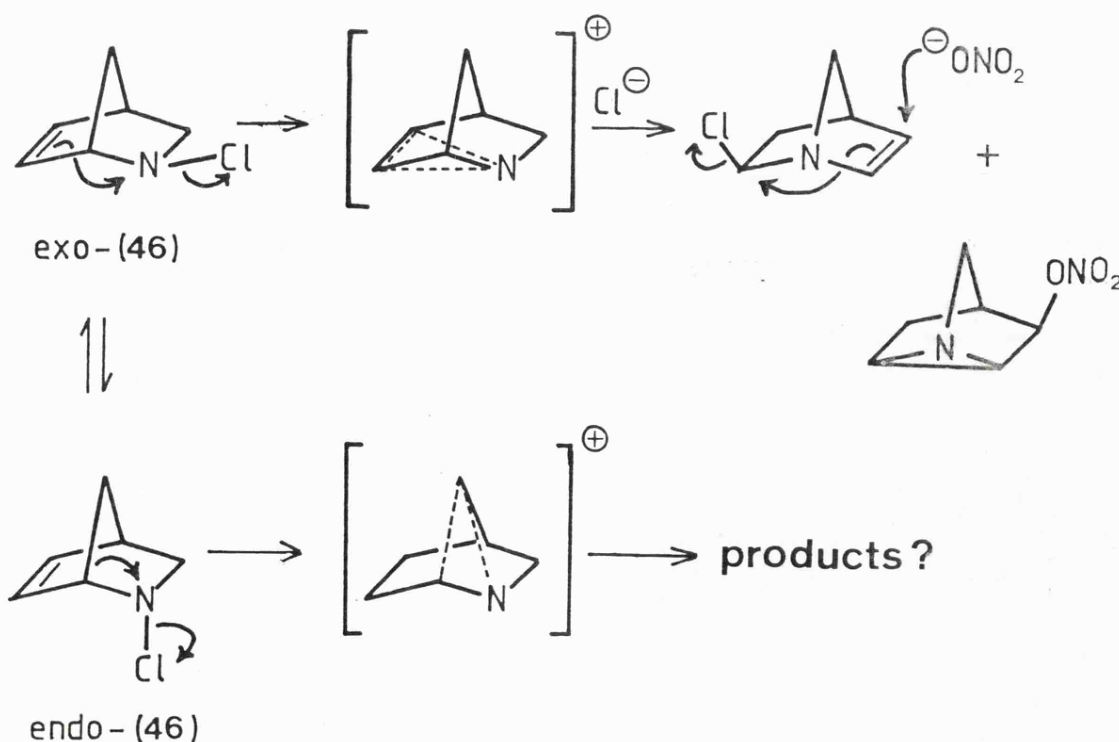


Figure 3.6

The real advantage of using nitrogen-containing systems is the availability of two potentially reactive configurations in the same mixture. Therefore, the opportunity to observe the isolated reaction of each of two diastereoisomeric, non-isoenergetic invertomers lies with compounds such as N-chloroaziridines, oxaziridines or N-chloro-7-azabicyclo(2.2.1)heptyl systems where the very high barrier to inversion has allowed the separation of invertomers in some cases. Most interestingly, the aziridine (74) (Figure 3.7) has been solvolysed in methanol¹¹⁰. The barrier to inversion in this compound will be ca.99kJmol⁻¹ (see Table 1.1, last entry) which means that the solvolysis could be conducted below 0°C without fear of inversion; however, no attempt was made to follow the fate of the more stable trans-invertomer at low temperature.

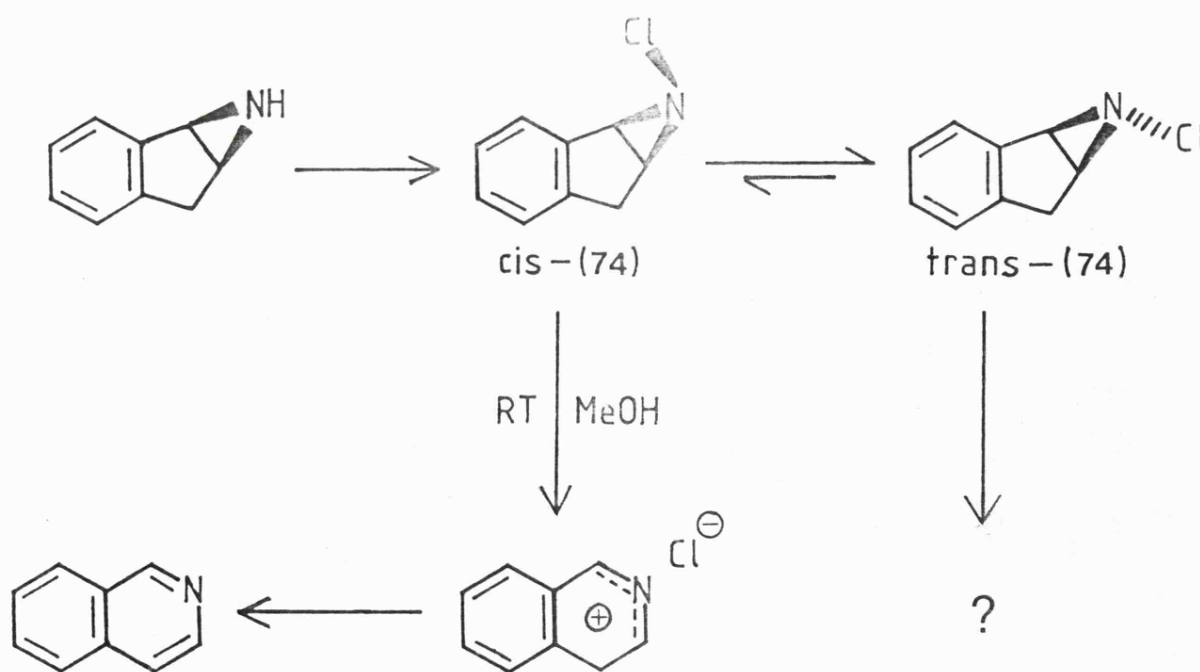


Figure 3.7

At the temperature at which the reaction was performed, the thermodynamically more stable trans-invertomer presumably underwent inversion to the less stable, but more reactive, cis-form. In this configuration, the allowed disrotatory ring opening assists the loss of the chloro group by overlap with the backside of the developing p-orbital on nitrogen and avoids the strained geometry of the analogous transition state for trans-(74).

There is, however, one example which stands clear in this area. The only reported instance of two diastereoisomeric invertomers reacting at different rates and by different pathways is the methanolysis of N-chloro-1,4-dihydronaphthalen-1,4-imine⁵⁸, (29b) (Figure 3.8).

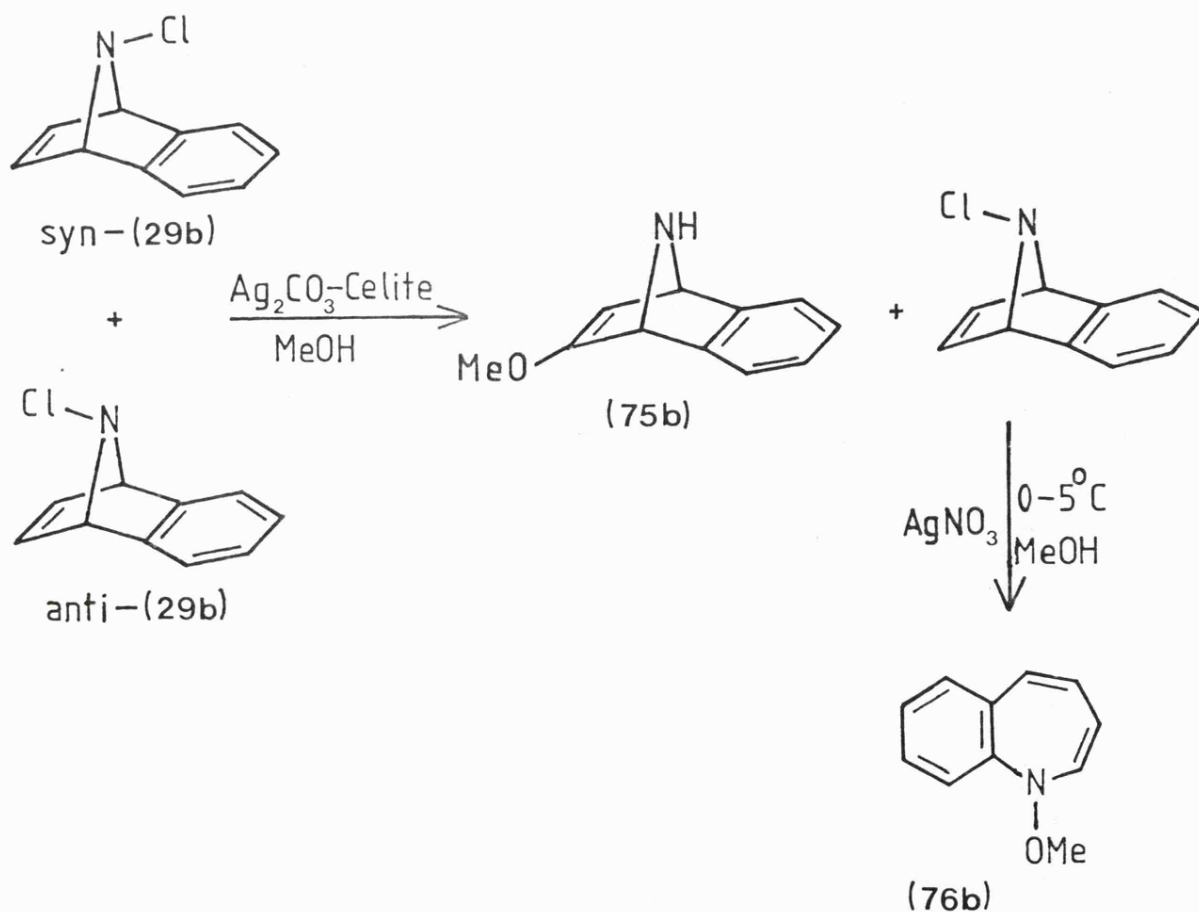


Figure 3.8

The inversion barrier in (29b) has been measured and found to be 98.2kJmol^{-1} and at room temperature therefore, the rate of inversion is low. This fact, combined with the greater reactivity of the syn-invertomer¹¹¹, allowed separation of the anti-invertomer from syn-. The syn-invertomer underwent solvolysis on silver carbonate-Celite¹¹² in methanol to give a product which was retained on the column packing, presumably as the carbonate salt; stereochemically pure anti-(29b) could then be eluted from the column with more methanol. By maintaining the temperature of the reaction mixture between 0°C and 5°C , pure anti-(29b) was then solvolysed to give a product whose structure was tentatively assigned as (76b). By performing the solvolysis under conditions of free inversion, only the hydrochloride of (75b) was obtained, the product of solvolysis of the more reactive syn-invertomer. Given the choice, the anti-invertomer of (29b) clearly preferred to react via prior inversion to syn-(29b). Thus, in this one elegant example, the combination of a high barrier to inversion, a facile separation of invertomers and solvolysis products stable under the conditions of the reaction, has allowed the observation of the fate of both amine invertomers.

The range of N-chloroamines available ((29a)-(29e)) provided an attractive opportunity to extend this interesting reaction. Furthermore, this type of solvolysis had bearing on several other areas of research.

When confined in a small, strained bicyclic system, the solvolysis of an N-Cl bond involves a transition state with an electron-deficient nitrogen atom. In some cases, this has been postulated as a formal "nitrenium ion"¹¹³ although in others the build-up of only partial positive charge on nitrogen is

sufficient to encourage the migration of σ - or π -electrons^{11,114} (Figure 3.9).

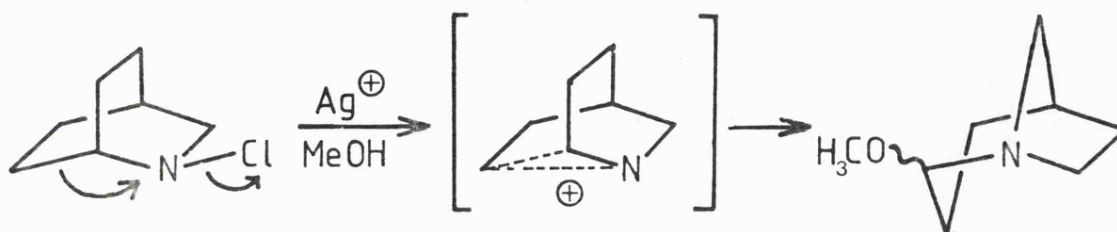


Figure 3.9

Although it is now clear that substrate structure is crucial in deciding whether a radical or ionic pathway is preferred¹¹⁵, such arrangements can only be triggered by some degree of positive charge at nitrogen, generated as the chlorine departs. For example, Schell has recently observed the imminium ion (77) (Figure 3.10) by ^{13}C nmr spectroscopy¹¹⁶.

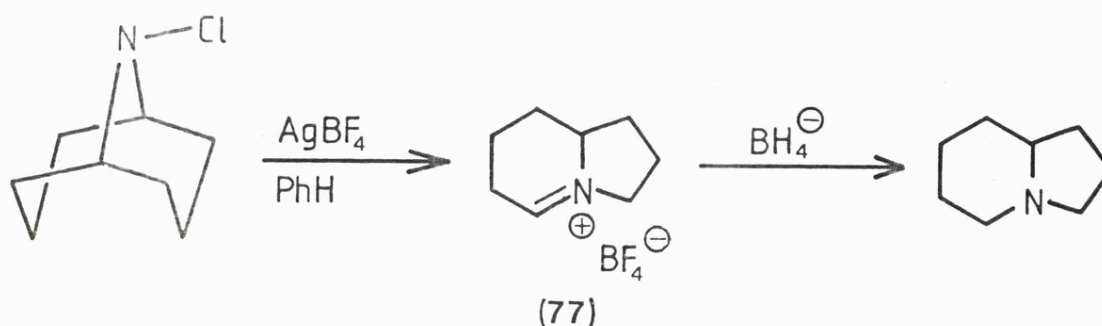


Figure 3.10

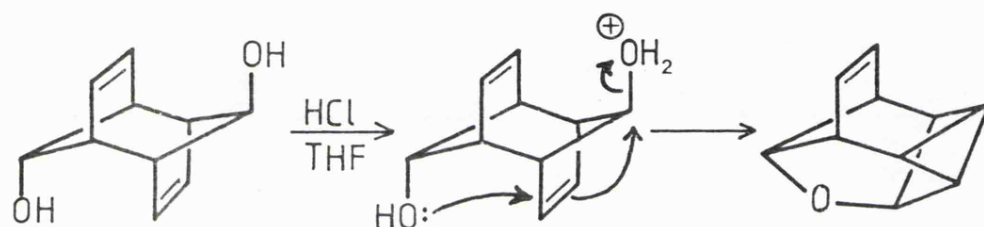
Rather surprisingly, however, there are few examples which demonstrate a pair of π -electrons providing anchimeric assistance to solvolysis of a strained azabicyclic amine. Previous work in these laboratories has shown that the

π -electrons of (46) (Figure 3.6) assist the departure of a leaving group in an extended rearrangement of the N-chloroamine when treated with silver nitrate (AgNO_3) in methanol¹¹.

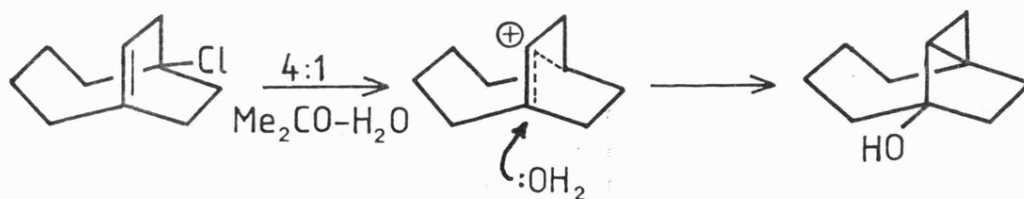
The dearth of examples of π -participation in azabicycles contrasts vividly with the abundance in analogous carbocyclic systems. Examples of anchimeric assistance to solvolysis by suitably disposed π -electrons continue to appear in the literature and some recent examples are selected in figure 3.11.

Reference

117



118



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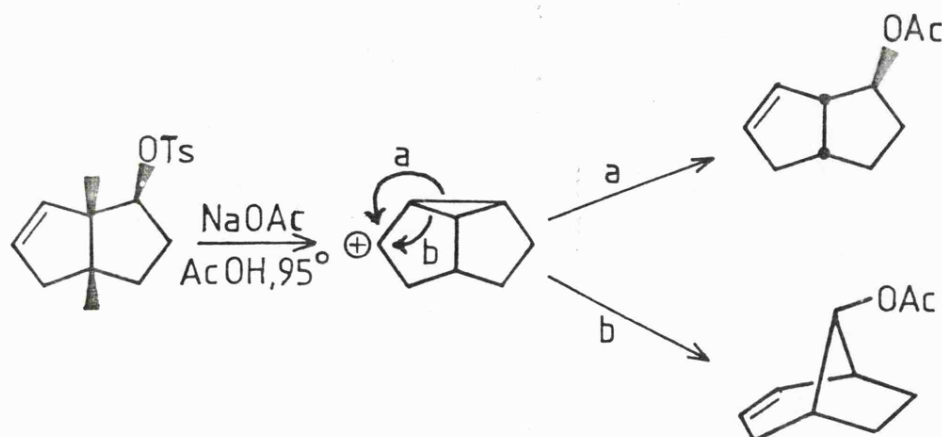


Figure 3.11

The solvolysis of the N-chloroamine⁵⁸ (29b) is, of course, a prime example of π -participation in a strained

azabicyclic compound and in this case, a different pair of π -electrons may assist the departure of the chlorine atom depending on whether the N-Cl bond lies syn- or anti- to the benzene ring. It seemed interesting, therefore, to investigate whether this order of reactivity was maintained as the electron density of the aromatic ring changed in (29a) to (29e).

Finally the investigation of the methanolysis of (29a)-(29e) would provide an excellent parallel to the work of Tanida on the effect of various substituents on the benzene ring on the relative rates of solvolysis of the brosylates¹²⁰ (78) (Figure 3.12). From this work, it emerged that an electron releasing substituent such as a methoxyl group accelerated the solvolysis by lowering the energy of the Wheland-type intermediate (79). It was of interest to observe whether a similar pattern of reactivity would emerge during the solvolysis of the anti-N-chloroamines (29) or (30).

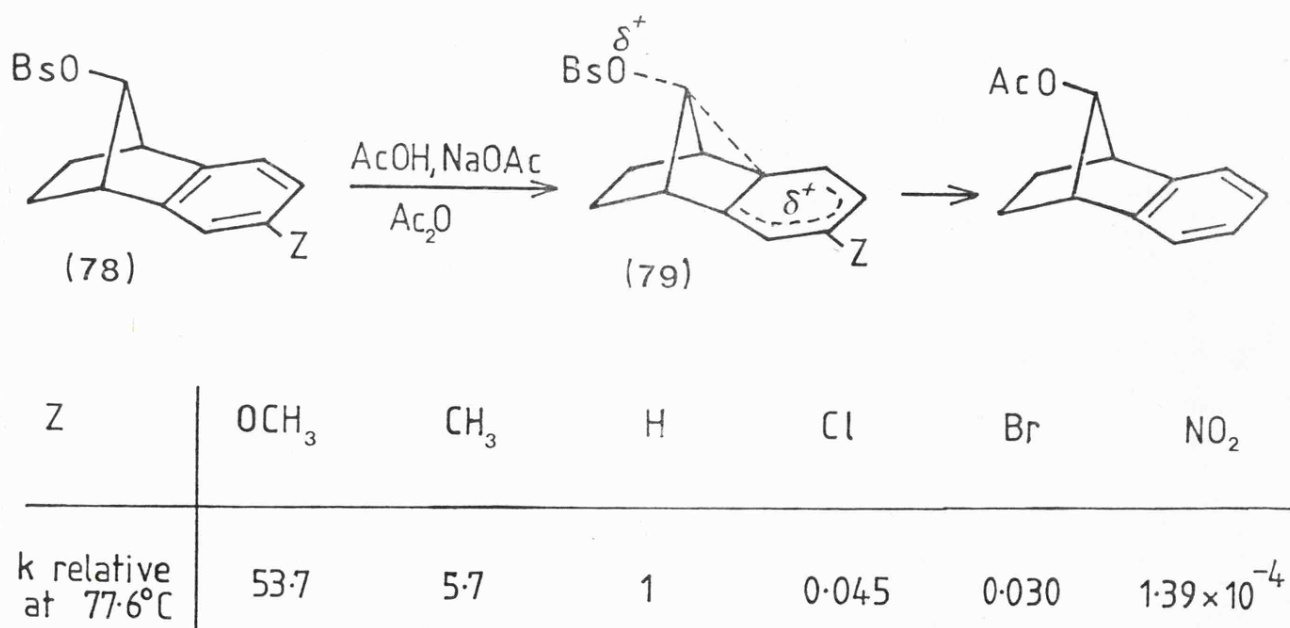


Figure 3.12

CHAPTER 4

THE QUATERNISATION OF SOME N-ALKYL-NAPHTHALEN-1,4-IMINES

When this work began in 1979, great interest^{lay} in reactions of norbornyl systems where the observed stereoselectivity was due to electronic, rather than steric, factors^{59,78,121,122,123,124}. The stereoselectivity of addition of a variety of electrophiles to the exocyclic double bond of 7-isopropylidenenorbornene derivatives (42) (Figure 2.16) was found to vary with the balance of electronic factors in these substrates^{78,121,122}.

In the reaction of (42) with N-bromosuccinimide, an increasing preference for attack of the electrophile from over the benzene ring (syn-attack) was observed as X varied from hydrogen to fluorine. This trend was generally similar to that shown in the low temperature N-chlorination of the amines (27) with NCS⁵⁹. This latter reaction is essentially an amine quaternisation. It was of interest, therefore, to see whether this pattern was repeated during the quaternisation of the N-methyl amines (24) and (26) in view of their straightforward synthesis and the particular advantages that quaternary salts offer for the study of stereoselectivity (see Chapter 3).

I. Results

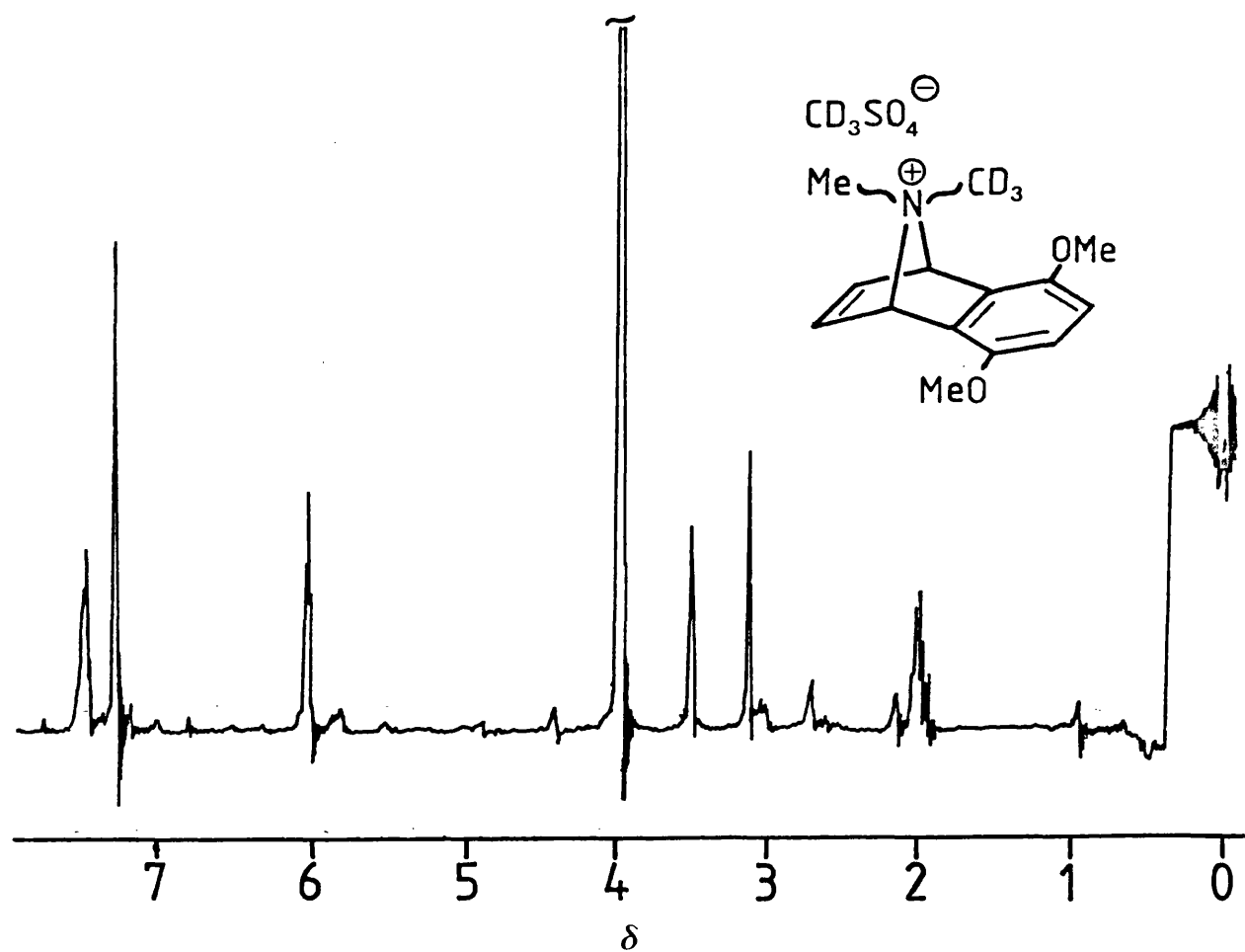
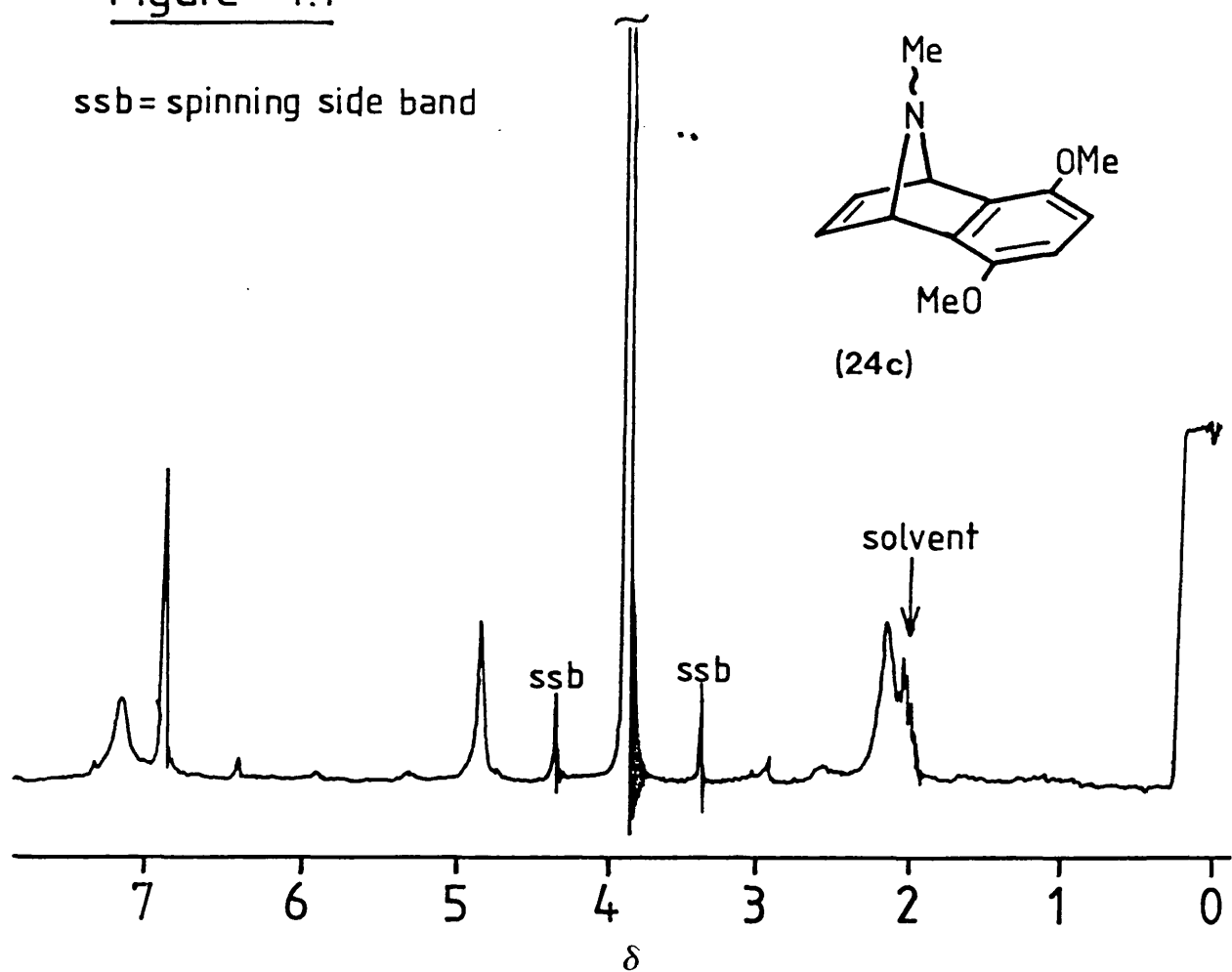
The synthesis of the amines used here have either been described earlier in Chapter 2 or are described in full in the experimental section.

The N-methyl amines (24a)-(24e) and (26a)-(26e) were dissolved in trideuterioacetonitrile (CD_3CN) and the alkylating agent was added directly to the solution from a graduated syringe. In each case, the whole experiment was conducted at room temperature in an nmr tube. In this way, the progress of the reaction could be monitored easily and, more significantly, so that any possible change in the ratio of diastereoisomeric quaternary products due to equilibration in the crude reaction mixture could be detected and measured. The ^1H nmr spectra of (24c) before and immediately after quaternisation with hexadeuteriodimethyl sulphate ($(\text{CD}_3)_2\text{SO}_4$) are shown in figure 4.1 as a typical example.

The creation of a positive charge on nitrogen caused a large downfield shift of the N-methyl signal in each amine. This formerly broad absorption (at ca. $\delta 2.10$) was split into two sharp singlets, (at ca. $\delta 3.4$ and $\delta 2.9$) which showed a total integrated intensity equivalent to three protons. The difference in the chemical, and therefore magnetic, environments of the methyl groups in the product salts syn- and anti-(80) (Figure 4.2) meant that the absorptions corresponding to these protons were separated by ca. 0.25-0.45ppm. Since the trideuteriomethyl group (CD_3) could not be observed by ^1H nmr spectroscopy, the integration of these methyl singlets provided an excellent measure of the relative amounts of each diastereoisomeric salt.

Figure 4.1

ssb = spinning side band



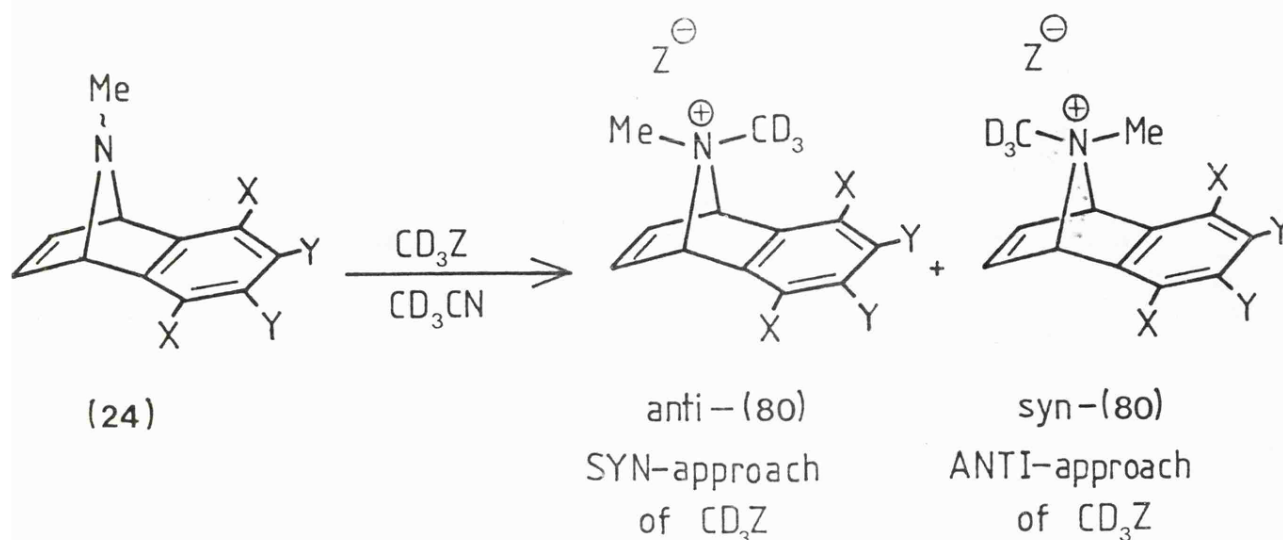


Figure 4.2

The amines (24b)-(24e) and (26b)-(26e) were quaternised with CD_3I , $(\text{CD}_3)_2\text{SO}_4$ and trideuteriomethyl fluorosulphonate (CD_3FSO_3). The analogous reactions of the N- CD_3 amines d_3 -(24) and d_3 -(26) and, for example, methyl iodide (MeI) were not performed because of the difficult syntheses of these deuterated amines.

Once more, the amines with the tetramethyl substituted benzene rings (24a) and (26a) showed very similar behaviour to the amines (24b) and (26b) and consequently were not alkylated with $(\text{CD}_3)_2\text{SO}_4$ and CD_3FSO_3 . The alkylating agents were chosen in view of the resurgence of interest in the principle that more reactive reagents show less positional or stereoselectivity^{121,125,126,127}. Based on a comparison of all ratios observed, some comment might then be made on the transition state for the reaction. Furthermore, in order to draw general conclusions about the way the stereoselectivity changed with the substituent in the aromatic ring in such substrates, a large number of ratios would be useful for comparison. The ratios observed are recorded in table 4.1.

Table 4.1

Compound	<u>Invertomer Ratio^a</u>		<u>CD₃I^b</u>		<u>(CD₃)₂SO₄^b</u>		<u>CD₃FSO₃^b</u>	
	<u>syn-l.p.:anti-l.p.</u>		<u>syn-attack:anti-attack</u>		<u>syn-attack:anti-attack</u>		<u>syn-attack:anti-attack</u>	
(24a)	30	70	40	60				
(24b)	29	71	41	59	42	58	41	59
(24c)	20	80	34	66	41	59	35	65
(24d)	18	82	17	83	31	69	29	71
(24e)	12	88	15	85	25	75	25	75
(26a)			60	40				
(26b)	6	94	59	41	50	50	51	49
(26c)	3	97	52	48	50	50	43	57
(26d)	3	97	36	64	40	60	37	63
(26e)	2	98	35	65	34	66	32	68

a. The ratios are recorded as the relative amounts of syn- and anti- lone pair (l.p.) as it is the lone pair on nitrogen, not the substituents, that are directly involved in the quaternisation process.

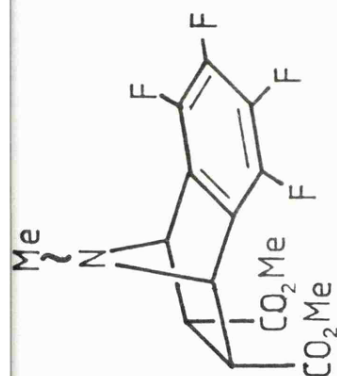
b. [±] 2%. Ratios are quoted as the relative amounts of quaternisation occurring from the syn- and anti- directions.

Although the ratios of diastereoisomeric quaternary salts in table 4.1 are quoted in terms of the amounts of syn- and anti- "attack" of alkylating agent, the mechanism of amine quaternisation is normally considered to be a bimolecular nucleophilic displacement (S_N2) by the nitrogen lone pair on the electron deficient carbon of the alkylating agent with retention of configuration about the amine. The amount of quaternary salt (80), in which alkylation has occurred with the lone pair anti- to the benzene ring, is measured by the integral of the singlet corresponding to the syn-methyl group in the ^1H nmr spectrum of syn-(80). The assignment of the N-methyl singlets to structures syn- and anti-(80) has already been discussed in detail in Chapter 2.

The ratios recorded in table 4.1 can be considered to be the result of kinetic control since no change was observed in any of them after complete quaternisation of the starting material. The samples were monitored for a further period corresponding to at least twice the time taken for the consumption of starting material and, in some cases, even longer. When these amines were quaternised with $(\text{CD}_3)_2\text{SO}_4$ and CD_3FSO_3 , reaction was immediate and by the time the ^1H nmr spectra were recorded, the starting amines had been completely consumed. Therefore, in order to eliminate the possibility that equilibration could have occurred during this brief period, selected examples ((24c) and (26c)) were reacted with $(\text{CD}_3)_2\text{SO}_4$ at -20°C in the probe of a 100MHz ^1H nmr spectrometer and spectra recorded as the reaction progressed and ratio emerged. No difference was observed between the final ratios observed in this way and those measured after reaction at room temperature.

It can be seen that the ratios of diastereoisomeric salts of each amine do not simply mirror the respective ground state amine invertomer ratios, particularly in the series of the amines (26a)-(26e). This would not be the case if the rate of quaternisation were faster than the rate of amine conversion. In addition, if quaternisation were faster than amine inversion then not only would the ratio of salts reflect directly the invertomer ratio but also the product ratio would not vary from one alkylating agent to another. Clearly, this is not the case and the ratios in table 4.1 may be assumed to reflect the differences in free energies of the transition states leading to the products, i.e. the Curtin-Hammett principle applies. Other amines prepared in connection with this research were also alkylated and the results were recorded in table 4.2. The quaternisation constituted attempts to broaden the range of substituents which might influence the reaction.

Table 4.2



Compound	Invertomer Ratio		(81e)		CD_3I		$(\text{CD}_3)_2\text{SO}_4$		CD_3FSO_5	
	syn-l.p : anti-l.p		syn-attack:anti-attack		syn-attack:anti-attack		syn-attack:anti-attack		syn-att:anti-att	
(65)	29	71 ^a	25(3.08)	75(3.28)	31(3.03)	69(3.21)	31(3.0)	69(3.2)		
(38e)	39	61			42(3.53)	58(3.20)				
(81e)					55(3.38)	45(2.93)				

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a. The anti-lone pair (l.p) configuration is defined as that with the lone pair syn- to the aromatic ring substituted with four hydrogen atoms.

II. Discussion

It can be seen from table 4.1 that in the series of amines (24a)-(24e), there is an overall preference for quaternisation anti- to the aromatic ring. This preference increases as the ring becomes increasingly electron deficient. It might be anticipated that anti-attack would be sterically slightly more favourable than syn-attack. However, in view of the minimal steric differences as the series is descended, the increasing preference for quaternisation to take place anti- to the benzene ring merely as the substituent on that ring changes must wholly be due to electronic factors.

This trend is quite opposite to that observed in the ratios for N-chlorination of the N-H amines⁵⁹ (27) under conditions of kinetic control. The increasing preference for the formation of the syn-chloro invertomer (Table 3.1) was explained by the increasingly favourable aromatic ring/succinimide interaction as the ring became electron deficient (Figure 3.5). The quaternisation results seem best explained by the increased electrostatic repulsion between the positive end of the quaternising agent dipole and the electron-deficient aromatic ring. This would disfavour syn-approach in the tetrahalosubstituted substrates (Figure 4.3).

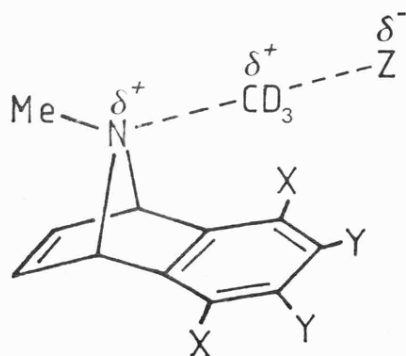


Figure 4.3

Although the preference for quaternisation to occur anti- to the ring might, at first sight, appear to follow from the fact that the preferred amine configuration in each of (24a)-(24e) is that with the lone pair anti- to the ring, the ratios upon quaternisation are sufficiently different to counter the suggestion that quaternisation occurs more rapidly than amine inversion. Disappointingly, however, the increase in reactivity of $\text{CD}_3\text{I} < (\text{CD}_3)_2\text{SO}_4 \leq \text{CD}_3\text{FSO}_3$ appears to have negligible effect on the product ratios. Typical of this observation are the results for the amine (65) (Table 4.2). The greatest loss of stereochemistry is no more than ca. 10% (for the reaction of (24d) and (24e) with CD_3I and CD_3FSO_3) and this is very small in energy terms. This result suggests that the transition states for the reactions with each type of alkylating agent occur at approximately similar points along the reaction path. The trend in product ratios with the variation in the ring substituent is the same whether the alkylating agent is CD_3I , $(\text{CD}_3)_2\text{SO}_4$ or CD_3FSO_3 , i.e. it suggests an "early", amine-like transition state.

With the series of amines (26a)-(26e), there is less preference for reaction to occur anti- to the benzene ring and this is as expected since the exo-2,3 protons clearly offer more steric hindrance to the approach of the electrophile. Consequently, there is a far greater proportion of the quaternary salt resulting from attack of the lone pair in the syn-configuration and, for example, 60% of the mixture of salts from the quaternisation of (26a) with CD_3I is the product corresponding to attack by the least favoured invertomer. These amines exist almost exclusively in the syn-methyl/anti-lone pair configuration in the ground state. Nonetheless, despite the greater steric congestion, the proportion of quaternary salt

syn-(82) (Figure 4.4) increases as the aromatic ring becomes electron deficient and again, this must surely be due to electronic factors as the series is descended. This only serves to underline the influence of the electron density of the aromatic ring during alkylation.

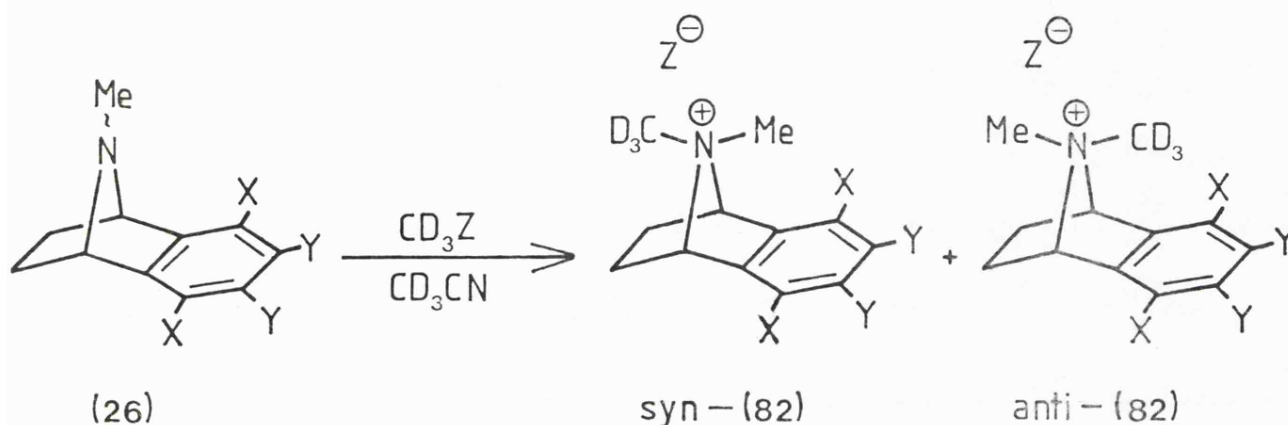
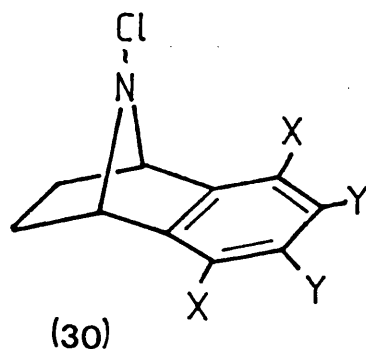


Figure 4.4

As with quaternisation of the series of amines (24a)-(24e), the trend in product ratios runs counter to that observed in the N-chlorination of secondary amines (28) under conditions of kinetic control (Table 4.3).

Indeed, it was these results which provided evidence of the influence of electronic factors during chlorination since, in each case, the major product by far ($\geq 80\%$) was that resulting from attack from the more hindered side of the amine¹¹. Whilst not denying the role of electronic forces in the quaternisations of the amines (26), the much greater steric bulk of the incoming electrophile during quaternisation (CD_3) as opposed to chlorination (Cl) presumably accounts for the smaller proportion of anti-attack in the former case compared to the latter (c.f. 94% for (30b) and 41% for the quaternisation of (26b) with CD_3I). The greater part played by steric hindrance in these quaternisations is corroborated by



	<u>Invertomer Ratio</u>	
	<u>syn-Cl : anti-Cl</u>	
(30a)	5	95
(30c)	6	94
(30d)	18	82
(30e)	20	80

Table 4.3

the insensitivity of the product ratio to the reactivities of the alkylating agents. Overall, the effect of the exo-2,3 protons is to increase the proportion of syn-attack by ca.10-20% compared to the series (24a)-(24e). This is almost as much as the increase in anti-attack upon descending both series (ca.15-25%).

The N-ethyl compounds (83b), (83e), (84b) and (84e) (Figure 4.5) were prepared in order to probe the effect of greater steric bulk at nitrogen on the quaternisation ratios. Furthermore, the presence of an ethyl group at nitrogen, where the ^1H nmr signal of the N-CH_2 group appeared as a quartet, allowed the use of non-deuterated methylating agents.

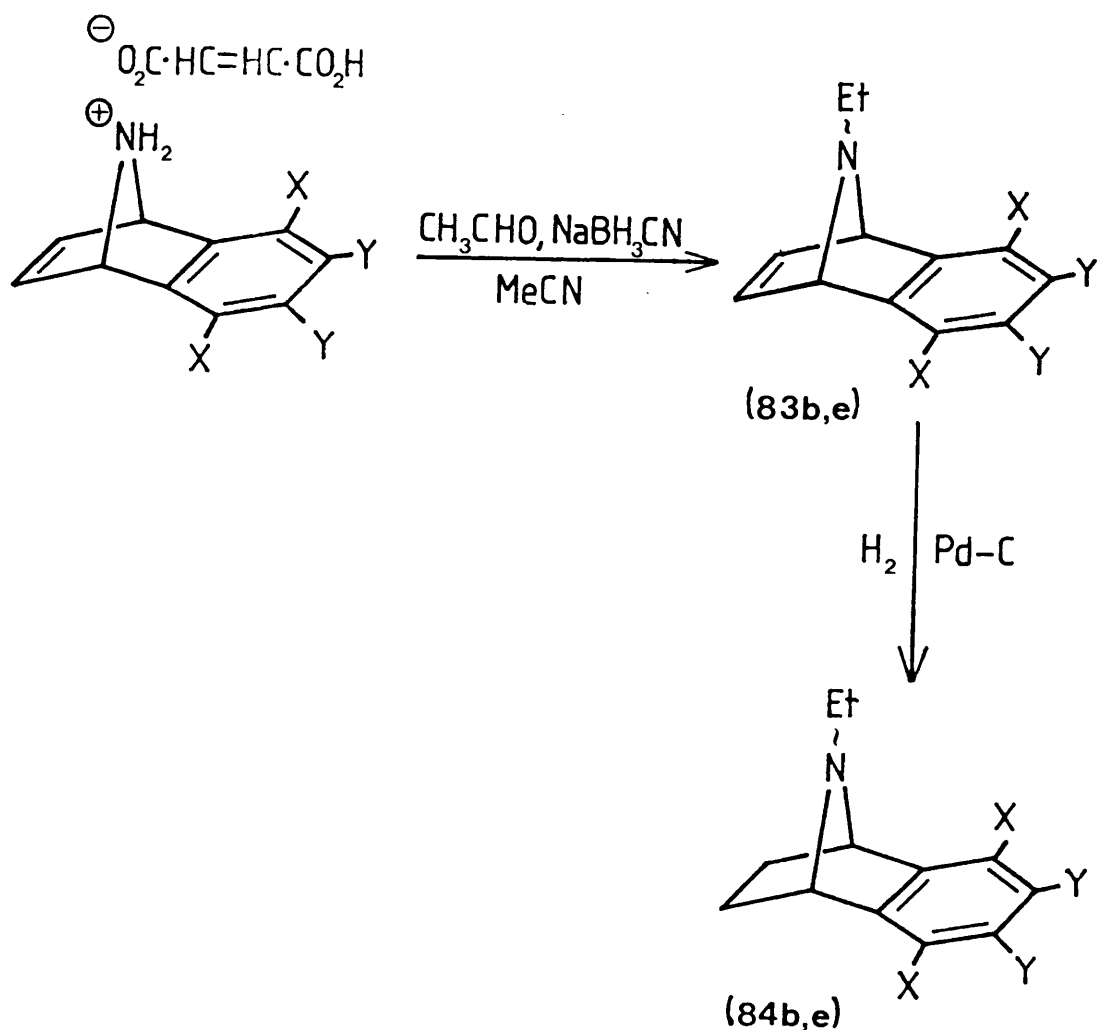


Figure 4.5

In this way, the effect on product ratios of less reactive alkylating agents such as methyl bromide (MeBr) could be investigated along with the effect of charged quaternising agents such as trimethyloxonium tetrafluoroborate ($\text{Me}_3\text{O}^+\text{BF}_4^-$, TMOTFB). If the transition state in figure 4.3 was representative of the reaction, it was hoped that the presence of a full positive charge on the incoming electrophile would encourage almost exclusive anti-quaternisation in the case of (83e) and (84e) because of the destabilising electrostatic interaction which would discourage attack syn- to the aromatic ring.

The quaternisation of the N-ethyl substrates led to a

pattern of major and minor methyl singlets and methylene quartets. These absorptions were analysed to yield the ratios of diastereoisomeric quaternary salts and a typical set of spectra is shown in figure 4.6 for the reaction of (84e) and MeBr.

The product ratios from quaternisation of the N-ethyl amines with MeBr, MeI and TMOTFB are recorded in table 4.4.

Table 4.4

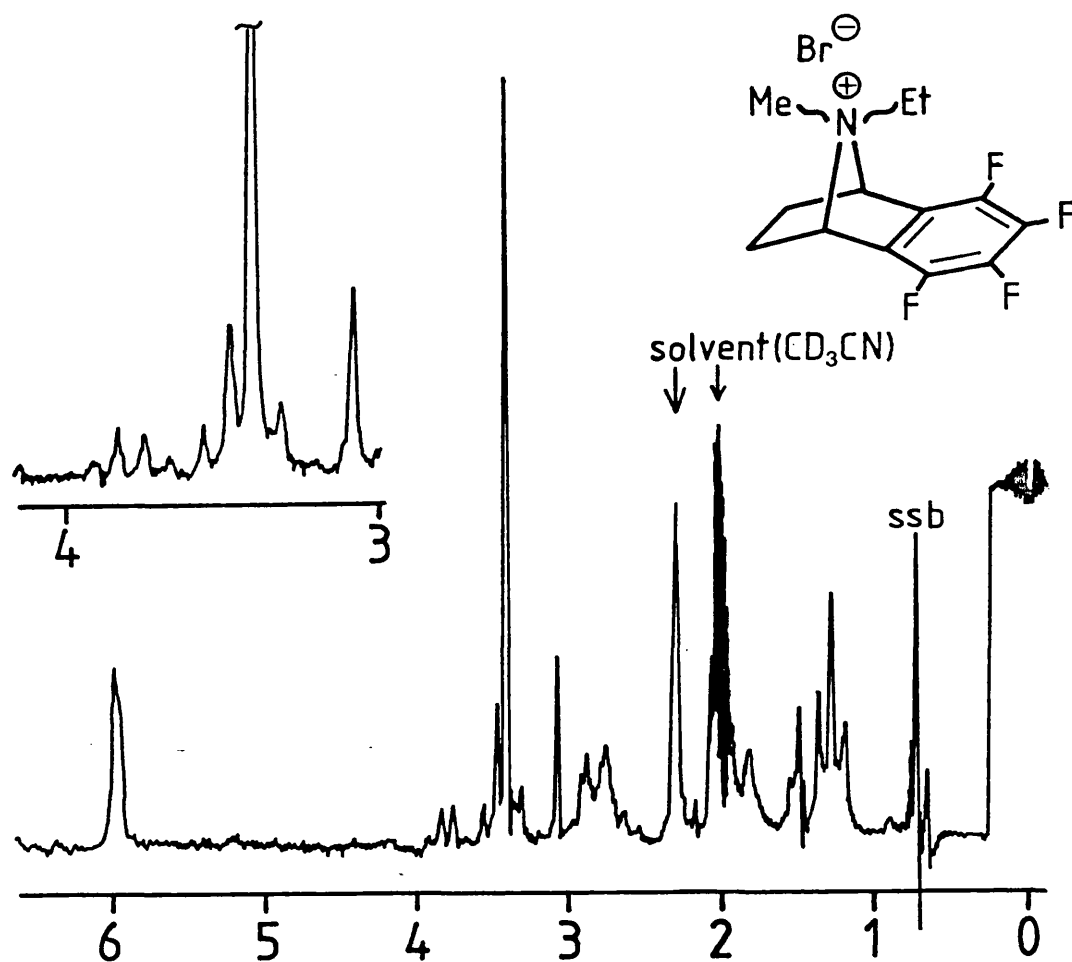
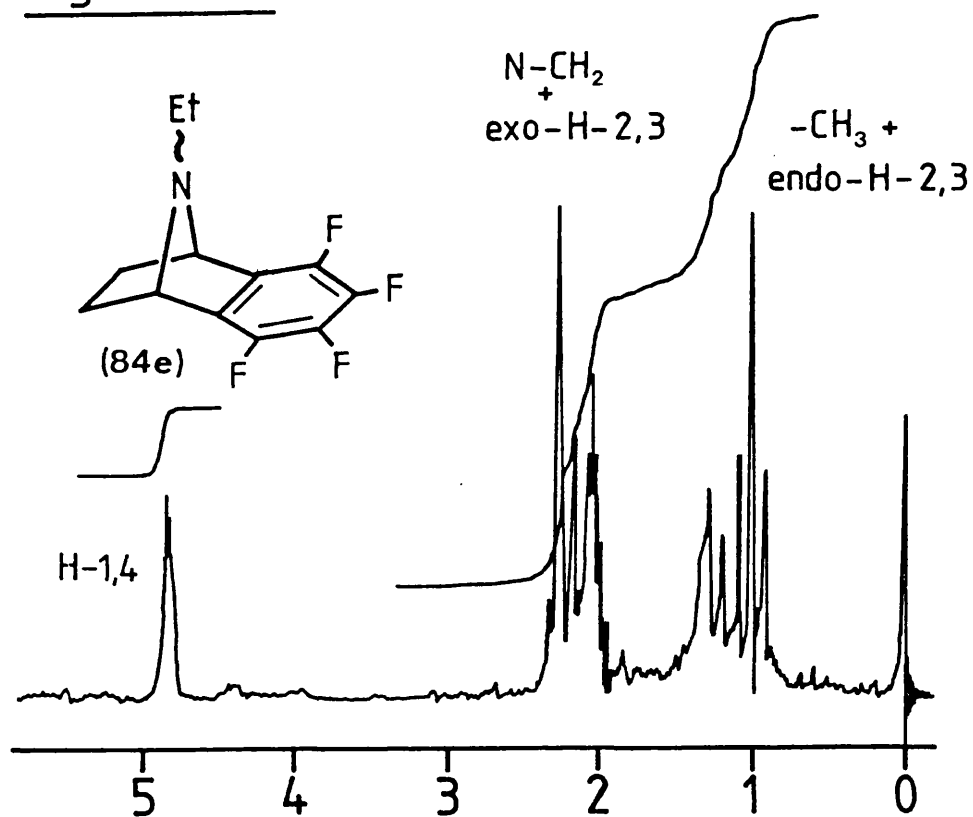
<u>Compound</u>	<u>MeBr</u> ^a	<u>MeI</u> ^a	<u>TMOTFB</u> ^a
	<u>syn-attack:anti-attack</u>	<u>syn- : anti-</u>	<u>syn- : anti-</u>
(83b)		47:53 ^b	37:63
(83e)		25:75 ^b	14:86
(84b)	67:33	60:40	
(84e)	39:61	38:62	35:65

a. $\pm$ 3%.

b. The errors associated with these ratios are much larger ($\pm$ 5%?) due to decomposition of the quaternary salt under the conditions of reaction.

The first point to note is that the ratios observed for the reaction of (84b) and (84e) with MeI are virtually identical to those for the reaction of (26b) and (26e) with CD₃I. This would suggest that the substitution of the bulkier ethyl group at nitrogen has no effect on the course of quaternisation. This conclusion is confirmed by a similar observation for the amines (83b) and (83e) where the ratios of diastereoisomeric products created upon reaction with TMOTFB closely resemble the ratios observed during the reaction of (24b) and (24e) with CD₃I. This latter observation also refutes the suggestion that the electron deficient aromatic ring disfavors syn-attack of the

Figure 4.6



lone pair on a alkylating agent more than a neutral one. The notion that the product ratios from the quaternisation of the N-methyl substrates could be a measure of the reactivity of the alkylating agent is further destroyed by the absence of any greater stereoselectivity during quaternisations with MeBr. The ratios are close to those observed for the reaction of (84b) and (84e) with MeI.

One other observation from experiments with N-ethyl compounds is noteworthy. The ratios from the reaction of (83b) and (83e) with MeI have much greater error placed on them due to the rapid decomposition of the quaternary salt. The addition of 0.5 molar equivalents of MeBr to (83b) dissolved in CD_3CN led initially to rapid formation of the quaternary salt (within 30 minutes as judged by ^1H nmr spectroscopy) but absorptions due to the diastereoisomeric salts began to disappear and, after 5 hours at room temperature, two products could be isolated. Petrol extraction of the concentrated nmr sample yielded 1-(N-ethyl-N-methyl)naphthylamine which was identified by similarity of the aromatic absorptions with those of authentic 1-(N,N-dimethyl)naphthylamine. The residue was identified as protonated starting material (nmr). This aromatisation has been noted frequently before^{63,74,128} and a mechanism of the formation of these products is suggested in figure 4.7.

In summary, the stereoselectivity observed during the quaternisation of the N-methyl amines (24) and (26) can be attributed to the variation in electron density of the aromatic ring as X and Y change. This is the first example of a stereoselective quaternisation where electronic factors play a

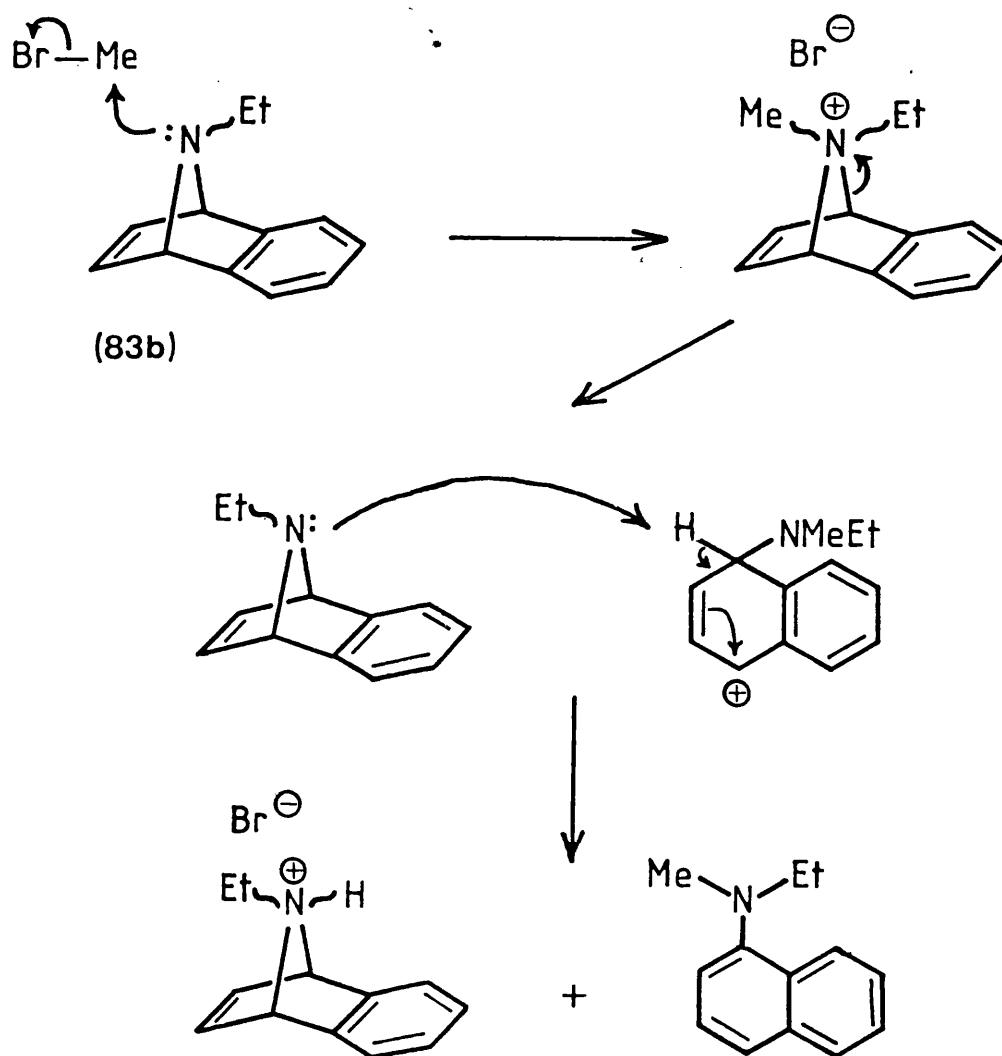


Figure 4.7

significant part in determining the relative amounts of diastereoisomeric salts. Prior to this, the only instance where the stereoelectronic effect of a double bond had been considered in this context was the quaternisation of 2-methyl-2-methyl-2-azabicyclo(2.2.2)oct-5-ene (85) (Figure 4.8) with CD_3I . However, the ratio of diastereoisomers was 1:1 indicating that the double bond had no effect over the preferred direction of quaternisation¹²⁹. Recent stereoselective quaternisations continue to be rationalised on the basis of steric congestion¹³⁰.

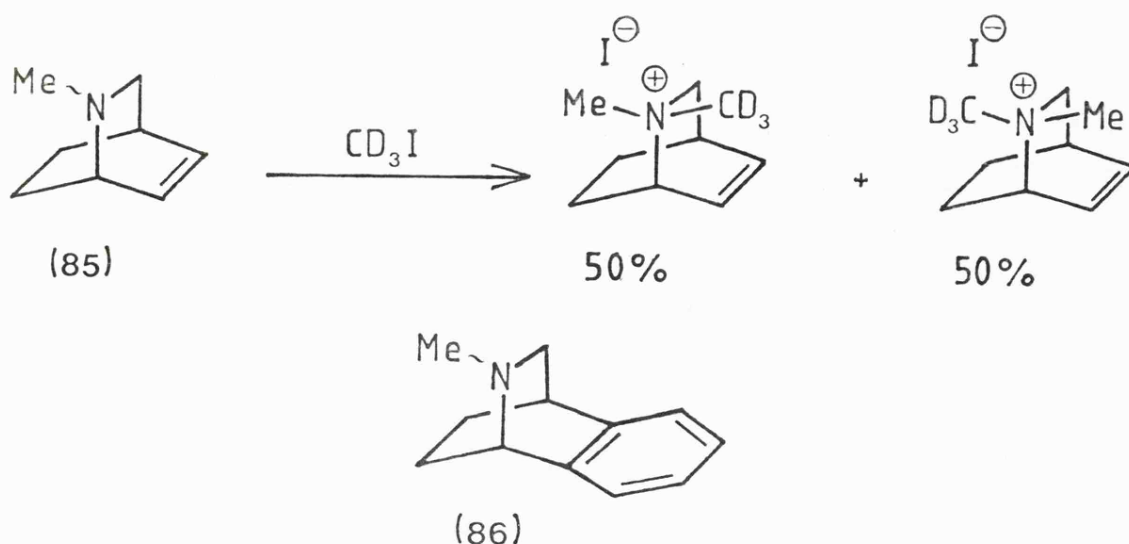


Figure 4.8

In contrast, preliminary experiments with the amine (86) where a benzene ring rather than an etheno group bridges the 1,4-positions showed a marked stereoselectivity (68:32) although no firm assignment of the respective stereochemistry of the major and minor products was possible.

With the N-chlorination of the amines (27) and (28) it is quite clear that the electronic factors are of paramount importance. However, with the quaternisation results presented here, the balance between steric and these same electronic forces appears much finer. This is possibly due to the greater bulk of the incoming group during the alkylation reactions and the lack of suitably disposed charges in the leaving group, charges which had played a key role during N-chlorination.

CHAPTER 5

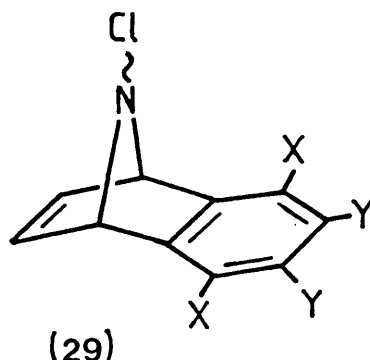
THE SOLVOLYSIS OF SOME SYN- AND ANTI-N-CHLORO-1,4-DIHYDRO-
NAPHTHALEN-1,4-IMINES

The N-chloroamine (29b) has previously provided a basis for the study of stereoelectronic control in the heterolysis of the N-Cl bond⁵⁸. To date, no other azabicyclic system presently available has an inversion barrier high enough to allow such a study. In view of the range of analogues available, (29a)-(29e), we were particularly attracted to an investigation of their solvolytic behaviour in order to probe the effect that the various substituents in the benzene ring might have upon the rate or course of the reaction. Furthermore, the previous study had been confined solely to (29b) and some doubt still remained over the structure of the product arising from the solvolysis of anti-(29b).

The solvolysis work will be presented under two headings: in section I, the evidence for the structures of the solvolysis products and the mechanism of their formation will be discussed. In the following section, observations concerning the relationship between the structure of each of the N-chloroamines and its relative reactivity will be examined.

I. The Structures of the Solvolysis Products¹³¹

Three N-chloroamines were investigated:- (29b), (29c) and (29e) (Figure 5.1). These were chosen because the substituents in the aromatic ring ranged widely from electron-donating (OMe) to electron-withdrawing (F).



- b. $X = Y = H$
- c. $X = OMe, Y = H$
- d. $X = Y = F$

Figure 5.1

Each mixture of syn- and anti-N-chloroamines was solvolysed at 0°C in methanol in the presence of silver salt. The N-chloroamines (29c) and (29e) were simply stirred in an ice-cold solution of methanolic $AgNO_3$ whilst (29b) was treated using Rautenstrauch's original procedure with silver carbonate-Celite. In this latter example, care was taken to ensure that the solvolysis proceeded under conditions of negligible inversion by performing the column and all subsequent manipulations at 0°C in a cold room.

Three products were isolated from the solvolysis of (29c) (Figure 5.2).

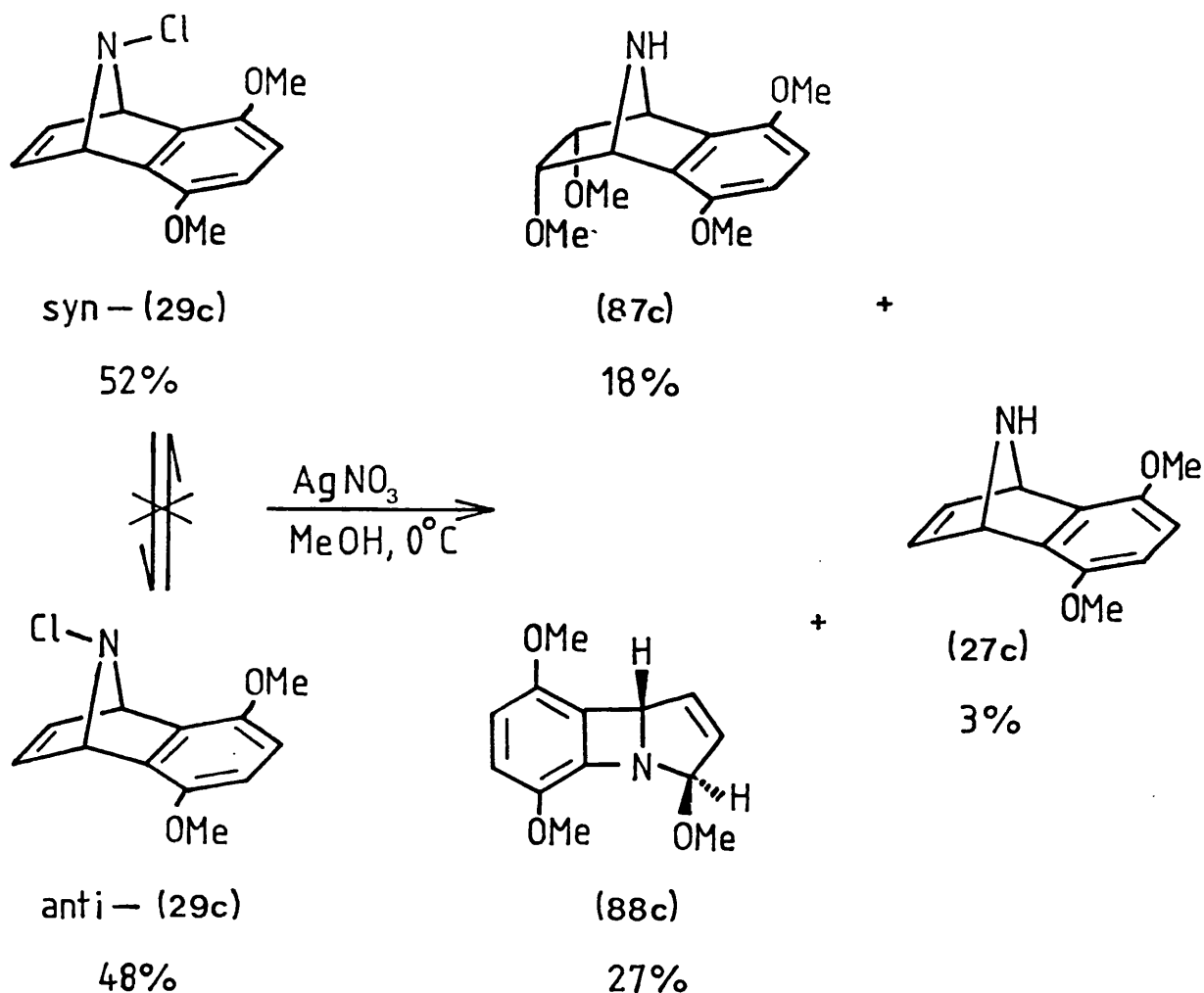


Figure 5.2

The amines (87c) and (88c) arise from the solvolysis of the syn- and anti-invertomers respectively of (29c). The yields quoted refer to those after chromatography. Although a variety of structures were considered for the amine (88c) based on spectral and analytical evidence alone, the choice of the 6,7-benzo-1-azabicyclo(3.2.0)-hept-3-ene system seemed reasonable in view of the literature precedent for analogous carbocyclic products from similar solvolyses in all-carbon systems^{10,11}.

When (29e) was treated similarly, only two products were isolated after work-up. These were the amines (27e), corresponding to simple dechlorination of starting material, and (87e), the product of solvolysis of syn-(29e) (Figure 5.3).

None of the amine (88e), corresponding to the solvolysis of anti-(29e), was ever isolated in any solvolysis of the fluorinated N-chloroamine.

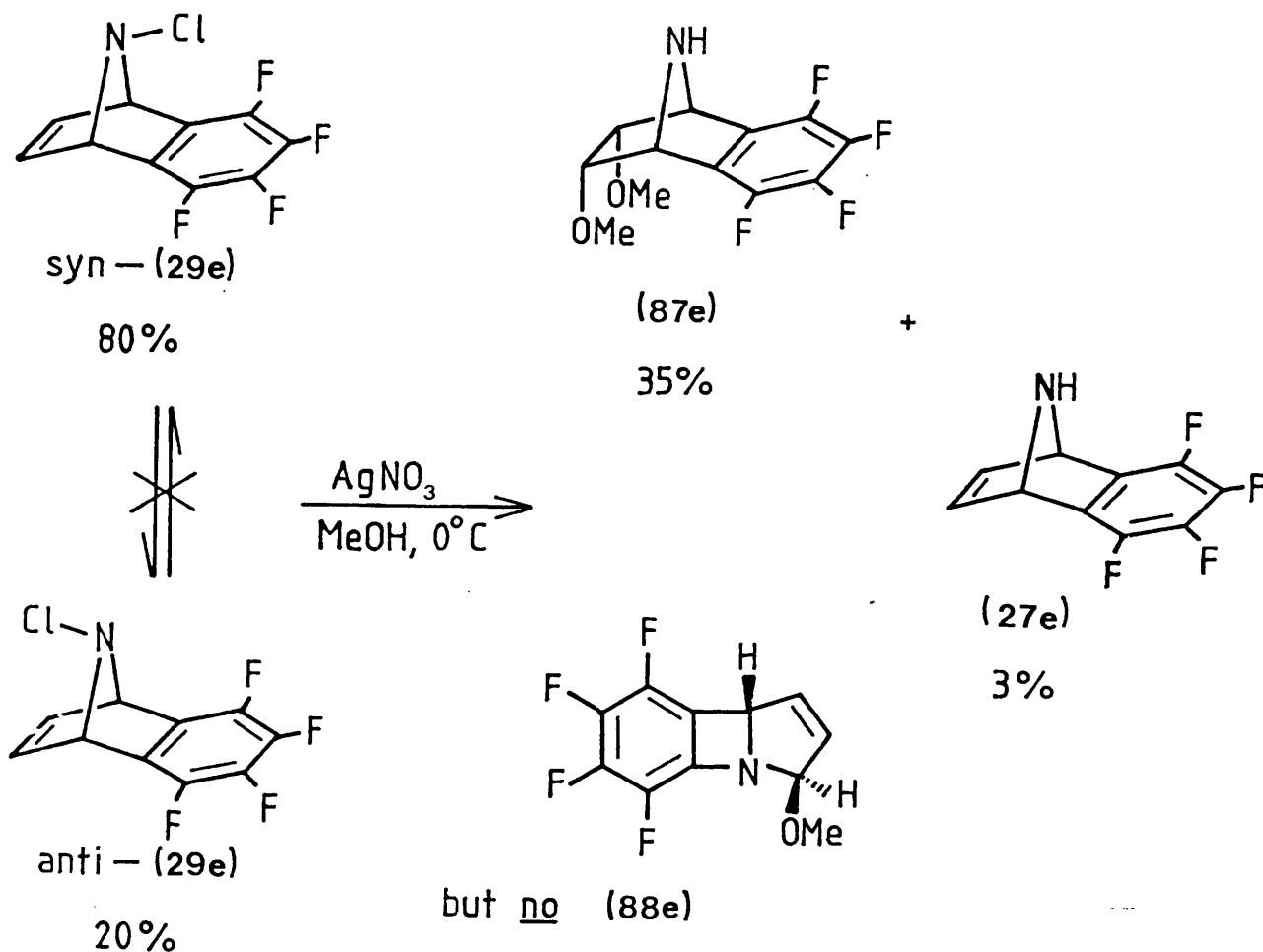


Figure 5.3

The amine (88b) (Figure 5.4) corresponds to the product which Rautenstrauch assigned the benzazepine structure (76b)⁵⁸. The amine (88b) arose from the solvolysis of anti-(29b). When a mixture of syn- and anti- (29b) was brought into contact with silver carbonate-Celite at 0°C , the stereochemically pure anti-(29b) could be eluted from the column after ca. 25 minutes; the anti-invertomer was then solvolysed at 0°C in methanolic AgNO_3 .

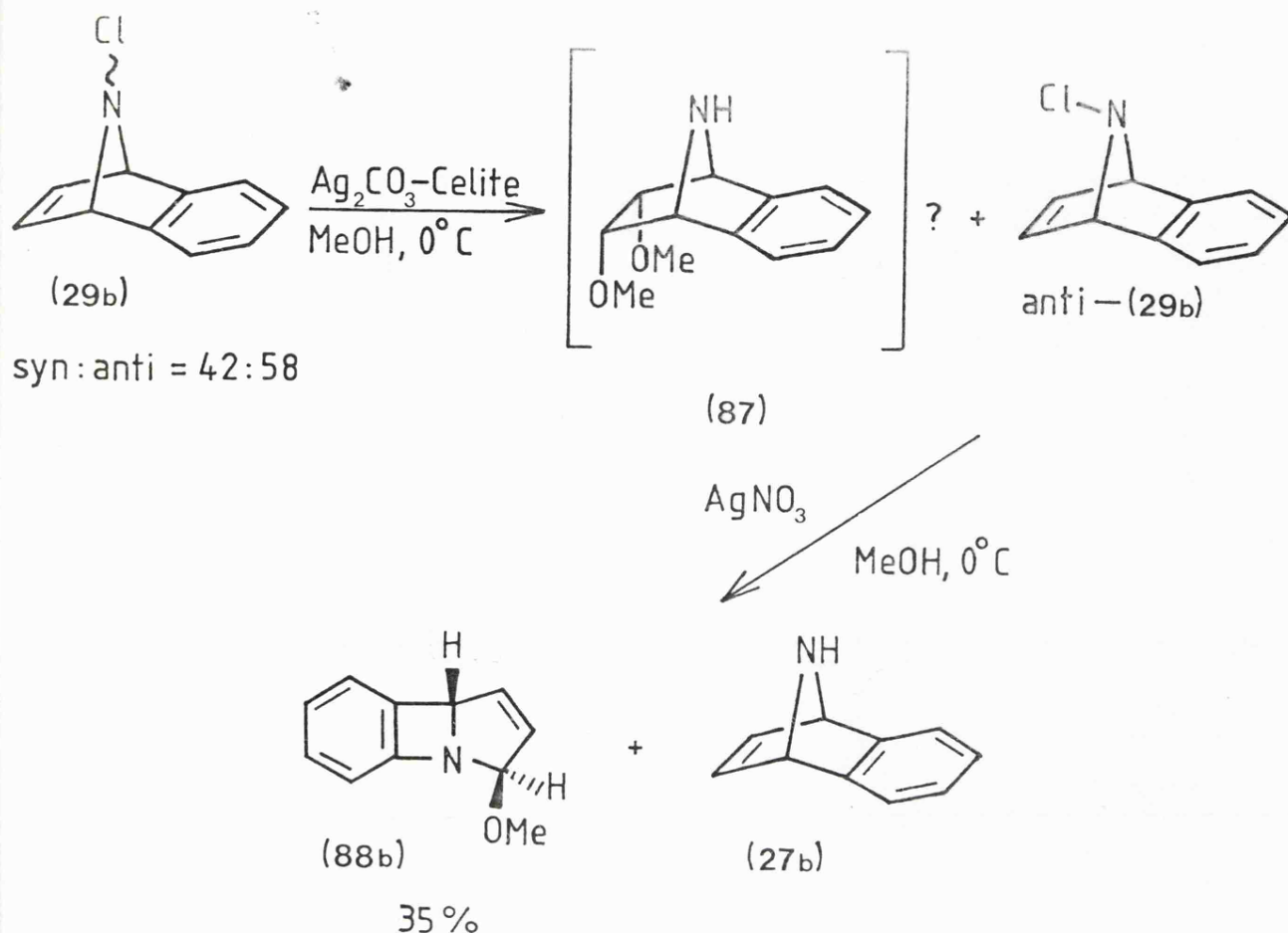


Figure 5.4

The product from the solvolysis of syn-(29b) could not, however, be recovered from the celite. On each occasion, the column material was stirred with base (2M or 4M K_2CO_3 or 2M NaOH solutions were used at various times), the celite was removed by filtration and the filtrate extracted with CH_2Cl_2 , but this always gave only traces of organic material whose ^1H nmr spectra bore no resemblance to that quoted for (75b) by Rautenstrauch or that of (87b), the revised structure for the product of syn-solvolysis*.

*The principal product isolated from the methanolysis of (29b) in solution at room temperature was characterised and assigned the structure (87b). Under conditions of free inversion, (29b) prefers to solvolyse by the more reactive syn-configuration⁵⁸. (See next section).

The amines (87c) and (87e) were stable, crystalline solids whilst (87b) could be purified by Kugelrohr distillation to give a viscous, pale yellow oil. In the mass spectrum of these amines, the molecular ion could only be observed at low temperature and low eV (35°C – 40°C , 40eV). Indeed, the molecular ion of (87b) (m/e 205) could not be observed under any conditions, although the $M+1$ ion, m/e 206, was recorded. However, satisfactory analytical results were obtained for this amine as its tetrafluoroborate salt. Satisfactory analyses were also obtained for (87c) and (87e). Intriguingly, the molecular ion of the amine (81e) (Figure 5.5) was also found to be very unstable and was observed only at low temperature and eV (50°C , 43eV).

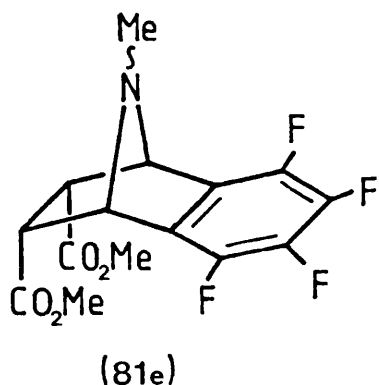


Figure 5.5

The amine (81e) similarly possesses 2,3-bis endo-substituents and, like (87b), (87c) and (87e), the major fragmentation was a retro Diels-Alder loss of the $\text{C}_2\text{-C}_3$ unit as the alkene to give the isoindole¹³².

Details of the structures (87b), (87c) and (87e) were confirmed by consideration of their ^1H nmr spectra and that of (87c) is shown in figure 5.6 as an example.

Figure 5.6

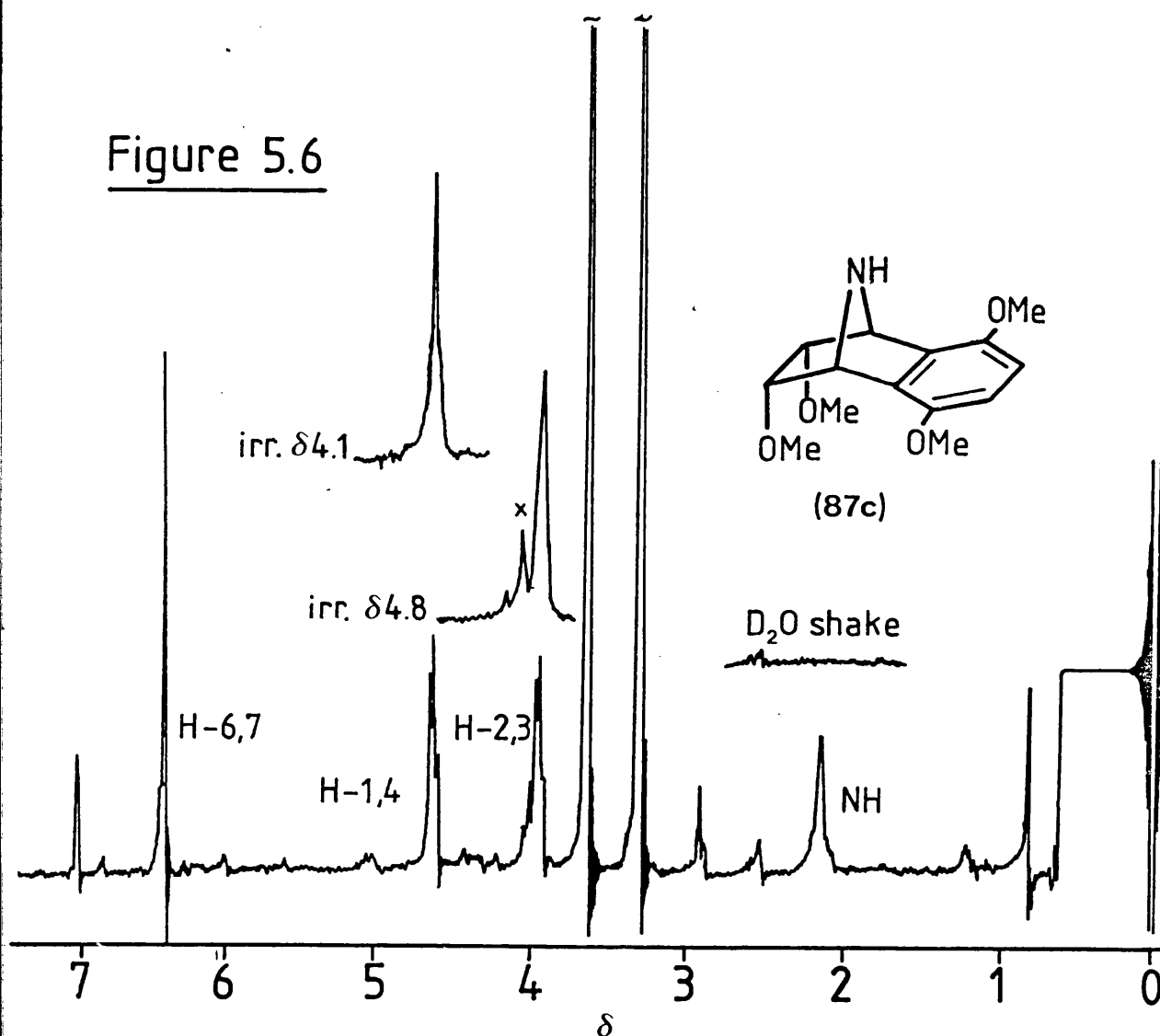


Figure 5.6

Each spectrum had several features in common. A broad singlet, exchangeable with D_2O , was observed at δ 2.5-2.0 and assigned to the NH proton in each case. A broad multiplet ($W_{\frac{1}{2}}=6\text{Hz}$) was present in each spectrum at virtually the same chemical shift (δ 4.1-4.03) and was ascribed to the exo-2,3 protons. The similarity of chemical shift of these protons is not surprising in view of the similarity of the magnetic environment in each amine and this was a deciding factor in their assignment. Homonuclear spin decoupling of these protons confirmed i) their position α - to the bridgehead 1,4-protons and ii) that H_2 and H_3 had the exo- configuration in each case

by virtue of the coupling between H_2 , H_3 and H_1 , H_4 ($W_{12}^1=6\text{Hz}$). The dihedral angle between H_1 , H_4 and endo- H_2 , H_3 protons would be ca. 90° and therefore J usually approaches 0Hz (see Figure 2.11). Greater variation was observed in the chemical shifts of the signals assigned to the bridgehead H_1 , H_4 protons and this was reasonable in view of their benzylic position. Furthermore, these absorptions - at δ 4.48 in (87b), 4.78 in (87c) and 4.93 in (87e) - showed the greater downfield shift (0.55-0.89ppm) on protonation that the H_2 , H_3 absorption (0.25-0.35ppm) thus confirming their position α - to nitrogen. Each spectrum contained a singlet at δ 3.35 which integrated for six protons against H_1 , H_4 and H_2 , H_3 (Figure 5.6). The infra-red spectrum of each amine showed a broad, weak resonance at 3290 cm^{-1} , confirming the presence of the $-\text{NH}$ group and, in the i.r. spectra of (87b) and (87e), there was a strong absorption at 2830 cm^{-1} , indicative of an $-\text{OMe}$ group.

None of these products from the syn-pathway exhibited a one proton multiplet around δ 6.76 (which had been assigned to the vinylic proton in (75b)⁵⁸) when their nmr spectra were recorded in CCl_4 or CDCl_3 . The presence of such a resonance is crucial to the consideration of (75b) and its analogues (75c) and (75e) as structures for these amines. Indeed, the ^1H nmr spectrum of (87e) is very simple, consisting of just four absorptions, all below δ 5.0 (Figure 5.7).

When (29b) was solvolysed in methanol alone for ca. 20 hours at room temperature, all the starting N-chloroamine was consumed and the ^1H nmr spectrum of the crude reaction mixture was shown to be a composite of protonated (27b) and (87b) by comparison with spectra of authentic protonated amines. The nmr spectrum of the reaction mixture after basification and extraction into

Figure 5.7

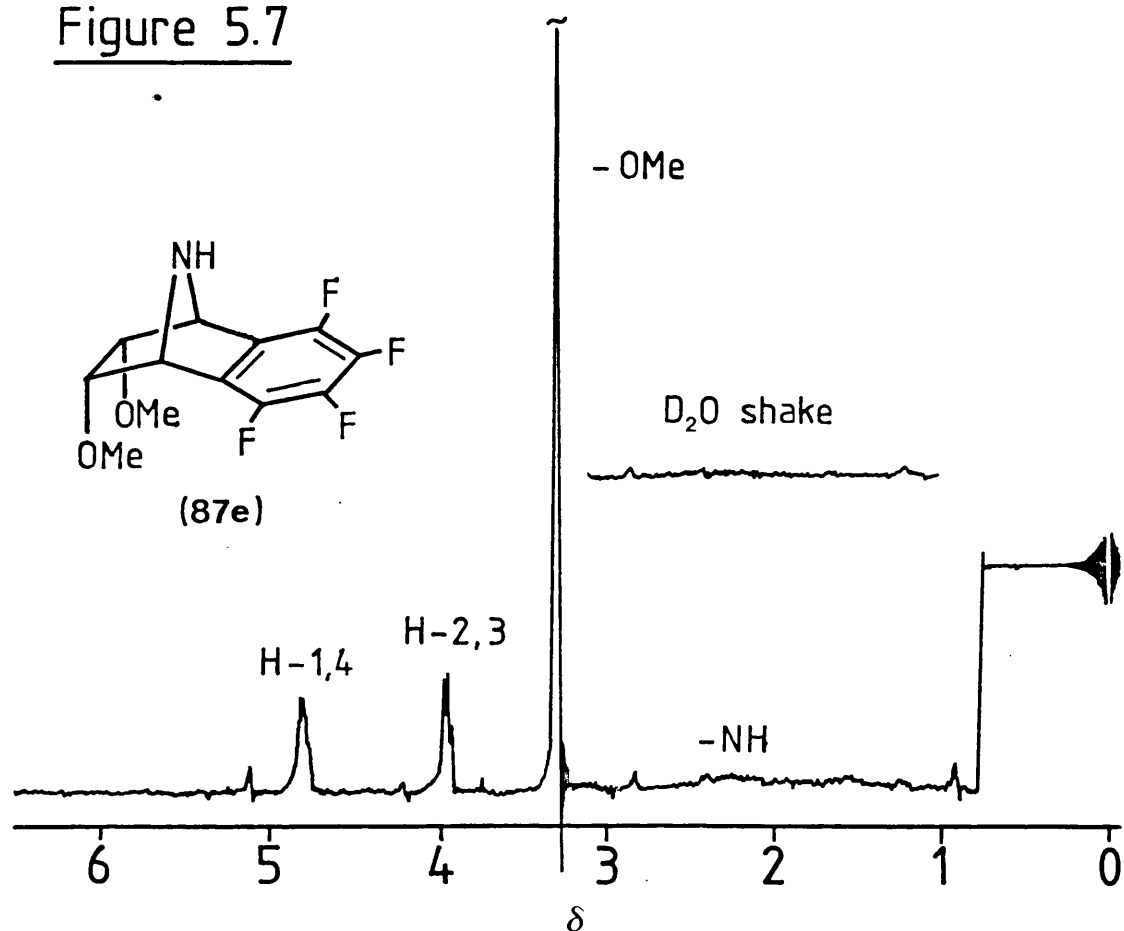


Figure 5.7

CH₂Cl₂, a mixture now of (27b) and (87b), showed a pattern of signals that was similar in some but not all respects to that quoted for (75b)⁵⁸ but we were unable to detect any (75b) (or its analogues in similar solvolyses) in any of these reactions.

That the amines (87b), (87c) and (87e) were the solvolysis products of the respective syn-N-chloroamines was confirmed by performing the methanolysis reactions at room temperature. Under these circumstances, Rautenstrauch had shown the syn-invertomer to be the more reactive⁵⁸. Thus, the amines arising from solvolysis of the anti-invertomers of (29b) and (29c) were assigned the structures (88b) and (88c) and not the previously suggested (76b) (and therefore by implication (76c)).

This revision of structure was supported by a substantial weight of evidence in which 400MHz ^1H nmr played a key role.

The amines (88b) and (88c) were both stable, crystalline solids at room temperature and satisfactory mass spectral and analytical data were obtained for each. The absence of any broad N-H absorption at ca. 3300cm^{-1} in the infra-red spectra of each amine suggested that they were tertiary. Perhaps the most interesting feature of the 100MHz ^{13}C nmr spectrum of (88b) (Figure 5.8) is the absorption at lowest field at 157.62ppm; this is typical of an aromatic carbon atom adjacent to nitrogen as in N,N-dimethylaniline¹³³ (Figure 5.9).

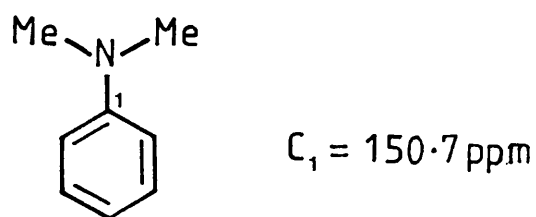
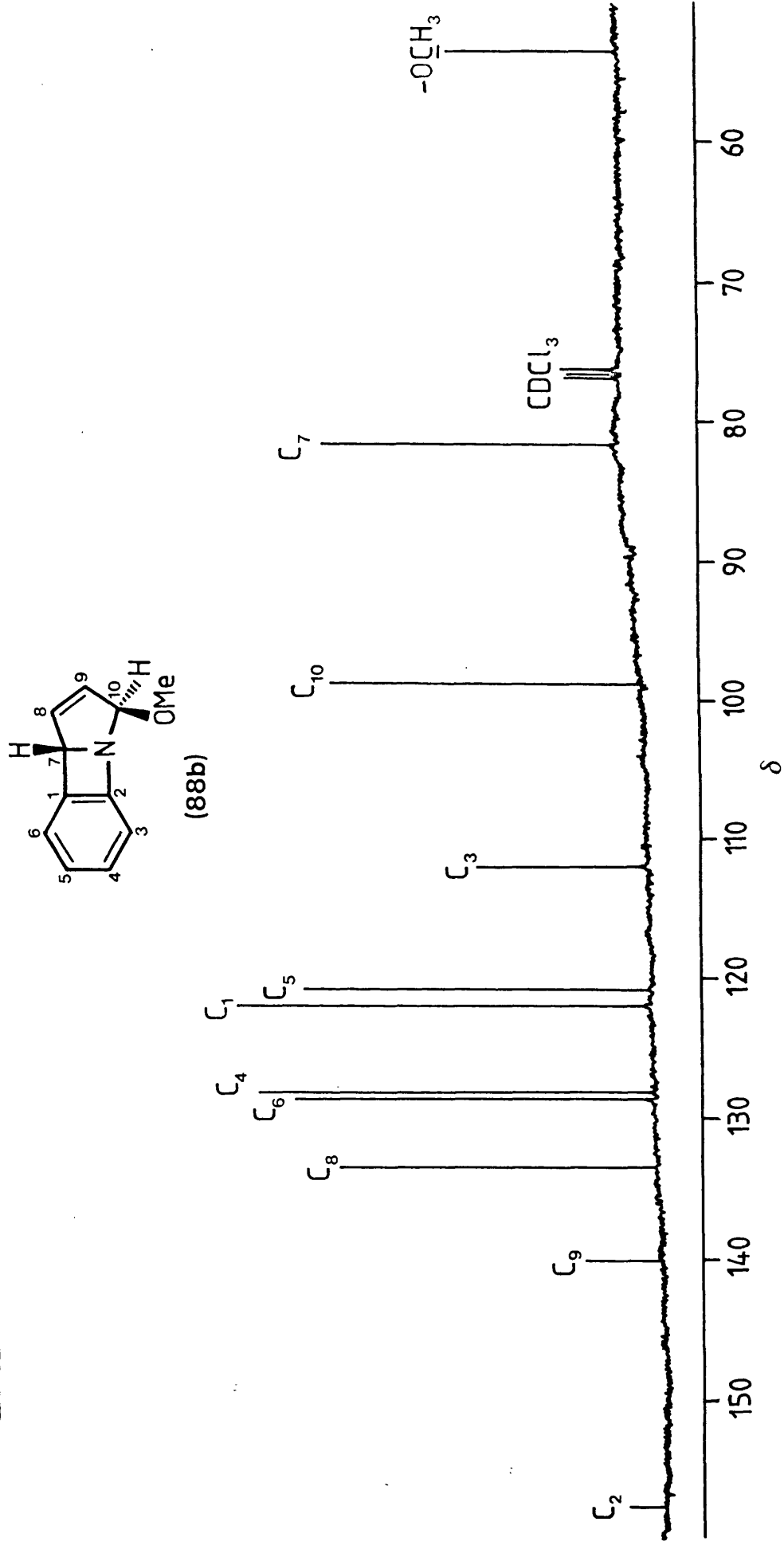


Figure 5.9

The ^{13}C nmr spectrum also indicated the presence of an -OMe group (53.53ppm) and only two vinylic carbon atoms (133.40 and 139.98ppm), not four as might be expected for the benzazepine structure (76b). The aromatic portion of the ^{13}C nmr spectrum of (88b) closely resembled that of 2-ethylaniline¹³⁴ (Figure 5.10) and this assisted the assignments as did calculation of the chemical shift of each carbon based on the structure (88b)¹³³.

The ^1H nmr spectrum of (88b) was as described by Rautenstrauch for (76b) (Figure 5.11). This spectrum contained a sharp, three-proton singlet at $\delta 3.33$ corresponding to a methoxy group together with three multiplet resonances at

Figure 5.8



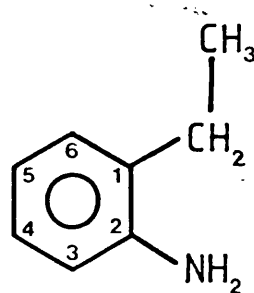
	<u>δ ppm from TMS</u>
	C_1 127.8
	C_2 144.1
	C_3 115.2
	C_4 126.6
	C_5 118.5
	C_6 128.2

Figure 5.10

δ 4.97, 5.63 and 6.24, integrating for 1:2:1 protons respectively. The analogous compound (88c) showed a similar spectrum (Figure 5.11) except that the AB system of the two aromatic protons overlapped with the most downfield absorption of the three between δ 5.2 and 6.35.

However, when (88b) was dissolved in d_6 -benzene and its spectrum recorded at 400MHz, the two proton signal at δ 5.63 separated into two further resonances, each integrating for one proton. Homonuclear spin decoupling experiments showed that all four protons were coupled to one another and a summary of the observed coupling constants is shown in figure 5.12. The 400MHz nmr spectrum of the amine (88c) showed an analogous pattern of doublets of triplets and similar coupling constants. The evidence for the proposed structure (88) will now be discussed exclusively for (88b) but a similar analysis applies for (88c).

Confirmation of the proposed structure for (88b) was aided by several other observations. Irradiation of the

Figure 5.11

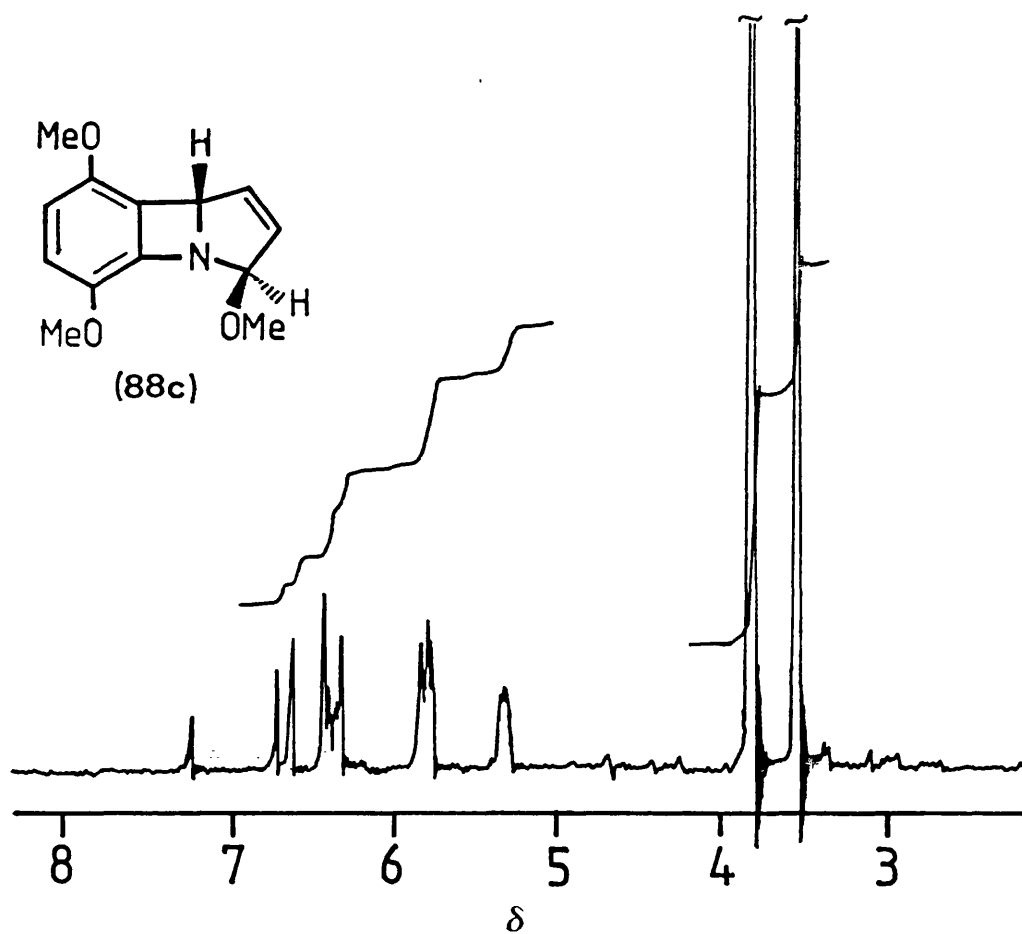
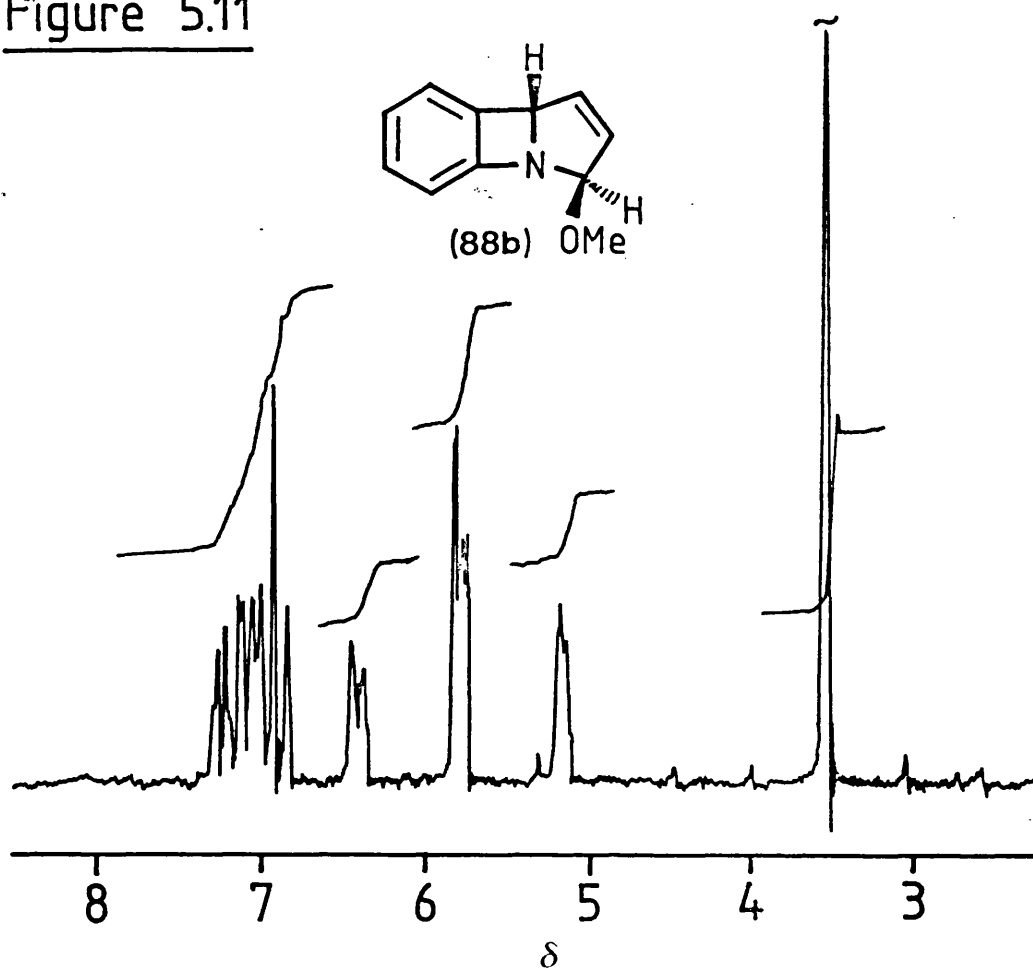
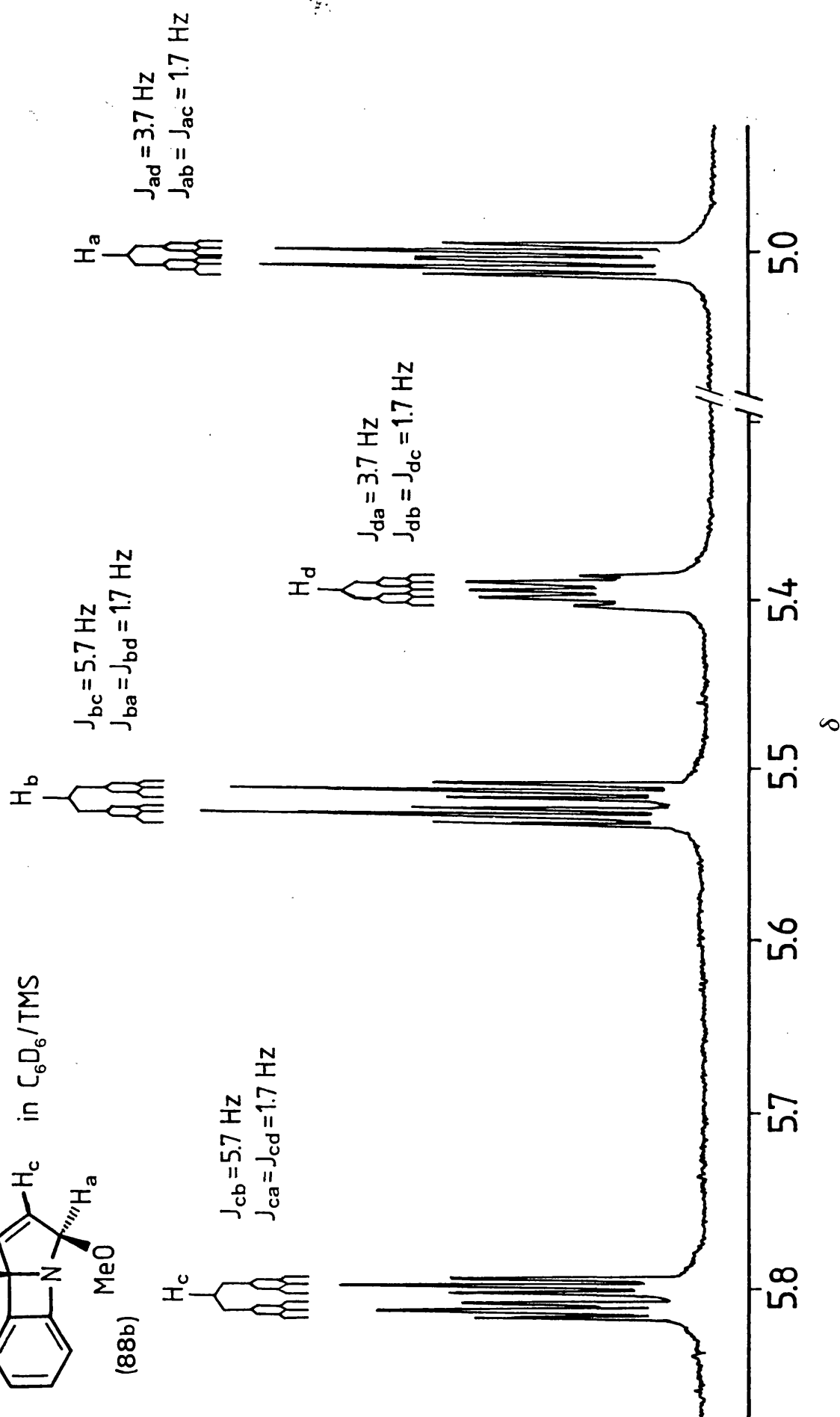
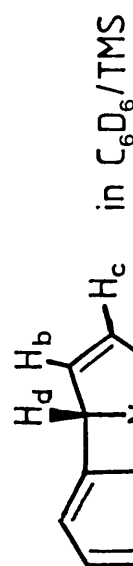
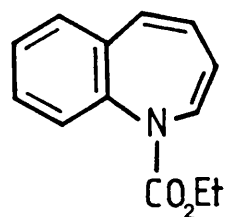


Figure 5.12



aromatic proton at δ 7.02 sharpened the absorption at δ 5.40 and hence showed that this was the benzylic proton, H_d (Figure 5.12). The signals assigned to H_a and H_d showed the greatest downfield shift on protonation with TFA indicating their proximity to nitrogen and therefore showing which absorptions were due to the more remote vinylic protons H_b and H_c which might reasonably be assumed to feel a much smaller influence from the positively charged nitrogen centre.

Furthermore, Anastassiou has recently prepared N-carbethoxy-1-benzazepine¹³⁵ (89) (Figure 5.13) and although no specific assignments were made, the multiplicities of the four olefinic protons and the magnitude of the coupling constants in the 1H nmr spectrum of (89) bear no resemblance to those observed for the supposed "benzazepine" (76b) (Figure 5.12).



(89)

1H nmr data (CDCl₃/TMS)

δ 7.5–7.1 (4H, m, Ar)

δ 6.86 (1H, d, $J=11$ Hz), 6.36 (1H, d, $J=7$ Hz),

6.24 (1H, dd, $J=11, 6$ Hz), 5.81 (1H, dd,

$J \sim 7, 6$ Hz)

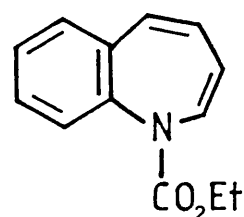
δ 4.23 (2H, q, $-OCH_2CH_3$), 1.26 (3H,

t, $-OCH_2CH_3$)

Figure 5.13

The fate of the benzazepine (76b) as a structure for this amine was sealed by the uptake of only one mole of hydrogen (nmr) upon hydrogenation over Pd-C and a comparison of the ultraviolet (UV) spectra of this hydrogenated product and its unsaturated precursor (86b); the position of the UV maxima in (88b) were unchanged after hydrogenation. This

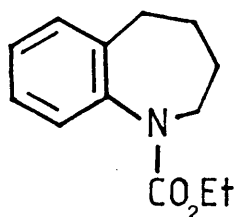
result would not be expected for the benzazepine (76b) and its tetrahydro analogue in view of the differences between the UV spectra of (89) and its tetrahydro analogue (90)¹³⁵ (Figure 5.14).



(89)

UV maxima in C₆H₁₄(nm)

306, 289, 245, 241, 228, 204



(90)

261, 229, 204

Figure 5.14

Having discarded the benzazepine structure (76b), the ¹H nmr spectral data was considered with respect to the novel structure (88b). The coupling of any three adjacent protons on the 1,2-fused-2,5-dihydro pyrrole moiety was rationalised straightforwardly by vicinal and allylic interactions but the coupling of H_a and H_d could arise in two different ways in such a system:-

i) W-Coupling across four single bonds via the nitrogen atom¹³⁶. This is shown by the heavily-linked pathway in A in figure 5.15 and requires H_a and H_d to be cis- to one another. Typically, such coupling constants are 0-1Hz.

ii) Transoid homoallylic coupling via the double bond^{136,137}. This is shown by the heavily-inked pathway in figure 5.15. The values of such coupling constants are typically 0-4Hz.

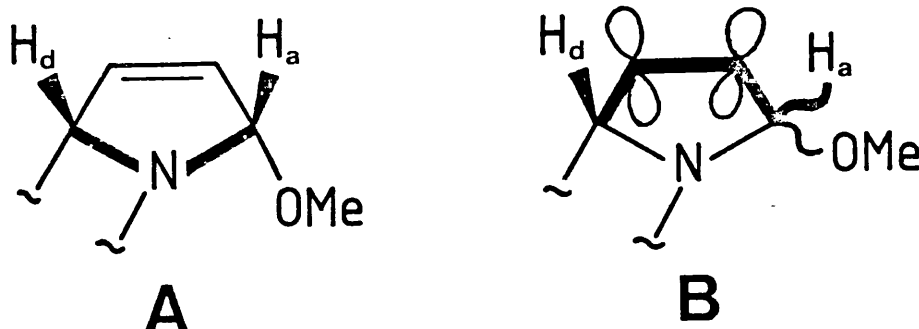


Figure 5.15

Which of these coupling mechanisms was operating here could be decided by a simple hydrogenation; if H_a and H_d no longer coupled to each other after such a process, then this would be strong evidence for homoallylic coupling. If H_a and H_d remained coupled then W-coupling would be implied and this would simultaneously solve the problem of determining the stereochemistry of the methoxy group since the required "W" arrangement would define the orientation of H_a and H_d . This would not rule out the possibility that both homoallylic and W-coupling contributed to $J_{a,d}$ since homoallylic coupling can arise when the protons concerned are cis- or trans- to one another¹³⁶.

In fact, the size of $J_{a,d}$ (3.7Hz) suggested homoallylic coupling between H_a and H_d and this was borne out by the results of hydrogenation over Pd-C (Figure 5.16).

The nmr signals due to H_b and H_c in (88b) and (88c) were removed upon hydrogenation along with the coupling between

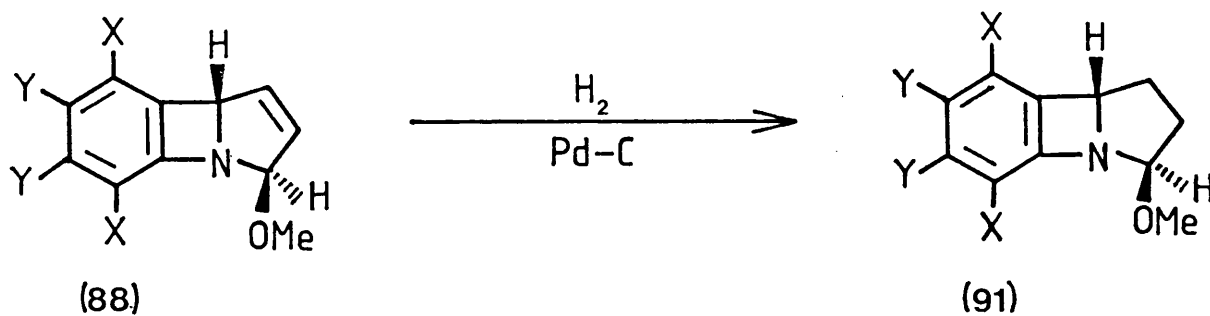


Figure 5.16

H_a and H_d , so proving the homoallylic interaction. The signal due to H_d in each amine remained downfield of that of H_a and this was suggested by protonation experiments with TFA where the signal due to H_d was shifted further downfield than that due to H_a . Further convincing evidence was afforded by irradiation of the signal at $\delta 5.28$ which sharpened the downfield half of the aromatic AB system of (91c) (Figure 5.17) thus proving its benzylic position.

Figure 5.17

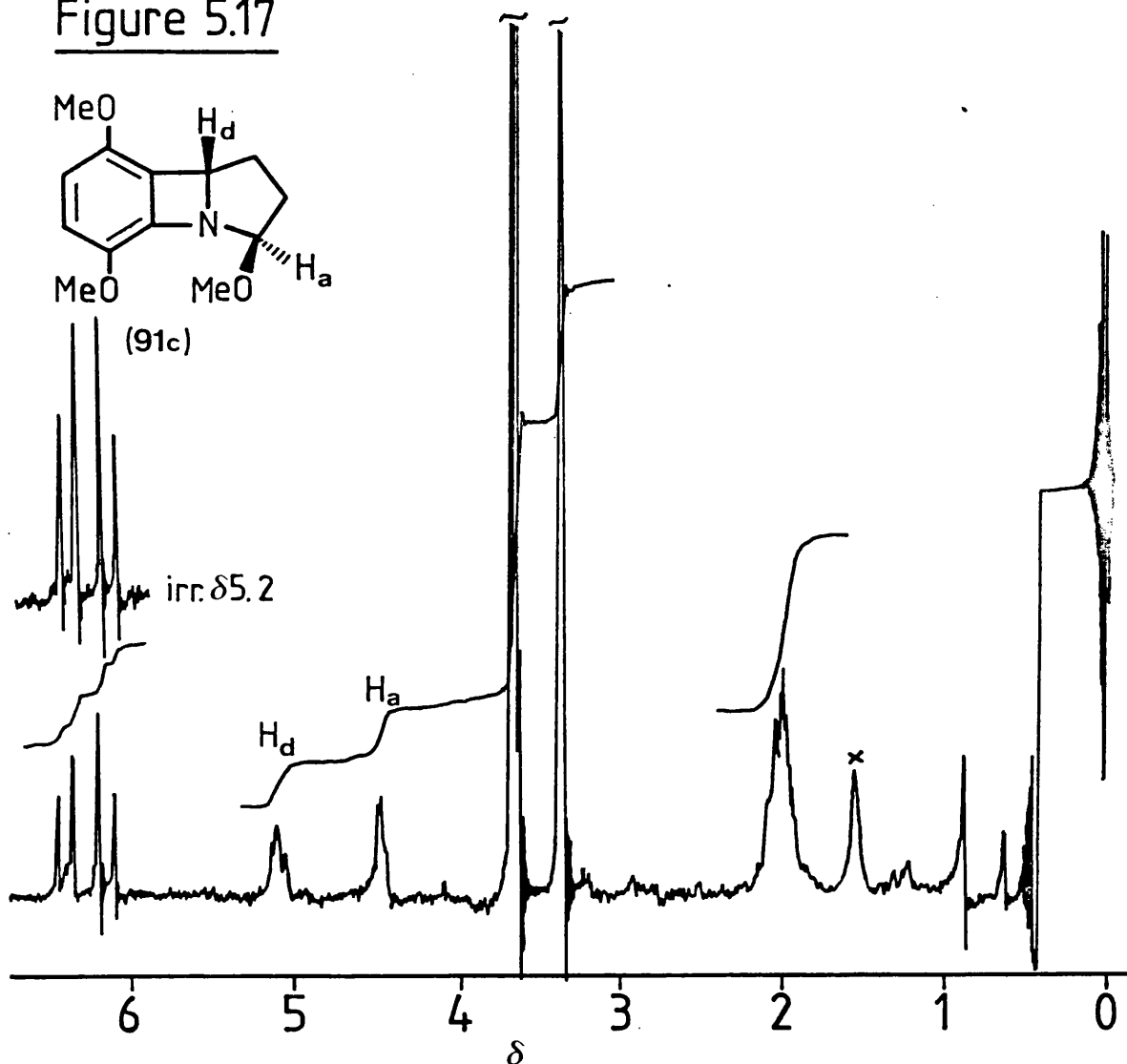
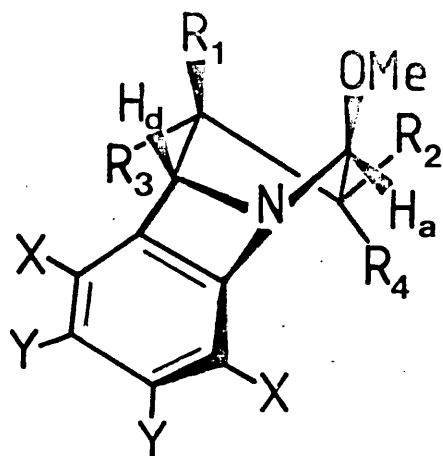


Figure 5.17

The stereochemistry of the methoxy group was determined by scrutiny of the 400MHz ^1H nmr spectra of the hydrogenated amines (91) and their deuterated analogues (92) and (93) (Figure 5.18), made by catalytic addition of deuterium gas.

Although the nmr signals due to H_a and H_d in (91b) and (91c) appeared complex at 90MHz, they were each simple doublets at 400MHz (Figure 5.19). Since H_a and H_d were both adjacent to a methylene not methine group, such multiplicities must arise from the fact that the angle between C-H_a and C-H_d and one of its neighbouring protons must be close to 90° ($J=0\text{Hz}$). This completely defined the conformation of the pyrrolidine ring



- (91) $R_1=R_2=R_3=R_4=H$
 (92) $R_1=R_2=D, R_3=R_4=H$
 (93) $R_1=R_2=H, R_3=R_4=D$

Figure 5.18

and also the stereochemistry of the methoxy group. The four possible stereoisomers are shown in table 5.1 along with a consideration of the bond angles between adjacent C-H bonds viewed along C-C bond joining them.

Only stereoisomer C can give rise to the multiplicities observed for H_a and H_d; in A, B and D, H_a and H_d would be expected to show some coupling to both their respective adjacent methylene protons. This defines the position of the methoxy group as on the β -face of the molecule, cis-to H_d.

This analysis was confirmed by the results of the addition of deuterium to the double bond. In the ¹H nmr spectrum of d₂-(91c), the signals due to H_a and H_d each consisted of overlapping singlet and doublet resonances where in the case of H_d, the singlet was the major resonance (55%) whilst for H_a, the doublet was the greater of the two (60%) (Figure 5.19). The nmr signals of H_a and H_d in d₂-(91b) showed the same pattern although in a different ratio. These spectra could be explained if the addition of deuterium had been non-stereospecific i.e.

Table 5.1

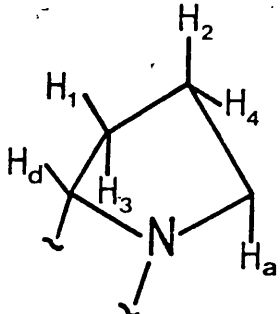
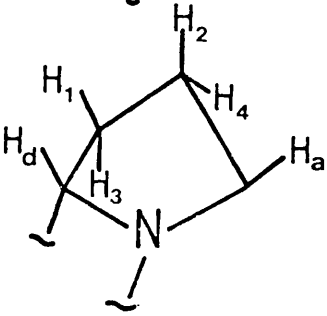
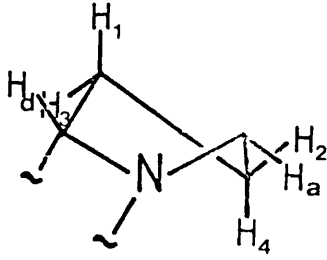
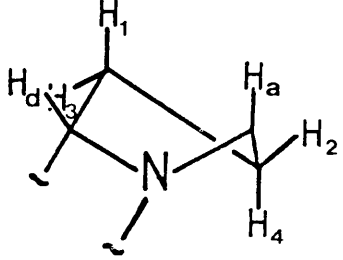
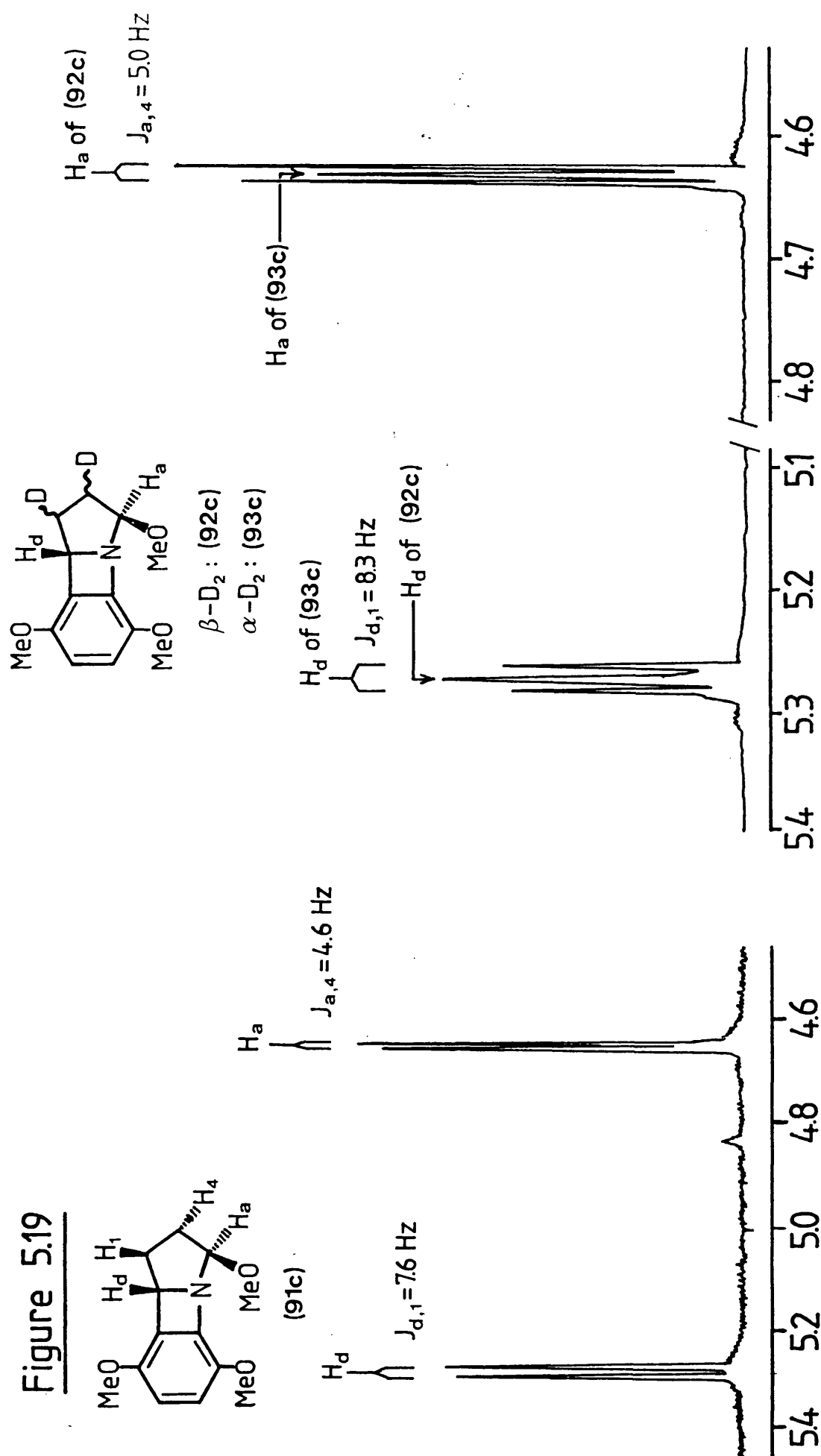
<u>Stereoisomer</u>	<u>Approximate Dihedral Angle Between H_x and H_y</u>		
	$H_d-H_1=10^\circ$, $H_a-H_2=180^\circ$,	$H_d-H_3=140^\circ$; $H_a-H_4=55^\circ$;	$H_d \neq$ doublet $H_a \neq$ doublet
	$H_d-H_1=10^\circ$, $H_a-H_2=60^\circ$,	$H_d-H_3=140^\circ$; $H_a-H_4=60^\circ$;	$H_d \neq$ doublet $H_a \neq$ doublet
	$H_d-H_1=40^\circ$, $H_a-H_2=90^\circ$,	$H_d-H_3=90^\circ$; $H_a-H_4=30^\circ$;	$H_d =$ doublet $H_a =$ doublet
	$H_d-H_1=40^\circ$, $H_a-H_2=50^\circ$,	$H_d-H_3=90^\circ$; $H_a-H_4=160^\circ$;	$H_d =$ doublet $H_a \neq$ doublet

Figure 5.19



the addition gave a mixture of (92) and (93) (Figure 5.18). The addition of deuterium to the β -face of (88c) ($R_1=R_2=D$ in figure 5.18) would remove coupling with H_d but not with H_a to produce the major singlet - major doublet pattern in the nmr spectrum. Similarly, addition to the α -face ($R_3=R_4=D$) would remove the coupling shown by H_a but not that by H_d . Therefore, the ratio of (92c):(93c) was 55:45 whilst that of (92b):(93b) was more exaggerated at 24:76.

We found also that such participation was not confined to the π -electrons of a benzene ring since the syn- and anti-invertomers of the naphtho-bridged system (40) underwent exactly analogous solvolysis reactions (Figure 5.20).

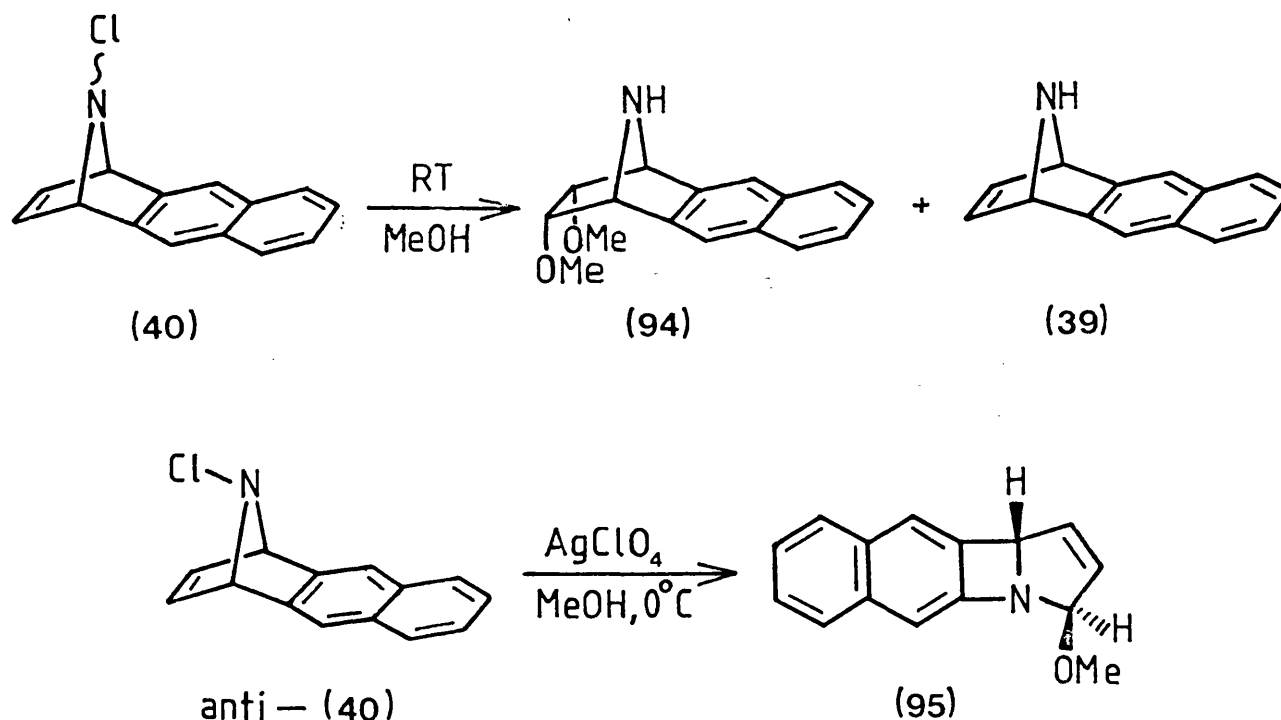


Figure 5.20

When the N-chloroamine (40) was allowed to stand at room temperature in methanol for three days, the amines (94) and (39) were isolated from the reaction mixture. At present, the evidence for the amine (94) rests solely on its nmr spectrum which shows two two-proton multiplets at δ 4.66 and 4.13 and a

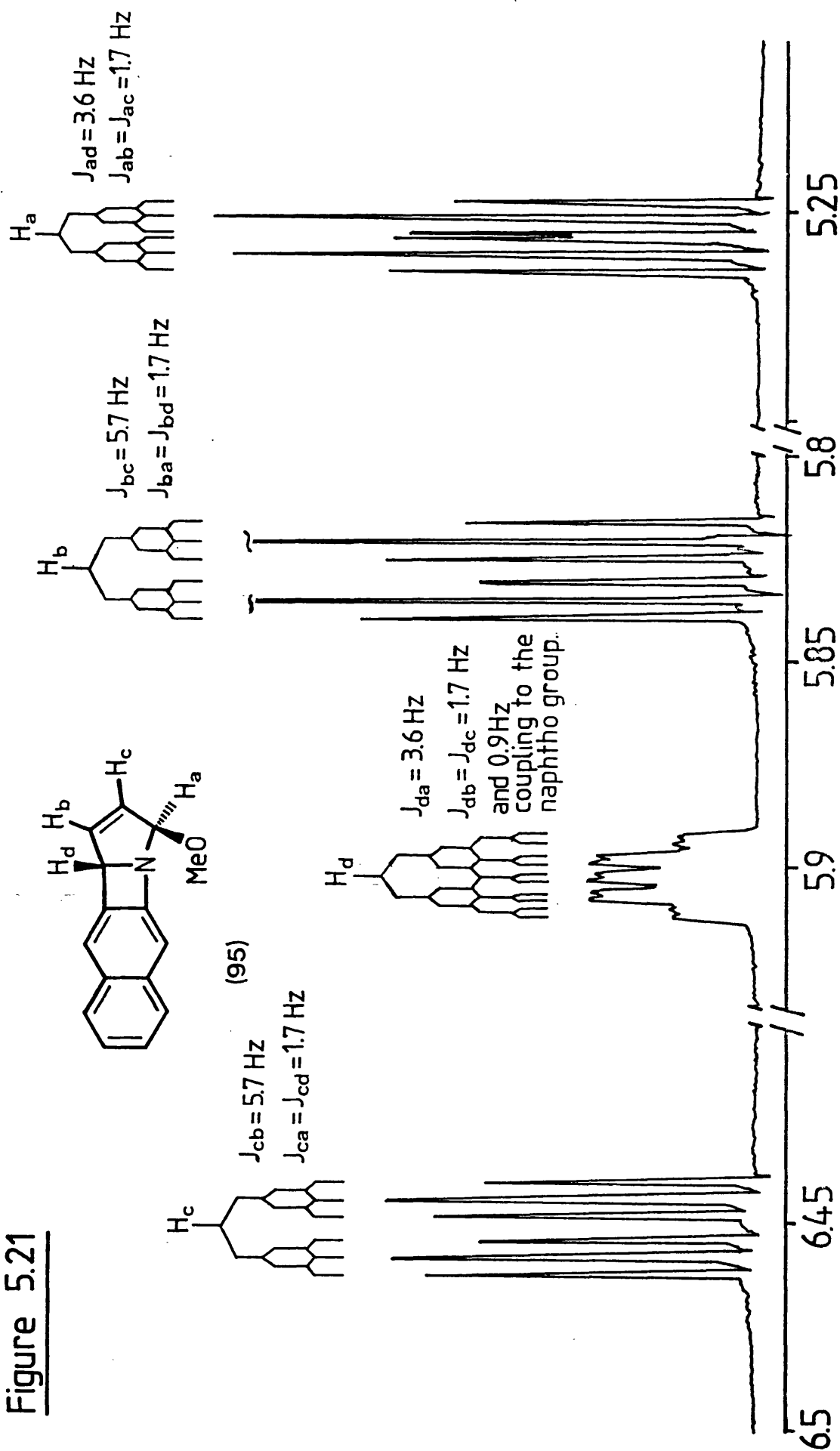
six-proton singlet at δ 3.36. This spectrum closely resembled that for (87b) and arises from participation of the π -electrons of the etheno-bridge in the solvolysis of syn-(40) which again appears to be the more reactive configuration under conditions of free inversion.

Rather fortuitously, syn- and anti- (40) could be physically separated in the attempted purification of (40) by extracting with trichlorofluoromethane at 0°C. The syn-invertomer was found to be soluble in this solvent but the anti-invertomer only sparingly so. Pure anti-(40) was then smoothly solvolysed at 0°C in methanolic AgClO_4 to give the amine (95) whose 90MHz ^1H nmr spectrum in CDCl_3 showed three multiplets in the ratio 1:2:1 at δ 6.36, 5.76 and 5.2, closely resembling the nmr signals of H_a - H_d of (88b) (Figure 5.11). At 400MHz the previously overlapping signals at 5.76 were resolved without the use of C_6D_6 and, as figure 5.21 shows, the multiplicities and coupling constants of these four absorptions were virtually identical to those observed for (88b) (Figure 5.12). This provided strong evidence in favour of structure (95). Satisfactory analytical and mass spectral data confirmed the formula $\text{C}_{15}\text{H}_{13}\text{NO}$.

Discussion

The most pleasing feature of the solvolyses is the way in which the structures of the products from methanolysis of syn- and anti-N-chloroamines parallel closely the products derived from analogous all-carbon bicyclic systems. The elegance of having both syn- and anti-configurations available in the same reaction mixture simply by choice of temperature is thus emphasised.

Figure 5.21



As has been noted earlier, the cis-fused bicyclo(3.2.0)heptyl ring system is commonly produced from the rearrangement of a suitably substituted bicyclo(2.2.1)heptyl moiety. The bicyclo(3.2.0)heptyl ring system has been isolated from the solvolyses of carbocycles such as (96)¹³⁸ and (97)¹³⁹ (Figure 5.22 (Figure 5.22) and shown to be intermediary in the rearrangement of tautomeric radicals¹⁴⁰ and cations¹⁴¹. The fundamental system, bicyclo(3.2.0)hepta-2,6-diene (98) has been prepared and characterised¹⁴².

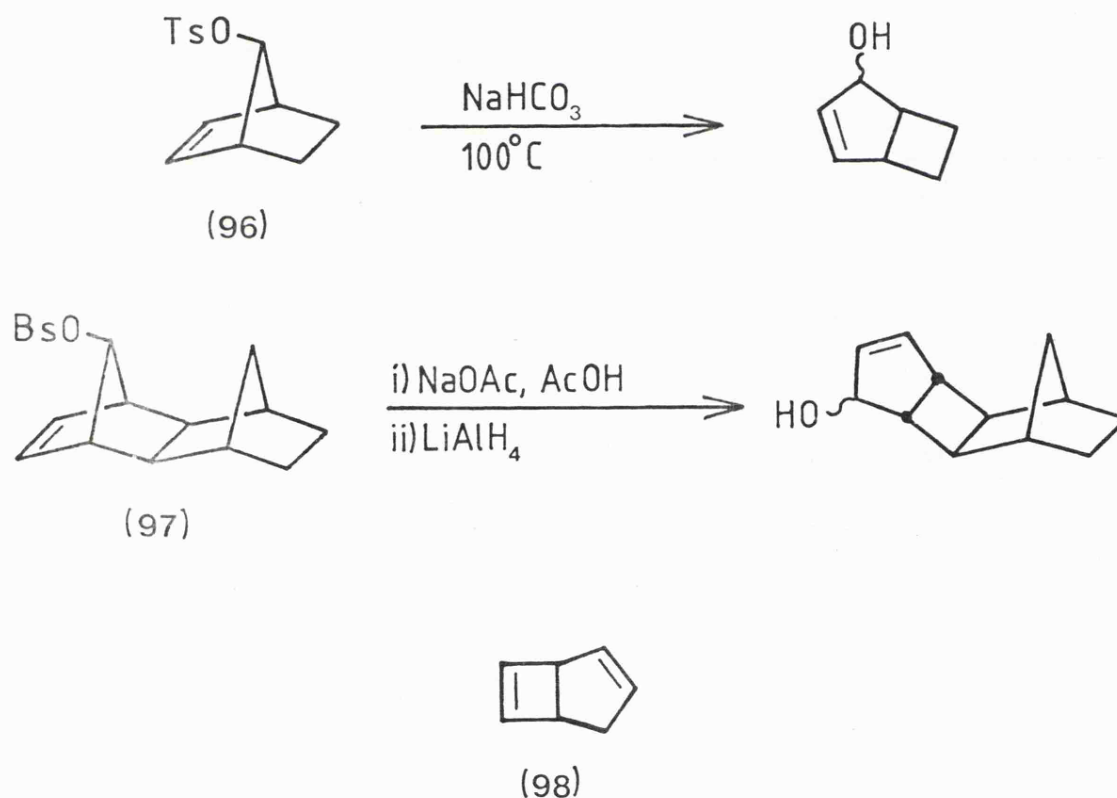


Figure 5.22

The precedent for the production of the amines (87) in all carbon systems lies with tricyclic products such as (99)¹⁴³ and (100)¹⁴⁴ (Figure 5.23) which has only been isolated when the leaving group at the 7-position is anti- relative to an adjacent π -bond.

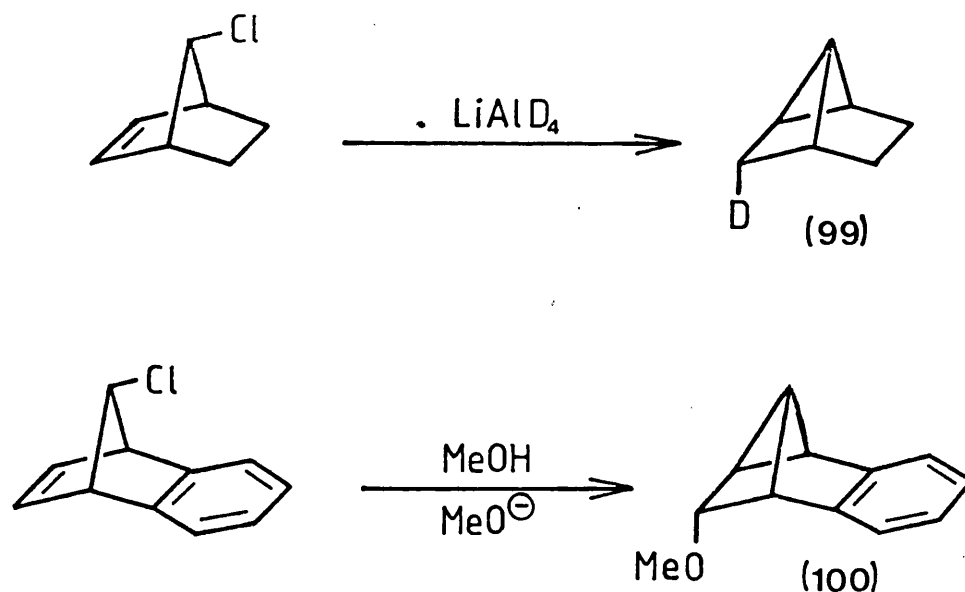


Figure 5.23

Rautenstrauch has proposed a similar intermediate in the mechanism for the formation of (75b)⁵⁸ and our results can be explained using the same strained, protonated aziridine structure (101) except that a second molecule of solvent performs the ring-opening step to give the observed bis-endo-methoxy products (87) (Figure 5.24).

The observed endo-ster^dchemistry of the methoxy groups is mechanistically reasonable if it is assumed that charge delocalisation in the transition state takes place via a non-classical ion. The presence of partial three-centre bonding on the exo-face in the transition state would force the approach of a solvent molecule from the endo-face. Although attack of methanol from the endo-face would still be the preferred direction in the case of the discrete ion (102), a small proportion of the product would undoubtedly be due to attack from the exo-face since a planar carbonium ion is involved. The absence of any such stereoisomer militates against a discrete carbonium ion.

Because of the skeletal rearrangement observed in the solvolysis of the anti-invertomer, there seems no reason not

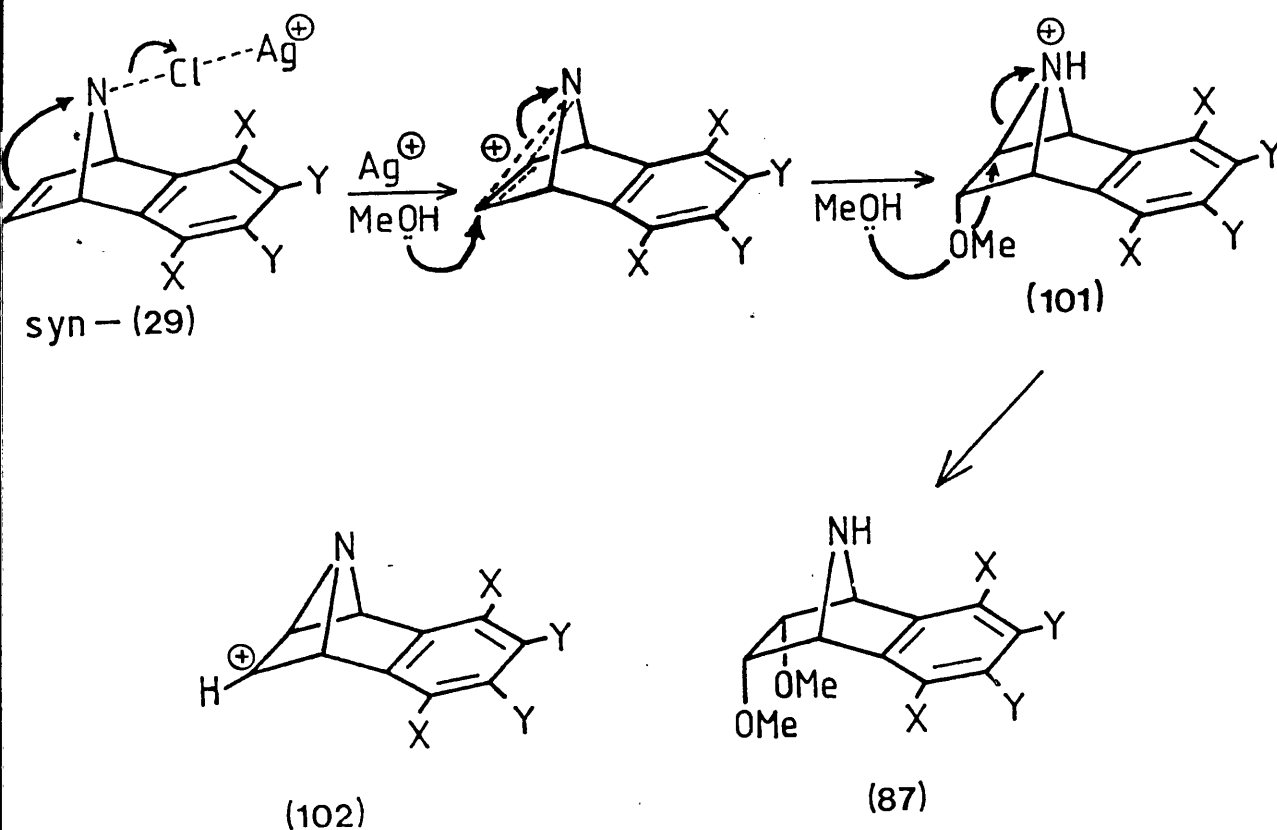


Figure 5.24

to assume that the main mechanistic pathway is heterolytic for both syn- and anti-N-chloroamines. The observation of skeletal rearrangement in N-chloroamine solvolyses is a strong indication that the transition state involves an electron-deficient nitrogen atom¹¹⁴ although a radical pathway can still compete with a heterolytic mechanism even under conditions favouring the latter¹¹⁵. The products of the solvolyses reported here suggest that a heterolytic mechanism dominates but the presence of small amounts of dechlorinated amine (27) indicates the intrusion of the homolytic pathway. This mechanism would proceed with the homolysis of the N-Cl bond to produce an aminyl radical and a chlorine radical, species which can abstract a hydrogen radical from a suitable source (presumably methanol the solvent) to produce amine and hydrogen chloride (Figure 5.25). Some support for this mechanism is found in the

observation that crude reaction mixtures consist of protonated species despite the expectation that the silver ion present would remove all available chloride ions as precipitated silver chloride.

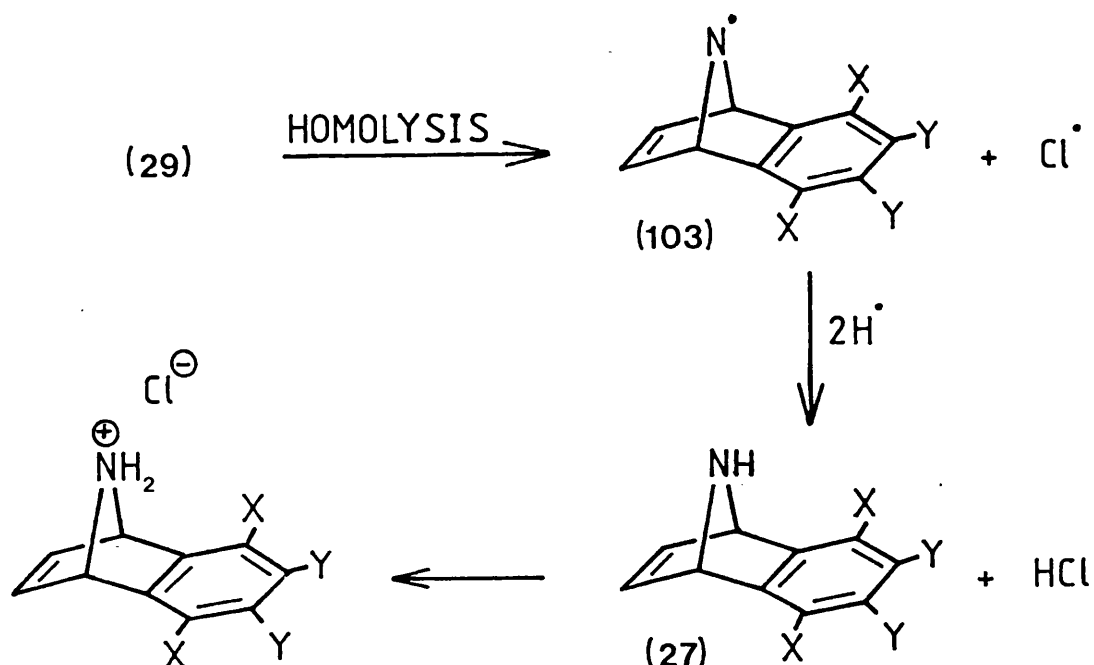
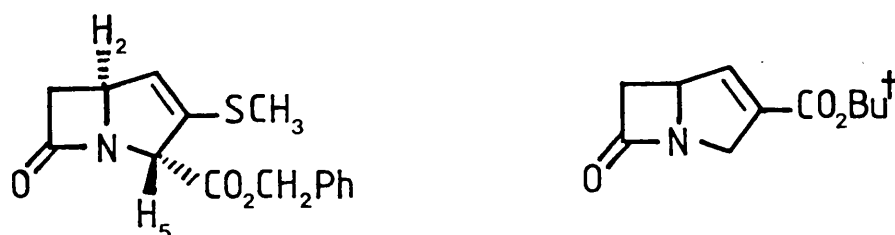


Figure 5.25

The production of amines and imines is typical of N-Cl solvolyses proceeding via a radical mechanism^{115d,145} although the imine derived from (103) would be in violation of Bredt's rule and further, would not be expected to survive the reaction conditions¹⁴⁵.

Despite numerous observations of bicyclo(3.2.0)heptyl systems, there has been no report of a 1,2-shift arising from π -participation by a benzene ring fused to a bicyclo(2.2.1)heptyl moiety. In every solvolysis involving such anchimeric assistance in all-carbon systems, the products have been those where the nucleophile has simply replaced the leaving group at the 7-position with retention of configuration^{85b,144,146}. The production of the tertiary amines (88b) and (88c) represents then the first example of such a

rearrangement. The cis-fused Δ^3 -azabicyclo(3.2.0)heptene ring system has been synthesised only in recent years as model compounds for and precursors to the β -lactam antibiotic thienamycin¹⁴⁷ and in the synthesis of Δ^1 -carbopenems¹⁴⁸ (Figure 5.26); the 6,7-fused benzene ring¹⁴⁹ makes the amines (88) completely novel structures.



Homoallylic coupling:

$$J_{2,5} = 3\text{Hz}$$

Figure 5.26

The stereospecificity of attack of methanol from the same face of the molecule as the former bridgehead proton H_d is a strong indication that no free carbonium ion can be involved in the rearrangement, despite its potential allylic position and being α - to a lone pair of electrons on nitrogen. The complete absence of the stereoisomer with the methoxy group trans- to H_d suggests a mechanism where a solvent molecule approaches the less hindered face of the positively charged intermediate to attack the benzylic carbon atom enabling the aryl ring to regain its aromatic sextet (Figure 5.27). If a free, planar carbonium ion were involved, some proportion of this other diastereoisomer could be anticipated.

Whether the carbonium ion intermediate has a symmetrical or asymmetrical structure i.e. (104) or (105) cannot be decided conclusively on the basis of the evidence presented

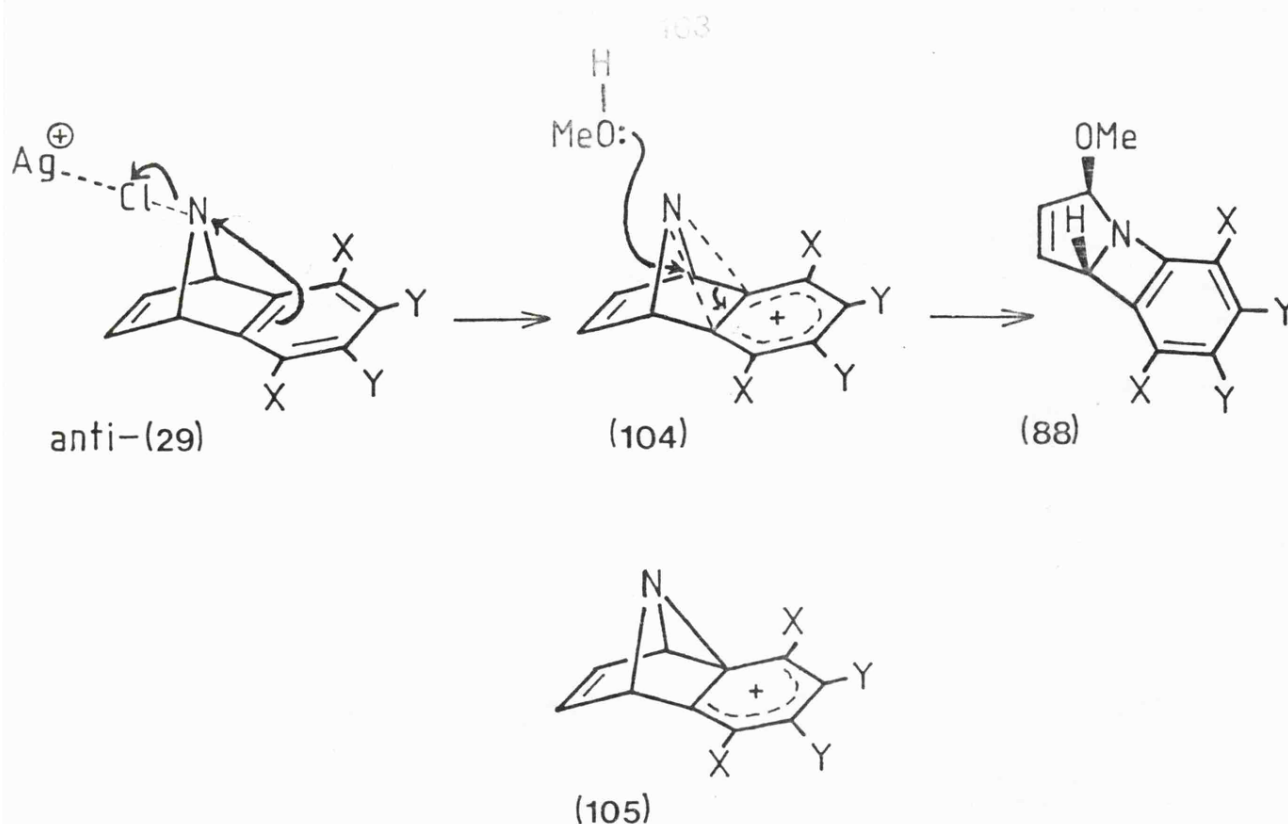


Figure 5.27

here. The symmetrical disposition of the substituent on the benzenoid ring means that any preference for (104) or (105) cannot be observed simply by studying the structure of (88). Tanida has tentatively suggested that the carbonium ion intermediate involved in the acetolyses of each of variously substituted brosylates (78)¹⁵⁰ (Figure 3.12) has a symmetrical structure analogous to (104), a view proffered on the basis that the transition state preceding it does indeed possess a symmetrical structure¹⁵¹.

Finally, the reason as to why anti-(29b) should prefer to undergo rearrangement whilst acetolysis of anti-9-chloro-1,4-dihydro-1,4-methanonaphthalene gives solely the anti-acetate¹¹¹ may in part lay with the increased electron density at the 7-position from the lone pair on nitrogen. This would be expected to deter the approach of a solvent molecule more than a carbon atom at the same position but this cannot be the complete answer. If the positively charged intermediate resembled (105) more than (104), then rearrangement would

relieve the strain accompanying the distorted aziridine ring. This seems reasonable in view of the unequivocal stereochemistry of the methoxy group.

Thus the solvolysis of N-chloro-7-azabicyclo(2.2.1)heptadienyl derivatives has been shown to give the aza-analogues of products which frequently appear in similar carbocyclic solvolyses, drawing the parallel between the two types of chemistry. The nitrogen containing systems, however, have the advantages that:-

i) the amounts of syn- and anti-N-chloroamine invertomers, and hence ultimately the amounts of (87) and (88), can be controlled by using "kinetic" or "thermodynamic" conditions during the chlorination reaction,

ii) the N-chloroamines may be solvolysed at low temperatures where they undergo negligible inversion. The products of reaction from each invertomer can be investigated without the need to separate the two configurations beforehand. Rather elegantly, it is possible to separate the less reactive anti-(29b) under such conditions and study its solvolysis independently.

11. Reactivity and Structure in the Solvolysis of N-Chloro-naphthalen-1,4-imines

In tandem with the solvolyses performed under conditions of no inversion (below 0°C), the N-chloroamines (29b), (29c) and (29e) were methanolysed at room temperature (20°C) in the absence of silver salt. Under these conditions, each N-chloroamine was free to invert during the solvolysis and the rate (which was much slower in the absence of silver salt) and products of each reaction were therefore dependent on the relative reactivities of the syn- and anti-configurations. The results of these solvolyses are shown in table 5.2.

Table 5.2

<u>N-Chloroamine</u>	<u>Reaction Time</u>	<u>Products (%Yield)^a</u>		
		<u>(27)</u>	<u>(87)</u>	<u>(88)</u>
(29b)	20 hours	11(10)	32(27)	-
(29c) ^b	16 hours	25(16)	47(37)	11(11)
(29e)	2 weeks	8 ^c	55(23)	-

a. Two yields are quoted. The first refers to the yield as measured from the ¹H nmr spectrum of the crude reaction mixture using a known weight of p-dibromobenzene as internal standard ($\pm$ 2%). The yield in parentheses refers to the isolated yield.

b. ~~A~~known weight of acetone was used as internal standard.

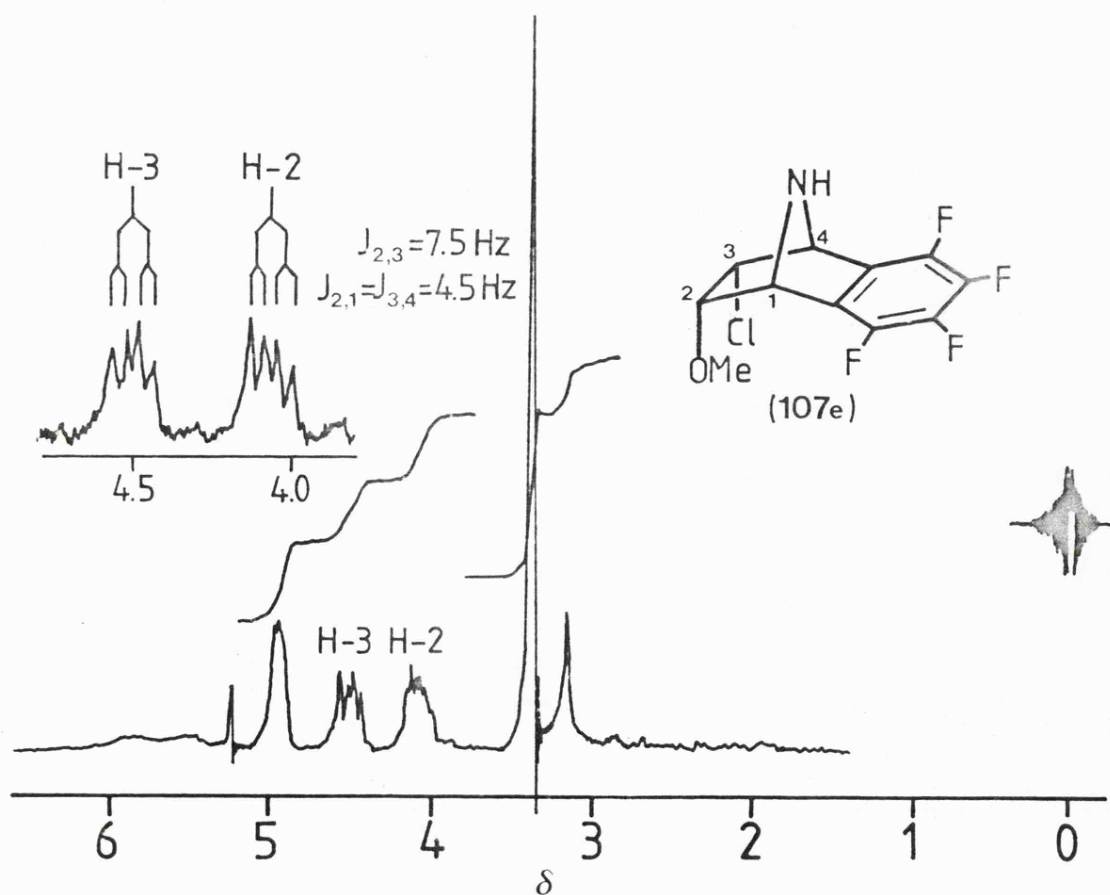
c. This amine could not be isolated pure from the mixture.

Rautenstrauch had shown that when the N-chloroamine (29b) was dissolved in methanol and allowed to stand at room temperature, the syn-configuration was the more reactive and all the solvolysis product was derived from this invertomer; anti-~~r~~reacted only via prior inversion to syn-. Indeed, as the results of table 5.2 show, the syn-configuration was clearly

the more reactive one for (29b) and (29e). The products other than dechlorinated amine can arise only by participation of the π -electrons of the etheno-bridge which, in turn, is possible only when the chloro group is in the syn-configuration.

The sluggish solvolysis of the fluorinated substrate (29e) was emphasised by the isolation of a third product in 8% yield (23% by nmr) after chromatography and recrystallisation. The infra-red spectrum showed the presence of a weak N-H stretching absorption at 3300cm^{-1} and the analytical and mass spectra data confirmed the formula $\text{C}_{11}\text{H}_8\text{NOF}_4\text{Cl}$. The ^1H nmr spectrum best fitted the structure (107e) (Figure 5.28) and the endo-stereochemistry was confirmed by the doublet of doublet multiplicities of H_2 and H_3 .

Figure 5.28



The stereochemistry of the chloro and methoxy groups also indicates a heterolytic mechanism for the formation of (107e) and its presence is most easily explained by competition between the chloride and methanol nucleophiles in solution.

However, the amine (88c) was isolated from the solvolysis of (29c) showing that even under conditions of free inversion the anti-pathway can effectively compete for the available N-chloroamine. Clearly, at this point the stabilisation gained from participation of the etheno-bridge is similar to that of the methoxy-substituted aryl ring where the +R effect can stabilise the developing positive charge.

It is in these room temperature solvolyses that the reactivity-aryl substitution pattern is most clearly shown. The electronic effects of the substituents have a direct influence on the rate and course of the reaction via the intermediates (105c), (105b) and (105e) (Figure 5.29).

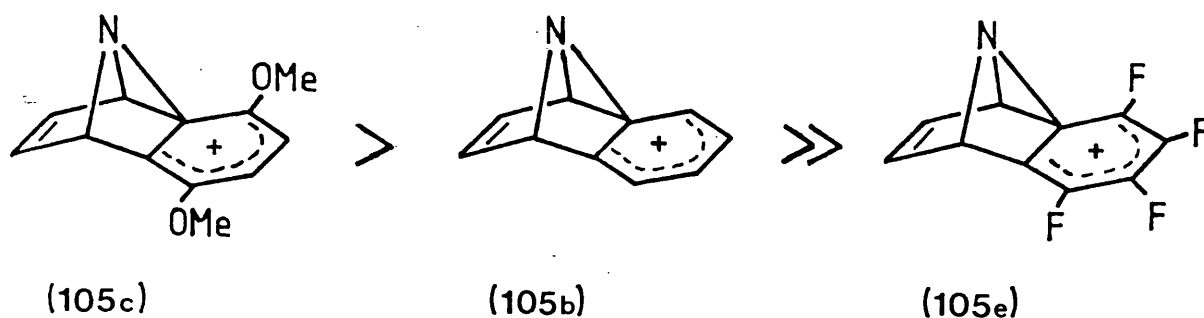


Figure 5.29

The tetrafluoro substituted N-chloroamine (29e) is least reactive to methanolysis and, even under conditions of negligible inversion (at -6°C in $\text{CD}_3\text{OD}/\text{AgClO}_4$ in the probe of an nmr spectrometer), the anti-invertomer failed to rearrange to the azabicyclic (88e). The fluorine substituents would be expected to raise the energy of the intermediate (105e) and hence the free energy of activation for reaction via the

anti-invertomer.

The N-chloroamine (29b) is considerably more reactive than (29e) although the syn-configuration is still favoured. A similar rate of solvolysis is observed for (29c) but the greater stabilisation afforded by the dimethoxybenzo group lowers the energy of (105c) relative to (105b) to the point where the anti- can compete with the syn-pathway in the solvolysis of (29c).

These results parallel closely Tanida's investigation of the rate of reaction as a function of the substituent in the aryl ring in the acetolyses of the brosylates (78)¹²⁰ (Figure 3.12). The variation could be neatly explained by the electron-withdrawing or donating effect of Z on a Wheland-type intermediate (79) (Figure 3.12).

Two other sets of observations helped confirm the greater reactivity of the aryl group when substituted with methoxy groups. The solvolysis of each of the N-chloroamines in CD₃OD was followed by nmr spectroscopy at low temperatures, in order to prevent interconversion of syn- and anti-invertomers. Using the bridgehead signals at ca.85.0 as the probe, the relative rates of disappearance of the two invertomers was monitored against an internal standard upon the addition of small amounts of soluble AgClO₄. In the nmr spectra of both (29b) and (29e), the bridgehead signal of the syn-invertomer disappeared the more quickly whilst the bridgehead signal of anti-(29c) clearly disappeared more rapidly, indicating the profound effect of the dimethoxy benzo group. Table 5.3 shows the yields of the solvolyses products estimated from the nmr spectra. Although the Curtin-Hammett principle does not apply here, the yields of the products d₆-(87) and d₃-(88) do not mirror the ratio of syn- and anti-starting N-chloroamines.

Presumably the competing radical pathway and the possibility of decomposition of starting material⁵⁸ intervene.

Table 5.3

<u>N-Chloroamine</u>	<u>Initial Ratio</u>	<u>Temperature(°C)</u>	<u>Products(%Yield)</u>		
	<u>syn- : anti-</u>		<u>d₆-(87)</u>	<u>d₃-(88)</u>	<u>(27)</u>
(29b)	72 : 28	-57	16 ^a	40 ^b	10 ^a
(29c)	63 : 37	-18	13 ^b	43 ^c	23 ^b
(29e)	20 : 80	-6	45 ^c	-	14 ^a

a. $\pm$ 2%

b. $\pm$ 3%

c. $\pm$ 5%

The neatest illustration of the higher reactivity of the anti-pathway when adjacent to a dimethoxybenzo group was provided by the solvolysis of the N-chloroamines (30b), (30c) and (30e) (Figure 2.1) in methanolic AgClO_4 at -40°C . Previous work in these laboratories had shown that compound (30b) gave the dechlorinated amine (28b)¹¹ (70%) under these conditions. Despite the fact that the nitrogen atom is constrained in a bicyclic system, the saturated N-chloroamine was reluctant to solvolyse and instead underwent a homolytic reaction¹¹⁵. The N-chloroamine (30e) was even less reactive under such conditions and after three hours at 55°C (oil bath temperature) in methanolic AgClO_4 , unchanged starting material was recovered from the mixture. However, when (30c) was warmed in methanolic AgClO_4 , the ^1H nmr spectrum of the mixture showed that starting material had been consumed completely. The reaction products included the amine (28c), and the rearranged amine (91c) was

isolated in 23% yield. The melting point and ^1H nmr spectrum of (91c) were identical to those of an authentic sample of (91c), prepared by hydrogenation of (88c) (Figure 5.30). Thus the presence of the methoxy groups means that participation by the aryl groups is now competitive with the radical pathway and produces (91c) directly. In view of the products from the solvolysis of (30b) under conditions of free inversion, it seems that only the anti-pathway is reactive by the heterolytic mechanism for (30c).

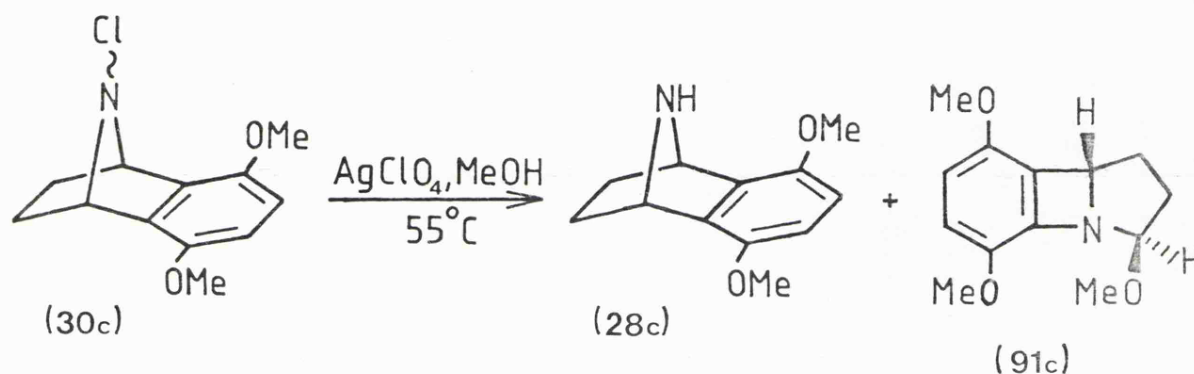


Figure 5.30

The anti-invertomer of (30c) was reactive even at low temperature. When stirred with AgClO_4 in dry methanol between -10 and -5°C , AgCl was slowly precipitated and the amine (91c) was again obtained directly in 53% yield, along with 20% of unchanged N-chloroamine. This unchanged starting material was presumably derived from the syn-invertomer but had equilibrated to a mixture of syn- and anti-(30c) under the conditions of the work-up (nmr). The melting point of (91c) obtained from this reaction was identical to that of authentic (91c) and the mixed melting point was not depressed.

Thus the reactivity of the 1,4-dihydro systems (29) has been shown to be strongly influenced by the nature of the substituents in the aryl ring; qualitatively at least, this

pattern of reactivity is the same as that observed in the 9-anti-1,2,3,4-tetrahydro-1,4-methanonaphthalene brosylates (78). Both syn- and anti-configurations are reactive for (29c) whilst for (29b) the syn-configuration is clearly the favoured one. The failure to observe (88e), the product of solvolysis of anti-(29e) is understandable in view of the proposed intermediate (105e); the decreased activity of the syn-pathway for (29e) is less easy to explain but may in part be due to the through-bond inductive effect of the tetrafluorobenzo-ring which would be expected to reduce the N-Cl polarisation (thus making departure of the chloride group more difficult) and reduce the ability of the etheno-bridge π -electrons to participate. We are reluctant to suggest through-space inductive effects between the two π -systems in view of the results of Chapter 2.

CHAPTER 5

APPENDIX:

THE REARRANGEMENT OF 11-CHLORO-1,2,3,4,9,10-HEXAHYDRO-
1,4-ETHENO-ANTHRACEN-9,10-IMINE

Introduction

The amine (110c) (Figure 5.31) was prepared in connection with previous work in these laboratories⁵⁹. It was designed to provide a fixed model to assist in distinguishing between syn- and anti-N-Cl configurations in (30c) by nmr spectroscopy¹¹.

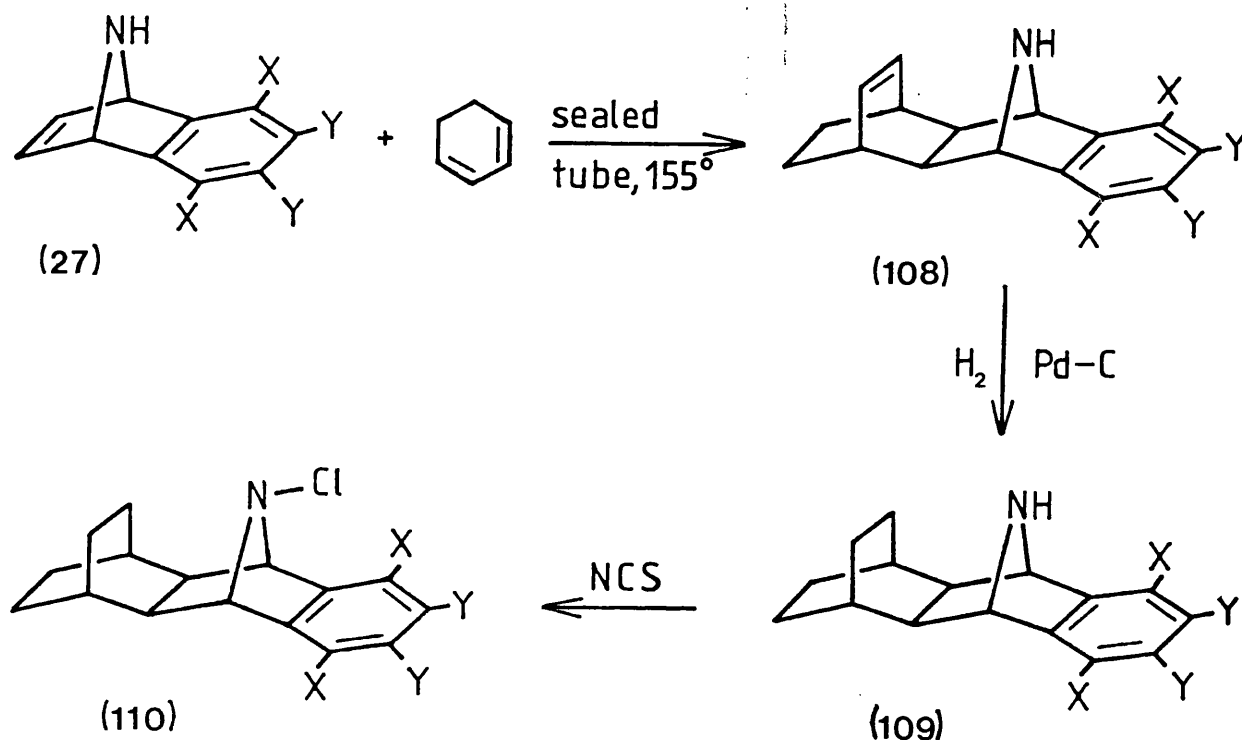
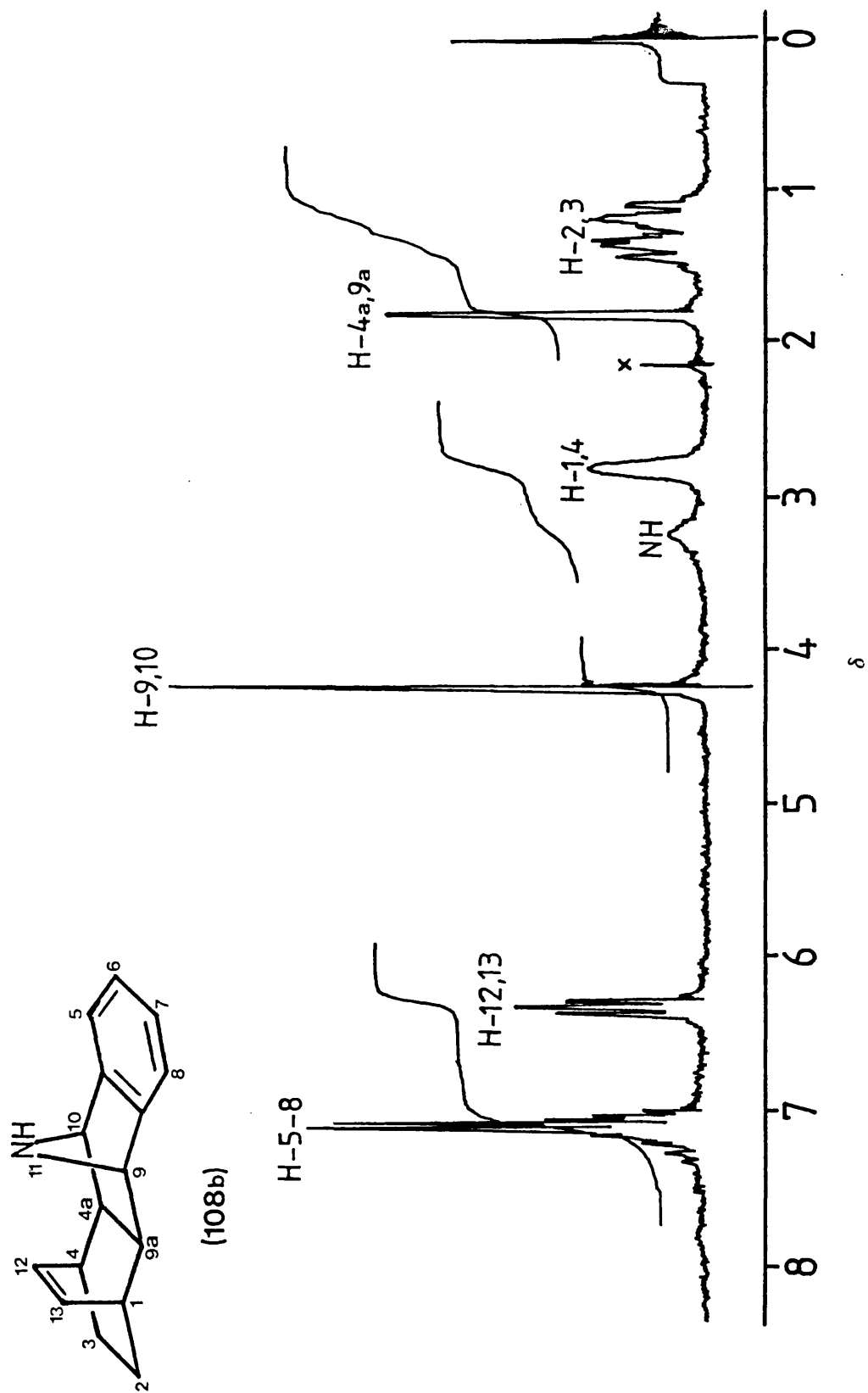


Figure 5.31

The Diels-Alder reaction between the amine (27) and cyclohexa-1,3-diene can, in principle, give rise to four stereoisomers but the ¹H nmr spectra of (108) exhibited singlet absorptions for the bridgehead protons adjacent to nitrogen (Figure 5,32).

This multiplicity is consistent only with exo-addition to the double bond of (27) because no coupling is expected^{74,152,153} between H₉, H₁₀ and H_{4a}, H_{9a} when these latter protons are in the endo-position. The question of the

Figure 5.32



orientation of the double bond in the bicyclohexenyl moiety was not pursued since hydrogenation to give (109) made its answer irrelevant. Nonetheless, we felt that if the stereoisomer (108) was the sole isolated adduct, then the p-orbitals of the proximate double bond would be ideally placed to overlap with the rearside of a developing p-orbital on nitrogen as a suitable leaving group departed. N-Chlorination would of necessity provide a leaving group in the required configuration (syn- to the aromatic ring) and the N-Cl bond generally had already been shown to undergo facile heterolysis with methanolic silver salts. Such a reaction would complement the work on π -participation in the solvolysis of N-chloro-2-^{11,154,155} and-7-azabicyclo(2.2.1)heptyl systems^{58,131,156} and the analogous solvolysis of the carbocyclic brosylate (111)¹⁵⁶ (Figure 5.33).

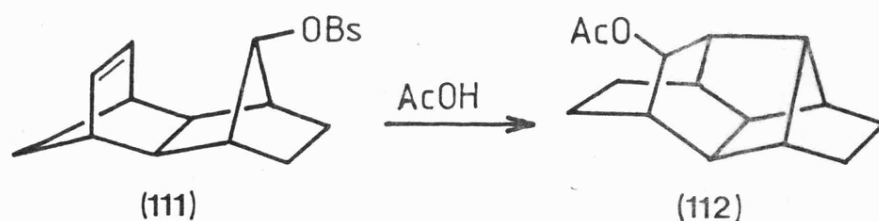
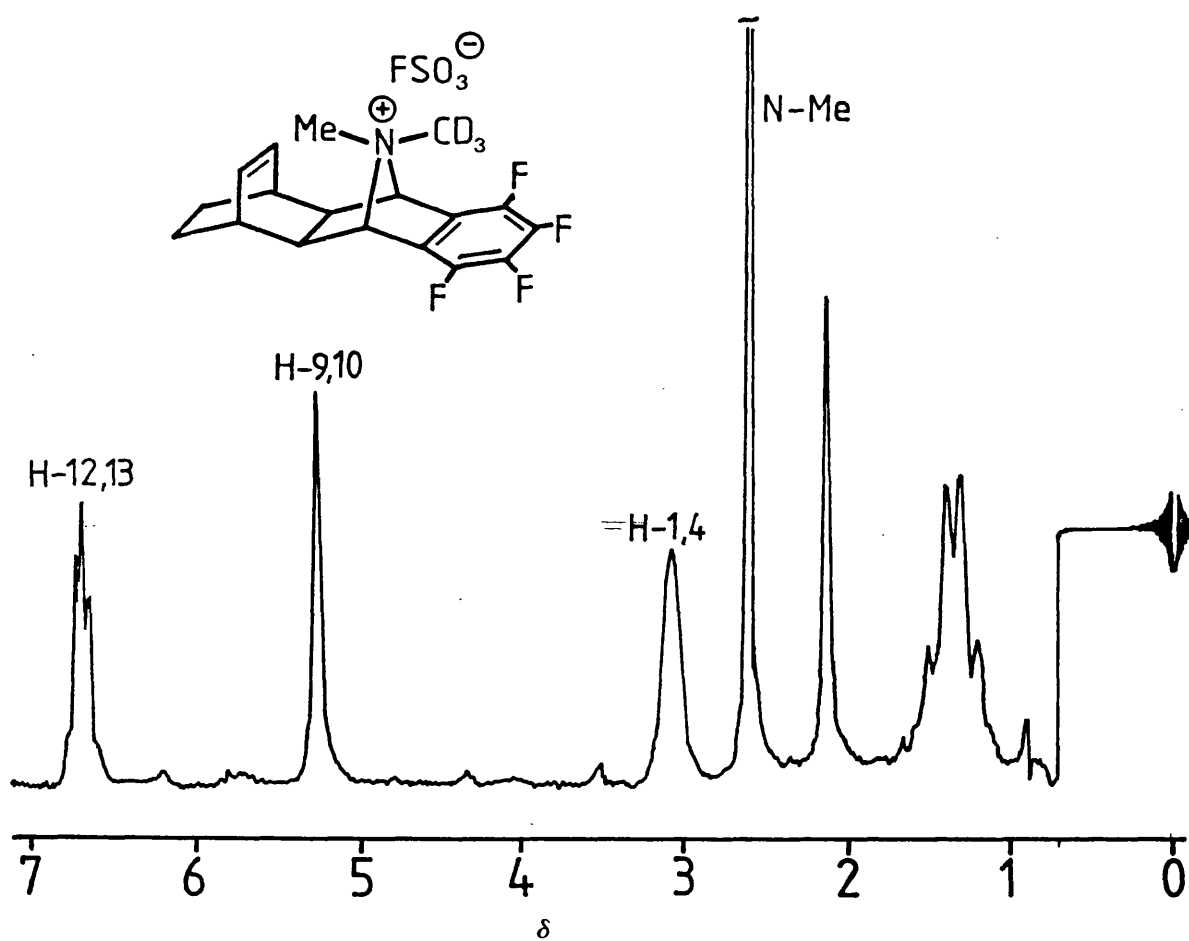
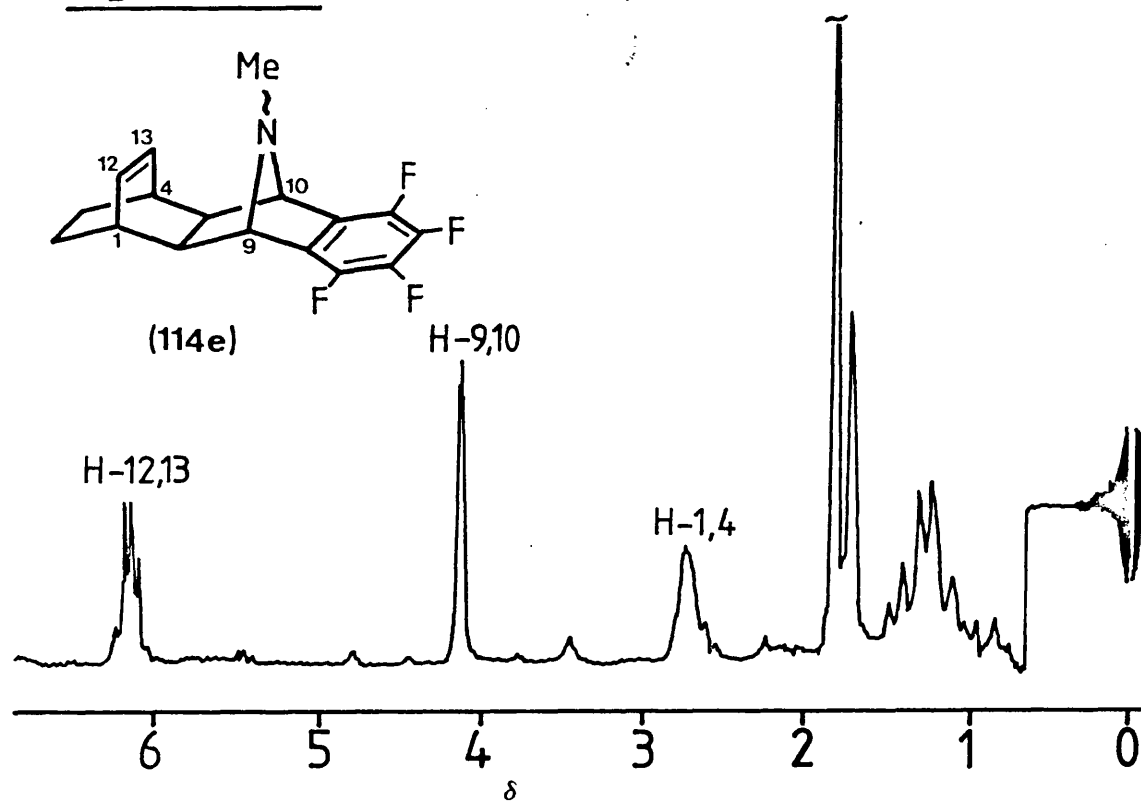


Figure 5.33

Inspection of molecular models suggested that (108) would be the preferred stereoisomer because the steric congestion between the 1,4-etheno and 9,10-imino bridge in this isomer is less than that between the 1,4-ethano and imino bridges of stereoisomer (113) (Figure 5.34).

Good evidence for the stereochemistry shown in (108) emerged as a result of the quaternisation of the amine (114e) (Figure 5.35) with CD_3FSO_3 in CDCl_3 . The absorption due to the

Figure 5.35



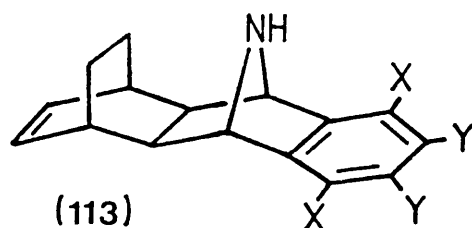


Figure 5.34

olefinic protons of (114e) was moved to lower field ($\delta 6.17 \rightarrow \delta 6.70$) upon quaternisation.

Whether the downfield shift of the olefin signal is due to the increased positive charge on nitrogen or the steric effect of the anti-methyl group (or both) may be considered less important than the fact that it occurs; certainly there is no such reason to expect such a shift in the alternate structure since the nitrogen is distant from the double bond (c.f. (113)).

During the course of this work, Sasaki has prepared the cycloadducts between the fulvenes (116a) and (116b) and the urethane (115) (Figure 5.36), to which the stereochemistry (117) was assigned.

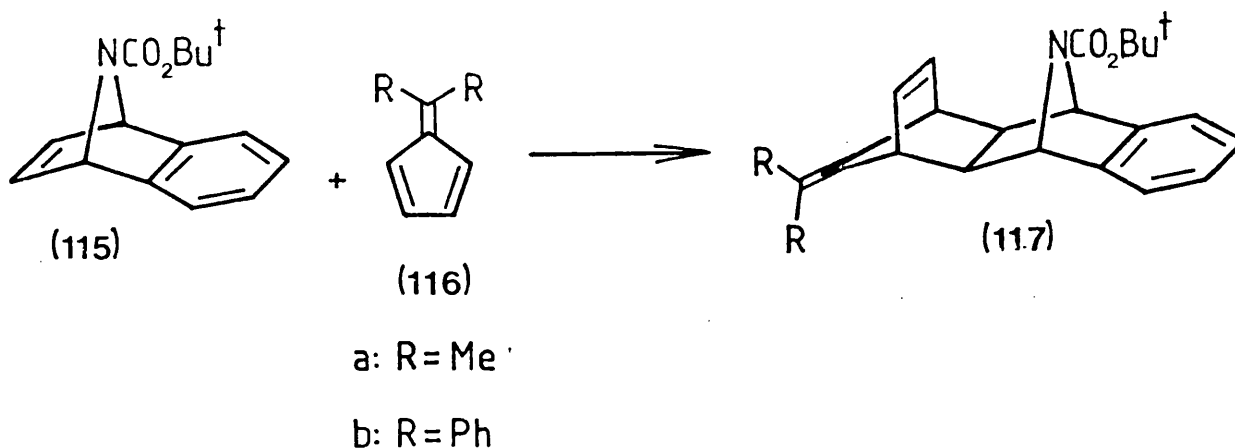


Figure 5.36

Indeed, the structure of the product from the heterolysis of the N-chloro derivatives of (108) should confirm the stereochemistry of the cycloadduct. To this end, the amine (108b) was prepared by the cycloaddition of cyclohexa-1,3-diene to (27b).

Results

The amine (108b) was chlorinated using NCS in CDCl_3 in the probe of an nmr spectrometer maintained at -60°C . The reaction was complete within 30 minutes at this temperature and gave the N-chloroamine (118b) (Figure 5.37), in which the bridgehead signals resonated at $\delta 4.44$.

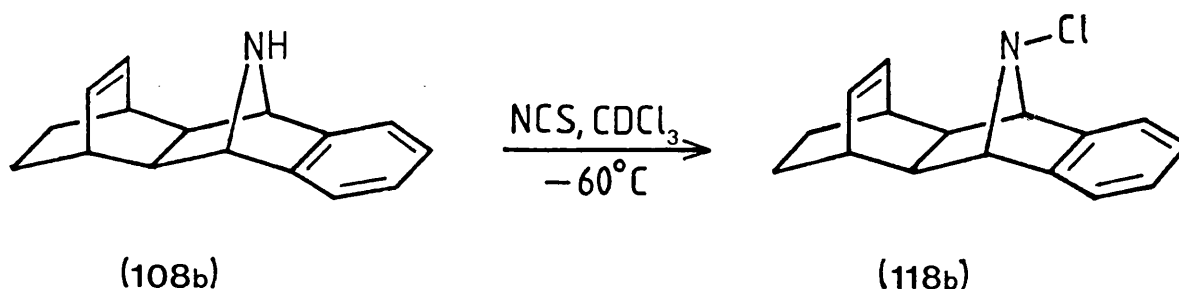


Figure 5.37

The solution containing (118b) was allowed to stand overnight at room temperature and then in an oil bath maintained at 50°C for 7 hours. Nmr spectra were recorded periodically until all the olefin absorption had disappeared.

The solution was then evaporated and taken into dichloromethane and the organic layer washed repeatedly with aqueous potassium carbonate to remove residual succinimide. After work-up, the components of the residue were separated by thick layer chromatography. After concentration of the organic extracts, the infra-red spectrum of the residue (39mg, 22%) showed neither the N-H absorption at 3300cm^{-1} nor the weak C=C absorption at 1620cm^{-1} which characterised the infra-red spectrum of the starting amine (108b).

The high resolution mass spectrum of the solvolysis product showed a molecular ion of 61% abundance at 257.0968 which indicated the molecular formula $\text{C}_{16}\text{H}_{16}\text{NCl}$ (Calculated : 257.09712) and hence the incorporation of chlorine into the product. In conjunction with the infrared spectrum, these data indicated the presence of a new tertiary amine with the loss of unsaturation in the 1,4-two-carbon bridge. The structure most consistent with these facts was the amine (120b) (Figure 5.38) arising by a mechanism analogous to that proposed for the formation of (112).

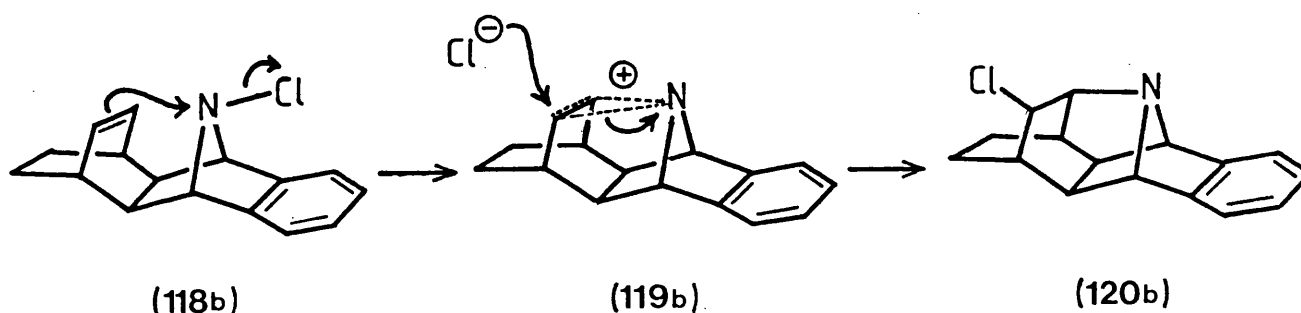


Figure 5.38

The stereochemistry of the chloro group would be expected to be as indicated in (120b) as a consequence of the intermediate non-classical ion (119b). Confirmation of the proposed structure was provided by the nmr spectrum of the product (Figures 5.39 and 5.40) and related spin decoupling experiments.

Figure 5.39

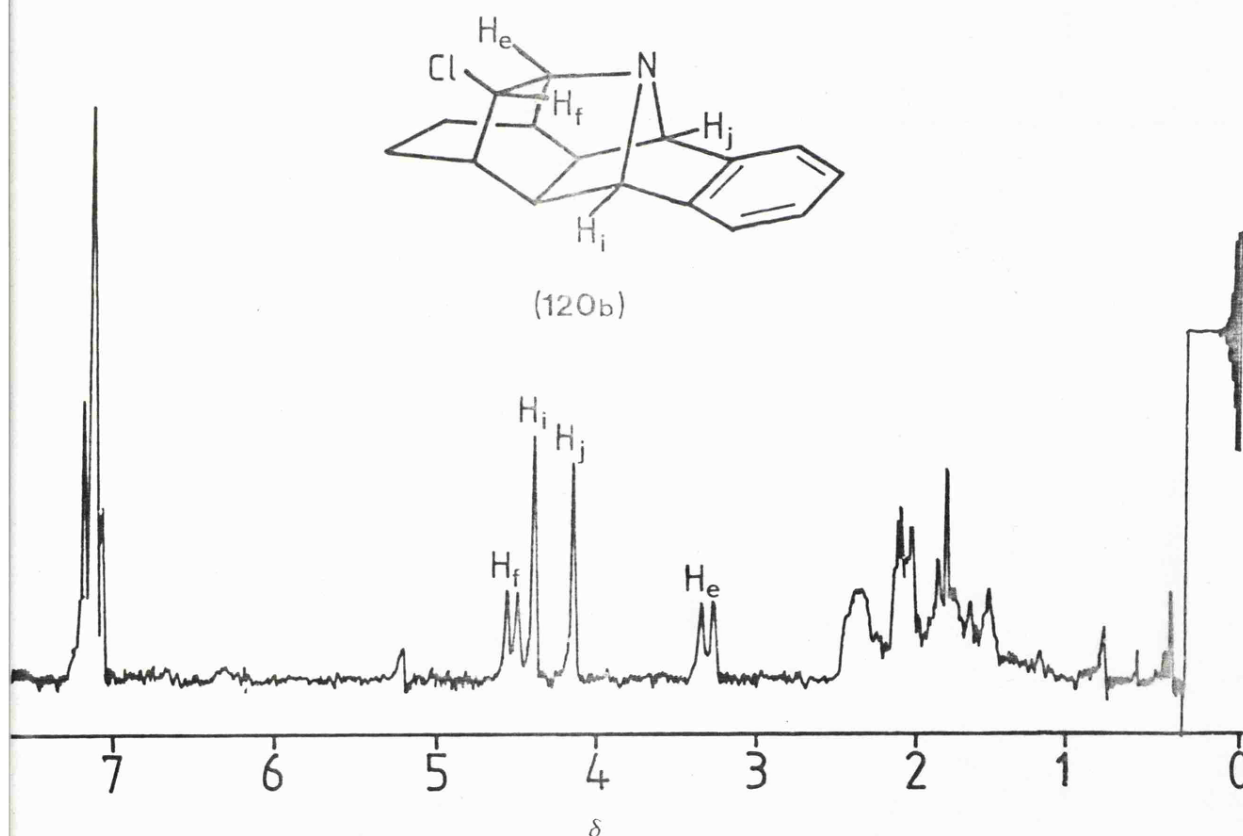


Figure 5.39

The singlet resonances at $\delta 4.41$ and $\delta 4.17$ were assigned to the bridgehead protons adjacent to nitrogen (H_i and H_j in figure 5.39) on the basis of the large downfield shift (0.86-0.90ppm) observed upon protonation with one equivalent of

Figure 5.40

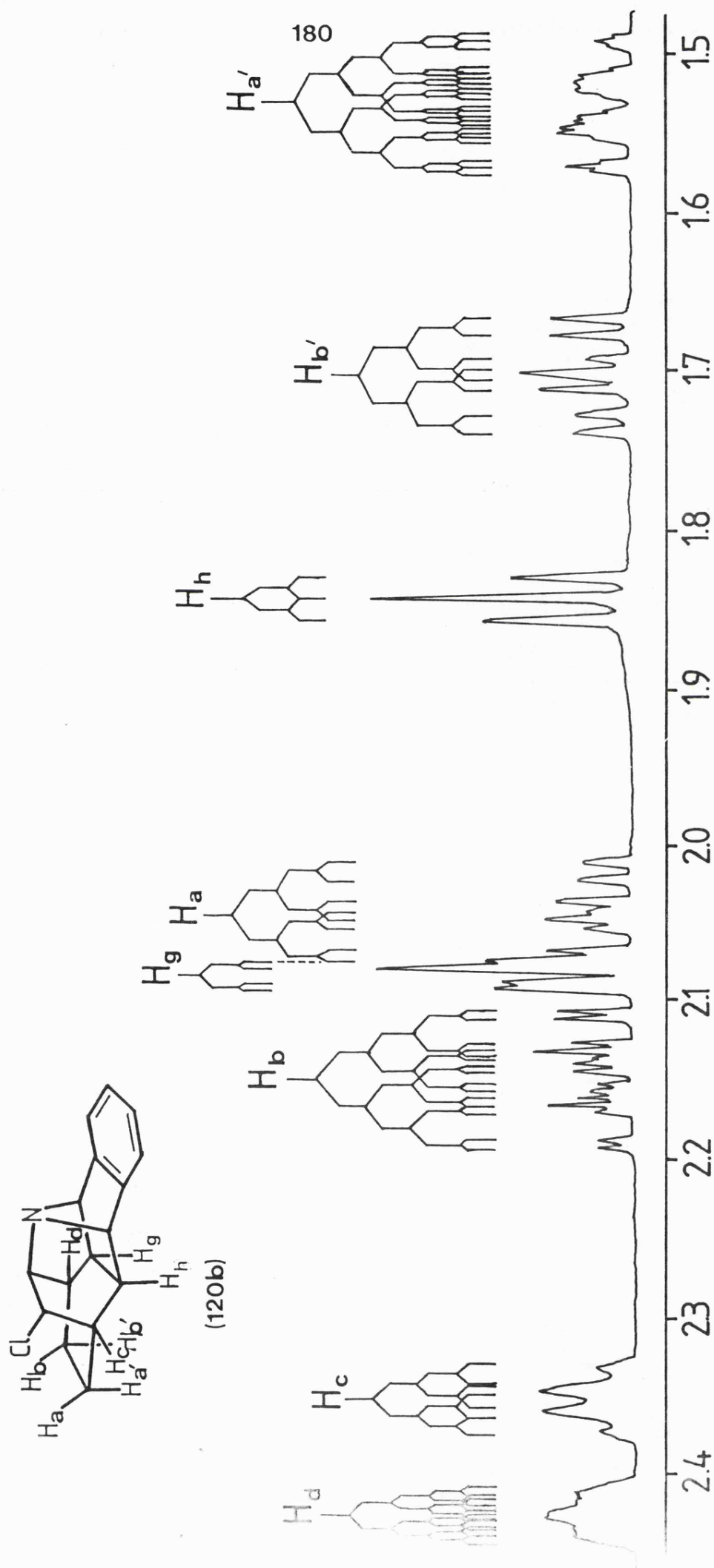


Figure 5.40 continued

Proton (H_x)	Multiplicity	Associated Coupling Constants (xy) in Herz
H_f	broad dd	$fc = 6.3$, $fa' = 1.4$, $fe = fd \leq 1$
H_e	broad d	$ed = 6.8$, $ef \leq 1$
H_d	broad dddd	$de = 6.8$, $db' = 5.6$, $db = 2$, $dg = 1.8$, $df \leq 1$
H_c	broad ddd	$cf = 6.3$, $ch = 5.4$, $ca' = 4.5$, $ce \leq 1$
H_b	dddd	$bb' = 13.4$, $ba' = 10$, $ba = 7.6$, $bd = 2$
H_g	dd	$gh = 5.4$, $gd = 1.8$, $ge \leq 1$ + unresolved coupling to H_j
H_a	broad ddd	$aa' = 13.5$, $ab = 10$, $ac = 4.5$, $ab' \leq 1$
H_h	broad t	$hg = hc = 5.4$ + unresolved coupling to H_j and H_i
$H_{b'}$	broad ddd	$b'b = 13.5$, $b'a' = 10.5$, $b'd = 3.6$, $ba' \leq 1$
$H_{a'}$	dddddd	$a'a = 13.5$, $a'b' = 10.5$, $a'b = 7.6$, $a'f = 1.4$, $a'e = 1$

TFA. Also, the observed singlets are consistent with the exo-orientation due to the lack of coupling with H_g and H_h . The doublet at $\delta 3.33$ also moved downfield by 0.7ppm upon addition of TFA and was therefore assigned to H_e , the remaining proton adjacent to nitrogen. The doublet at $\delta 4.55$ in the spectrum of (120b) was characteristic of a proton attached to a carbon bearing a chlorine. For example, the analogous protons in 2,3-dichloro-2-azabicyclo(2.2.1)heptane¹⁵² and 2-chloro-2-azabicyclo(2.2.2)octane¹⁵⁷ resonate at $\delta 4.42$ and $\delta 4.18$ respectively. This doublet was assigned to H_f and, as expected, experienced a much smaller downfield shift upon addition of TFA (0.25ppm). However, the fact that the signal assigned to H_f experienced a downfield shift of any kind is crucial evidence for justifying structure (120b) over other plausible rearranged structures such as (121b) and (122b) (Figure 5.41). These molecules could be produced by migrations of the 1,4 and 4,4a σ -bonds respectively, to a formal positive charge sited on C-13.

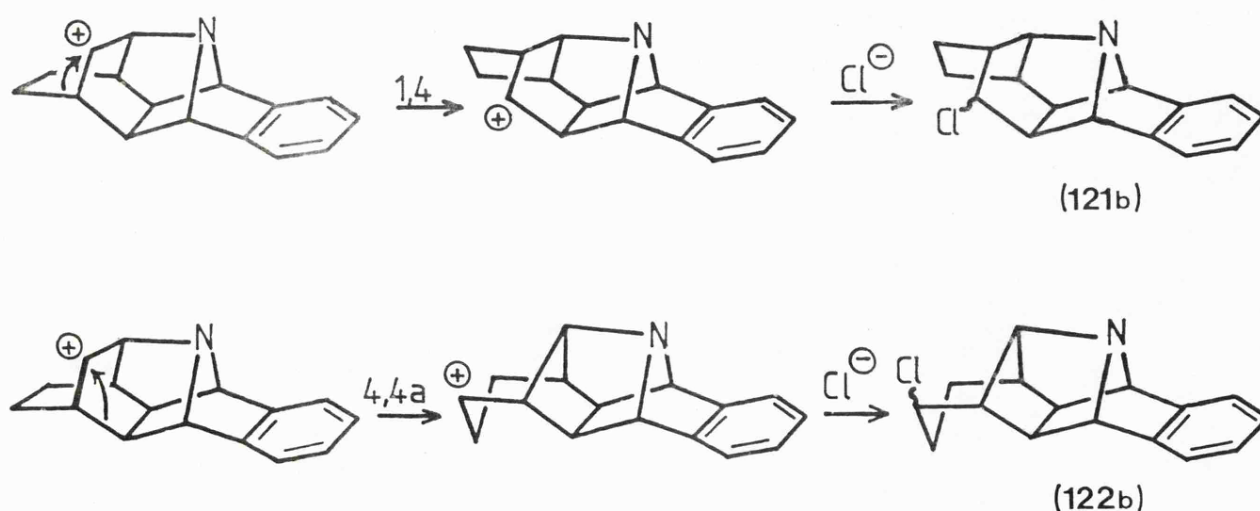


Figure 5.41

In each of the amines (121b) and (122b), however, the proton attached to the carbon bearing the chloro group would

be remote from the nitrogen atom and thus less sensitive to protonation effects.

Double irradiation of the signal due to H_f located the bridgehead proton H_e at $\delta 2.36$. Conversely, irradiation of the signal H_e caused the doublet multiplicity due to H_f to collapse to a singlet. Irradiation of H_e simplified the absorption at $\delta 2.42$ which was thus assigned to H_d ; this vicinal relationship was confirmed when irradiation at $\delta 2.42$ caused collapse of the signal to a singlet. Sequential irradiation in this manner allowed the assignment of all the protons of (120b). The protons H_i ($\delta 4.38$) and H_j ($\delta 4.14$) were assigned by analogy with the amine (34) where the bridgehead signals occurred at $\delta 4.2$ and $\delta 3.9$ respectively⁷².

An inspection of a molecular model of (120b) suggested that the stereochemistry of the chloro group on C-13, resulting from rearside attack on the non-classical ion^{156,158} (119b), was in accord with the lack of resolvable coupling between H_e and H_f . (The dihedral angle was ca. 90°). However, irradiation of each signal led to a very slight sharpening of the other suggesting that the transmission of spin information was not totally negligible. The same model suggested that H_e and H_f would couple much more strongly if the chloro group were in the epimeric position on the same carbon where the dihedral angle was now ca. 30° . As in the case of the methanolysis of the N-chloroamines (29b) and (29c), the stereochemistry of the incoming group was evidence of a reaction proceeding with anchimeric assistance via a non-classical ion whose geometry determined the position of attack of the nucleophilic species.

This rearrangement provides further evidence for the stereochemistry of the cycloadduct (108b), with the etheno bridge on the same side of the molecule as the imino bridge. The ease

with which this rearrangement proceeds in a solvent which is considerably less polar than methanol and, further, in the absence of silver ion, emphasises the anchimeric assistance that suitably orientated π -electrons can offer.

CHAPTER 6

EXPERIMENTAL

Experimental

General

Diethyl ether, tetrahydrofuran (THF) and dioxan were refluxed over and distilled from lithium aluminium hydride. These solvents were dried initially over sodium wire. "Ether" refers to diethyl ether.

Methanol (MeOH) and dichloromethane (CH₂Cl₂) were refluxed over and distilled from calcium hydride.

Acetonitrile was refluxed over and distilled from phosphorus pentoxide.

Light petrol refers to the fraction boiling between 40° and 60°C which was dried over sodium wire.

All organic solutions were dried over anhydrous magnesium sulphate and the drying agent was removed by filtration through a sintered glass funnel prior to evaporation in vacuo.

Microanalyses were performed by CHN Analysis Ltd. of South Wigston, Leicester.

Melting points were determined using a Kofler hot stage apparatus and are uncorrected.

Instrumentation

¹H nmr spectra were recorded on Varian Associates T60, EM-390 and Jeol JNM-PS100 spectrometers. 400MHz spectra were recorded by Drs. O. Howarth and E. Curzon using facilities provided by the SERC at the University of Warwick. 220MHz spectra were recorded by PCMU, Harwell. Spin decoupling experiments were carried out on the EM-390 instrument and variable temperature work on the PS100 spectrometer.

Unless otherwise stated, all spectra were measured using

deuteriochloroform (CDCl_3) as solvent and chemical shifts are given in ppm(δ) from internal tetramethylsilane (TMS). Signal characteristics are described using the standard abbreviations:

(s) - singlet, (d) - doublet, (t) - triplet,
(q) - quartet, (m) - multiplet, (dt) - doublet of triplets,
etc. (br) - broad.

Coupling constants (J) are given in Herz (Hz) and $W_{\frac{1}{2}}$ refers to the width of an absorption at half-height, measured in Hz.

When a pair of signals was integrated to obtain a ratio, the ratio was the average of five or ten integrations carefully recorded. When the overlap of signals made such integrations less accurate, the relative areas were measured using a planimeter. Once again, the ratio was taken as the average of ten planimeter readings.

Routine and low temperature ^{13}C nmr spectra were recorded using a Jeol JNM FX60 spectrometer which for the ^{13}C nucleus had an operating frequency of 15.4 MHz. The 100 MHz spectra were recorded using facilities of the University of Warwick. Chemical shifts are recorded in ppm(δ) downfield from TMS.

Infra red spectra were measured on Perkin-Elmer 237 and 257 machines using 0.1mm sodium chloride solution cells and CH_2Cl_2 as solvent. The position of absorptions are given in wave wavenumbers (cm^{-1}) and described by the standard abbreviations:-

(s) - strong, (m) - medium, (w) - weak, (br) - broad.

Mass spectra were measured using a VG Micromass 16 Spectrometer. The data is given in m/e units; the mass peak is designated by M^+ and the base peak with an asterisk.

Ultraviolet spectra were recorded using a Pye-Unicam SP800 spectrophotometer. The positions of maxima are given in nanometres (nm) and the extinction coefficient, ϵ , follows each absorption in parentheses.

Preparation of N-Trimethylsilylpyrrole^{61,159}

Freshly distilled pyrrole (23.0g, 0.34m) and hexamethyldisilazane (30.4g, 0.19m) were refluxed under dry N₂ for 6h at 110°C with a few crystals of ammonium sulphate. Direct distillation of the reaction mixture through a 25cm Vigreux column gave N-trimethylsilylpyrrole as a colourless oil (26.6g, 56%) b.p. 71°-78°C (60mmHg) (lit. 150°-151°C).

δ (CCl₄) 6.52 (m, 2H), 6.06 (m, 2H),
0.35 (s, 9H).

In an alternative route to this N-substituted pyrrole, the potassium salt of pyrrole was treated with chlorotrimethylsilane but with the attendant hazard of the use of potassium metal.

Preparation of N-Ethoxycarbonylpyrrole¹⁶⁰

A 1l three-necked r.b.flask was flushed with dry N₂ and flame-dried. Pyrrole (70.0g, 1.04m) in 375ml of dry THF was stirred at 0°C as small pieces of potassium metal (38.6g, 0.99m) were added. The metal dissolved rapidly and the mixture was stirred overnight at room temperature under N₂. The potassio-pyrrole was cooled to 0°C and ethyl chloroformate (108.5g, 1.0m) in 75ml of dry THF was added slowly over ca. 45min. The mixture was stirred at 0°C for 1h, at room temperature for a further hour and then allowed to stand overnight.

Ether (300ml) and water (400ml) were then added and the organic phase separated. The aqueous layer was extracted with more ether (3 x 100ml) and all organic extracts were combined, dried and concentrated in vacuo. Distillation afforded N-ethoxycarbonylpyrrole, b.p. 69°-72°C (17mmHg) (lit. 180°C) as a colourless, sweet-smelling oil (19.30g, 55%).

δ (CCl₄) 7.06 (m, 2H), 6.03 (m, 2H),
 4.23 (q, 2H), 1.3 (t, 3H).

A further fraction was collected (15.6g) b.p. 64°-69°C (17mmHg), which contained 81% of the desired N-ethoxycarbonylpyrrole (nmr).

Preparation of 1,2-Dibromo-3,4,5,6-tetramethylbenzene¹⁶¹

1,2,3,4-Tetramethylbenzene (50.0g, 0.37m) in 150ml of glacial acetic acid was treated with bromine (45ml, 2.3 molar equivalents) in 75ml of glacial acetic acid. After standing overnight, the thick, white precipitate was filtered off and washed successively with dilute alkali and water. After drying, 1,2-dibromo-3,4,5,6-tetramethylbenzene (92.2g, 84%) was isolated, m.p. 150°-160°C (lit. 208°C). Repeated recrystallisation from chloroform failed to improve the value of the melting point.

m/e 294, 292*, 290 (1:2:1, M⁺), 211, 209, 131.

Preparation of 5,6,7,8-Tetramethyl-1,4-dihydronaphthalen-1,4-imine (27a)¹⁶².

A 1l three-necked r.b. flask was flushed with dry N₂ and flame-dried. 1,2-Dibromo-3,4,5,6-tetramethylbenzene (25.0g, 0.09m) was placed in the flask along with N-trimethylsilylpyrrole (23.0g, 0.17m) in 285ml of dry THF. The whole apparatus was cooled to -78°C. The addition of n-BuLi (1.6M, 60ml) in six portions from a syringe caused the solid to dissolve and the solution became cherry-red in colour. It was stirred at -78°C for 1h and then brought to room temperature over over 1-2h.

After stirring overnight, the reaction mixture was poured into water (350ml) and the organic phase separated. The aqueous layer was extracted with ether (3x100ml). All

organic extracts were combined, dried and concentrated in vacuo. The resultant dark red oil was treated with fumaric acid (10.5g, 0.095m) in 150ml of hot propan-2-ol. Upon cooling, buff coloured crystals of the fumarate salt of the amine were precipitated (8.6g, 32%).

The amine could be liberated by treatment with 2M NaOH solution. After extraction with CH_2Cl_2 , work-up afforded the amine (27a) as a white solid. Vacuum sublimation (0.01mm Hg, oil bath 100°C) gave fine white crystals, m.p. $77^\circ\text{--}79^\circ\text{C}$.

δ	6.96 (m, 2H), 5.06 (m, 2H), 3.00 (br, s, NH), 2.22 and 2.1 (s, each 6H).
m/e	199^* (M^+), 184, 173, 157.
ν_{max}	3260(w), 3000(m), 2920(m), 2860(m), 1450(m), 1350(m), 1350(s), 1190(m), 1095(m), 1055(m), 1025(m), 860(s), 835(s) cm^{-1} .

Preparation of 1,4-Dihydronaphthalen-1,4-imine (27b)^{51,62a,62b,130}

A 1l three-necked r.b. flask, fitted with a condenser and two 250ml dropping funnels, was flushed with dry N_2 and flame-dried. N-Ethoxycarbonylpyrrole (25.0g, 0.18m) in 300ml of dry dioxane was brought to reflux and then isoamyl nitrite (27.0g, 0.23m) and anthranilic acid (25g, 0.19m), each dissolved in 100ml of dry dioxane, were added at similar rates so that the addition took 1h. A rapid evolution of gas occurred and the solution became deep cherry-red in colour. The solution was refluxed for a further 15-20min. after the addition was complete.

The nmr spectrum of a sample indicated the presence of a cycloadduct by a characteristic bridgehead signal at δ 5.52 (in CDCl_3) and new ethyl group absorptions at δ 4.0(q) and

1.15(t)^{62b}. The adduct was not isolated and the bulk of the solvent was removed under reduced pressure. The residual dark brown oil was treated with 17% sodium hydroxide solution (285ml) and the mixture refluxed to effect hydrolysis. Its progress was monitored by nmr spectroscopy. Upon completion, the mixture was extracted with ether (5 x 100ml) and the organic extracts combined, dried and the solvent removed in vacuo. Distillation of the dark oil gave 1,4-dihydronaphthalen-1,4-imine(27b) (13.3g, 52%), b.p. 88^o-92^oC(0.4mmHg) (lit. 60^oC, 0.4mmHg).

δ (CCl₄) 7.20-6.62 (br,m,6H), 4.73(m,2H), 2.70 (br,s,NH).
 $\nu_{\max}$ (liquid film) 3200(br,m), 3060(s), 2980(s),
 1450(s), 1345(s), 1290(m), 1270(s),
 1200(m), 1125(m), 1080(m), 1040(m),
 1000(m), 855(s), 830(s), 750(s),
 730(s)cm⁻¹.

Preparation of 2-Chloro-1,4-dimethoxybenzene¹⁶³

This was prepared in the standard fashion by the O-alkylation of chlorohydroquinone with dimethyl sulphate in basic ethanol. Upon reaction of chlorohydroquinone (102.7g, 0.72m) with an excess of dimethyl sulphate (1.8 molar equivalents), the title compound (96.4g, 78%) was isolated after distillation, b.p. 92^o-108^oC (0.5mm Hg) (lit.¹⁶⁴ 123^o-124^oC (15mmHg)).

δ 6.83-6.33 (m,3H), 3.67 and 3.57 (each s,
 total 6H).

Preparation of 5,8-Dimethoxy-1,4-dihydronaphthalen-1,4-imine(27c)

(References 61,165)

1-Chloro-2,5-dimethoxybenzene (20.0g, 0.115m) was treated successively with n-BuLi (1.6M, 80ml) and

N-trimethylsilylpyrrole (17.0g, 0.122m) at -78°C in dry ether. The mixture was allowed to warm to room temperature (ca.2h) and was then poured into water (500ml). The organic layer separated and the aqueous layer was washed with further ether (2 x 100ml). The extracts were combined, dried and the solvent removed in vacuo to give a brown oil which crystallised in the cold. Repeated recrystallisation from ether gave the amine (27c) (3.5g, 15%) as white crystals, m.p. $84^{\circ}\text{--}85^{\circ}\text{C}$ (lit. $80^{\circ}\text{--}81^{\circ}\text{C}$).

δ	6.96 (m, 2H), 6.45(s, 2H), 5.20(m, 2H), 3.73(s, 6H), 2.77 (br, s, NH).
ν_{max}	3270 (w), 2940 (m), 2830 (m), 1610 (m), 1495 (s), 1465 (m), 1435(m), 1345 (m), 1240 (s), 1070 (s), 995 (m), 965 (m), 855 (s), 830 (s) cm^{-1} .

Preparation of 5,6,7,8-Tetrafluoro-1,4-dihydronaphthalen -1,4-imine (27e)⁶¹

This amine was prepared using a similar method as that used to prepare (27c). Tetrafluorobenzene (generated in situ from pentafluorobenzene (20.0g, 0.12m) and n-BuLi (1.6M, 75ml)) and N-trimethylsilylpyrrole (18.9g 0.14m) afforded, after work-up, the amine (27e) as a pale brown oil. Bulb-to-bulb distillation of this oil gave (27e) (5.1g, 20%) as a colourless oil (b.p 142°C , 0.2mmHg) which crystallised below 0°C .

δ	7.00 (m, 2H), 5.30 (m, 2H), 2.87 (br, s, NH).
ν_{max}	3270 (w), 3010 (w), 1635 (w), 1490 (s), 1350 (m), 1260 (m), 1185 (m), 1120 (m), 1085 (s), 1045 (s), 945 (s), 900 (m), 850 (s), 815 (s) cm^{-1} .
m/e	215 (M^+), 189*, 162.

Preparation of 5,6,7,8,9-Pentamethyl-1,4-dihydronaphthalen-1,4-imine (24a), 9-Methyl-1,4-dihydronaphthalen-1,4-imine (24b) and 9-Methyl-5,8-dimethoxy-1,4-dihydronaphthalen-1,4-imine (24c)

In a typical procedure, sodium cyanoborohydride⁶⁸ (400mg, 6.4mmol), the fumarate salt of 5,8-dimethoxy-1,4-dihydronaphthalen-1,4-imine (27c) (927mg, 2.9mmol) and 40% formaldehyde solution (1.1ml, 14.7mmol) were stirred overnight in 35ml of acetonitrile. Ether was then added to the reaction mixture and the flask contents were washed with acid (0.6M HCl, 3x30ml). The combined acid extracts were made basic (2M NaOH, 40ml) and the basic, aqueous layer extracted finally with CH₂Cl₂ (4 x 50ml). The combined organic extracts were dried and concentrated to give crude (24c), which was recrystallised from ether-light petrol (450mg, 71%). Vacuum sublimation (0.4mmHg, oil bath 100°C), gave white crystals of the amine, m.p. 83°-84°C (lit.¹⁶⁵ 84°-86°C).

Physical and spectroscopic data for (24a), (24b) and (24c) are enumerated in table 6.1.

Preparation of 9-Methyl-5,6,7,8-tetrachloro-1,4-dihydronaphthalen-1,4-imine (24d)³⁶ and 9-Methyl-5,6,7,8-tetrafluoro-1,4-dihydronaphthalen-1,4-imine (24e)^{36,63,64}.

Only these two amines could be prepared by the direct cycloaddition of the substituted benzyne to N-methylpyrrole. Their preparation has been reported previously by Callander and co-workers (24e) and by Gribble and co-workers (24d). Physical and spectroscopic data and the yields obtained of (24d) and (24e) are shown in table 6.1 and 6.2.

Preparation of the 9-Methyl-1,2,3,4-tetrahydronaphthalen-1,4-imines (26a), (26b), (26c) and (26e)

In a typical procedure, 9-methyl-5,6,7,8-tetrafluoro-1,4-dihydronaphthalen-1,4-imine (24e) (1.30g, 5.7mmol) was

Compound	M.p/B.p(°C)	Yield	$\delta(\text{CDCl}_3)$	m/e	$\nu_{\text{max}}(\text{cm}^{-1})$
(24a)	95-98	22	6.8(br, 2H), 4.56(br, 2H), 2.16 and 2.10(br, s, 15H)	213 [*] (M ⁺), 198 187, 172	2940(m), 2850(m), 1440(m), 1250(m), 1105(m), 805(s)
(24b)	142 (0.2mmHg)	54	7.13-6.82(br, m, 6H), 4.36(br, 2H), 2.05(br, 3H)	157 [*] (M ⁺), 142 133, 115	2940(s), 2860(s), 2770(m), 1610(w), 1440(s), 1295(s), 1190(m), 1130(m), 1095(s), 1005(m), 970(s), 905(s), 840(m), 800(s)
(24c) ¹⁶⁵	83-84	71	6.92(m, 2H), 6.83(s, 2H), 4.7(m, 2H), 3.71(s, 6H), 2.11(br, s, 3H)	217 [*] (M ⁺), 202 191, 177, 128	2940(s), 2830(s), 2780(m), 1610(m), 1490(s), 1460(s), 1240(s), 1215(s), 1175(m), 1105(m), 1065(s), 985(s), 965(m), 785(s)
(24d) ^{36, 63}	154-155	16	6.9(m, 2H), 4.76(m, 2H), 2.21(s, 3H)	295(M ⁺), 280 269 [*] , 233	2950(w), 2870(w), 2795(w), 1350(m), 1305(m), 1205(w), 1110(m)
(24e) ^{64, 36}	72-73.5	56	6.87(m, 2H), 4.81(m, 2H), 2.13(br, s, 3H)	229(M ⁺), 214, 203 [*] , 187	2950(w), 2860(w), 2790(w), 1490(s), 1385(w), 1300(m), 1205(w), 1115(m), 1045(s), 1005(s), 1005(w), 990(m), 935(m)

Compound ^a	<u>C-1,4</u>	<u>C-2,3</u>	<u>C-5,6</u>	<u>C-7</u>	<u>C-8,11</u>	<u>C-9,10</u>	<u>X,Y</u>
(24a) ^b Major	72.20	143.63	145.58	38.70	131.55	133.11	18.57,
Minor	72.98	140.00	146.48	37.66	127.91	132.20	17.66
(24b)	70.88	143.32	146.95	36.39	122.99	124.24	
	71.76	137.88	149.25	35.41	119.66	123.65	
(24c)	68.91	143.76	135.07	36.91	150.18	109.70	55.46
	69.33	138.21	135.07	35.88	146.64	109.23	55.61
(24d)	72.35	143.37	147.12	36.76	127.77	128.81	
	72.50	138.78	148.91	35.12	126.93	128.21	
(24e)	69.17	143.15	- ^c	36.69	- ^c	- ^c	
	71.39	138.16	- ^c	35.11	- ^c	- ^c	

a. All spectra measured in CDCl₃/TMS at 100MHz frequency and at -55^o C.

b. Spectrum measured at 15.4MHz frequency.

c. Signals due to the aromatic carbons could not be resolved due to ¹³C-¹⁹F coupling.

dissolved in 30ml of an appropriate solvent (ethyl acetate or methanol) and hydrogenated over palladium-charcoal in a Parr apparatus, for 2h at a pressure of 20psi. The catalyst was removed by filtering the mixture through Celite and the catalyst was washed with further solvent. The solvent was removed under pressure to afford 9-methyl-5,6,7,8-tetrafluoro-1,2,3,4-tetrahydronaphthalen-1,4-imine (26e) (1.23g, 93%), m.p. 76°-79°C.

In the case of (24d), the easy hydrogenolysis of the aromatic carbon-chlorine bonds meant that milder conditions were required. Thus, Adam's catalyst (Pt(II)O_2) was used with 10psi of hydrogen for ca. 10 min.

Physical and spectroscopic data of the reduction products are given in tables 6.3 and 6.4.

Preparation of the 1,4-Dihydro-2,3-exo-dideuterionaphthalen-1,4-imines d_2 -(26b), d_2 -(26c) and d_2 -(26e)^{13,73}

The reductions were performed in methanol with palladium-charcoal as catalyst. The heterogeneous mixtures were stirred overnight under a balloon filled with deuterium gas. The catalyst was removed by filtration through a pad of Celite and the solvent removed in vacuo.

The ^1H nmr and mass spectral data of these analogues are given in table 6.5.

Preparation of 2-Methyl-4,5,6,7-tetrafluoroisoindole^{61,62a,166,167}

A 100ml r.b. flask was flushed with dry N_2 and rinsed with dry CH_2Cl_2 . 3,6-Di(2-pyridyl)-1,2,4,5-tetrazine¹⁶⁸ (3.0g, 13mmol) in 10ml of dry CH_2Cl_2 was stirred as 9-methyl-5,6,7,8-tetrafluoro-1,4-dihydronaphthalen-1,4-imine (24e) (2.78g, 12mmol) in 20ml of dry CH_2Cl_2 was added dropwise. The heterogeneous mixture was stirred for 6h at

Table 6.3

Compound	M.p./B.p. (°C)	$\delta(\text{CDCl}_3)$	m/e	$\nu_{\text{max}}(\text{cm}^{-1})$
(26a) ^a	100-103	4.10(m, 2H), 2.15-2.00 (m, 17H), 1.07(m, 2H)	215(M ⁺), 200, 187*, 172	2950 (s), 1450 (m), 1265 (br, m) 1195 (m), 1095 (m), 1005 (w), 840 (m).
(26b) ^{62b}		7.13(m, 4H), 4.05(m, 2H), 2.05(m, 5H), 1.18(m, 2H)	159(M ⁺), 144 131*, 111, 90	2960 (s), 1450 (s), 1340 (m), 1265 (br, s), 1200 (s), 1085 (s), 970 (s), 840 (s).
(26c) ^b	108-110.5	6.60(s, 2H), 4.27(m, 2H), 3.7(s, 6H), 2.03(m, 5H), 1.18 (m, 2H)	219(M ⁺) 204, 191*, 176, 148, 133	2945 (s), 2830 (sh), 1495 (s), 1460 (s), 1250 (s), 1200 (m), 1165 (m), 1090 (s), 1030 (m), 992 (m), 965 (m), 850 (m).
(26d)	134.5-136.5	4.35(m, 2H), 2.10(m, 5H), 1.25(m, 2H)	297(M ⁺), 282, 269*, 254, 235 1090 (m).	1360 (s), 1200 (m), 1155 (s).
(26e)	76-79	4.38(m, 2H), 2.03(m, 5H), 1.23(m, 2H)	231(M ⁺), 216, 203*, 188, 162 1290 (s), 1095 (s), 1065 (s), 1035 (s), 950 (s), 915 (m), 885 (s), 810 (s).	2790 (m), 1490 (s), 1380 (s), 1125 (m), 1115 (s), 990 (m).

a. $\text{C}_{15}\text{H}_{21}\text{N}$ requires C 83.67% H 9.83% N 6.50%. Found C 83.60% H 9.78% N 6.53%.

b. $\text{C}_{13}\text{H}_{17}\text{NO}_2$ requires C 71.21% H 7.81% N 6.41%. Found C 71.14% H 7.96% N 6.28%.

Table 6.4 ^{13}C Nmr Spectral Data (δ) of the Amines (26a)-(26e)

Compound ^a	<u>C-1,4</u>	<u>C-2,3</u>	<u>C-5,6</u>	<u>C-7</u>	<u>C-8,11</u>	<u>C-9,10</u>	<u>X,Y</u>
(26a)	66.75	26.62	139.99	35.58	127.26	132.85	16.36, 15.97
(26b)	67.53	26.88	144.80	35.32	121.55	126.23	
(26c)	64.67	26.23	133.24	35.19	149.21	109.99	55.32
(26d)	68.44	25.58	143.24	35.58	127.00	130.51	
(26e) ^b	66.62	27.66	- ^c	36.49	- ^c	- ^c	

a. All spectra measured in CDCl_3 at room temperature.

b. Spectrum measured in CH_2Cl_2 .

c. Not resolvable due to extensive ^{13}C - ^{19}F coupling.

Table 6.5

<u>Compound</u>	<u>$\delta(\text{CDCl}_3)$</u>	<u>m/e^a</u>
d_2 -(26b)	7.2(m, 4H), 4.27(s, 2H), 2.15(s, 3H), 1.25(s, 2H)	161(M^+), 145, 131 [*] , 116, 103, 90
d_2 -(26c)	6.62(s, 2H), 4.25(s, 2H), 3.75(s, 6H), 2.03(s, 3H), 1.17(s, 2H)	219(M^+), 203, 191 [*] , 176, 161, 148
d_2 -(26e)	4.48(s, 2H), 2.08(s, 3H), 1.24(s, 2H)	233(M^+), 203 [*] , 188, 162

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a. Analysis of the mass spectra of these compounds revealed $\geq 97\%$ incorporation of deuterium.

room temperature. The mixture was left to stand overnight after which time the solvent was removed in vacuo and the crimson solid remaining was sublimed (oil bath 130°C, 0.05mmHg) to give 2-methyl-4,5,6,7-tetrafluoroisoindole (2.13g, 86%), as pale yellow crystals, m.p. 151°-154°C (lit. 178°C).

δ 7.08 (m, 2H), 3.96 (s, 3H).
 m/e 203* (M+), 188, 175, 162, 143.

Preparation of 9-Methyl-5,6,7,8-tetrafluoro-2,3-dimethoxycarbonyl-1,4-dihydronaphthalen-1,4-imine (38e)¹⁶⁹

2-Methyl-4,5,6,7-tetrafluoroisoindole (1.02g, 5mmol) was dissolved in 25ml of dry CH₂Cl₂ and dimethyl acetylene dicarboxylate (0.62ml, 5mmol) was added to the stirred solution via syringe. Stirring was continued for 3h. After this time, the solution was dried, filtered and the solvent removed in vacuo to give, after recrystallisation from ether-acetone, the 1:1 adduct (38e) (890mg, 51%), m.p. 122°-124°C.

δ 5.18 (s, 2H), 3.8 (s, 6H), 2.23 (s, 3H).
 $\nu_{\max}$ 2950 (w), 1715 (s), 1630 (w), 1480 (s), 1430 (m), 1260 (m), 1225 (m), 1160 (m), 1105 (m), 1080 (m), 930 (w) cm⁻¹.
 m/e 345(M⁺), 315, 286, 272, 256, 203*, 189, 162.
 C₁₅H₁₁NO₄F₄ requires C 52.18% H 3.21% N 4.06%
 found C 52.04% H 3.29% N 4.03%

Preparation of 11-Methyl-1,2,3,4-tetrafluoro-9,10-dihydroanthracen-9,10-imine (65)^{36,63}

A 100ml three-necked r.b. flask, fitted with two 50ml dropping funnels and a reflux condenser, was flushed with dry N₂ and flame-dried. The vessel was charged with dry magnesium turnings (227mg, 9.4mmol) in dry THF (2ml). A few drops of a

solution of 2-bromofluoro-benzene (1.52g, 8.7mmol) in THF (2ml) were added and the Grignard reaction rapidly ensued. As the flask was cooled in ice, the remaining 2-bromofluorobenzene solution was run in. When the metal had dissolved, 2-methyl-4,5,6,7-tetrafluorisoindole (1.74g, 8.6mmol) in 15ml of dry THF was added and the darkening solution heated under reflux for 1h.

The reaction mixture was cooled, transferred to a separating funnel and extracted with acid (1M HCl, 4 x 10ml). The combined acid extracts were made basic (2M NaOH, 30ml) and the basic aqueous layer was extracted with CH₂Cl₂ (5 x 50ml). The combined organic extracts were dried and evaporated to give 11-methyl-1,2,3,4-tetrafluoro-9,10-dihydroanthracen-9,10-imine (65) which was recrystallised from light petrol (280mg, 12%), m.p. 83^o-86^oC.

δ	7.43-6.93 (m, 4H), 5.21 (s, 2H), 2.25 (br, s, 3H).
$\nu_{\max}$	2950 (w), 2870 (w), 2790 (w), 1500 (s), 1485 (s), 1330 (m), 1270 (m), 1115 (m), 1095 (m), 1045 (m), 995 (m), 955 (m), 925 (m) cm ⁻¹ .
m/e	279 [*] (M ⁺), 264, 250, 237, 203, 188, 162.

Preparation of 11-Ethoxycarbonyl-1,4-dihydro-anthracen-1,4-imine^{62b,170}

This was prepared using the method described for 1,4-dihydronaphthalen-1,4-imine (27b). N-ethoxycarbonylpyrrole (4.2g, 0.03m) and naphthalene, generated in dry refluxing dioxan from 2-amino-3-naphthoic acid (5.0g, 0.027m) and isoamyl nitrite (3.5g, 0.03m), gave the desired cycloadduct. The solvent was removed under reduced pressure to give 9.0g of a dark red

oil. This was absorbed onto basic alumina (30g, Woelm) and this alumina placed carefully on top of a further 120g of basic alumina. The column was eluted with ether and the first compound removed was 11-ethoxycarbonyl-1,4-dihydroanthracen-1,4-imine (3.43g, 49%). It recrystallised from ether-acetone as colourless needles, m.p. 125^o-126^oC.

δ	7.78-7.21 (m, 6H), 6.88 (m, 2H), 5.62 (m, 2H), 4.03 (q, 2H), 1.17 (t, 3H).
$\nu_{\max}$	3040 (s), 2970 (w), 1710 (s), 1370 (m), 1325 (m), 1245 (m), 1095 (m), 870 (m) cm ⁻¹ .
m/e	265 (M ⁺), 238, 236, 220, 192, 165 [*] .
C ₁₇ H ₁₅ NO ₂	requires C 76.96% H 5.70% N 5.28% found C 77.25% H 5.78% N 5.28%

Preparation of 11-Methyl-1,4-dihydroanthracen-1,4-imine (37)¹⁷¹

Lithium aluminium hydride (150mg, 4mmol) was slurried with sodium-dried ether (25ml) and cooled to 0^oC. 11-Ethoxycarbonyl-1,4-dihydroanthracen-1,4-imine (300mg, 1.1 mmol) was dissolved in ether (50ml) and added slowly to the slurry from a dropping funnel. The cooling bath was removed and the mixture was refluxed for 45min. After cooling, the excess of LiAlH₄ was destroyed cautiously with water and the mixture filtered through Celite. The aqueous phase was separated and washed with further ether (2 x 25ml). The combined organic extracts were then washed with acid (2M HCl, 4 x 10ml), the acid washings made basic (2M NaOH, 50ml) and the basic layer was extracted with CH₂Cl₂ (4 x 25ml). The CH₂Cl₂ solution was dried and the solvent was evaporated to yield crude (37) (177mg, 78%). The solid was recrystallised from light petrol as white crystals, m.p. 91^o-94^oC (lit. 94.5^o- 95.5^oC).

δ	7.27-7.30 (m, 6H), 6.8 (br, 2H), 4.55 (br, 2H). 2.15 (br, 3H).
$\nu_{\max}$	3040 (w), 2960 (w), 2750 (w), 1415 (w) 1100 (m) 880 (m), 805 (s) cm^{-1} .
m/e	207* (M^+), 192, 178, 165.

Protonation Experiments

1) A solution of approximately 50mg of amine in ca. 0.2ml of CDCl_3 was slowly added, in drops, to a rapidly stirred mixture of 1:4 trifluoroacetic acid/deuteriochloroform (0.2ml). The whole solution was transferred to an nmr tube and the spectrum recorded with TMS as internal standard. All operations were carried out at ambient temperatures. The solutions were then allowed to stand in the dark at room temperature for 7 days and the ratio of trifluoroacetate salts ascertained again after this interval. The solvent was removed and the mixture of trifluoroacetate salts then redissolved in CDCl_3/TMS and the nmr spectrum recorded. A slight excess of amine was then added and any further change in the ratio of protonated amine salts was recorded.

2) The amine (24e) (76mg, 0.3 mmol) was dissolved in CFCl_3 (Arcton II) (20ml) and placed in a burette. The solution was dripped very slowly (2-3h) into rapidly stirred TFA (2ml) contained in a narrow sample tube to provide a depth of acid, enabling a vortex to be created. Nitrogen was blown gently over the surface of the acid to evaporate the volatile Arcton. The ratio was checked as soon as the addition was complete and any changes were monitored over a period of time,

A similar experiment using 73mg of (24d) in 26ml of CFCl_3 was performed.

Preparation of 9-Methyl-5,6,7,8-tetrafluoro-2,3-bis-endo-methoxycarbonyl-1,2,3,4-tetrahydronaphthalen-1,4-imine (81e)

The amine (38e) (400mg, 1.2 mmol) was dissolved in ethyl acetate (40ml) and hydrogenated over Pd-C for 2h at 20psi. The catalyst was removed by filtration through Celite and evaporation of the solvent gave the title compound quantitatively. It recrystallised from ether-acetone as colourless needles, m.p. 143^o-145^oC.

δ 4.58 (m,2H), 3.67 (m,2H), 3.53 (s,6H),
2.03 (s,3H).

ν_{max} 2950 (w), 1745 (s), 1500 (s), 1435 (w),
1290 (m), 1200 (m), 1115 (m), 1040 (m),
950 (w), 820 (w) cm⁻¹.

m/e 347 (M⁺), 328, 316, 285, 273, 256, 228,
203^{*}, 188, 162.

C₁₅H₁₃NO₄F₄ requires C 51.88% H 3.77% N 4.03%
found C 51.86% H 3.83% N 4.08%

Preparation of 2-Methyl-5,6-benzo-2-azabicyclo(2.2.2)oct-7-en-3-one

The compound was prepared in the manner described by Sheinin et al¹⁷². 1-Methyl-2-pyridone (15.10g, 0.14m) and freshly prepared 2-diazonium benzene carboxylate¹⁷³ (20.3g, 0.14m) (generated from 2-amino benzoic acid (19.0g, 0.14m), isoamyl nitrile (19.24g, 0.16m) and trifluoroacetic acid (1ml) in 150ml of THF) gave the title compound (2.55g, 10%).

δ 7.36-6.70 (m,6H), 4.96 (dd,1H,J=3,6Hz),
4.56 (dd,1H,J=3,6Hz), 2.81 (s,3H).

Preparation of 2-Methyl-5,6-benzo-2-azabicyclo(2.2.2)octan-3-one

2-Methyl-5,6-benzo-2-azabicyclo(2.2.2)oct-7-en-3-one (1.0g, 5.4mmol) was dissolved in ethyl acetate (50ml) and

hydrogenated over palladium/charcoal in a Parr apparatus for $1\frac{1}{2}$ h at 20psi. The catalyst was removed by filtration through Celite and the solvent dried, filtered and the solvent removed to give 2-methyl-5,6-benzo-2-azabicyclo(2.2.2)octan-3-one (920mg, 91%)

δ 7.20 (m, 4H), 4.46 (m, 1H), 3.83 (m, 1H),
2.90 (s, 3H), 2.08 (m, 2H), 1.90 (m, 2H).

Preparation of 2-Methyl-5,6-benzo-2-azabicyclo(2.2.2)octane(86)

A 250ml three-necked r.b. flask was flushed with dry N_2 and flame-dried. Lithium aluminium hydride (1.0g, 26 mmol) was added cautiously to 75ml of dry ether. A solution of 2-methyl-5,6-benzo-2-azabicyclo(2.2.2)octan-3-one (920mg, 4.9mmol) in 50ml of dry ether was then allowed to run in slowly from a dropping funnel. The mixture was stirred and heated at reflux for $2\frac{1}{2}$ h under N_2 . After the mixture had cooled, excess reducing agent was destroyed by cautious addition of ether saturated with water. The solution was filtered through Celite and the celite washed with further ether. The dried ether extracts were concentrated to give 2-methyl-5,6-benzo-2-azabicyclo(2.2.2)octane (86) (776mg, 91%) as a pale yellow oil. Bulb-to-bulb distillation afforded a colourless oil, b.p. $80^\circ C$ (0.1mmHg).

δ 7.15 (m, 4H), 3.58 (m, 1H), 3.25 (dd, 1H,
J=1.5, 10Hz), 2.95 (m, 1H), 2.31-1.18
(envelope, 8H(NCH_3 2.00)).
m/e 173 (M^+), 156, 144*, 130, 115.

Preparation of 9-Ethyl-1,4-dihydronaphthalen-1,4-imine (83b) and 9-Ethyl-5,6,7,8-tetrafluoro-1,4-dihydronaphthalen-1,4-imine(83e)

N-Ethylation of the respective secondary amines (27) was

performed using the procedure for N-methylation described by Anderson and co-workers⁶¹ but using acetaldehyde instead of formaldehyde.

The fumarate salt of 1,4-dihydronaphthalen-1,4-imine (27b) (1.25g, 4.8 mmol), sodium cyanoborohydride (600mg, 9.6 mmol) and acetaldehyde (2ml, 36 mmol) were stirred for 24h in acetonitrile (50ml). After column chromatography (Al_2O_3 , ether), 9-ethyl-1,4-dihydronaphthalen-1,4-imine (83b) was isolated as a yellow oil (199mg, 23%). Bulb-to-bulb distillation afforded a colourless oil, b.p. 140°C , 0.15mmHg.

The physical and spectroscopic data of (83b) and (83e) are shown in table 6.6.

Preparation of 9-Methyl-1,2,3,4-tetrahydronaphthalen-1,4-imine (84b) and 9-Ethyl-5,6,7,8-tetrafluoro-1,2,3,4-tetrahydronaphthalen-1,4-imine (84e)

The compounds (83b) and (83e) were hydrogenated over palladium-charcoal in the fashion described for (24e). Physical and spectroscopic data of (84b) and (84e) are given in table 6.6.

Preparation of 11-Methyl-5,6,7,8-tetrafluoro-1,4-etheno-1,2,3,4,9,10-hexahydroanthracen-9,10-imine (114e)¹⁵³

9-Methyl-5,6,7,8-tetrafluoro-1,4-dihydronaphthalen-1,4-imine (24e) (1.0g, 4.4 mmol) and cyclohexa-1,3-diene (2.1g, 26 mmol) were sealed in a thick-walled Pyrex tube and placed in an oven at 136°C for 24h. After the tube had cooled, it was opened and the dark red oil washed into a dropping funnel with ether. The organic solution was washed with acid (2M HCl, 5x15ml), the combined acid washings made basic (2M NaOH, 90ml) and the basic aqueous layer extracted with ether (4 x 30ml). The combined organic extracts were dried and evaporated to give the title compound (114e) (626mg, 57%). It recrystallised from light petrol to give white crystals, m.p. 138°C - 131°C .

Table 6.6

Compound	Yield(%)	M.p./B.p($^{\circ}$ C)	δ	m/e	$\nu_{\max}(\text{cm}^{-1})$
(83b)	23	140(0.15mmHg)	7.33-6.33(br,m,6H), 4.57(m,2H), 2.27(br, 2H), 1.00(t,3H)	171 * (M $^+$), 156, 145, 129	2960 (m), 2840 (w), 1670 (w), 1450 (m), 1375 (m), 1270 (w), 1120 (m), 1090 (m), 995 (w), 790
(83c) ^a	31		6.91(br,m,2H), 4.96 (m,2H), 2.26(br,q, 2H), 1.00(t,3H)	243(M $^+$), 217 200 * , 189	2960 (m), 2840 (w), 1490 (s), 1380 (m), 1355 (w), 1295 (m), 1200 (m), 1175 (m), 1120 (m), 1040 (s), 935 (s), 810 (s).
(84b)	79		7.13(m,4H), 4.17(m, 2H), 2.33-1.93(m,4H), 1.18(m,2H), 1.00(t,3H)	173(M $^+$), 159, 145 * , 129, 117, 89	2890 (s), 1450 (m), 1380 (m), 1280 (br,m), 1200 (m), 1085 (m), 905 (s).
(84e) ^b	97		4.52(m,2H), 2.33-2.00 (m,4H), 1.23(m,2H), 1.00(t,3H)	245(M $^+$), 218 * , 207, 189, 162, 151, 143	2970 (s), 1490 (s), 1385 (s), 1293 (s), 1205 (m), 1135 (m), 1105 (m), 1090 (m), 1075 (m), 1035 (s), 1030 (s), 968 (m), 905

a. Analysed as its tetrafluoroborate salt : $\text{C}_{12}\text{H}_{10}\text{NBF}_8$ requires C 43.54% H 3.05% N 4.23%

found C 43.57% H 3.07% N 4.40%

b. Analysed as its tetrafluoroborate salt : $\text{C}_{12}\text{H}_{12}\text{NBF}_8$ requires C 43.28% H 3.63% N 4.21%

found C 42.94% H 3.67% N 4.25%

δ	6.17 (m, 2H), 4.13 (m, 2H), 2.73 (br, 2H), 1.82 (s, 3H), 1.73 (m, 2H), 1.53-1.00 (m, 4H).
$\nu_{\max}$	2940 (m), 2860 (w), 1490 (s), 1475 (s), 1375 (m), 1250 (m), 1110 (m), 1045 (m), 990 (m), 945 (m), 900 (w) cm^{-1} .
m/e	309 (M^+), 294, 280, 268, 237, 216, 203*, 188, 162.
$\text{C}_{17}\text{H}_{15}\text{NF}_4$	requires C 66.01% H 4.89% N 4.53% found C 66.04% H 4.90% N 4.53%

Amine Quaternisations

In a typical procedure, the amine (25-50mg) was dissolved in d_3 -acetonitrile (0.4-0.5ml) and the solution placed in an nmr tube. The quaternising agent was delivered directly into the amine solution from a syringe and the tube shaken. When d_3 -methyl iodide (CD_3I) was used, a five molar excess was added. The more reactive d_6 -dimethyl sulphate ($(\text{CD}_3)_2\text{SO}_4$) and d_3 -methyl fluorosulphonate (CD_3FSO_3) were added to only 1.5-2.5 molar excess. The nmr spectrum was recorded immediately after the addition and, if quaternisation were slow, subsequent spectra were taken until all starting material had disappeared. The reactions were conducted at room temperature.

If the quaternary ammonium salt precipitated from solution, a minimum quantity of D_2O (2-3 drops) was added to ensure complete dissolution although this was required in only a few cases.

In a typical experiment, the ratio of diastereoisomeric quaternary salts was determined by integration of the two N-methyl signals in the ^1H nmr spectrum of the crude reaction mixture. The chemical shift of the syn- and anti-N-methyl signals in the quaternary salts were 0.6-1.2ppm downfield of

the signal due to the amine N-methyl signal because of the positive charge created on nitrogen. The ratio was the average of ten careful integrations of these new N-methyl signals, which were measured over expanded sweep widths of 5 or 2ppm. When the overlap of signals made these integrations less accurate, a planimeter was used to measure the relative area and the ratio obtained as the average of ten readings. Integration of the quartet against the triplet absorption in the ^1H nmr spectrum of ethyl benzene gave a maximum error limit of $\pm 2\%$.

After quaternisation was complete, the ratio of products was monitored by nmr for a period of at least twice the reaction time in order to check for equilibration. Complete quaternisation of the amine had occurred before an nmr spectrum could be obtained when $(\text{CD}_3)_2\text{SO}_4$ and CD_3FSO_3 were used. Thus, in certain examples, these quaternisations were repeated at -20°C in the probe of an nmr spectrometer and the emerging ratio of quaternary salts followed upon addition of the quaternising agent at this temperature. By following the ratio in this way, any chance of equilibration of the ratio of salts between the addition of quaternising agent and recording the ^1H nmr spectrum could be monitored.

Analytical data for some quaternary salts (as the monomethylsulphate derivatives) is given below. The quaternary salts derived from the amines (24) were unstable to recrystallisation or decomposed on storage.

<u>Amine Salt</u>	<u>m.p. (°C)</u>	<u>Calculated (%)</u>			<u>Found (%)</u>		
		C	H	N	C	H	N
(26b) $C_{13}H_{19}NSO_4$	134.5-136	54.72	6.71	4.91	54.78	6.84	4.87
(26c) $C_{15}H_{23}NSO_6$	147-149	52.16	6.71	4.06	52.19	6.65	4.02
(26e) $C_{13}H_{15}NF_4SO_4$	160-161.5	43.70	4.23	3.92	43.67	4.18	3.88

Preparation of 9-Chloro-1,4-dihydro- and 1,2,3,4-tetrahydro-naphthalen-1,4-imines (29) and (30)

General procedure⁵⁸

The amine (2-3 mmol) was dissolved in 10ml of dry ether and cooled to 0°C. N-Chlorosuccinimide (1.1 molar equivalents) was added in one portion and the mixture stirred rapidly in the dark under dry N₂ for 2h. The solvent was removed in vacuo whilst the flask was immersed in ice-water and the residue was then extracted with cold Arcton (5 x 5ml). The combined organic extracts were dried, filtered and the solvent removed at 0°C to produce the crystalline N-chloroamines. The N-chloro-1,4-dihydronaphthalen-1,4-imines were markedly light sensitive and were stored in the dark at -40°C. Each N-chloroamine was prepared only as required in order to avoid decomposition on storage. The ¹H nmr data of the N-chloroamines used in this work are given in table 6.7.

Solvolysis of 9-Chloro-1,4-dihydronaphthalen-1,4-imine (29b) at 0°C.

The N-chloroamine (29b) (718mg, 4 mmol) was dissolved in a minimum of ice-cold methanol and placed onto a 15cm chromatography column packed at 0°C with silver carbonate-Celite in dry methanol. The column was allowed to stand for 25 min. at

Table 6.7Compound δ

(29b)	syn-Cl: 7.40-7.13 (m, 4H), 7.17 (m, 2H, $W_{\frac{1}{2}}=4.5\text{Hz}$), 4.86 (m, 2H, $W_{\frac{1}{2}}=4.5\text{Hz}$) anti-Cl: 7.13-6.87 (m, 4H), 6.82 (m, 2H, $W_{\frac{1}{2}}=4.5\text{Hz}$), 5.06 (m, 2H, $W_{\frac{1}{2}}=4\text{Hz}$)
(29c)	syn-Cl: 6.95 (m, 2H, $W_{\frac{1}{2}}=4.5\text{Hz}$), 6.62 (s, 2H), 5.1 (m, 2H, $W_{\frac{1}{2}}=4\text{Hz}$), 3.77 (s, 6H) anti-Cl: 6.85 (m, 2H, $W_{\frac{1}{2}}=3\text{Hz}$), 6.55 (s, 2H), 5.27 (m, 2H, $W_{\frac{1}{2}}=4.5\text{Hz}$), 3.72 (s, 6H)
(29e)	syn-Cl: 6.97 (m, 2H, $W_{\frac{1}{2}}=5\text{Hz}$), 5.18 (m, 2H, $W_{\frac{1}{2}}=4.5\text{Hz}$) anti-Cl: 6.90 (m, 2H, $W_{\frac{1}{2}}=4.5\text{Hz}$), 5.33 (m, 2H, $W_{\frac{1}{2}}=5\text{Hz}$).

0°C in a cold room and then the column was thoroughly eluted with further cold methanol. The solvent was removed in vacuo in the cold and the ^1H nmr spectrum of the product showed the presence of anti-(29b) only.

The anti-invertomer was dissolved in 5ml of ice-cold methanol and added to 15ml of rapidly stirred methanolic silver nitrate (1.0g) at 0°C. The mixture was stirred in an ice-water bath for 15min. after which time it was filtered and extracted with light petrol (4 X 20ml). The organic extracts were combined, dried and the solvent removed in vacuo to give 6,7-benzo-5-methoxy-1-azabicyclo(3.2.0)hept-3-ene (88b) (140mg). The methanol layer was concentrated to dryness and extracted with dichloromethane to yield a further sample of (88b) (365mg). This material was chromatographed on basic alumina using 1:1 petrol-ether as eluant to give pure (88b) (102mg). The total yield was 242mg (35%). The solid was recrystallised several times from light petrol, m.p. 61°-62.5°C (lit.⁵⁸ 61°-62°C).

^1H nmr $\delta(\text{C}_6\text{D}_6)^*$ 7.12 (m, 1H, Ar), 6.78 (d, 2H, Ar), 6.63 (d, 1H, Ar),
5.81 (dt, H_c , $J_{c,b} = 5.7$, $J_{c,a} = 1.7$, $J_{c,d} = 1.7\text{Hz}$)
5.52 (dt, H_b , $J_{b,c} = 5.7$, $J_{b,a} = 1.7$, $J_{b,d} = 1.7\text{Hz}$),
5.40 (dt, H_d , $J_{d,a} = 3.7$, $J_{d,b} = 1.7$, $J_{d,c} = 1.7\text{Hz}$),
5.00 (dt, H_a , $J_{a,d} = 3.7$, $J_{a,b} = 1.7$, $J_{a,c} = 1.7\text{Hz}$),
3.38 (s, 3H, OMe).

ν_{max} 2930 (w), 2820 (w), 1590 (s), 1450 (s),
1355 (s), 1185 (s), 1105 (s), 1085 (s),
1040 (s), 985 (s), 805 (w) cm^{-1}

m/e 173 (M^+), 158, 141*, 114, 88

^{13}C nmr δ 157.62 (C_2), 139.99 (C_9), 133.40 (C_8),
128.57 (C_6), 128.04 (C_4), 121.86 (C_1),

120.63 (C₅), 112.16 (C₃), 98.80 (C₁₀),
81.70 (C₇), 53.53 (C₁₁).

λ_{max} (Cyclohexane) 215(4974), 232(6488), 284(2919)

C₁₁H₁₁NO requires C 76.28% H 6.40% N 8.09%

found C 76.15% H 6.49% N 8.09%

* Spectrum at 400MHz operating frequency.

Solvolysis of 9-Chloro-5,8-dimethoxy-1,4-dihydronaphthalen-1,4-imine (29c) at 0°C

The N-chloroamine (29c) (606mg, 2.5 mmol) was dissolved in 15ml of ice - cold dry methanol and added to 5ml of ice-cold methanolic silver nitrate (800mg). The heterogeneous mixture was stirred at 0°C for 30min. in the dark under dry N₂. The mixture was poured into water and 2M NaOH (20ml) added. The basified aqueous layer extracted with CH₂Cl₂ (4 X 25ml). The combined organic extracts were dried and concentrated in vacuo to give a brown oil (550mg) which was adsorbed onto basic alumina (2.0g). This alumina was placed on top of a prepacked column of alumina (Al₂O₃) and the column eluted with ether. This gave, in order of elution, 6,7-(8,11-dimethoxybenzo)-5-methoxy-1-azabicyclo(3.2.0)hept-3-ene (88c), m.p. 64.5°-67°C (159mg, 27%).

δ^* 6.68 and 6.40 (dd, 2H, Ar, AB system, $J_{AB}=9\text{Hz}$),
6.38 (dt, H_c, $J_{c,b}=5.7, J_{c,a}=1.7, J_{c,d}=1.7\text{Hz}$),
5.80 (dt, H_b, $J_{b,c}=5.7, J_{b,a}=1.7, J_{b,d}=1.7\text{Hz}$),
5.79 (dt, H_d, $J_{d,a}=3.5, J_{d,c}=1.7, J_{d,b}=1.7\text{Hz}$),
5.31 (dt, H_a, $J_{a,d}=3.5, J_{a,c}=1.7, J_{a,b}=1.7\text{Hz}$),
3.82 and 3.80 (s, total 6H, ArOMe), 3.55 (s, 3H, OMe).

*Spectrum in CDCl₃ at 400MHz operating frequency.

$\nu_{\max}$	2940 (m), 2830 (w), 1580 (m), 1485 (s), 1425 (s), 1325 (m), 1230 (s), 1105 (s), 1075 (s), 1015 (s), 980 (s), 845 (s) cm^{-1} .
m/e	233 (M^+), 218, 202*, 190, 174, 160.
$\lambda_{\max}$ (Cyclohexane)	217.5(13431), 237(6567), 290(3134).
$\text{C}_{13}\text{H}_{15}\text{NO}_3$	requires C 66.94% H 6.48% N 6.00% found C 66.87% H 6.49% N 5.98%

Further elution with ether gave 5,8-dimethoxy-2,3-bis-endo-methoxy-1,2,3,4-tetrahydronaphthalen-1,4-imine (87c)
m.p. $154^{\circ}\text{--}156^{\circ}\text{C}$ (122mg, 18%).

δ	6.62 (s, 2H, Ar), 4.78 (m, 2H, $W_{\frac{1}{2}}=5\text{Hz}$, H_1, H_4), 4.08 (m, 2H, $W_{\frac{1}{2}}=5\text{Hz}$, H_2, H_3), 3.75 (s, 6H, ArOMe), 3.42 (s, 6H, OMe), 2.06 (br, s, NH, exchangeable with D_2O).
$\nu_{\max}$	3290 (w), 2990 (m), 2830 (m), 1635 (w), 1495 (s), 1300 (m), 1245 (m), 1200 (m), 1085 (m), 995 (m), 795 (s) cm^{-1} .
m/e	265 (M^+), 234, 177*, 162, 147, 134, 119.
$\text{C}_{14}\text{H}_{17}\text{NO}_4$	requires C 63.38% H 7.22% N 5.28% found C 63.04% H 7.08% N 5.43%

The column was stripped with methanol and, from this residue, 5,8-dimethoxy-1,4-dihydronaphthalen-1,4-imine was isolated by firstly column and then thick-layer chromatography, The total yield of material was 20mg (3%), the ^1H nmr spectrum of which was identical to that of authentic (27c).

Solvolysis of 9-Chloro-5,6,7,8-tetrafluoro-1,4-dihydronaphthalen-1,4-imine (29e) at 0°C

The N-chloroamine (29e) (350mg, 1.4 mmol) and finely ground silver nitrate (500mg) were stirred for 40min. in ice-cold dry methanol in the dark under dry N_2 . The mixture was

then filtered, poured into 50ml of 0.1M K_2CO_3 solution and the aqueous phase was extracted with CH_2Cl_2 (4 X 20ml). The combined organic extracts were dried and the solvent removed in vacuo to give a yellow oil (344mg) which crystallised in the cold. Repeated recrystallisation from ether-light petrol gave 5,6,7,8-tetrafluoro-2,3-bis-endo-methoxy-1,2,3,4-tetrahydronaphthalen-1,4-imine (87e) m.p. 140° - $142.5^{\circ}C$ (111mg, 35%).

δ	4.93 (m, 2H, $W_{\frac{1}{2}}=5Hz$, H_1, H_4), 4.04 (m, 2H, $W_{\frac{1}{2}}=5Hz$, H_2, H_3), 3.38 (s, 6H, OMe), 2.33 (br, s, NH, exchangeable with D_2O).
ν_{max}	3300 (w), 2930 (m), 2830 (m), 1500 (s), 1390 (m), 1200 (m), 1115 (m), 1075 (m), 1025 (m), 980 (m), 935 (m), 805 (m) cm^{-1} .
m/e	277 (M^+), 262, 246, 215, 202, 189*, 162, 88.
$C_{12}H_{11}NO_2F_4$	requires C 51.99% H 4.00% N 5.05%
	found C 51.81% H 3.96% N 5.26%

The mother liquors from the recrystallisation were shown to contain further (87e) (25mg, 8%) and (27e) (9mg, 3%) by integration against an internal standard (p-dibromobenzene) in the 1H nmr spectrum of the mixture. These two amines could not be separated successfully by chromatography.

Solvolysis of 9-Chloro-1,4-dihydronaphthalen-1,4-imines (29) at Ambient Temperature

General Procedure

The N-chloroamines (0.7-1.6 mmol) were dissolved in a minimum of dry methanol (5-10ml) and allowed to stand at ambient temperature in the dark under dry N_2 . The progress of each reaction was monitored by 1H nmr spectroscopy. After completion,

the solvent was evaporated and the residue taken into CH_2Cl_2 and then treated with 0.1M K_2CO_3 solution. The aqueous phase was washed further with portions of CH_2Cl_2 and the combined and dried organic extracts concentrated in vacuo.

The products from the solvolysis of (29b) and (29c) were each separated by thick-layer chromatography using alumina plates and 1:1 dichloromethane/ethyl acetate as solvent. The products from the solvolysis of (29e) were separated by flash chromatography¹⁷⁴ on Keisegel using ethyl acetate as solvent. During this latter separation, the novel amine 5,6,7,8-tetrafluoro-2-endo-chloro-3-endo-methoxy-1,2,3,4-tetrahydronaphthalen-1,4-imine (107e) was isolated in 8% yield (38mg). Recrystallisation from ether-petrol gave an analytically pure sample, m.p. $132^\circ\text{--}133^\circ\text{C}$.

δ	4.96 (m, 2H, $W_{\frac{1}{2}}=8\text{Hz}$, H_1, H_4), 4.5 (dd, 1H, $J=7.5$, 4.5Hz, H_3), 4.06 (dd, 1H, $J=7.5$, 4.5Hz, H_2), 3.13 (br, s, NH).
ν_{max}	3300 (w), 2930 (w), 2830 (w), 1500 (s), 1385 (m), 1300 (m), 1200 (m), 1125 (s), 1075 (s), 1005 (m), 975 (m), 935 (s), 805 (s) cm^{-1} .
m/e	283 (M^+), 280, 246, 214, 203, 189*, 162.
$\text{C}_{11}\text{H}_8\text{NOF}_4\text{Cl}$	requires C 46.91% H 2.86% N 4.97% Cl 12.59%
	found C 46.89% H 2.96% N 5.01% Cl 12.69%

The amine (87b) was the principal product from the solvolysis of (29b). It was purified by bulb-to-bulb distillation and analysed as its tetrafluoroborate salt which sublimed above 275°C .

δ	7.40-7.0 (m, 4H, Ar), 4.50 (m, 2H, $W_{\frac{1}{2}}=6\text{Hz}$, H_1, H_4), 4.03 (m, 2H, $W_{\frac{1}{2}}=6\text{Hz}$, H_2, H_3), 3.28 (s, 6H, OMe), 2.46 (br, s, NH).
ν_{max}	3300 (w), 2980 (s), 2920 (s), 2820 (s), 1455 (s), 1350 (m), 1200 (s), 1145 (s), 1110 (s), 1070 (s), 1030 (s), 995 (s), 885 (s), 850 (s), 790 (s) cm^{-1} .
m/e	206 (M+1), 190, 174 [*] , 158, 142, 118.
$\text{C}_{12}\text{H}_{16}\text{NBF}_4\text{O}_2$ requires	C 49.18% H 5.50% N 4.78%
found	C 48.75% H 5.57% N 4.79%

The yields of products isolated from these solvolyses are collected in table 5.2, page 165.

Hydrogenation of 6,7-Benzo-5-methoxy-1-azabicyclo(3.2.0)hept-3-enes (88b) and (88c)

General Procedure

The amine (10-20mg) was dissolved in ether (10ml) and 0.5-1mg of Pd-C catalyst added. The heterogeneous mixture was stirred in a 25ml r.b. flask which was flushed for ca. 10min. with dry N_2 . The system was then evacuated once (water pump pressure) and hydrogen (or deuterium) gas admitted from a balloon. The reaction mixture was stirred overnight after which time the catalyst was filtered off through a pad of Celite and the filter cake washed copiously with ether. The solvent was dried and concentrated to yield the product quantitatively. The physical and spectral data of the amines (91-93b) and (91-93c) are collected in table 6.8.

Preparation of 1,4-Dihydroanthracen-1,4-imine (39)

11-Ethoxycarbonyl-1,4-dihydroanthracen-1,4-imine (750mg, 2.8 mmol) was hydrolysed by heating under reflux with NaOH (4.0g) in 1:1 methanol-water (30ml). The progress of the reaction was monitored by TLC and after 8h, the mixture was

Compound	$\delta(\text{CDCl}_3)^a$	$\nu_{\text{max}}(\text{cm}^{-1})$	$\underline{m/e}$	$\lambda_{\text{max}}(\text{nm})$
(91b)	^b 7.28-6.87(m, 3H, Ar), 6.82(d, 1H, Ar), 5.2 (m, H _d), 4.43(m, H _a), 3.43(s, 3H, OMe), 2.13-1.83 (m, 4H)	2930(s), 1720(w), 1585(m), 1445(s), 1375(m), 1350(m), 1185(s), 1075(s), 1035(s), 985(m), 930(m), 800(m).	175(M ⁺), 160, 143*, 132, 115	218(4613), 233(5250), 285(2227)
(91c) ^c	6.65 and 6.40(dd, 2H, 2H, Ar, AB system, J _{AB} =9Hz)1495(s), 5.28(d, H _d , J=7.6Hz), 4.64(d, H _a , J=4.6Hz), 3.80(s, 3H), 3.78(s, 3H) 3.49(s, 3H), 2.18-1.93 (m, 4H).	2950(m), 2830(w), 1585(m), 1430(m), 1245(s), 1160(m), 1075(s), 1030(m), 790(m).	235*(M ⁺), 220, 204, 188, 174, 162, 145, 130	221(9214), 239(5857), 291(2571)

Compound	$\delta(\text{CDCl}_3)^a$	$\nu_{\text{max}}(\text{cm}^{-1})$	m/e	$\lambda_{\text{max}}(\text{nm})$
$\text{d}_2-(91\text{b})^d$	7.18-6.92(m, 3H, Ar), 6.66(d, 1H, Ar), 5.23 (H_d :s for(92b)), and $\text{d}, \text{J}_{\text{d}, \text{R}}^1=8.3\text{Hz}$ for (93b)), 4.47 (H_a :d, $\text{J}_{\text{a}, \text{R}}^4=4.6\text{Hz}$ for(92b) and s for (93b)), 3.48(s, 3H), 2.16-1.89(m, 2H)		177(M^+), 162, 144*, 134, 117, 104	
$\text{d}_2-(91\text{c})^d$	5.64 and 6.40(dd, 2H, Ar, AB system, $\text{J}_{\text{AB}}=9\text{Hz}$) 5.27(H_d :s for(92c) and $\text{d}, \text{J}_{\text{d}, \text{R}}^1=8.3\text{Hz}$ for (93c)), 4.63(H_a :d, $\text{J}_{\text{a}, \text{R}}^4$ =5.0Hz for(92c) and s for(93c)), 3.8(5, 3H), 3.48(s, 3H), 2.14-1.92 (m, 2H)		237*(M^+), 222, 206, 190, 175, 162, 147, 132, 119, 94	
			a. 400MHz. b. 90MHz.	
			c. m.p. 67-69°C. $\text{C}_{13}\text{H}_{17}\text{NO}_3$ requires C 66.36% H 7.28% N 5.95%. Found C 66.27% H 7.25% N 5.97%.	
			d. MS reveals $\geq 99\%$ incorporation of D_2 .	

cooled and diluted with water. The aqueous layer was extracted with CH_2Cl_2 (4 X 30ml) and the combined organic extracts were dried, combined and evaporated. The product appeared as a canary yellow gum which crystallised in the cold. The amine (39) was purified by bulb-to-bulb distillation (0.1mmHg, 130°C) to give a pale yellow solid (425mg, 78%). A small sample was recrystallised from ether, m.p. $111^\circ\text{--}113^\circ\text{C}$.

δ	7.33–7.25 (m, 6H), 6.83 (m, 2H, $W_{\frac{1}{2}}=3\text{Hz}$), 4.95 (m, 2H, $W_{\frac{1}{2}}=3\text{Hz}$), 3.00 (br, s, NH).
ν_{max}	3260 (w), 3000 (m), 1415 (w), 1355 (m), 1260 (w), 1085 (m), 1035 (m), 885 (m), 865 (s), 835 (s) cm^{-1} .
m/e	193 (M^+), 165, 144 [*] , 128.

Room Temperature Solvolysis of 11-Chloro-1,4-dihydroanthracen-1,4-imine (40)

The amine (39) (31mg, 0.16 mmol) was treated with NCS (30mg, 0.22 mmol) in CDCl_3 at -50°C . The consumption of starting material at this temperature was followed by ^1H nmr spectroscopy and upon completion of chlorination^{*} the solvent was removed in vacuo. The residue was dissolved in a minimum of dry methanol (1ml) and allowed to stand at room temperature for three days. The solution was washed with 2M NaOH (2ml) and the aqueous layer extracted with CH_2Cl_2 . The combined organic extracts were dried and the solvent removed in vacuo. Thick-layer chromatography (alumina, 1:1 dichloromethane/ethyl acetate) gave the dechlorinated amine (39) (5mg, 16%) by TLC comparison and 2,3-bis-endo-methoxy-1,2,3,4-tetrahydroanthracen-1,4-imine (94) (16mg, 40%).

δ	7.85-7.55 (m, 4H, Ar), 7.50-7.28 (m, 2H, Ar), 4.66 (m, 2H, $W_{\frac{1}{2}}=6\text{Hz}$, H_1, H_4), 4.13 (m, 2H, $W_{\frac{1}{2}}=6\text{Hz}$, H_2, H_3), 3.36 (s, 6H, OMe), 2.33 (br, s, NH).
ν_{max}	3300 (w), 2980 (m), 2930 (m), 2830 (m), 1500 (m), 1450 (w), 1350 (m), 1310 (m), 1195 (m), 1140 (s), 1105 (s), 1070 (m), 1025 (s), 990 (s), 875 (m), 790 (s) cm^{-1} .

$^{*}(40) : \delta$	7.78-7.22 (m, 6H), 6.86 (syn-Cl) and 6.76 (anti-Cl) (each m, total 2H, $W_{\frac{1}{2}}=4\text{Hz}$), 5.22 (anti-Cl) and 5.02 (syn-Cl) (each m, total 2H, $W_{\frac{1}{2}}=5\text{Hz}$).
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Solvolysis of Anti-11-Chloro-1,4-dihydroanthracen-1,4-imine
at 0°C.

The amine (39) (408mg, 2.1 mmol) was stirred at 0°C in 1:1 ether/dichloromethane with NCS (350mg, 2.6 mmol) for ca.2h. In attempting to extract the N-chloroamine into Arcton (ca.30ml), it was found that the syn- and anti-invertomers were partially separated, because the syn-invertomer was considerably more soluble than the anti-invertomer. The organic extracts were combined and evaporated to give an orange solid (275mg) which consisted of syn- and anti-(40) in the ratio 67:32 (nmr) (m/e 227, 229 (M^+ , 3:1). The residue (216 mg) consisted of pure anti-(40) together with the by-product succinimide as shown by ^1H nmr spectroscopy. Integration indicated the presence of ca.60mg of pure anti-(40) in the mixture.

This residue was dissolved in ice-cold methanol (10ml)

and stirred with AgClO_4 (123mg) under dry N_2 in the dark for 1h. After this time, the mixture was filtered and evaporated and the residual brown oil taken into 0.1M K_2CO_3 solution (50ml) and extracted with CH_2Cl_2 (6 X 10ml). The combined extracts were washed with water (50ml) and then dried, filtered and concentrated to give a brown oil (62mg). This was absorbed onto basic alumina and this alumina placed on top of a pre-packed column of alumina (3.0g). The column was eluted with light petrol-ether (1:1) and the first seven fractions were combined on the basis of TLC to give 6,7-naphtho-5-methoxy-1-azabicyclo(3.2.0)hept-3-ene (95) m.p. $112^\circ\text{--}113^\circ\text{C}$ (38mg, ca. 59%).

δ^* 7.77-7.17 (m, 6H, Ar), 6.45 (dt, H_c , $J_{cb}=5.7$, $J_{ca}\approx J_{cd}=1.7\text{Hz}$), 5.90 (dt, H_d , $J_{da}=3.6$, $J_{db}=J_{dc}=1.7\text{Hz}$), 5.82 (dt, H_b , $J_{bc}=5.7$, $J_{ba}=J_{bd}=1.7\text{Hz}$), 5.25 (dt, H_a , $J_{ad}=3.6$, $J_{ab}=J_{ac}=1.7\text{Hz}$), 3.57 (s, 3H, OMe).

ν_{max} 3040 (w), 2920 (w), 2810 (w), 1625 (w), 1605 (w), 1415 (m), 1350 (w), 1300 (w), 1185 (m), 1145 (m), 1100 (s), 1085 (s), 1075 (s), 1035 (m), 980 (m), 855 (m), 800 (w) cm^{-1} .

m/e 233 (M^+), 208, 193^{*}, 180, 165, 152,

λ_{max} (Cyclohexane) 220.5(14300), 239(24000), 266.5(3300), 276(3700), 288(2400), 334(1500)nm.

High resolution MS (m/e) Calculated for $\text{C}_{15}\text{H}_{13}\text{NO}$: 223.09971

Found for $\text{C}_{15}\text{H}_{13}\text{NO}$: 223.09920

$\text{C}_{15}\text{H}_{13}\text{NO}$ requires C 80.69% H 5.8% N 6.2%
found** C 80.55% H 5.88% N 6.24%

* Spectrum recorded in CDCl_3 at 400MHz operating frequency.

** Figures corrected for ash content (0.6%).

Solvolysis of 9-Chloro-5,8-dimethoxy-1,2,3,4-tetrahydro-naphthalen-1,4-imine (30c) at 0°C

The N-chloroamine (30c) (112mg 0.46 mmol) was dissolved in ice-cold dry methanol (5ml) and added to methanolic AgClO_4 (110mg) (3ml) which was maintained at a temperature between 0°C and -10°C by means of an ice-salt bath. The heterogeneous mixture was stirred rapidly in the dark under dry N_2 . The progress of the reaction was monitored by TLC and further portions of AgClO_4 (4 X 100mg) were added over the next 9h. After this time, the solvent was removed in vacuo and the residue treated with water (10ml) and 0.1M K_2CO_3 solution (25ml). The aqueous phase was extracted with CH_2Cl_2 (3 X 10ml) and the organic extracts were dried and concentrated. The aqueous phase was made further basic by the addition of 2M NaOH and extracted once more with CH_2Cl_2 . The total organic extract (90mg) was separated into its components by thick-layer chromatography. 6,7-(8,11-Dimethoxybenzo)-5-methoxy-1-azabicyclo(3.2.0)heptane (91c), m.p. 67.5°C-69.5°C (58mg, 53%), the ^1H nmr spectrum of which was identical to that of authentic (91c). The melting point of a mixed sample showed no depression. The starting material (30c) was also isolated (22mg, 20%) (nmr, m/e 239, 241 (3:1, M^+)).

Solvolysis of 9-Chloro-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-1,4-imine (30c)

The N-chloroamine (30c) (114mg, 0.47 mmol) was dissolved in dry methanol (10ml) and the solution warmed in an oil bath (55°C). AgClO_4 (200mg) was added and within 30 seconds, AgCl began to precipitate. The mixture was stirred for 45min. in the

dark under dry N_2 . The dark brown mixture was filtered and evaporated to dryness. The oil was taken into CH_2Cl_2 (20ml) and 0.1M K_2CO_3 solution was added (20ml). The aqueous phase was extracted with further CH_2Cl_2 (3 X 20ml). The combined organic extracts were dried and concentrated to give a brown oil (106mg). Preparative thick-layer chromatography (Silica, ether) gave 6,7-(8,11-dimethoxybenzo)-5-methoxy-1-azabicyclo (3.2.0)heptane (91c) (26mg, 23%), m.p. 67° - $68.5^{\circ}C$, which showed a 1H nmr spectrum identical to that of authentic (91c). The dechlorinated amine (28c) (30mg, 26%) was also isolated (nmr).

Solvolysis of 9-Chloro-5,6,7,8-tetrafluoro-1,2,3,4-tetrahydronaphthalen-1,4-imine (30e)

The N-chloroamine (30e) (435mg, 1.7 mmol) was dissolved in dry methanol (10ml) in a 50ml r.b. flask and the solution was warmed in an oil bath at $55^{\circ}C$. $AgClO_4$ (716mg) was added and the mixture was stirred in the dark under N_2 for 3h at the same temperature. The solvent was removed in vacuo and CH_2Cl_2 (50ml) and water (30ml) were added. The two phases were shaken and separated. The aqueous layer was extracted with further CH_2Cl_2 (2 X 10ml). The combined organic extracts were dried, concentrated and chromatographed on alumina using ether as the eluant. Unchanged starting material (276mg, 65%) was recovered (nmr).

Low Temperature Solvolysis of 9-Chloro-1,4-dihydronaphthalen-1,4-imines (29b), (29c) and (29e)

In a typical procedure, the N-chloroamine (29c) (41mg, 0.17 mmol) and p-dibromobenzene (16mg, 0.067 mmol) were dissolved at $0^{\circ}C$ in ice-cold d_4 -MeOH (ca. 0.5ml) and the solution transferred to an nmr tube which was maintained at $-60^{\circ}C$. The

^1H nmr spectrum of the solution was recorded at -57°C and the initial ratio of syn- and anti-(29c) was calculated by integration of the H_1 , H_4 signals at δ 5.08 and 5.24 respectively.

The spectrum was recorded as small portions of AgClO_4 (ca. 35mg) were added and the rate of loss of syn- and anti-invertomers measured by integration against the internal standard. The crude yields of the products (27c), d_6 -(87c) and d_3 -(88c) were also calculated using the known weight of internal standard. Finally, when all the starting material had been consumed, the solution was diluted, made basic (K_2CO_3 solution) and then extracted with CH_2Cl_2 ($2 \times 2\text{ml}$). The extracts were combined, dried and evaporated. The nmr spectrum of this residue was compared against spectra of pure, authentic (27c), (87c) and (88c) to ensure that these were the products of the solvolysis. The yields of products from the solvolyses of (29b), (29c) and (29e) are given in table 5.3.

Preparation of 1,4-Etheno-1,2,3,4,9,10-hexahydroanthracen-9,10-imine (108b)

1,4-Dihydronaphthalen-1,4-imine (27b) (750mg, 5.2 mmol) and cyclohexa-1,3-diene (2.09g, 26 mmol) were placed in a thick-walled Pyrex tube, the tube sealed and heated in an oil bath at 155°C for 23h. After cooling, colourless, needle-like crystals had appeared which were taken into CH_2Cl_2 and washed with acid (2M HCl , $4 \times 10\text{ml}$). The combined acid extracts were made basic (2M NaOH , 50ml) and the basic layer was extracted with CH_2Cl_2 ($4 \times 25\text{ml}$). The combined organic extracts were dried and the solvent removed in vacuo. The solid residue sublimed at 130°C (0.3mmHg) to give the title compound (108b) (560mg, 48%). A small portion was recrystallised from ether to provide the analytical sample, m.p. $118^\circ\text{--}120^\circ\text{C}$.

δ	7.32-6.96 (m, 4H, Ar), 6.32 (m, 2H, H ₁₂ , H ₁₃), 4.22 (s, 2H, H ₉ , H ₁₀), 3.24 (br, s, NH), 2.80 (m, 2H, H ₁ , H ₄), 1.80 (s, 2H, H _{4a} , H _{9a}), 1.52-1.00 (m, 4H).
ν_{max}	3300 (w), 3020 (m), 2920 (s), 2850 (m), 1620 (w), 1450 (m), 1375 (m), 1035 (m), 895 (m), 835 (m), 815 (s) cm ⁻¹ .
m/e	223 (M ⁺), 206, 194, 178, 165, 143, 117 [*] , 89.
C H N	requires C 86.05% H 7.67% N 6.27% found C 86.16% H 7.71% N 6.25%

Preparation and Heterolysis of syn-11-Chloro-1,4-etheno-
1,2,3,4,9,10-hexahydroanthracen-9,10-imine (118b)

The amine (108b) (150mg, 0.67 mmol) was dissolved in CDCl₃ (ca. 0.4ml) and the solution transferred to an nmr tube. The tube and its contents were cooled to -60°C by means of a dry ice-acetone bath. NCS (122mg) was added and the solution agitated with a glass rod. The tube was placed in the probe of a 100MHz nmr spectrometer which had been cooled previously to -50°C. The progress of the chlorination was followed by recording the nmr spectrum over the next hour. The consumption of the amine (108b) was monitored by the disappearance of the H₉, H₁₀ proton signal at δ 4.22 and the N-chloroamine (118b) gave the following spectrum:

δ	7.24 (m, 4H, Ar), 6.34 (m, 2H, H ₁₂ , H ₁₃), 4.44 (s, 2H, H ₉ , H ₁₀), 2.84 (m, 2H, H ₁ , H ₄), 1.92 (m, 2H, H _{4a} , H _{9a}), 1.28 (m, 4H, H ₂ , H ₃).
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The solution of the N-chloroamine was allowed to stand at room temperature overnight and then in an oil bath maintained at 55°C for ca. 7h. The decomposition of (118b) was monitored

by the disappearance of the H_{12}, H_{13} -olefin absorption in the 1H nmr spectrum. The solvent was evaporated and the residue dissolved in 0.1M K_2CO_3 solution (50ml). This aqueous layer was washed several times with CH_2Cl_2 (combined extracts totalled 50ml). The organic extracts were dried and evaporated in vacuo (140mg). Preparative TLC (SiO_2 , ethyl acetate doped with a few drops of ammonia solution) gave the amine (120b) (39mg, 23%). It recrystallised from ether-acetone, m.p. 173° - $175.5^{\circ}C$.

$\delta(400MHz)$ 7.16 (m, 4H, Ar), 4.54 (broad dd, $H_f, J_{fc}=6.3$, $J_{fa'}=1.4, J_{fe}=J_{fd}\leq 1Hz$), 4.41 (s, H_j), 4.17 (s, H_i), 3.33 (broad d, $H_e, J_{ed}=6.8, J_{ef}\leq 1Hz$), 2.42 (broad dddd, $H_d, J_{de}=6.8, J_{db'}=3.6, J_{db}=2$, $J_{dg}=1.8, J_{af}\leq 1Hz$), 2.35 (broad ddd, $H_c, J_{cf}=6.3$, $J_{ch}=5.4, J_{ca}=4.5, J_{ce}\leq 1Hz$), 2.15 (dddd, H_b , $J_{bb'}=13.4, J_{ba'}=10, J_{ba}=7.6, J_{bd}=2Hz$), 2.09 (dd, $H_g, J_{gh}=5.4, J_{gd}=1.8, J_{ge}\leq 1Hz$), 2.04 (broad ddd, $H_a, J_{aa'}=13.5, J_{ab}=10, J_{ac}=4.5, J_{ab'}\leq 1Hz$), 1.85 (broad t, $H_h, J_{hg}=J_{hc}=5.4Hz$), 1.70 (broad ddd, $H_{b'}, J_{b'b}=13.4, J_{b'a'}=10.5, J_{b'd}=3.6, J_{b'a}\leq 1Hz$), 1.53 (dddddd, $H_{a'}, J_{a'a}=13.5, J_{a'b'}=10.5, J_{a'b}=7.6, J_{a'f}=1.4, J_{a'c}=1Hz$).

ν_{max} 3030 (w), 2950 (s), 2870 (m), 1710 (w), 1470 (m), 1460 (m), 1325 (w), 1185 (m), 1170 (m), 1005 (w), 985 (m), 965 (w), 920 (m), 850 (s) cm^{-1} .

High Resolution MS (m/e) : Calculated for $C_{16}H_{16}NCl=257.09712$;

Found = 257.0968

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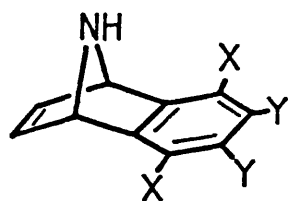
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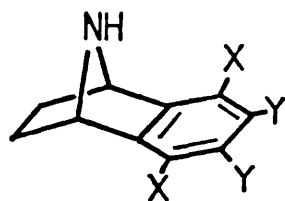
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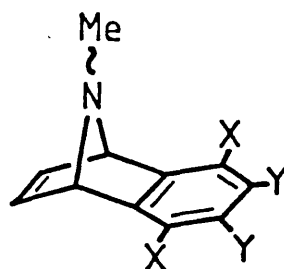
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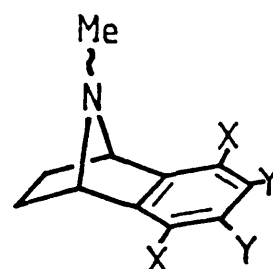
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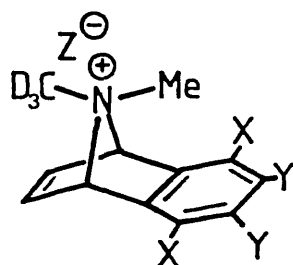
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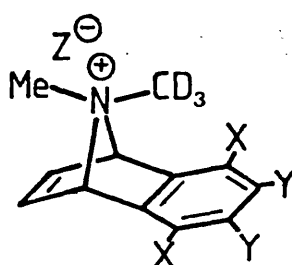
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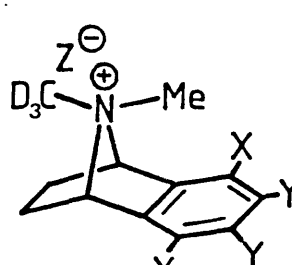
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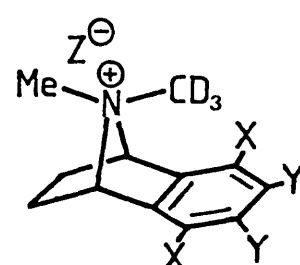
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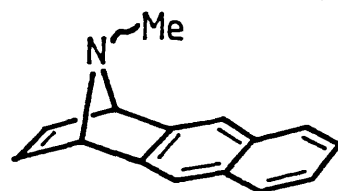
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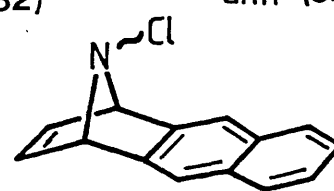
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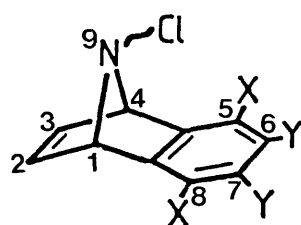
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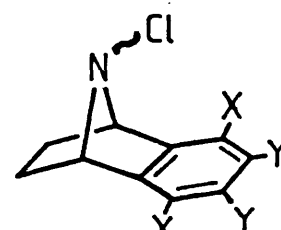


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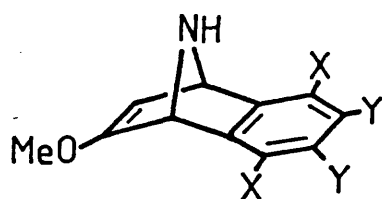


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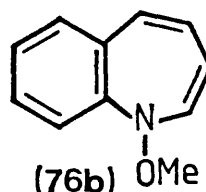
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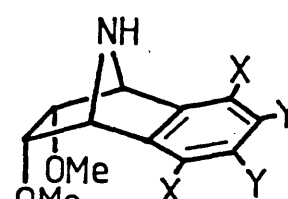
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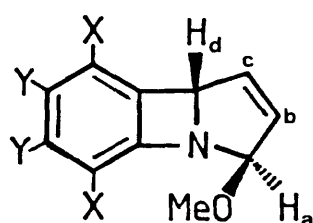
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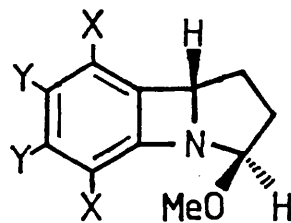
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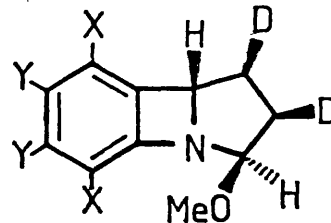
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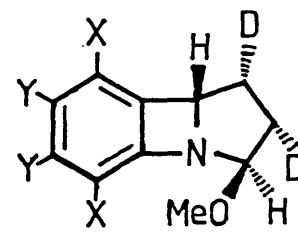
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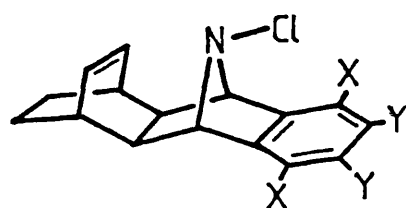
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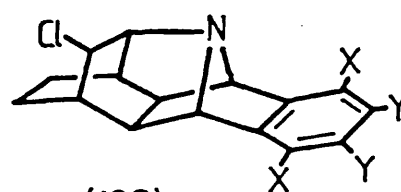
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Abstract

Slow Inversion at Nitrogen and its Consequence for some Azabicyclic Systems by M.L. Durrant

The chemistry of a range of N-methyl-1,4-dihydro- and 1,2,3,4-tetrahydronaphthalen-1,4-imines has been investigated.

Inversion at nitrogen is slow in these amines and can be observed by ^1H nmr spectroscopy. The invertomer ratios of both series have been measured and, in each amine, the major invertomer has been assigned the syn-configuration (that with the N-methyl group syn- to the aromatic ring). On the basis of a comparative study, it was concluded that homoconjugative interaction of the lone pair and adjacent π -electrons is only a minor factor affecting the preferred configuration at nitrogen.

The inversion barriers of the dihydronaphthalen-1,4-imines have been measured and the values obtained gave further proof of the barrier-raising ability of the 7-azabicyclo(2.2.1) heptadienyl group. The inversion barriers were found to vary slightly with the substituents on the aromatic rings but no clear reasons for this variation emerged.

The members of both series of amines were quaternised with various alkylating agents. The ratios of the diastereoisomeric quaternary salts formed varied with the substituents on the aromatic rings. This variation was thought to be due to the prevailing electronic forces in view of the minimal steric differences between the amines in each series.

The high inversion barriers ($>95\text{kJmol}^{-1}$) of N-chloro-1,4-dihydronaphthalen-1,4-imines allowed the study of the separate chemistries of the two invertomers. At 0°C with silver salts in methanol (conditions of negligible inversion), each invertomer solvolysed with assistance from adjacent π -electrons. The structures and stereochemistries of the products reflected this assistance and further, the ability of the aryl group to participate in the heterolysis of the anti-N-Cl bond varied predictably as a result of substitution with electron-withdrawing or releasing groups. The anti-invertomer rearranged to the novel 6,7-benzo-1-azabicyclo(3.2.0) hept-3-ene system.

Under conditions of free inversion (ambient temperature, no silver salt), the products from the methanolyses reflected the relative reactivities of syn- and anti-invertomers. The less reactive invertomer (anti-) "reacted" only via prior inversion to the more reactive (syn-).