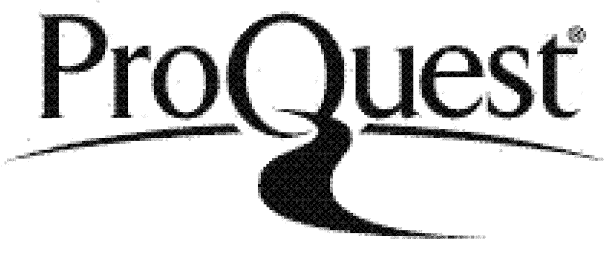
A Study of Some Strained Azabicyclic Compounds & Their Rearrangement Reactions.

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

by

J. W. Davies



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STATEMENT

The experimental work in this thesis, submitted for the degree of Doctor of Philosophy, entitled 'A Study of some Strained Azabicyclic Compounds and their Rearrangement Reactions' has been carried out by the author in the Department of Chemistry of the Leicester University between October 1981 and November 1984. This work has not been, and is not currently being, presented for any other degree.

J.C.W. Davies.

University of Leicester

31st July 1985.

To Mum, Dad, Jackie and Neal.

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Abstract

A Study of some Strained Azabicyclic Compounds and their Rearrangement Reactions by J.W.Davies

The barriers to nitrogen inversion were determined for several 1-methyl-2-azabicyclo[2.1.1]heptyl systems. The rearrangement chemistry of the N-chloro derivative was investigated. This underwent silver-ion catalysed solvolysis to afford 4-methoxymethyl-2-methyl-1-pyrroline and also rearranged in the presence of alumina with retention of chlorine to give 2-methyl-2-chloro-1-azabicyclo[2.1.1]-hexane, a novel ring system. The hydrochloride salt of this chlorine-retaining product rearranged with aqueous base to afford 4-hydroxymethyl-2-methyl-1-pyrroline.

A study of 1,2,3,4-tetrafluoro-9,10-dihydroanthracen-9,10-imines showed that electronic influences exhibit subtle effects on the mode of kinetically-controlled chlorination at the 11-position and on the preferred orientation of the chlorine substituent under conditions of thermodynamic control. The influence of aryl substituents on the rate of aryl participation during silver-ion catalysed solvolysis was also investigated.

The heterolytic rearrangement of 9-chloro-1,4-dimethyl-2,3-dihydronapthalen-1,4-imines required the use of novel solvolytic conditions. Unlike their 1,4-dihydro analogues, these preferred rearrangement to benzo(f)-5H-azepines which themselves underwent an extensive series of rearrangements.

Investigation of 7-chloro-1,7-diazabicyclo[2.2.1]heptane provided evidence that the effect of raising the barrier to nitrogen inversion by electronegative substituents arose predominantly from lone pair - lone pair repulsions. The ^{15}N NMR signals of a variety of systems containing the 7-azabicyclo[2.2.1]heptyl skeleton were observed downfield of the most shielded examples reported for several classes of amine. X-ray crystallographic studies of two 9-chloro-2,3-dihydronapthalen-1,4-imines, each possessing a different stereochemistry at nitrogen, showed that the position of the chlorine atoms exerts influence on the structure of the remainder of the 7-azabicyclo[2.2.1]heptyl skeleton.

CONTENTS

ABBREVIATIONS

Me-	Methyl-
Et-	Ethyl-
^{n}Bu-	^{n}Butyl-
Ac-	Acetyl-
Ph-	Phenyl-
Ts-	Toluene-p-sulphonyl-
NBS	N-Bromosuccinimide
NCS	N-Chlorosuccinimide
DMAD	Dimethylacetylenedicarboxylate
PTAD	4-Phenyl-1,2,3,4-triazoline-3,5-dione
DMF	Dimethylformamide
DMSO	Dimethylsulphoxide
DEPT	distortionless enhancement by polarisation transfer
COSY	correlated spectroscopy
NOE	nuclear Overhauser effect

CHAPTER ONE

INTRODUCTION

Author's note.

The spelling of naphthalene is incorrect throughout this thesis.

1.I Pyramidal Nitrogen Inversion

In the ground state of any simple primary, secondary or tertiary amine the outer valence electrons of the nitrogen atom can be considered to be in sp^3 hybridised orbitals. Out of the four sp^3 hybrids, three are normally available for σ-bond formation to other atoms, whereas the fourth sp^3 hybrid is occupied by an unshared pair of electrons and is known as the lone pair. The three σ-bonds and the lone pair are approximately tetrahedrally disposed about the nitrogen atom and by passage through a trigonal, sp^2-hybridised transition state, the two possible forms of the tetrahedron may be interconverted as shown in Figure 1:1.

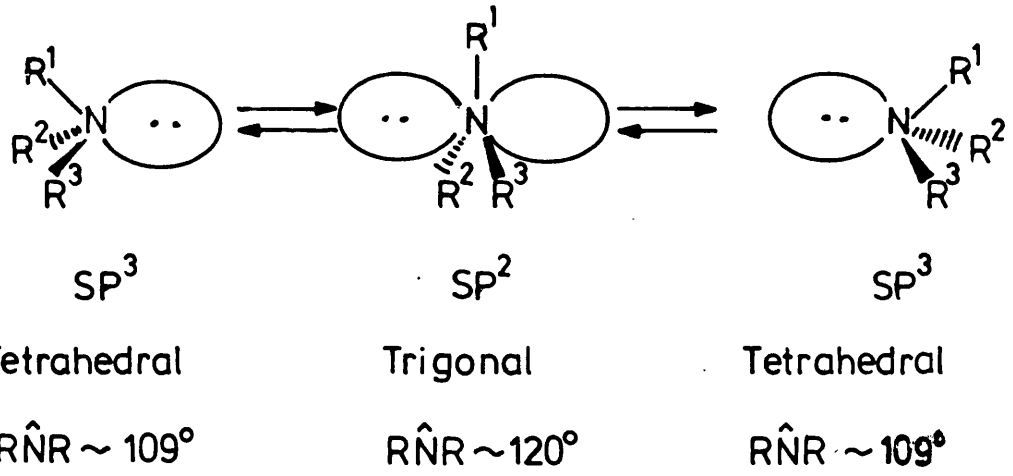


Figure 1:1

The two forms of the tetrahedron are known as invertomers and the process of interchange between them is known as pyramidal nitrogen inversion.[1,2,3,4]

The energy barrier to inversion ($\Delta G^{\neq}$) is the energy required to rehybridise the tetrahedral sp^3 form to the approximately trigonal sp^2 form, where the three substituents and the nitrogen atom lie roughly in the same plane* and the lone pair occupies a p-orbital whose axis is perpendicular to this plane, (fig. 1:2).

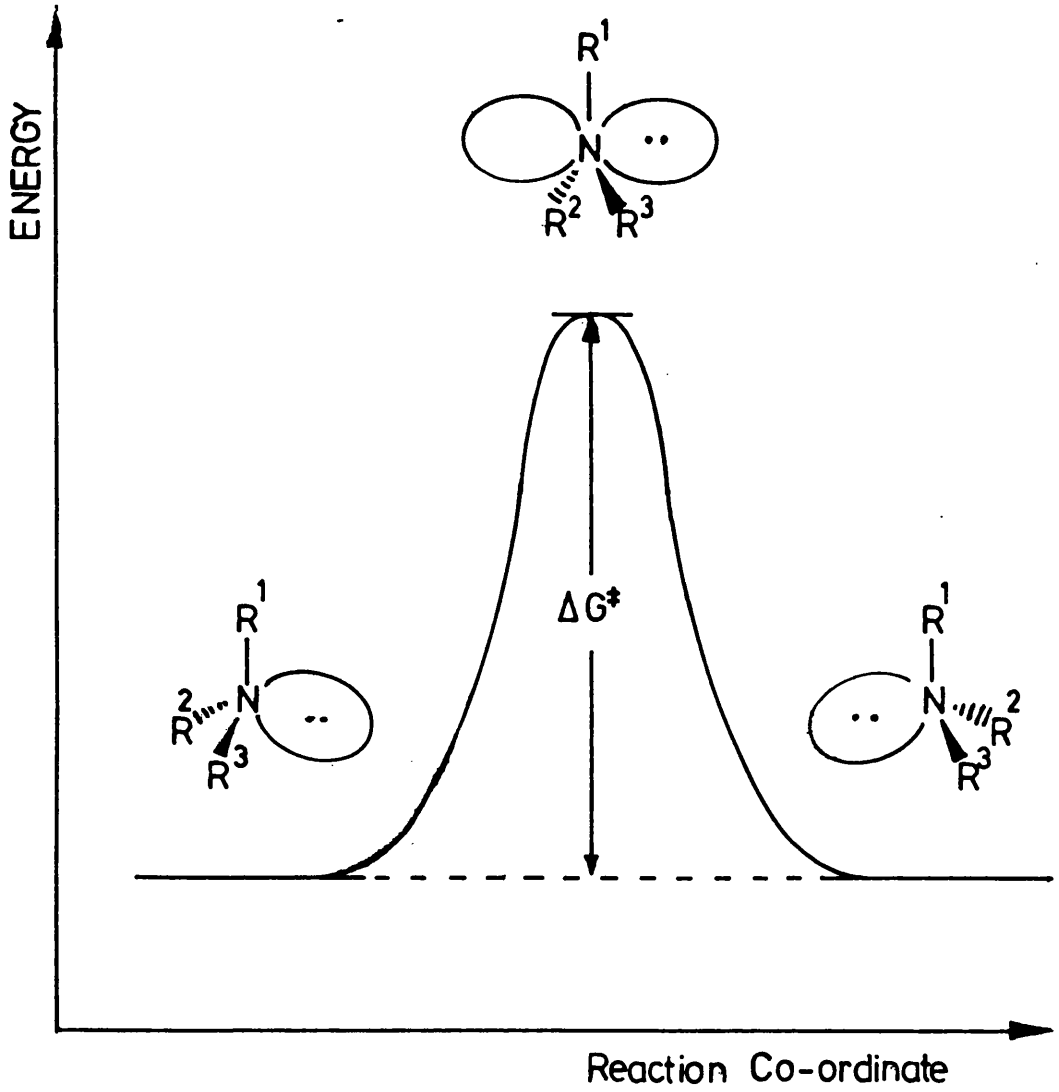


Figure 1:2

*This is only strictly true if the invertomers are enantiomeric.

Several alternative mechanisms for inversion in amines have been proposed;[2] of these only quantum-mechanical tunneling is thought to be of any importance. This operates in ammonia and other simple amines in which usually at least one ligand is hydrogen or deuterium. These compounds commonly have low barriers in the range 4 - 24 kJ mol^{-1}.

In simple amines, where the three ligands attached to the nitrogen atom are dissimilar and the lone pair is considered a fourth such ligand then the nitrogen atom becomes a chiral centre and the invertomers become enantiomers. Unlike their carbon analogues, resolution of enantiomers is not possible for the majoriy of amines since they are rapidly interconverted by nitrogen inversion.

The resolution of enantiomers in four-coordinate nitrogen compounds is possible, e.g. in amine oxides and quaternary ammonium salts. In these compounds the barrier to interconversion is high due to the fact that the interconversion of enantiomers can only occur via a dissociation-recombination mechamism.

For some more complicated amines there is no longer an enantiomeric relationship between invertomers. The invertomers in these compounds are diastereoisomers and as such possess different physical and chemical properties.

There are several classes of three-coordinate nitrogen compounds that do however possess high inversion barriers, some sufficiently high to afford configurational stability at nitrogen at normal temperatures ($\Delta G^{\ddagger} > 92$ kJ mol^{-1})[4]. This then allows for either the resolution of enantiomers or the separation of diastereoisomers. Compounds with such high barriers are of especial interest. Study of these

compounds may increase our knowledge of the effects of structural features on inversion barriers and thus lead to a better understanding of nitrogen inversion in general. Further compounds which possess barriers high enough for the configuration at nitrogen to be stable may allow the study of the stereochemical consequences of rearrangements taking place at nitrogen.

There are several factors that influence the magnitude of the barrier to inversion at nitrogen which fall broadly into two main categories, being steric and electronic effects.

Steric Effects

a) Non-bonded interactions

Non-bonded interactions may be either attractive or repulsive in nature. Attractive interactions are generally too small to be of any great significance but repulsive interactions are much stronger and the presence of bulky substituents can have a considerable effect on inversion barriers.

Non-bonded repulsions may be either increased or diminished on going from the ground state to the transition state during inversion. When a small alkyl substituent on nitrogen, such as methyl, is replaced by a large group, such as t-butyl, the barrier to nitrogen inversion will be lowered, as on going to the transition state the bond angle at nitrogen ($C\hat{N}C$) increases from $\sim 109^{\circ}$ to $\sim 120^{\circ}$ and thus any strain present in the ground state can be relieved to some extent at the transition state. This effect can be

illustrated by comparison of the barriers for the aziridines (1) and (2) in table 1:1. In certain other cases, where substituents more distant from nitrogen cause increased steric congestion in the ground state, then that ground state becomes destabilised with respect to the transition state and so the barrier is also lowered. An example of this can be seen in the N-methyl azetidines (3) and (4), where dimethyl substitution of the azetidine ring causes such a destabilisation and thus lowers the inversion barrier. However if steric crowding is increased on going to the transition state, as in (5), then the transition state is destabilised and the barrier is increased, (table 1:1).

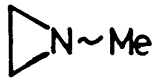
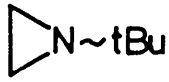
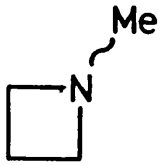
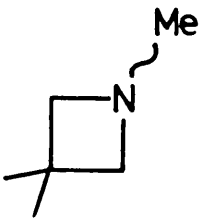
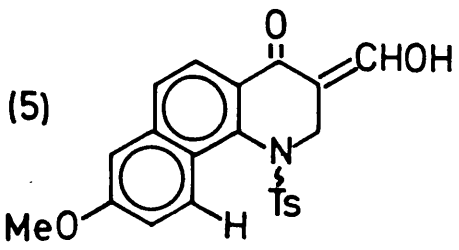
		barrier to inversion, $\Delta G^{\ddagger}$ (kJ/mol)[1,2]
(1)		81·1
(2)		71·1
(3)		42·7
(4)		37·0
(5)		96·2[5]

Table 1:1

b) Ring strain

In pyramidal inversion the trigonal sp^2 transition state requires a $\hat{CNC}$ angle of ~120°. The incorporation of the inverting nitrogen into a small ring causes the angle strain in the transition state to be higher than that in the ground state. An example of this is N-methyl aziridine, the $\hat{CNC}$ angle is ~60°, which is far from the unstrained tetrahedral angle (~109°) but even further from the normal 120° angle of the transition state. The increased transition-state strain raises the inversion barrier greatly with respect to unstrained amines. The very high barrier for nitrogen inversion in aziridines was predicted,[6] long before it was tested and shown that some aziridines exhibit configurational stability even at room temperature.[7]

Table 1:2 shows the increase in inversion barrier as the ring size (and hence the $\hat{CNC}$ angle) contracts. The increase in barrier on going from azetidine ($\hat{CNC}$ ~96°) to aziridine ($\hat{CNC}$ ~60°) is further enhanced because the lone pair in aziridines has more s character than that of a normal sp^3 lone pair and thus requires more energy to reach the pure p-orbital character of the lone pair at the transition state.

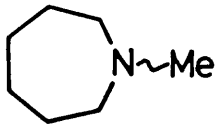
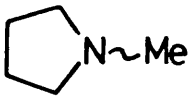
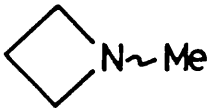
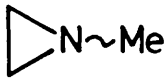
	barrier to inversion $\Delta G^{\ddagger}$ (kJ/mol)[1,2]
	28·4
	33·9
	42·6
	81·1

Table 1:2

c) The bicyclic effect[1]

The inversion barrier is further raised by bridging the azamonocycle with one or more carbon atoms. This bicyclic effect may be partially due to increased molecular rigidity imparted by the bridging carbon atoms thus raising the angle strain at nitrogen, (table 1:3).

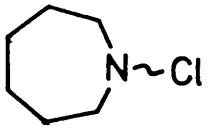
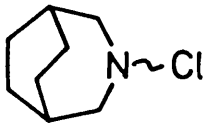
	barrier to inversion [2] $\Delta G^{\ddagger}$ (kJ/mol)
	38·5
	42·3

Table 1:3

In table 1:4 it can be seen that as the rigidity of the bicyclic system increases, so the barrier to inversion is raised.[8]

barrier to inversion, $\Delta G^{\ddagger}$ (kJ/mol) [8]

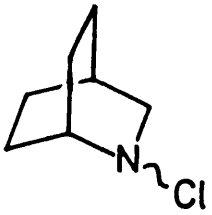
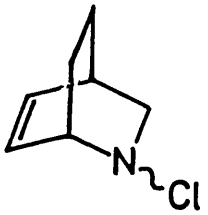
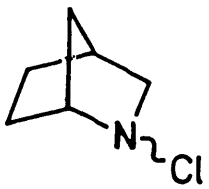
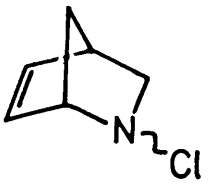
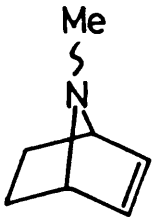
			
44·3	48·5	51·0	64·0

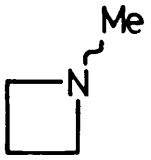
Table 1:4

The most remarkable effect however is found in 7-azabicyclo[2.2.1]heptanes and related systems, which have inversion barriers almost as high as those found in aziridines.[1] The $C\hat{N}C$ angle in these systems is thought to be ~96°,[9] similar to that found in azetidines but the inversion barriers are much larger. This extraordinary effect has not yet been fully accounted for although some tentative suggestions have been made,[1,10] (table 1:5). Further discussions about these systems and their anomalously high barriers will be considered later in the present work.

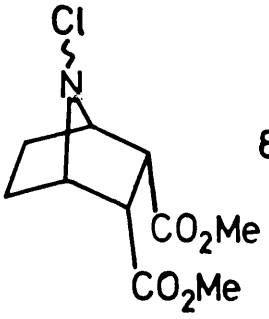
barrier to inversion, $\Delta G^{\ddagger}$ (kJ/mol)



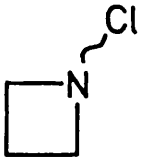
62·3[11]



42·7[2]



87·1[1]



56·0[2]

Table 1:5

Electronic Effects

a) Conjugative effects

When a substituent has π-orbitals which are capable of conjugation with the lone pair on nitrogen, delocalisation of electrons is greater in the transtition state than in the ground state. In the transition state the lone pair is in a pure p-orbital which is able to overlap more effectively than when it is in a sp^3-orbital in the ground state. Conjugation lowers the barrier to nitrogen inversion by stabilisation of the transition state, several examples of this can be seen in table 1:6.

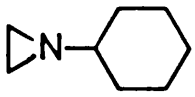
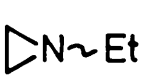
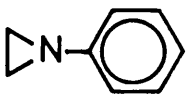
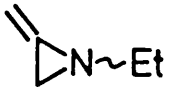
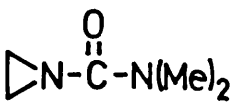
	barrier to inversion, $\Delta G^{\ddagger}$ (kJ/mol)[1]		
	78·7		81·2
	49·0		43·1
			41·1

Table 1:6

b) Substituent electronegativity

When a substituent on nitrogen is sufficiently electronegative it will withdraw electron density from the nitrogen atom. Since the more distant electron density is more readily removed, the lone pair on the nitrogen assumes greater s character. This effect raises the barrier since the lone pair needs to be in a pure p-orbital in the transition state.

c) Lone pair - lone pair repulsion

If the substituent on nitrogen possesses lone pairs, the barrier to inversion may increase due to repulsive interactions with the nitrogen lone pairs. These interactions are greater in the transition state than in the ground state, (fig. 1:3).

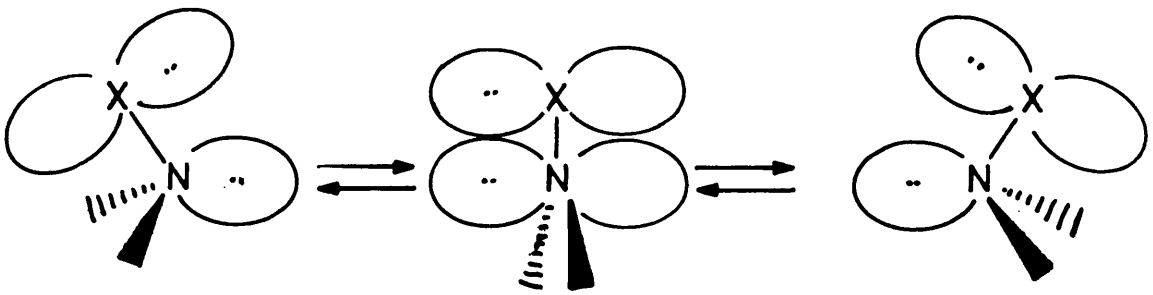


Figure 1:3

It is not easy to separate the influences of the electronegative effect and lone pair - lone pair repulsion, since most atoms that are electronegative also are likely to possess lone pairs of electrons. However further discussion of this will be taken up later in this present work. Table 1:7 illustrates the combined effect of these variables on the barrier to inversion by a comparison of alkyl-substituted azacycles with corresponding heteroatom-substituted species.

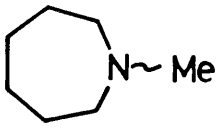
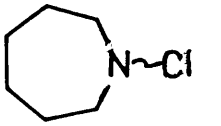
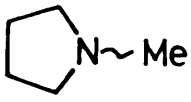
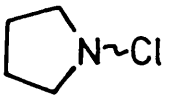
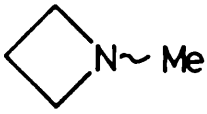
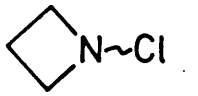
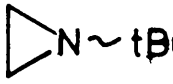
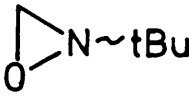
	barrier to inversion, $\Delta G^{\ddagger}$ (kJ/mol)[1]		
	28·5		38·5
	35·2		43·1
	42·7		56·1
	71·1		138·1

Table 1:7

1.II The Determination of Inversion Barriers and Invertomer Ratios

Inversion barriers

Inversion barriers in amines may be measured by a variety of methods. The choice of which technique is most appropriate depends largely on the structure of the molecule and the magnitude of the barrier measured. Barriers in the range 0 - 20 kJ mol^{-1} are normally measured by microwave spectroscopy and to a lesser extent by IR spectroscopy. These techniques have provided the barriers for low molecular weight amines such as ammonia and methylamine.

In amines with high barriers to inversion (> 96 kJ mol^{-1}), the isolation of invertomers becomes feasible. The first-order rate constants for inversion may then be measured at several temperatures by appropriate spectroscopic means (NMR, UV, IR or polarimetry).

For compounds whose inversion barriers lie outside the limits for measurement either by microwave/IR spectroscopy or by classical kinetic methods, the method of choice is dynamic NMR spectroscopy. The barriers susceptible to DNMR are in the range 20 - 100 kJ mol^{-1}. The measurement is simple and is made with the sample at thermodynamic equilibrium. The inversion process must bring about exchange between two magnetically distinct sites at a rate which is slow[4] on the NMR timescale. The NMR signals due to those sites must be sufficiently separated for temperature-dependant coalescence to be observed.

When nitrogen inversion is quite slow on the NMR timescale two distinct signals may be observed. As the rate of inversion is raised by an increase in temperature then the

two peaks broaden. The peaks coalesce when the rate of inversion is comparable to the frequency difference at slow exchange. If the temperature is further raised, the inversion becomes so rapid that, on the timescale of the observation, the sites are no longer distinct and a single sharp peak is produced, located at the weighted average of the slow exchange frequencies.

The temperature at which the signal broadening is a maximum is called the coalescence temperature (Tc). The rate constant for inversion at this temperature (kc) may be obtained from the expression (1:1), where $\Delta\nu$ is the frequency separation of the two sites at slow exchange.

$$k_c = \frac{\pi\Delta\nu}{\sqrt{2}} \qquad (1:1)$$

The free energy of inversion at coalescence ($\Delta G^{\ddagger}_c$) can be calculated by use of the Eyring equation, (1:2).[4]

$$k_r = \frac{k_b}{h} \exp\left(\frac{-\Delta G^{\ddagger}}{RT}\right) \qquad (1:2)$$

k_r = rate constant

k_B = Boltzmann's constant

h = Planck's constant

R = gas constant

T = absolute temperature

$$\Delta G_c^{\ddagger} = 19{\cdot}12 T_c [10{\cdot}32 + \log_{10} \frac{T_c}{k_c}] \quad (1{:}2a)$$

This method is only strictly applicable to systems in which the population of invertomers at equilibrium are identical[12] but with modifications its use can be extended to other systems.[13] 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, though this is possible to quite a high degree of accuracy.[4] It is now possible by computer-based lineshape analysis of spectra to utilise all the data contained therein and obtain accurate values for all the activation parameters associated with inversion.

Care must be taken not to confuse other temperature - dependent processes with nitrogen inversion. One of the more common processes encountered is hindered rotation about bonds. This can arise in amides,[4] sulphenamides,[14] hydroxylamines,[15] hydrazines[16] and even some simple amines.[17] Another conformational phenomena to be considered is ring inversion. For example, piperidine ring inversion occurs with a similar energy of activation to that found for nitrogen inversion;[18,19] the two processes become difficult to disentangle.[20]

Historically, ^{1}H NMR spectroscopy was most commonly used in the estimation of inversion barriers. More recently, especially with the development of sensitive FT NMR spectrometers, other nuclei have been increasingly used to study

nitrogen inversion; these include ^{13}C, ^{15}N and ^{19}F where appropriate. ^{13}C NMR is of especial use as the spectra produced are often much less complicated than ^{1}H NMR spectra; this is mainly due to the wider range of chemical shifts and the lack of coupling. It is usually possible to use ^{13}C NMR to study coalescence for more than one set of signals although the slow relaxation of the ^{13}C nucleus constitutes a drawback which affects the accuracy of integration of absorptions. The use of ^{15}N NMR has been minimal until recently due to the low natural abundance of this nucleus and its low sensitivity. However with the advent of more sensitive, higher-field NMR spectrometers the study of this nucleus at natural abundance has become possible, avoiding the need for ^{15}N-enriched samples.

Invertomer ratios

In many cyclic amines the two invertomers have a diastereomeric relationship. In such cases the invertomer ratio (and hence the free energy difference) can be obtained by direct integration of NMR spectra provided that the interconversion on the NMR timescale is slow and also that signals due to an atom at one exchanging site (at least) appear at different chemical shifts. The degree of accuracy of such measurements depends largely on the separation of the signals. Problems due to signal overlap are normally confined to ^{1}H NMR and can often be alleviated by measurements at high field. In ^{13}C NMR signal overlap is less likely and invertomer ratios are usually directly measurable (as was the case for piperidine[21,22]). Care must be exercised in ^{13}C NMR because of variations in the relaxation rates

for ^{13}C nuclei.

Those amines having non-equivalent invertomers tend also to have unequal distributions of invertomers due to steric and/or electronic influences, (table 1:8).

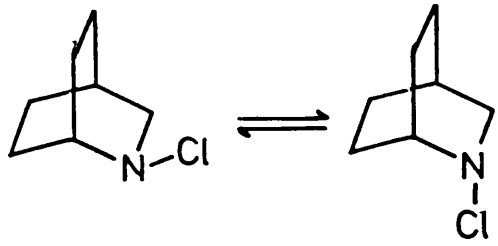
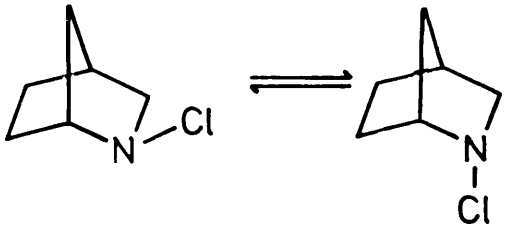
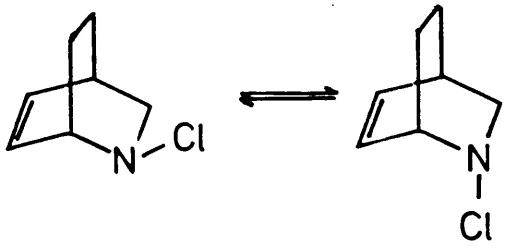
	% exo Chlorine at equilib.	:	% endo Chlorine at equilib.
	50	:	50
	75	:	25
	9	:	91

Table 1:8

Steric influences seem to be the predominant factor for determining the invertomer preferences shown in the azabicycles of table 1:8.[8] There are, however, systems in which electronic effects appear to be of significance. It was observed by Morishima[23] that the 7-azabicyclo[2.2.1]-

hepta-2,5-diene system has an invertomer ratio determined by the acidity of the solution in which it has been dissolved, (table 1:9).

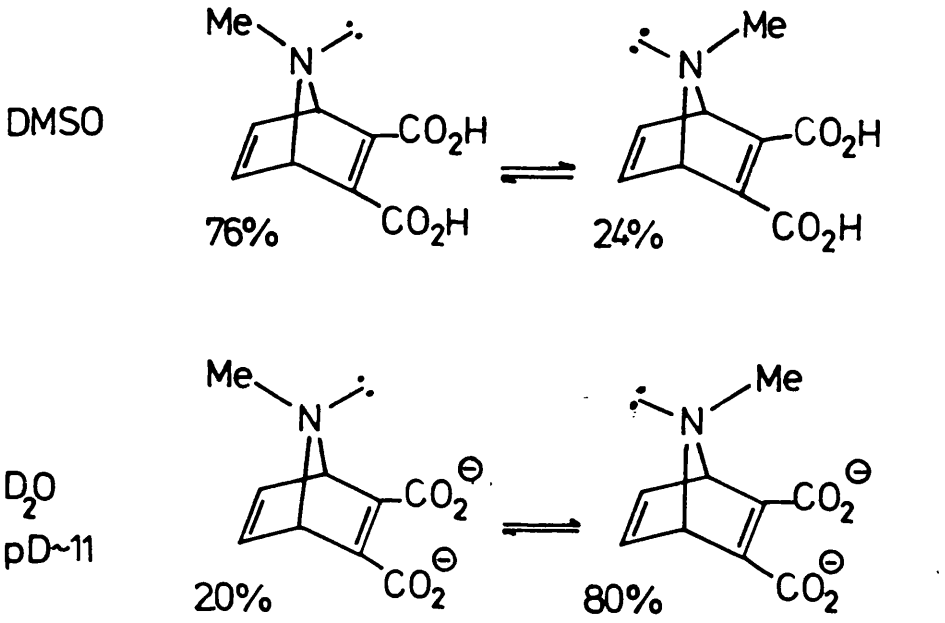


Table 1:9

Morishima explained his observations by proposing a repulsive bis-homoallyl interaction between the nitrogen lone pair and the π-bonds. The invertomer ratio was thought to reflect the balance between the two interactions. In DMSO, the non-ionised acid groups withdraw electron density from the substituted π-bond reducing its repulsive interaction. When ionised, however, the electron density of the substituted π-bond is increased and the balance of interactions reversed. Later works have suggested that the size of the bis-homoallyl interaction may have been overestimated.[24,25]

It is possible that the observed variation in invertomer ratios results mainly from differential solvation of the ionised and the non-ionised forms of the molecule.

1.III Intramolecular Rearrangements of N-chloroamines in Neutral Media*

The rearrangement of N-chloroamines has long been of interest for both theoretical and synthetic reasons. The theoretical discussions have in the past centred around the intermediacy of nitrenium ions[30] (now often referred to as aminylium ions[29]) in solvolytic rearrangements of N-chloroamines.

Nitrenium ions are divalent nitrogen species possessing two unpaired electrons and a unit positive charge.[30] They are isoelectronic with carbenes (formally having the possibility of existing in singlet and triplet states) and should resemble carbenium ions in character.

Investigations into the solvolysis of 2-chloro-2-azabicyclo[2.2.2]octane in methanol, assisted by the presence of silver nitrate, showed alkyl migration to occur giving 2-methoxy-1-azabicyclo[3.2.1]octane.[31,32]

Gassman pointed out that this rearrangement could proceed by two possible routes, each requiring the migration of an alkyl group along with its pair of electrons. Figure 1:4 shows the two possible pathways.

*This section excludes discussion of the Hofmann-Löffler-Freytag reaction, reviews of which are available.[26-29]

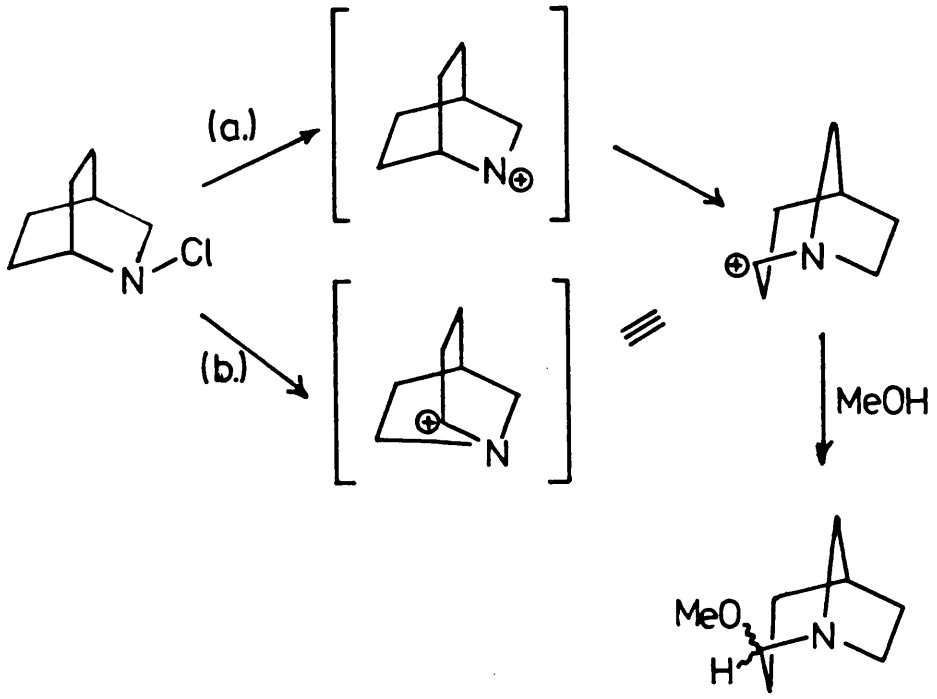


Figure 1:4

The first pathway (a), which Gassman himself favoured, involved the formation of a nitrenium ion as a discrete intermediate, whilst the second (b) suggested a concerted process with simultaneous loss of chloride during alkyl migration.

The cyclisation reactions shown in figure 1:5 were investigated by Gassman et al.[33,34] For these reactions the presence of discrete nitrenium ion intermediates was postulated; however such reactions (and others like them) were later shown to be radical in nature.[35,36]

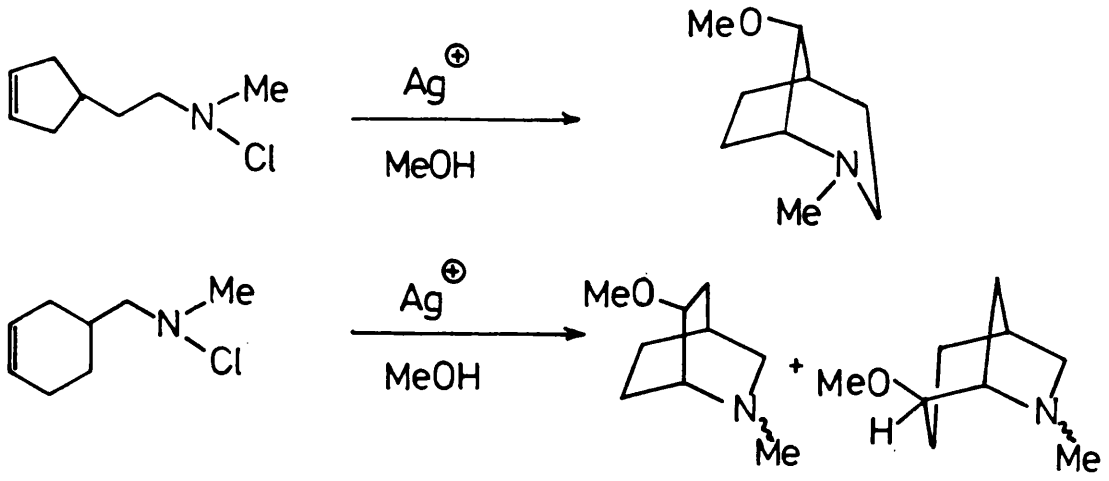


Figure 1:5

Furstoss et al.[37] extended these studies to the elaborated systems shown in figure 1:6; these reactions were also thought to proceed via radical pathways.

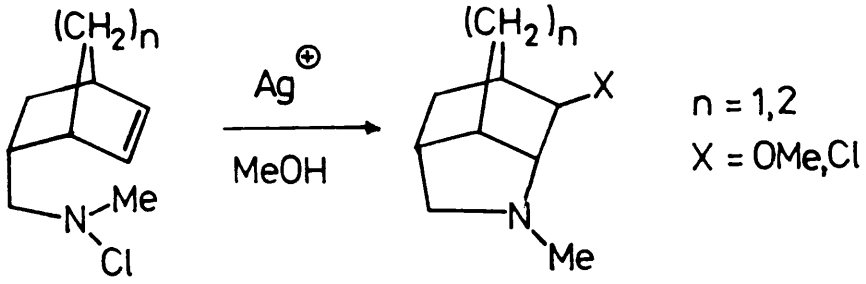


Figure 1:6

It must be noted that there are two classes of reaction in which it is thought likely that a mechanism involving an electron-deficient nitrogen centre operates. The first of these is the rearrangement of N-chloroanilines. Gassman et al.[38,39] proposed a mechanism involving an anilinium ion intermediate (figure 1:7), although the positive charge must be extensively delocalised over the aromatic ring.

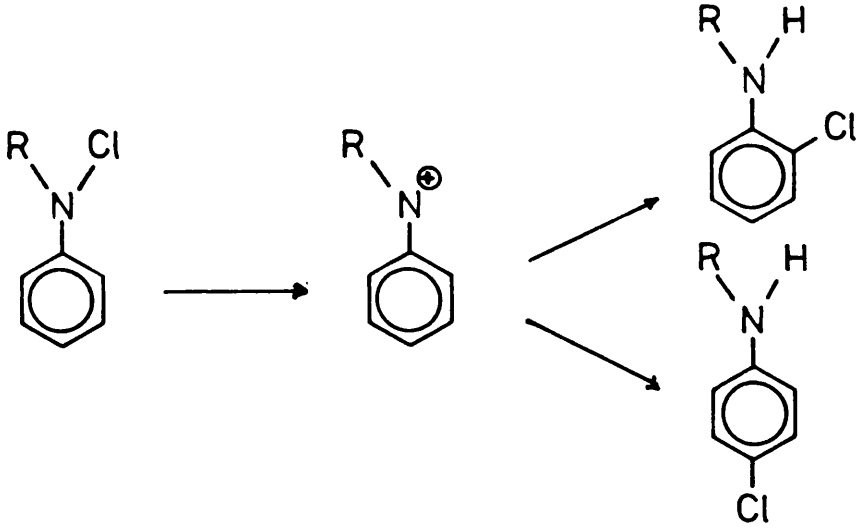


Figure 1:7

The second class of reactions is that in which silver-ion-catalysed bond migration to nitrogen occurs with re-arrangement or ring expansion. Examples of such reactions can be seen in figure 1:8.

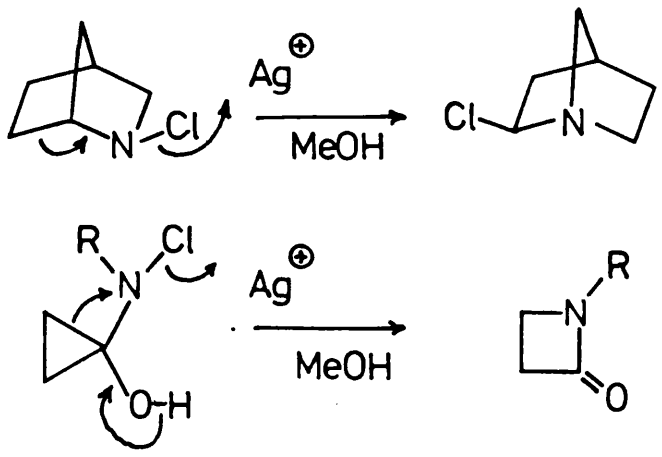


Figure 1:8

These reactions are not thought to involve radical intermediates, since the products obtained under conditions known to favour radical pathways are quite different, even when using the same substrate,[32,40] (figure 1:9).

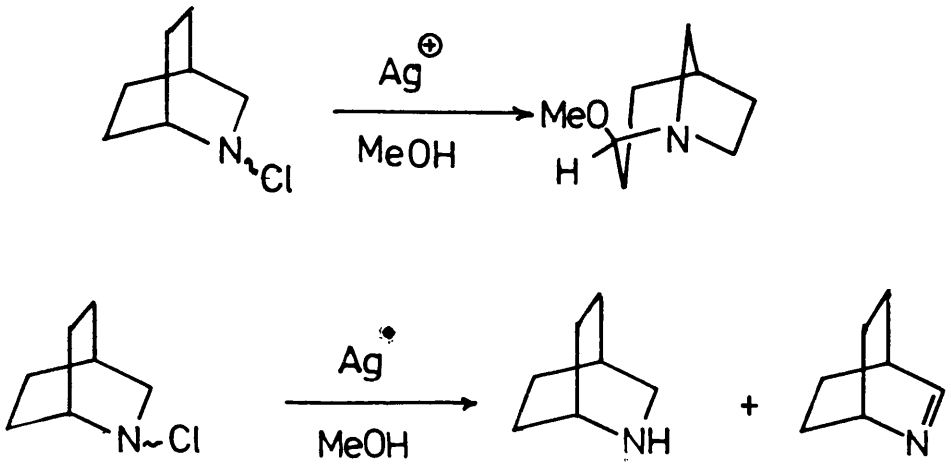


Figure 1:9

Gassman et al.[41] showed that there was a disparity between the products obtained under radical and ionic conditions, (figure 1:10).

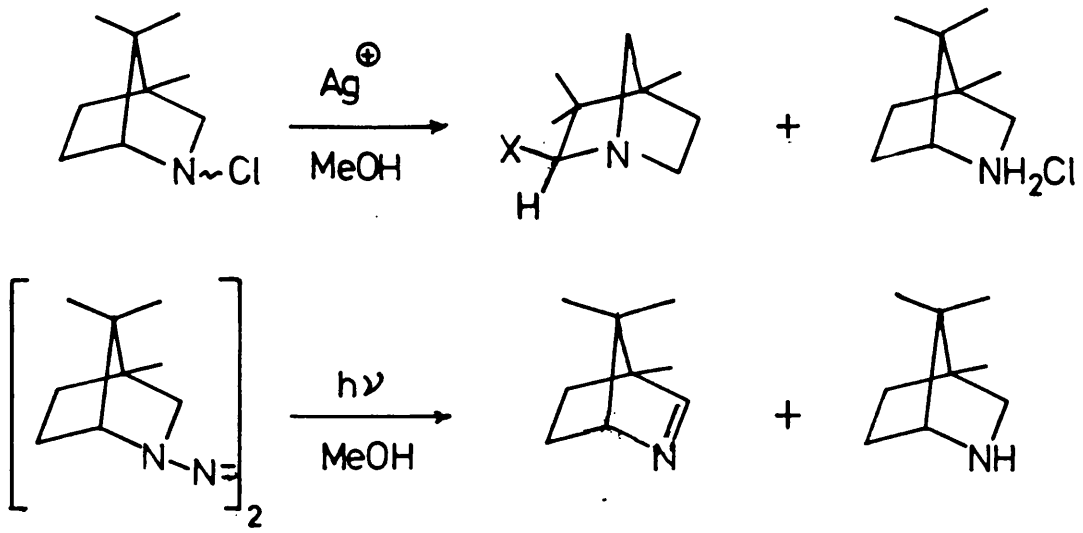


Figure 1:10

It seems therefore (from figures 1:9 and 1:10) that the production of the "parent" secondary amine* and endocyclic imine are characteristic of a reaction proceeding via an aminyl radical.

The diversity of products obtained from silver-ion promoted rearrangements of certain bicyclic N-chloroamines led Gassman[30] to postulate a scheme in which discrete nitrenium ions are involved, (figure 1:11).

*The term "parent" secondary amine will be used to describe the secondary amine from which the reacting N-chloroamine would normally be prepared directly.

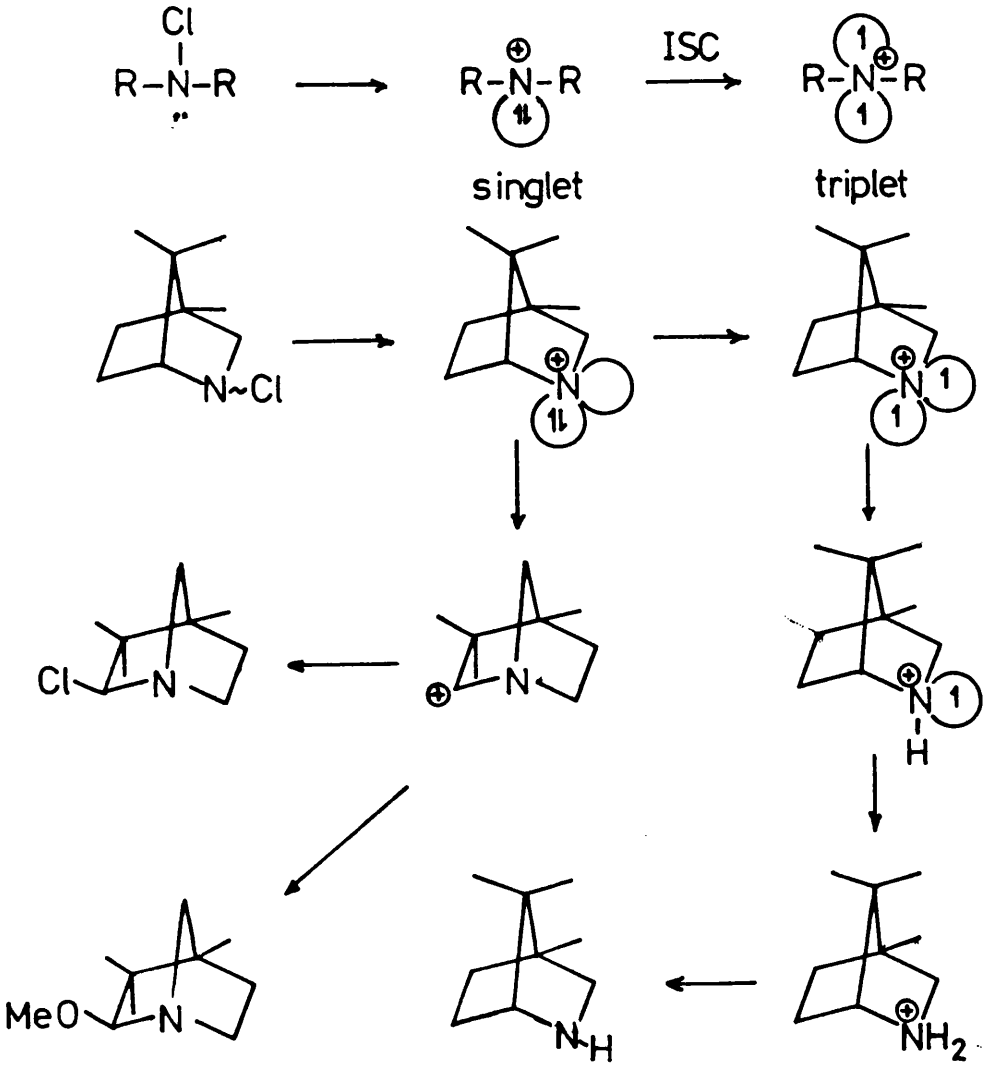
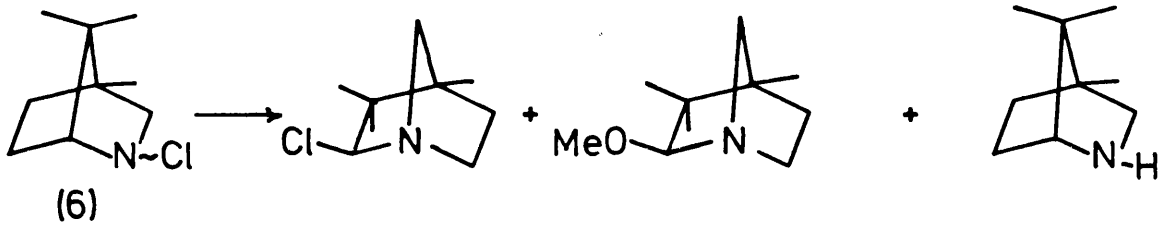


Figure 1:11

Gassman proposed that the singlet nitrenium ion was formed first, but that some intersystem crossing (ISC) to the triplet form also occured; the singlet and triplet nitrenium ions then gave rise to different products. However, the theory that nitrenium ions could exist as discrete species brought with it certain problems. Gassman et al.[41] recorded the failure to observe the production of endocyclic imine

in the reactions of figure 1:11, even though the triplet nitrenium ion would involve a nitrogen radical cation that might be expected to give rise to such a product, as it resembles the aminyl radical produced in homolytic reactions.

Also, the methanolysis of 4,7,7-trimethyl-2-chloro-2-azabicyclo[2.2.1]heptane (6) afforded a significant proportion of product in which chlorine was retained.[43] The rate of this reaction increased (ca. 2000x) when catalysed by silver ion, but more surprisingly the proportion of chlorine-retaining product also increased, (figure 1:12).



(6)

a.) MeOH, $T_{1/2}$ ~83min. 59% 20% 7%

b.) $Ag^{\oplus}$/MeOH, $T_{1/2}$ <1min. 78% 8·5% 4%

Figure 1:12

Gassman suggested that the silver-ion-catalysed reaction (b) must proceed in a concerted manner via a very tight ion-pair or a very highly concerted transition state in which the chloride ion is never entirely free,[43] (fig. 1:13). The uncatalysed reaction (a) must also proceed by a similar transition state to that shown in figure 1:13 (but without the silver-ion).

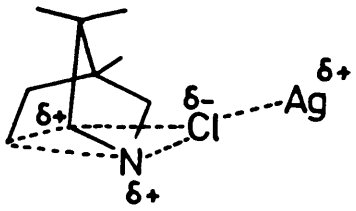


Figure 1:13

Both of the rearrangement reactions (a) and (b) of figure 1:12 that gave rise to chlorine-retaining products must have proceeded faster than chloride-ion could move away. The rate of these reactions, therefore, does not accord with the formation of discrete nitrenium ions (with long enough lifetimes for ISC to occur). It must therefore be concluded that the evidence for the existence of discrete nitrenium ions is not entirely satisfactory and that in many cases the proposal of a highly concerted transition state often provides a more acceptable explanation of the data.

Gassman et al.[44] also studied the rearrangement of 1,7,7-trimethyl-2-chloro-2-azabicyclo[2.2.1]heptane (7)

isomeric with (6) and found that this also gave a complex mixture of products, (figure 1:14).

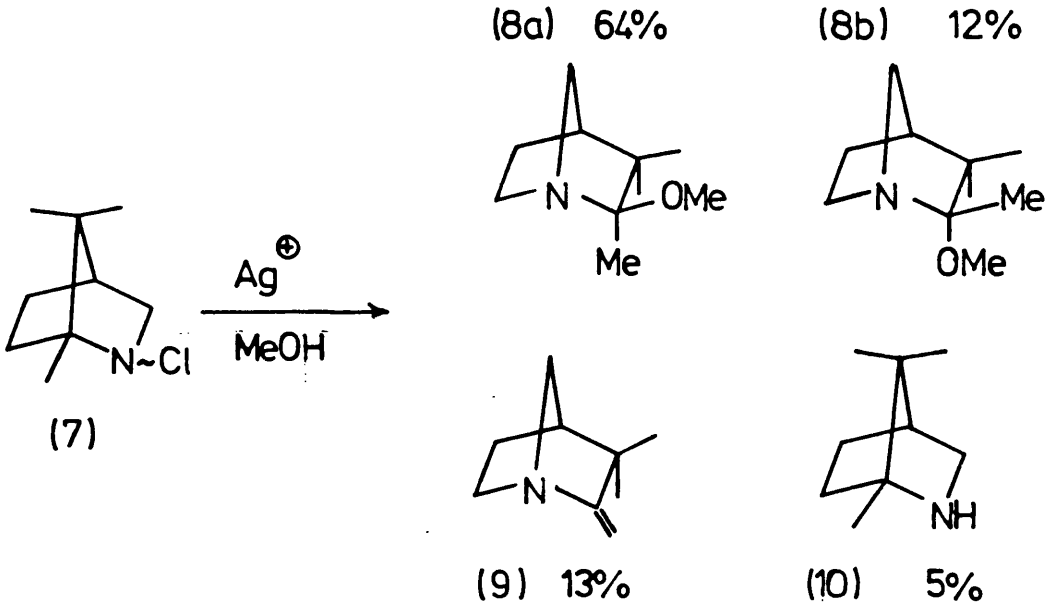


Figure 1:14

In the above reaction no chlorine-retaining products were observed. Gassman et al. explained that this was because the departure of the chloride-ion would be facilitated by the stability of the remaining tertiary carbenium ion (11).[44] This would subsequently be attacked by the nucleophilic methanol, (figure 1:15).

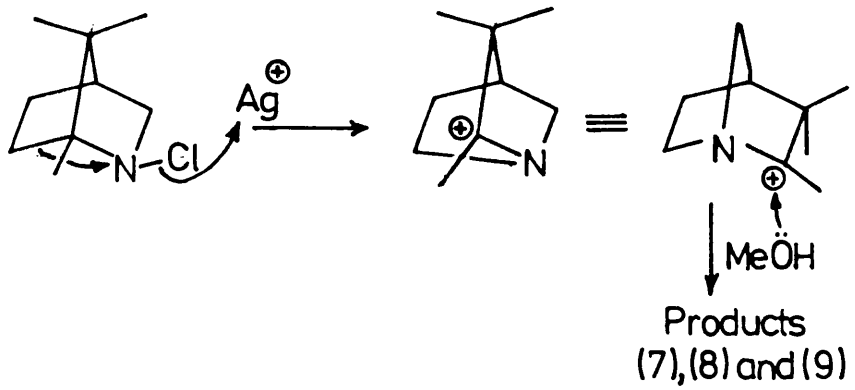


Figure 1:15

Malpass and Walker completed studies on the solvolytic rearrangements of 2-chloro-2-azabicyclo[2.2.1]hept-5-ene (12) and 2-chloro-2-azabicyclo[2.2.2]oct-5-ene (15),[45] (figure 1:16).

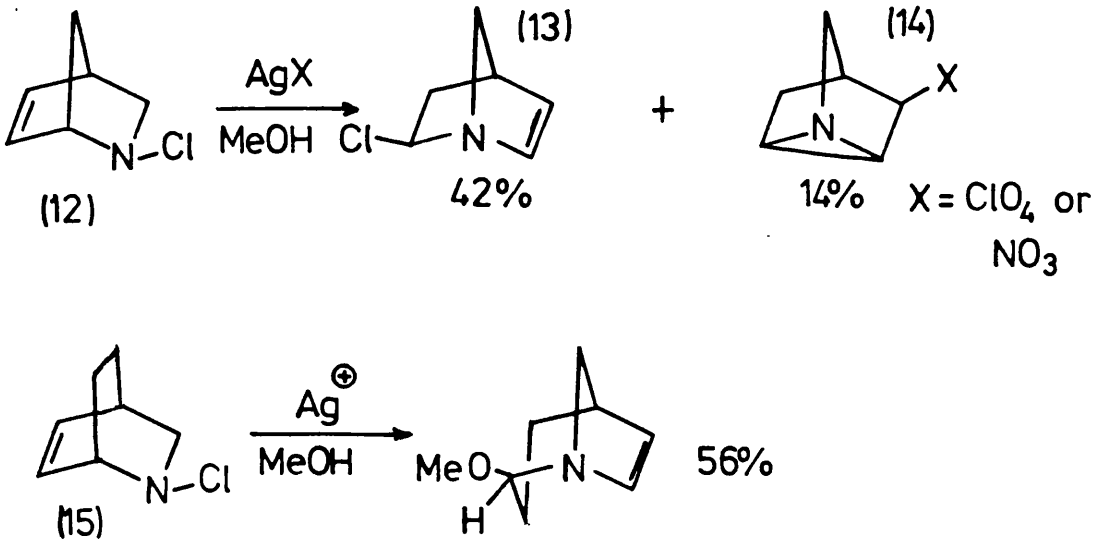


Figure 1:16

The solvolyses of both (12) and (15) afforded products which resulted from the migration of the etheno-bridge; thus both reactions were considered as proceeding with π-participation. In the case of (15) it was considered significant that no evidence of sp^3-C migration was observed, which might have been expected (see figure 1:14). The rearrangement of the more highly strained (12) was thought to proceed via a highly-concerted transition state to afford the chlorine-retaining product (13). The minor product formed in the rearrangement of (12) was shown to arise from further solvolytic rearrangement of (13), (figure 1:17).

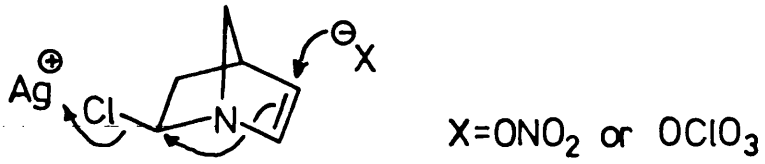
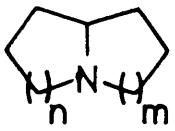


Figure 1:17

Other investigations into the solvolytic behaviour of strained azabicyclic systems (both saturated and unsaturated) have been carried out with systems in which the leaving group on nitrogen is a species other than chloride-ion,[44,46,47] however further discussion of these lies beyond the scope of this section.

Finally, mention must be made of the investigations of Schell et al.[48] which involve the development of rearrangement reactions of bicyclic N-chloroamines in order to synthesise ring systems (17 a-d) commonly found in alkaloid structures, (figure 1:18).



		n	m
17	a	1	1
	b	1	2
	c	1	3
	d	2	3

Figure 1:18

Preliminary rearrangements proved unsatisfactory because the intermediate iminium ion was often readily oxidised to afford an unwanted acetal[48,49] and the production of the desired amine was also hampered by formation of large quantities of secondary "parent" amine (probably via a homolytic route), (figure 1:19).

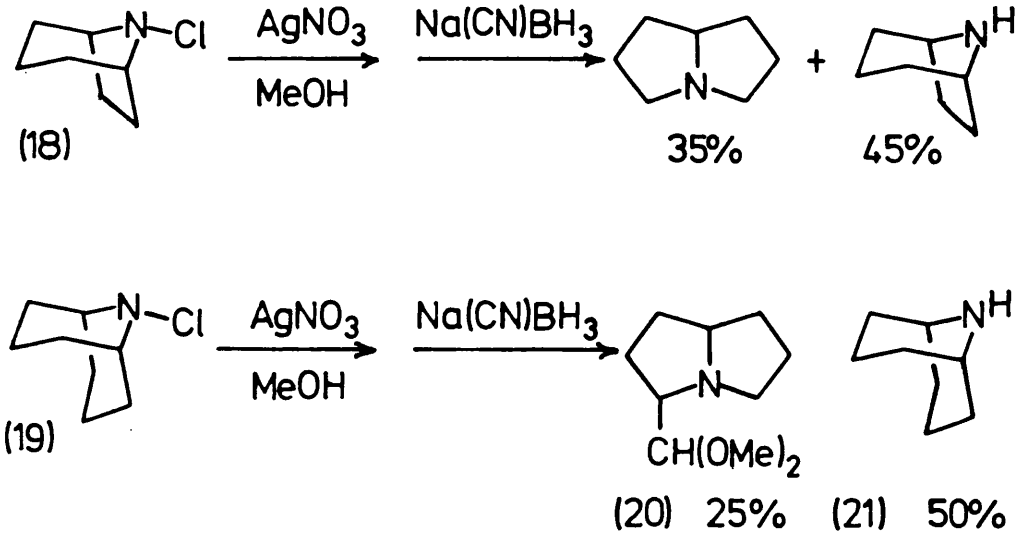


Figure 1:19

It was noted, however, that the iminium ion intermediate could be prepared and protected from oxidation by precipitation from solution prior to reduction; this occured when benzene was used as solvent in place of methanol. Under these conditions the quantity of "parent" secondary amine was also dramatically reduced, (figure 1:20).

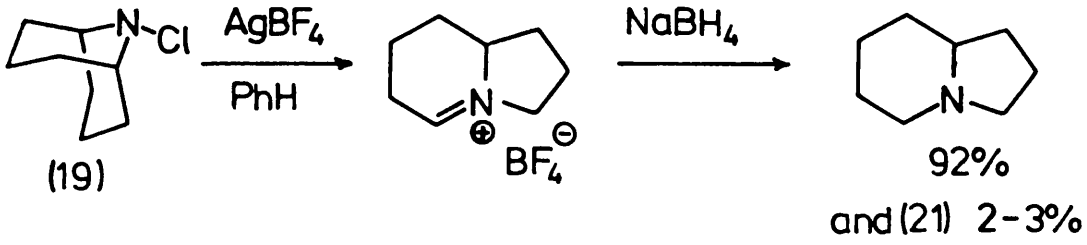
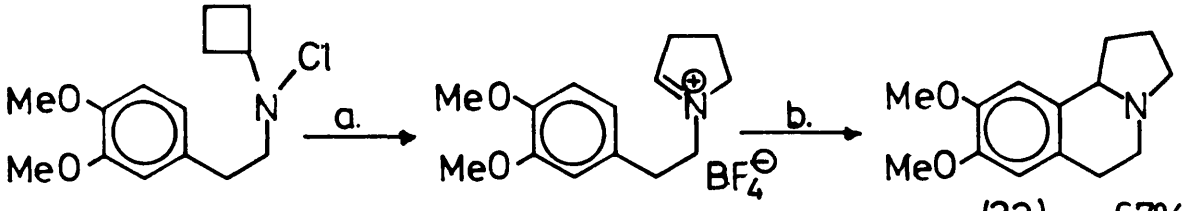


Figure 1:20

This methodology proved to be applicable to several similar bicyclic N-chloroamines,[49] the quantity of secondary amine produced in every case being minimal. Schell et al.[50] further applied this approach to the preparation of the pyrrolideine (22), (figure 1:21).



(22) 67%

a. $AgBF_4$, PhH, 50°C, 30min

b. Conc. HCl, 1h, basic work-up. (Pictet-Spengler)

Figure 1:21

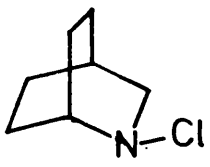
In this case the use of an aprotic solvent did not completely suppress the dechlorination reaction since 10 - 12% of the "parent" secondary amine was also produced.

CHAPTER 2

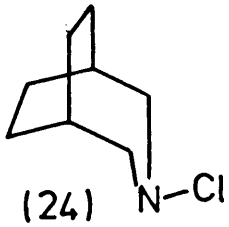
A STUDY OF THE BARRIER TO NITROGEN INVERSION AND THE REARRANGEMENT REACTIONS OF 1-METHYL-2-CHLORO-2-AZABICYCLO[2.1.1]HEXANE

2.I Introduction

The study of nitrogen inversion has long established that in azamonocycles the barrier to nitrogen inversion generally increases with decreasing ring size.[1] In larger, less strained systems, however, the study of nitrogen inversion can be complicated by ring inversion. Lehn and Wagner introduced two-carbon bridges across six- and seven-membered rings to give the 2-azabicyclo[2.2.2]octane and 3-azabicyclo-[3.2.2]nonane systems[51] in which nitrogen inversion was the sole temperature-dependent process. They also reported the measurement of inversion barriers for the N-chloroamine derivatives of these systems (23) and (24), (figure 2:1).



(23)

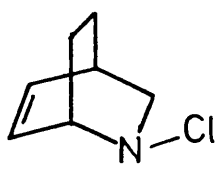


(24)

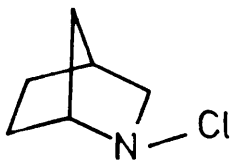
	(23)	(24)
Barrier to Inversion (kJ/mol)	44.3	42.2

Figure 2:1

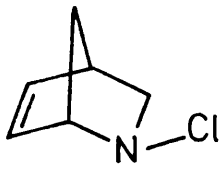
Malpass and Tweddle prepared 2-azabicyclo[2.2.2]oct-5-ene, 2-azabicyclo[2.2.1]heptane and 2-azabicyclo[2.2.1]-hept-5-ene systems[52] and subsequently measured the inversion barriers for their N-chloroamine derivatives (25 - 27),[8] (figure 2:2).



(25)



(26)



(27)

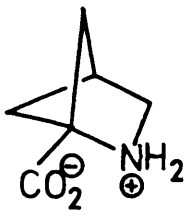
Barrier to Inversion (kJ/mol)	46·7	50·2	60·0

Figure 2:2

On going from (25) to (27) the flexibility and size of the all-carbon bridges were reduced. This raised the strain in the molecule as a whole. Thus the angle strain at nitrogen and consequently the barrier to inversion were also raised.

The production of a system more strained than (27) required further reduction in the size of the carbon bridges. This led to the investigation of the 2-azabicyclo[2.1.1]-hexane system, for which it was hoped that the further increase in barrier would be substantial.

The first example of this system to be isolated was an amino acid found in the seeds of the legume Atelia herbert smithii.[53] The compound 2,4-methanoproline (28) acts as a defence against predatory insects. Its structure was confirmed by X-ray crystallography, (figure 2:3).



(28)

Figure 2:3

The total synthesis of (28) was accomplished, separately, by two groups.[54,55] In each case the key step involved a [2+2] photocycloaddition to form the 2-azabicyclo[2.1.1]hexane skeleton, (figure 2.4).

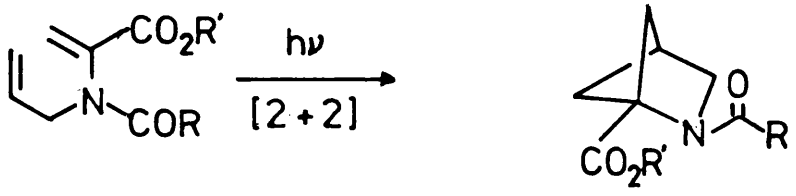
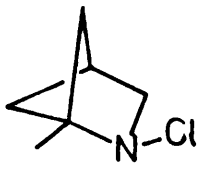


Figure 2:4

It was realised that modification and extension of these synthetic routes would provide a 2-azabicyclo[2.1.1]-hexane derivative (29) for which the study of inversion barriers and rearrangement reactions would be possible, (figure 2:5).



(29)

Figure 2:5

The choice of chlorine as the other substituent on nitrogen in (29) has important consequences. The inversion barrier is raised due to its electronegativity and lone pairs. Also due to its ease of removal as chloride-ion, it provides a useful substituent for the study of rearrangement reactions taking place at nitrogen. In view of these reasons and bearing in mind the considerable number of N-chloroazabicycles available for comparison, the synthesis of (29) was attempted.

2.II Synthesis and Spectroscopic Investigations

The preparation of the intermediate azabicycle (31) closely followed the methodology previously devised by both Pirrung[54] and Clardy et al.[55] The diene (30) used for the [2+2] cycloaddition reaction differed slightly from those previously used and therefore required slightly modified photolysis conditions (figure 2:6). A benzoyl substituent on nitrogen was preferred because later, when reduced to a benzyl group, it could be readily removed by hydrogenolysis.

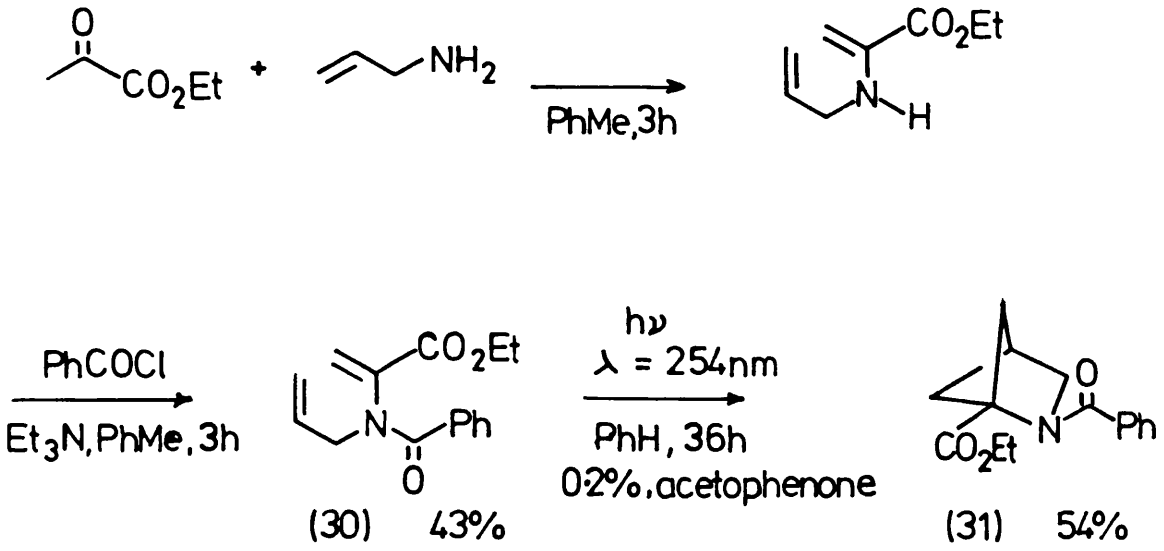


Figure 2:6

The conversion of (31) to 2-benzyl-2-azabicyclo[2.1.1]-hexane (34) was achieved by the use of established reductive procedures, (figure 2:7).

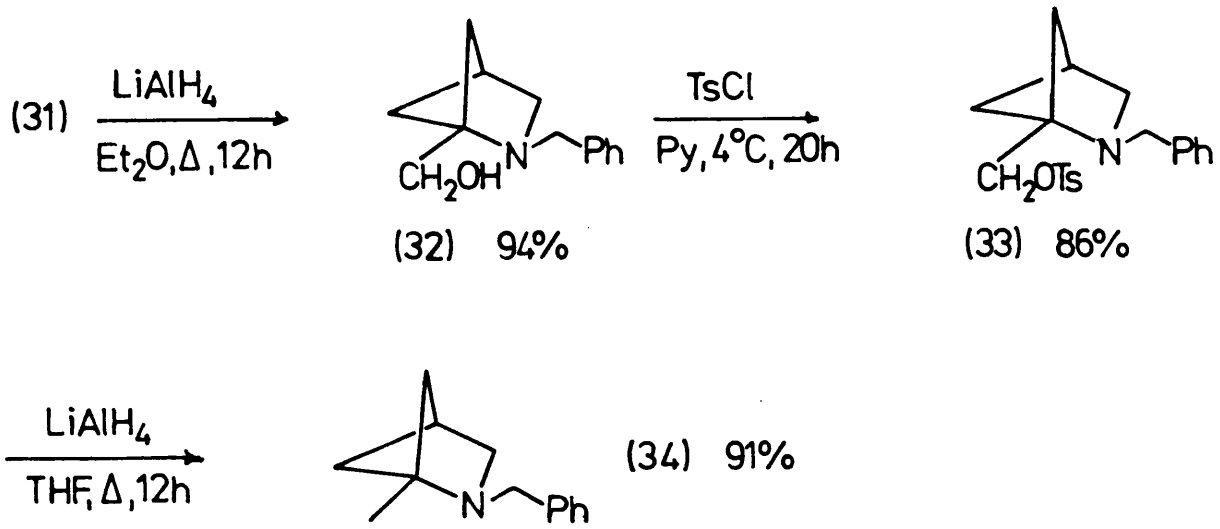


Figure 2:7

With the synthesis of (34) accomplished, its ^{1}H NMR spectrum was observed at room temperature (figure 2:8). The spectrum contained three broad singlets and a multiplet, the two downfield singlets being of greater interest. The absorption at ca. 3.5ppm arose from the methylene protons of the N-benzyl group; the absorption at ca. 2.4ppm was the result of accidental equivalence of the protons of the methylene group α- to nitrogen and the bridgehead proton.

When the ^{1}H NMR spectrum was measured at -103°C, the signals from the N-benzyl methylene protons and the protons of the methylene α- to nitrogen had both separated into two distinct peaks (figure 2:9). The ^{1}H NMR of (34) was then further observed at frequent temperature intervals between -100°C and -81°C. Both pairs of signals coalesced as the temperature was raised (figure 2:9). The coalescence

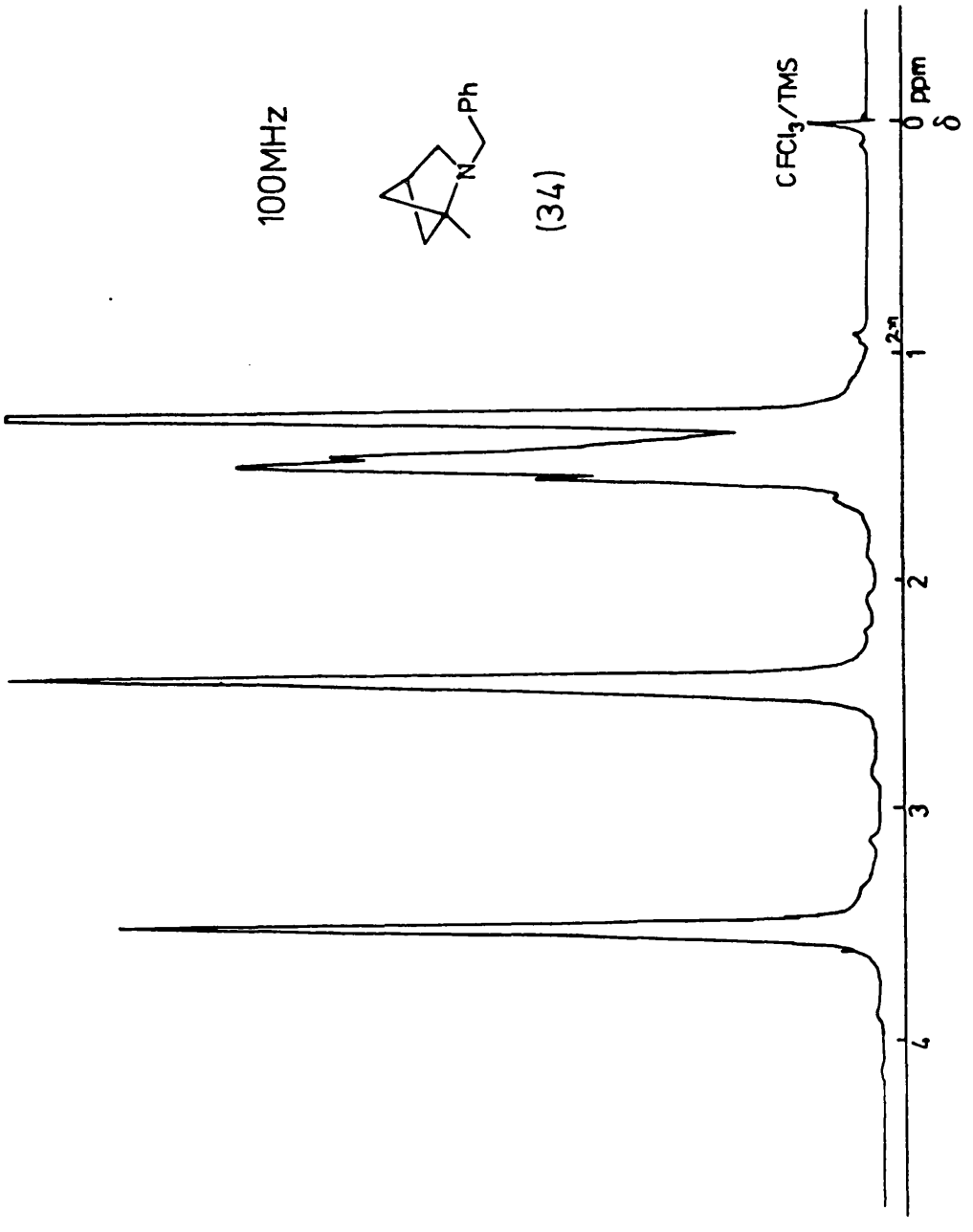


Figure 2:8

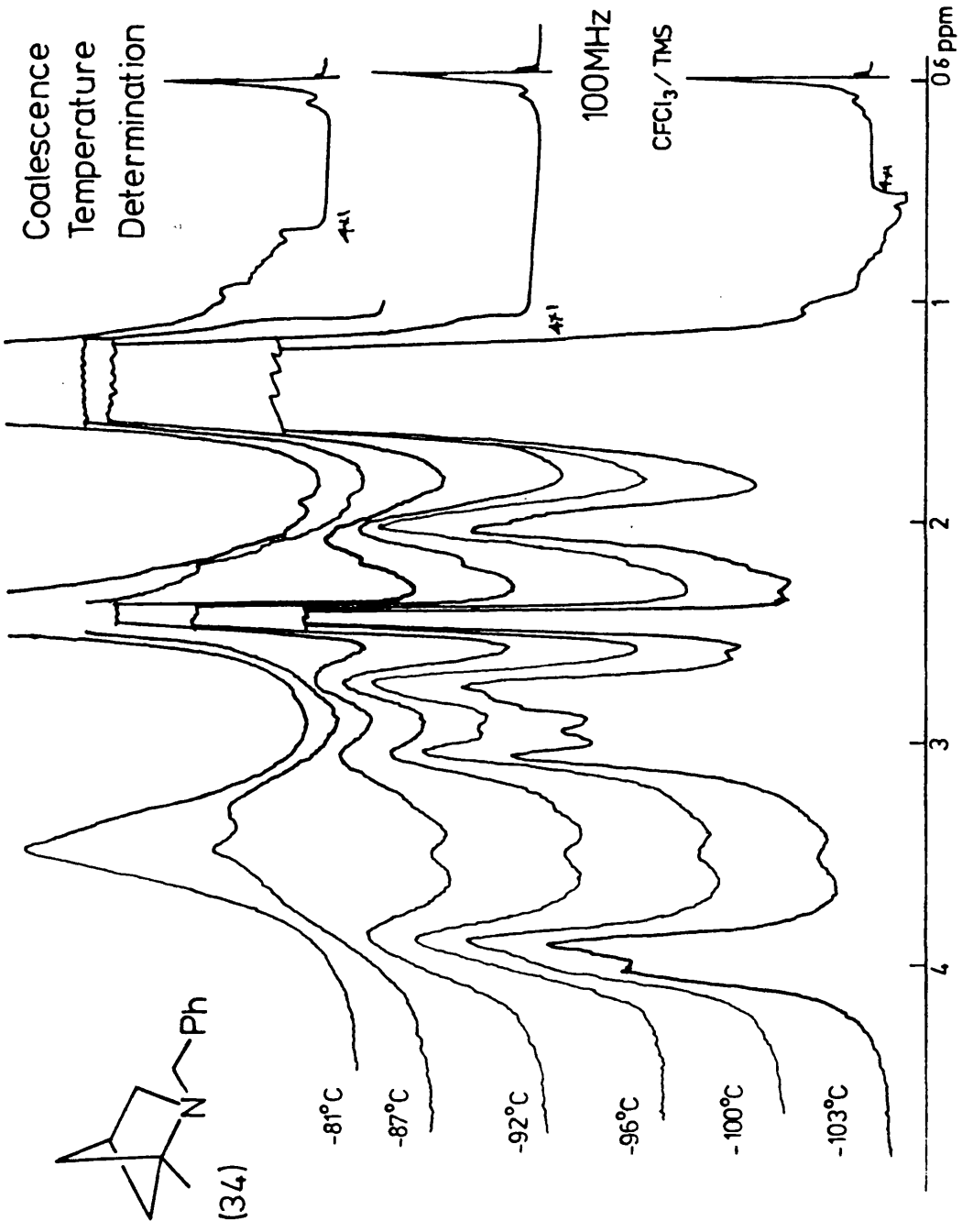

Coalescence
Temperature
Determination
100MHz
$CFCl_3$ / TMS
δ ppm
-81°C
-87°C
-92°C
-96°C
-100°C
-103°C
Ph
N
(34)

Figure 2:9

temperatures (Tc) were estimated and the inversion barriers ($\Delta G^{\neq}$) calculated directly, (table 2:1).

Table 2:1

Compound (34)	$\Delta\nu$ (-103°C)	Tc (±5°C)	$\Delta G^{\neq}$ (±1kJmol^{-1})
benzylic methylene H's	95 Hz	-85°C	36.4 kJmol^{-1}
methylene H's α- to nitrogen	68 Hz	-87°C	37.0 kJmol^{-1}

Averaged Value for Barrier to Inversion ($\Delta G^{\neq}$) 36.7 kJmol^{-1} ±1 kJmol^{-1}

Comparison with certain other N-alkyl azacycles shows that despite the anticipated extra strain in the system the inversion barrier was not raised significantly (table 2:2).

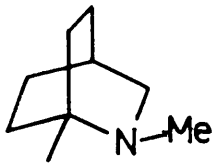
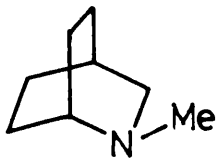
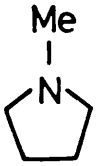
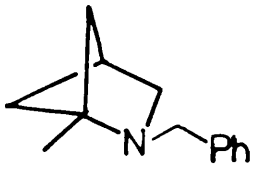
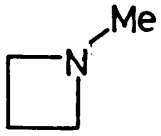
		Barrier to Inversion, $\Delta G^{\ddagger}$ (kJ/mol)
(35)		29.1[56]
(36)		35.3[51,56]
(37)		36.3[1]
(34)		36.7
(3)		42.6[1]

Table 2:2

It should be noted that N-benzyl substituted compounds generally have slightly lower barriers to inversion than their N-methyl analogues due to their greater steric bulk. Although the barrier for (34) is substantially higher than that for the 1-methyl-2-azabicyclo[2.2.2]octane (35) it is significantly lower than the value found for N-methyl azetidine (3) and is very similar to that for N-methyl pyrrolidine (37).

The further conversion of (34) to the N-chloroamine (29) was then carried out. The synthesis involved the removal of the benzyl group by hydrogenolysis. The amine thus produced was rather volatile and was therefore converted to, and isolated as, its hydrochloride salt (38).* The N-chloroamine (29) was prepared by direct treatment of (38) with sodium hypochlorite solution (figure 2:10) and was stable in solution for several weeks if stored cold ($4^{o}C$).

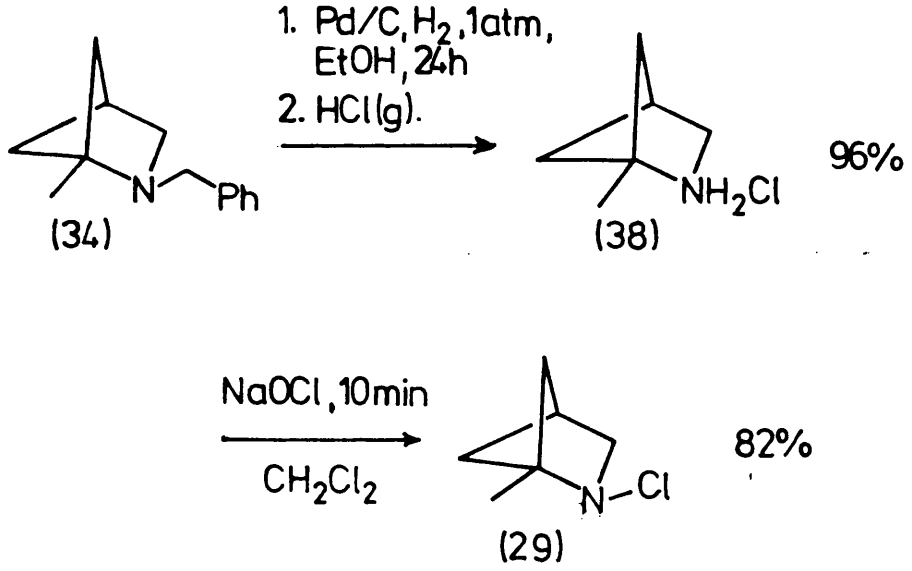


Figure 2:10

The ^{1}H NMR spectrum of the N-chloroamine (29) was measured at room temperature. It was obvious, from the general form of the spectrum, that unlike the N-benzyl derivative (34) the N-chloroamine was undergoing slow

*The hydrochloride salt was highly hygroscopic, therefore the amine was fully characterised as its picrate salt.

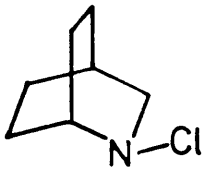
inversion on the NMR timescale. The ^1H NMR spectra showed temperature-dependent coalescence as the temperature of the solution was increased (figure 2:11). The coalescence temperature (Tc) was estimated and the barrier to inversion ($\Delta G^{\neq}$) was calculated, (table 2:3).

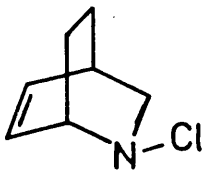
Table 2:3

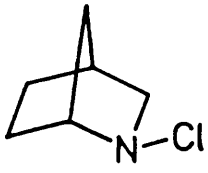
N-chloroamine (29)	$\Delta\nu$ (25°C)	Tc (±3°)	$\Delta G^{\neq}$ (± kJmol^{-1})
methylene H's α- to nitrogen	52 Hz	73°C	71.5 kJmol^{-1}

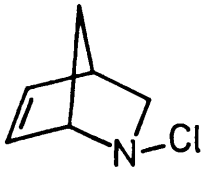
Comparisons can be made with a variety of strained N-chloroazabicycles, (table 2:4).

Barrier to Inversion
$\Delta G^{\ddagger}$ (kJ/mol)

(23)  44·3

(25)  46·7

(26)  50·2

(27)  60·0

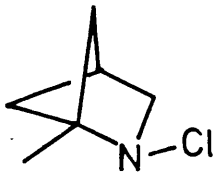
(29)  71·5

Table 2:4

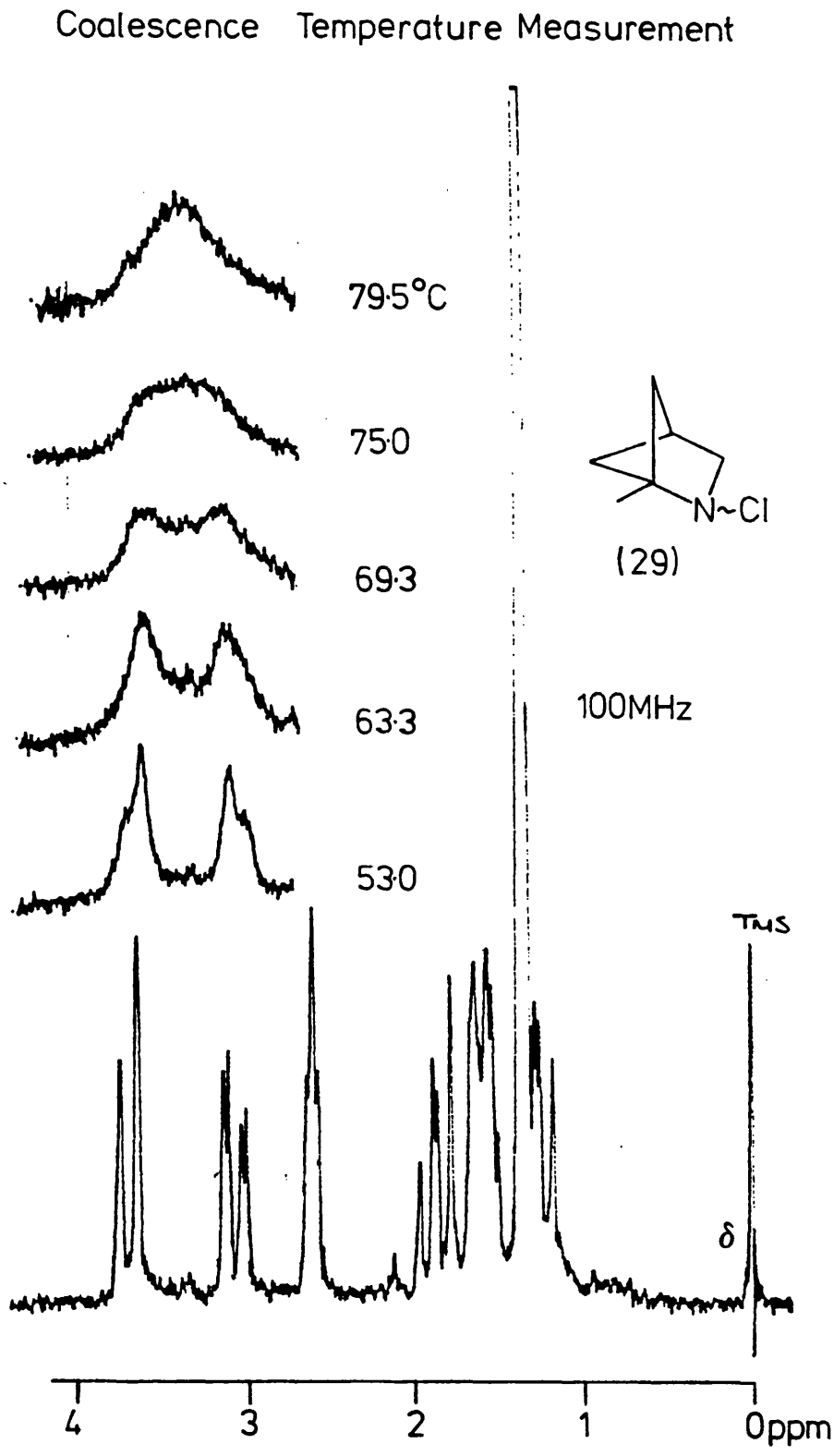

Coalescence Temperature Measurement
79·5°C
75·0
69·3
63·3
53·0
N~Cl
(29)
100MHz
TMS
δ
4
3
2
1
0ppm

Figure 2:11

The increase in barrier on going from (26) to (29), (11.3 $kJmol^{-1}$), is much greater than the increase going from (23) to (26), (5.9 $kJmol^{-1}$). This shows that as the ring size diminishes the effect on ring strain becomes increasingly large and consequently the barrier increase becomes correspondingly greater. The significant increase in barrier height from (26) to (29) is nevertheless insufficient to cause the configuration at nitrogen to become fixed, even at moderately low temperatures.

The ^1H NMR of (29) provided further interest. At 100 MHz the spectrum was not totally resolved but on going to higher field (400 MHz) a more complete analysis was possible (figure 2:12). The analysis was aided by the use of a COSY experiment[57] (figure 2:13). The data are tabulated in table 2:5.

The position of the chlorine substituent relative to the adjacent methylene protons H_b and H_a was assigned by comparisons with similar systems, (table 2:6).

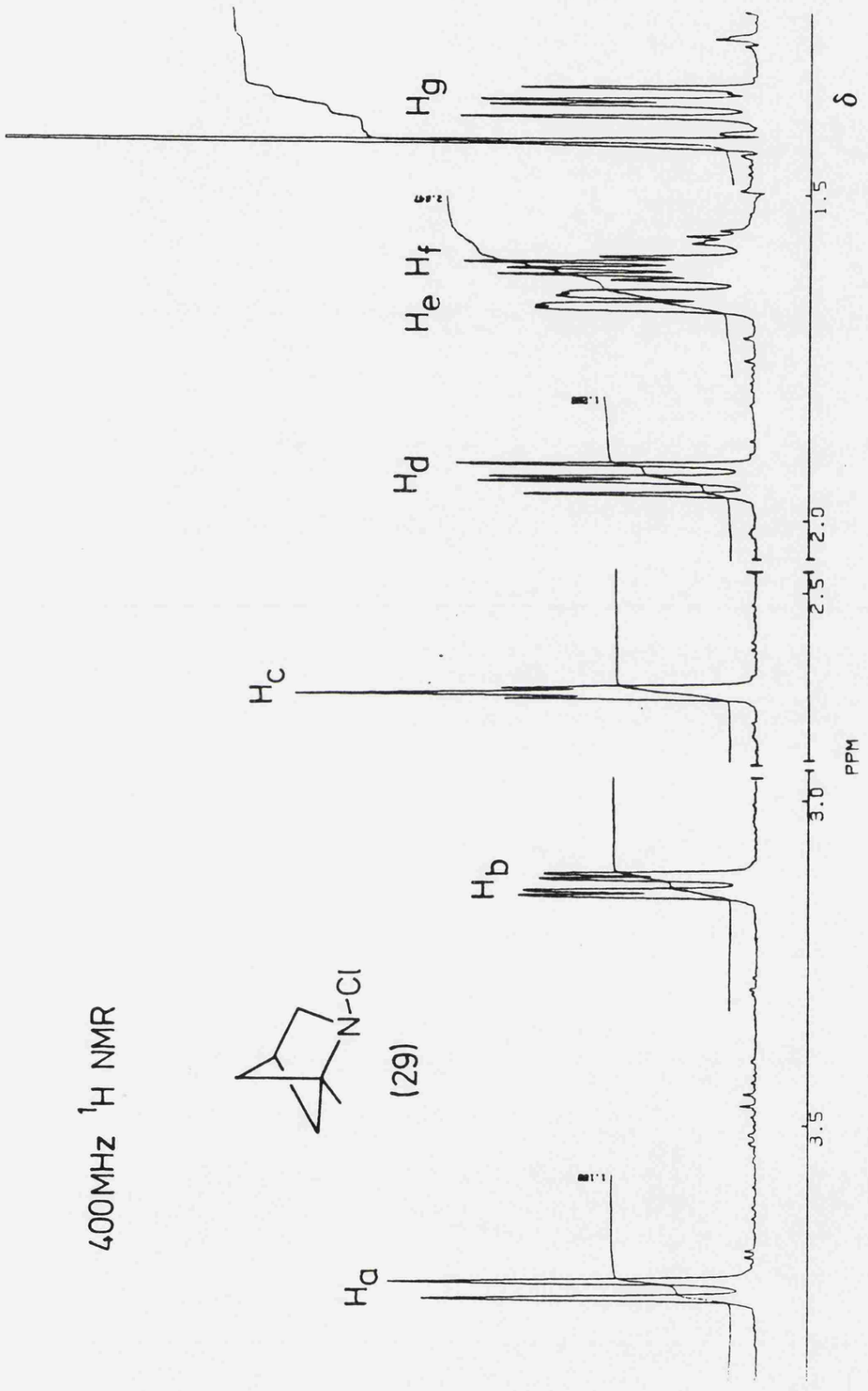


Figure 2:12

(29) COSY Spectrum

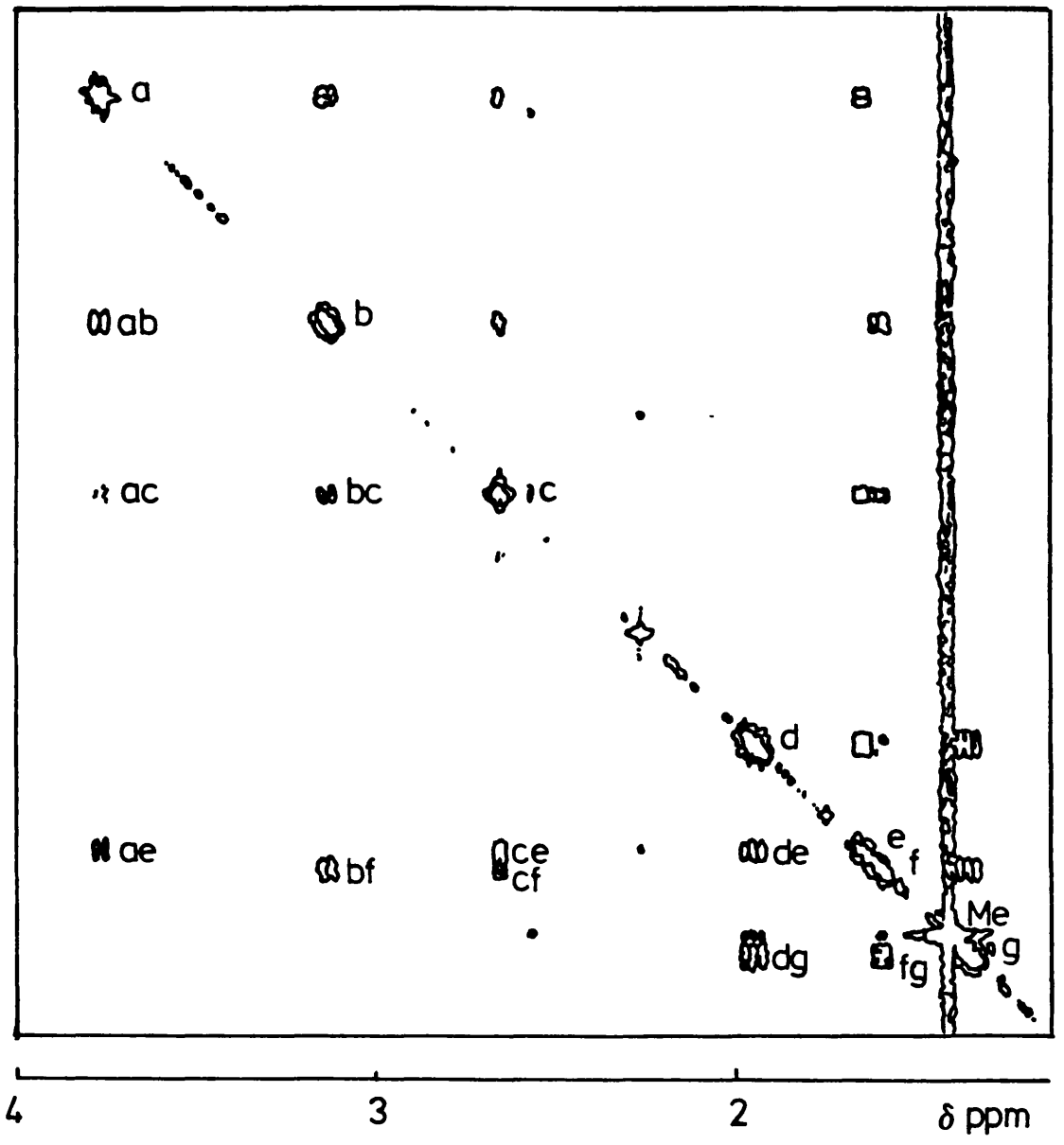


Figure 2:13

g	Me	f	e	d	c	b	a	
1.36	-	7.57	-	10.54	-	-	-	g
	1.42	-	-	-	-	-	-	Me
		1.62	-	-	3.17	3.13	-	f
			1.67	7.73	3.17	-	1.69	e
				1.94	-	-	-	d
					2.65	-	-	c
						3.13	10.25	b
							3.75	a

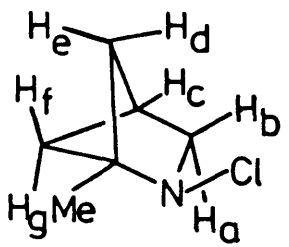


TABLE 2:5

Chemical shifts (δ, ppm) along diagonal.

Coupling constants (J, Hz) off-diagonal.

δ_H (400 MHz; $CDCl_3$)

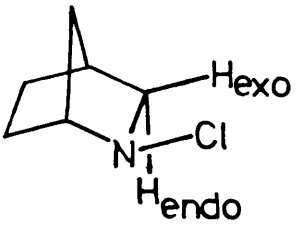
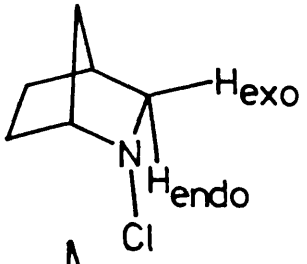
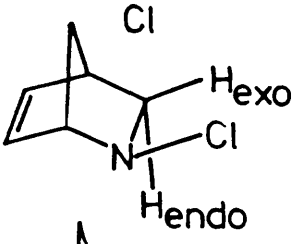
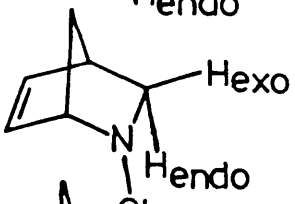
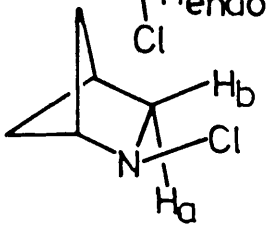
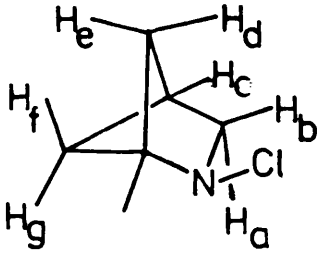
		Chemical Shifts δ ppm		Shift of proton on bringing an adjacent Chlorine into line, $\Delta\delta$
		$H_{exo.}$	$H_{endo.}$	
		2·98	3·20	-0·43 H_{exo} -0·83 H_{endo}
(26)		3·41	2·37	
		ca. 3·1	ca. 3·1	-0·54 H_{exo} -1·06 H_{endo}
(27)		3·64	2·04	
		H_b	H_a	
(29)		3·13	3·75	-0·62 H_b

Table 2:6[8]

In the case of (29) the two invertomers are clearly isoenergetic being enantiomers. The coupling information provided by high-field ^1H NMR also proved interesting. There is an apparent asymmetry in the molecule, betrayed by the coupling information. Thus H_b shows long-range W coupling with H_f (J = 3.13Hz), which is analogous to the coupling of H_a with H_e (J = 1.69Hz). Both these long-range interactions can be observed in the COSY experiment, (figure 2:13). The appreciable difference in these couplings tends to imply that the molecule is to some degree twisted, probably by the steric bulk of the chlorine substituent, enhancing one W-interaction to the detriment of the other, (figure 2:14).

(29)

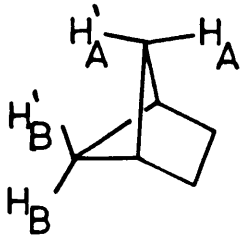


$J_{dg} = 10{\cdot}5Hz$

Figure 2:14

The second striking feature of the coupling information is the size of the interaction between H_d and H_g (J = 10.54Hz). This coupling is also clearly observable in the COSY experiment and such a large interaction must indicate that the bridgehead carbon atoms are rigidly held in close proximity to each other. The all - carbon

analogue of this system (39) also exhibits the same type of coupling,[58] although the coupling constants are somewhat smaller, (figure 2:15).

(39) 

J_{AB} = 6-8 Hz

Figure 2:15

2.III Rearrangement Reactions

a) Rearrangements Involving Internal Return of Chlorine

One of the more intriguing results in certain silver-catalysed solvolyses of strained bicyclic N-chloroamines is the isolation in high yields of rearranged products in which the chlorine has been retained. Gassman[59] first noted the large proportion of internal return of chlorine in the rearrangements of 2-azabicyclo[2.2.1]heptane derivatives, (figure 2:16).

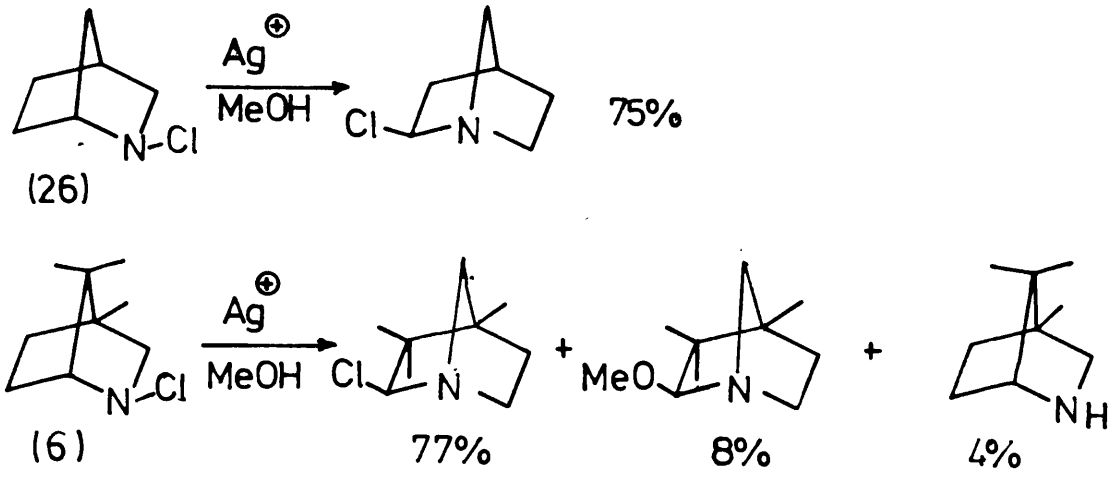
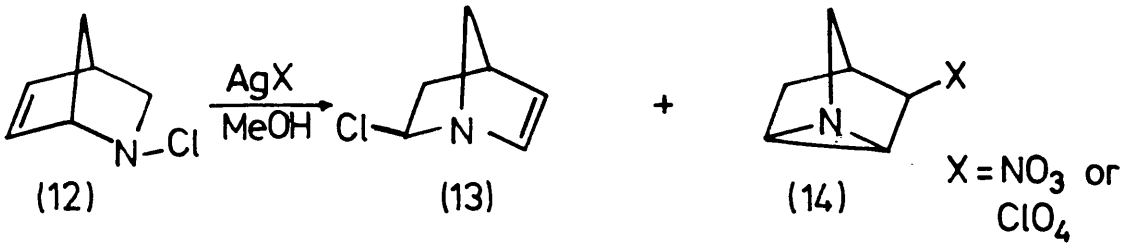


Figure 2:16

Malpass and Walker[45] also noted a similar retention of chlorine in the silver-catalysed rearrangement of 2-chloro-2-azabicyclo[2.2.1]hept-5-ene (12), (figure 2:17).



(12) (13) (14)

Figure 2:17

As postulated by Gassman,[30] it seems likely that such rearrangements involve either a very tight ion-pair or a highly concerted transition state at nitrogen, (figure 2:18).

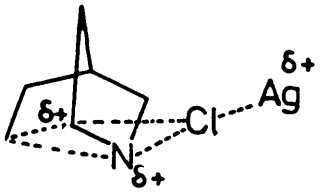


Figure 2:18

It seems that there are two major requirements which need to be fulfilled for internal return of chlorine to occur under these solvolytic conditions. Firstly, the carbon to which the chlorine migrates should be a secondary centre and secondly, the azabicycle itself apparently must contain sufficient strain for the migration to occur before the chlorine is removed by silver-ion as silver chloride.

There was no internal return of chlorine in 1,7,7-

trimethyl-2-chloro-2-azabicyclo[2.2.1]heptane (7)[44] because the centre to which the chlorine would migrate is a tertiary one and can readily form a more stable tertiary carbenium ion (11), allowing complete removal of chloride by silver-ion, (figure 2:19).

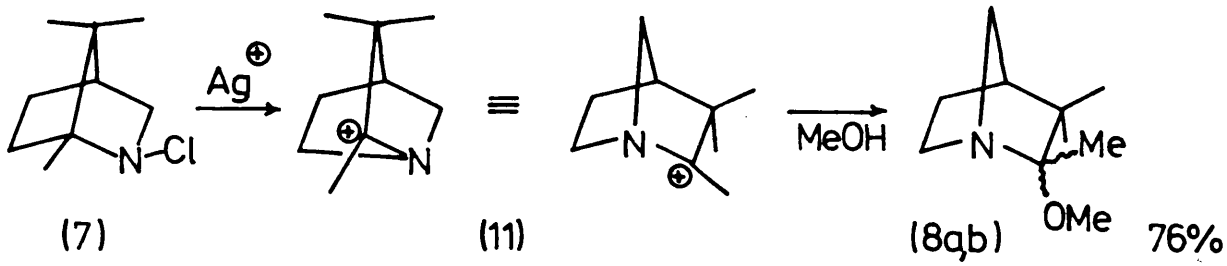


Figure 2:19

The less strained 2-chloro-2-azabicyclo[2.2.2]octane (23) also rearranged solvolytically without internal return of chlorine,[31] (figure 2:20).

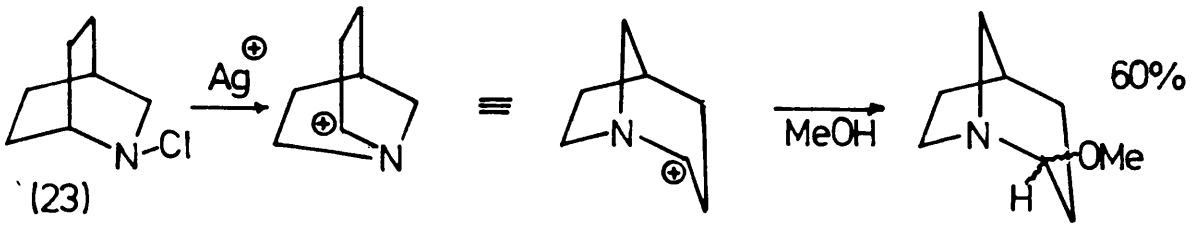


Figure 2:20

In certain rearrangements, such as that previously described in figure 2:17, the product of internal return of chlorine (13) is unstable with respect to the reaction conditions and undergoes further rearrangement to give the secondary product (14). Thus, silver-ion-catalysed rearrangements of bicyclic N-chloroamines only lead to chlorine-retaining products in certain cases, and usually in these cases they

are produced along with other side-products or secondary products.

Malpass and Walker[45] found that some of these problems could be avoided by using chromatographic alumina as a mild catalyst* to promote such rearrangements, (figure 2:21).

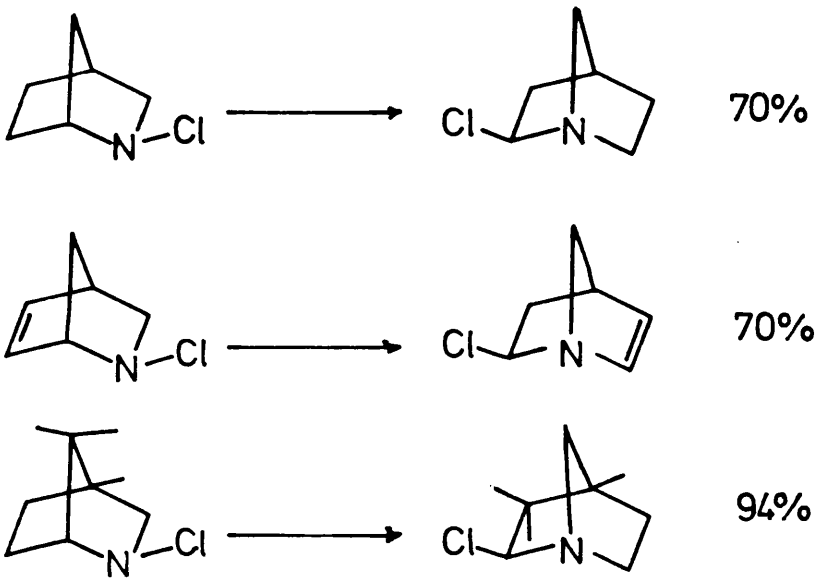


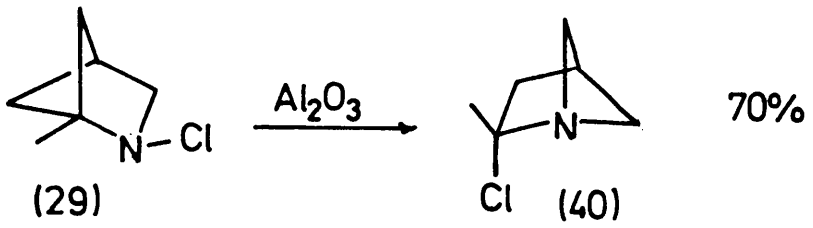
Figure 2:21

In each rearrangement, the chlorine-containing compound was produced cleanly. There were no side-products or further

*Reviews of the use of alumina to promote other reactions are available.[60]

reactions and the yields were equal to or better than those recorded for the analogous silver-ion-catalysed reactions.

When 2-chloro-2-azabicyclo[2.1.1]hexane (29) was reacted under conditions of alumina catalysis, rearrangement occured to give 2-chloro-2-methyl-1-azabicyclo[2.1.1]hexane (40), (figure 2:22). This is the first recorded derivative of the 1-azabicyclo[2.1.1]hexane system.



(29) (40)

Figure 2:22

The structure of (40) was elucidated by the use of high-field (400 MHz) ^{1}H NMR, (figure 2:23), and with the aid of a selective decoupling experiment, (table 2:7).

Table 2:7

Effects of simultaneous irradiation of H_f and H_g.

Chemical Shift (δ, ppm)		Coupling Constants Remaining	Coupling Constants Lost
2.19	H_a	11.6Hz, 0.9Hz	2.4Hz
2.33	H_b	10.4Hz	7.0Hz
2.47	H_c	11.6Hz, 1.1Hz	3.0Hz
3.03	H_d	10.4Hz	6.7Hz
3.03	H_e	1.1Hz, 0.9Hz	-
3.32	H_f	decoupled at 3.33 ppm	
3.36	H_g		

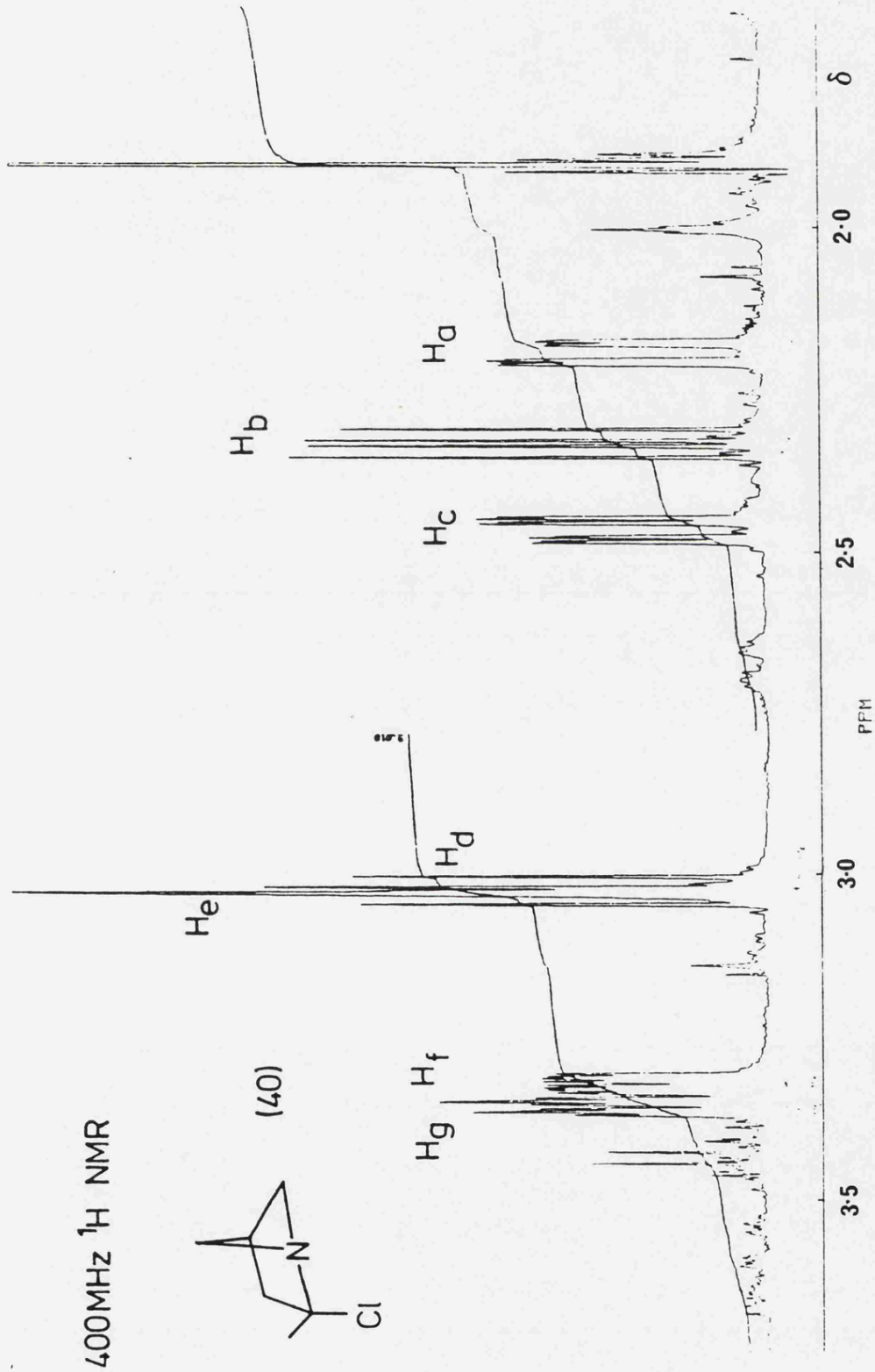


Figure 2:23

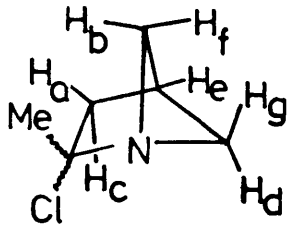


Figure 2:24

When H_f and H_g were irradiated simultaneously, a large W-coupling (J = 10.4Hz) between H_b and H_d could be seen. There were also smaller W-couplings between H_c and H_f (J = 3.0Hz), and between H_a and H_g (J = 2.4Hz). This helped to locate the relative positions of H_f and H_g within the molecule. The relative positions of the chlorine and the methyl group with respect to the rest of the molecule were found by NOE difference spectra from the methyl group, (figure 2:25). The protons that showed the largest NOE's were H_a and H_b, (figure 2:26).

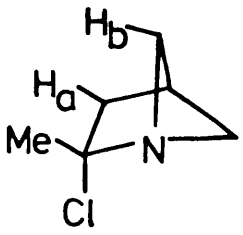


Figure 2:26

The final assignments of the spectrum of (40) are shown in table 2:8.

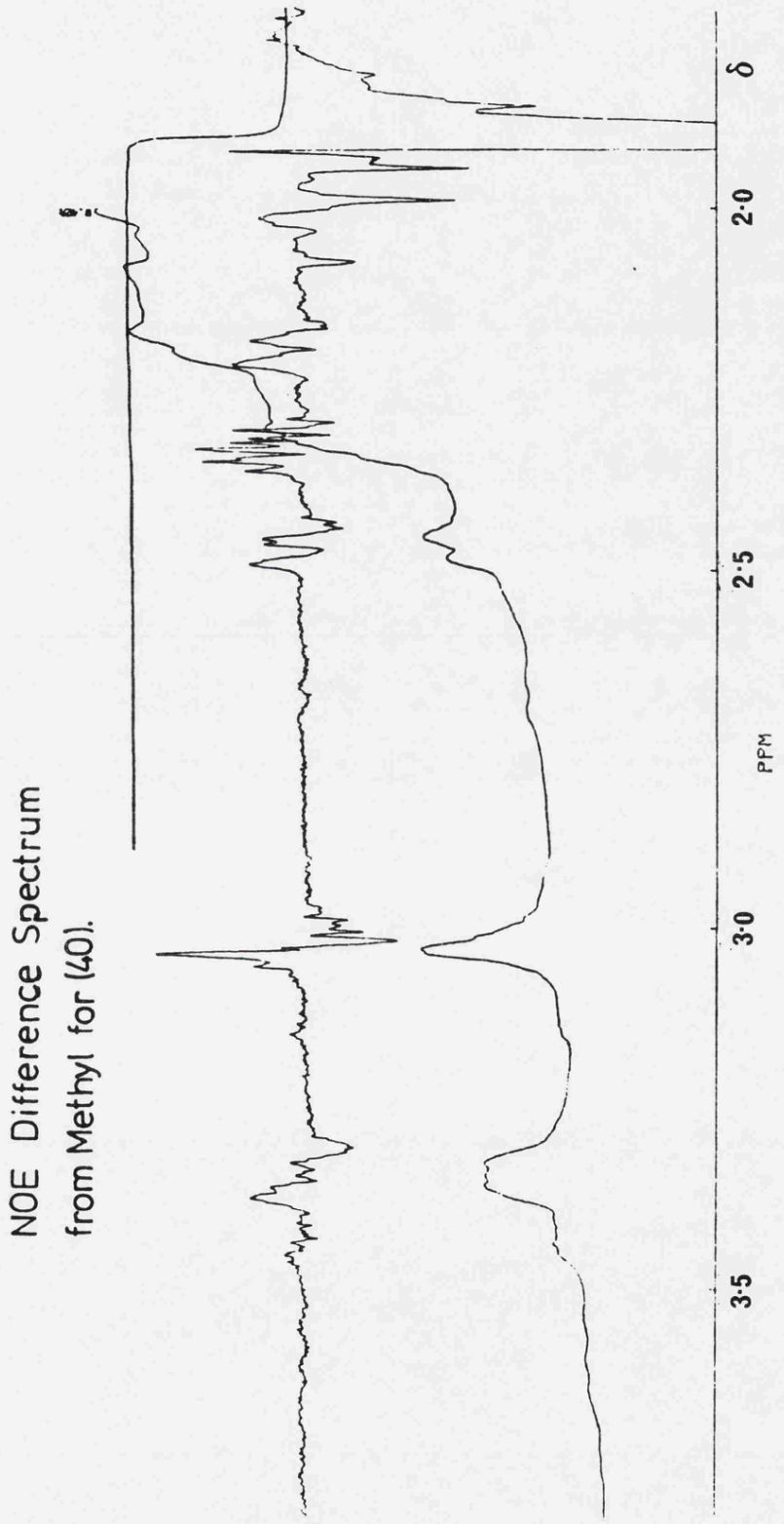


Figure 2:25

Me	a	b	c	d	e	f	g	
1.90	-	-	-	-	-	-	-	Me
	2.19	-	11.6	-	0.9	-	2.4	a
		2.33	-	10.4	-	7.0	-	b
			2.47	-	1.1	3.0	-	c
				3.03	-	-	6.7	d
					3.03	-	-	e
						3.32	1.8	f
							3.36	g

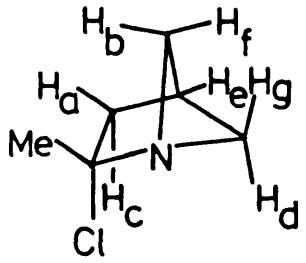


TABLE 2:8

Chemical shifts (δ, ppm) along diagonal.

Coupling constants (J, Hz) off-diagonal.

δ_H (400MHz; $CDCl_3$)

The rearrangement to form (40) seems to be a further example of chlorine retention in strained azabicycles occuring via a very tight ion-pair or a highly concerted transition state, (figure 2:27).

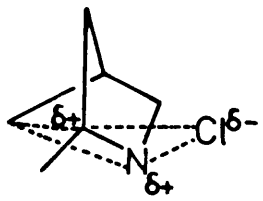


Figure 2:27

The retention of chlorine is quite a surprising result on the basis of Gassman's work (see figure 2:19). The presence of a methyl group α- to nitrogen should encourage the formation of a discrete tertiary carbenium ion (41) which would be subsequently intercepted by solvent to give (42), (figure 2:28).

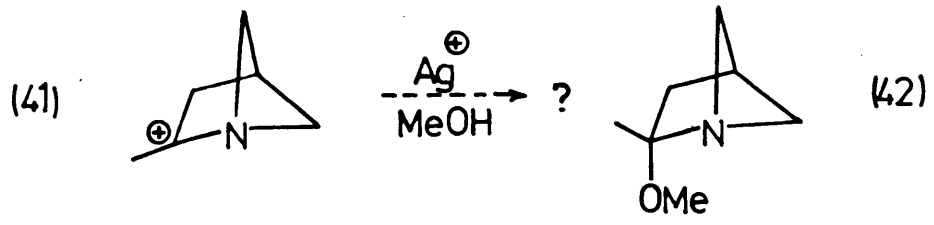


Figure 2:28

It was considered that it might be possible to obtain (42) by solvolytic rearrangement of (29) in the presence of silver-ion. However the unexpected product which was isolated when this reaction was attempted, was the 1-pyrroline

derivative (43), (figure 2:29).

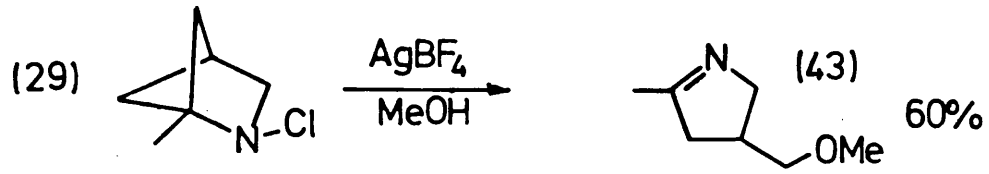


Figure 2:29

It was thought at first that the mechanism might involve the formation of the chlorine-retained product (40) which could then further rearrange under the reaction conditions, (figure 2:30).

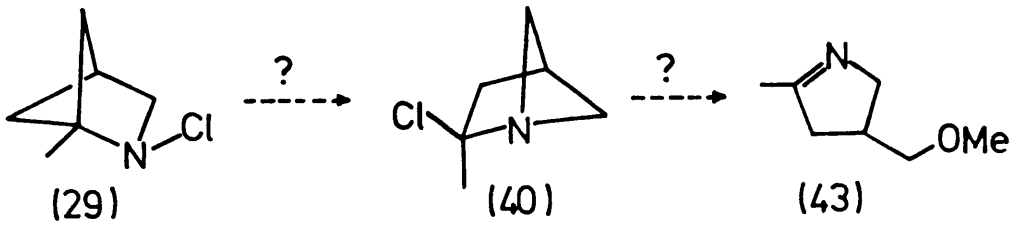


Figure 2:30

However, when (40) was subjected to similar reaction conditions only unchanged (40) was recovered (46% yield). Therefore the proposed mechanism involves removal of chloride by silver-ion to produce the relatively stable tertiary carbenium ion (41), followed by nucleophilic attack of methanol on the bridging carbon atom to cause ring opening and imine formation, (figure 2:31).

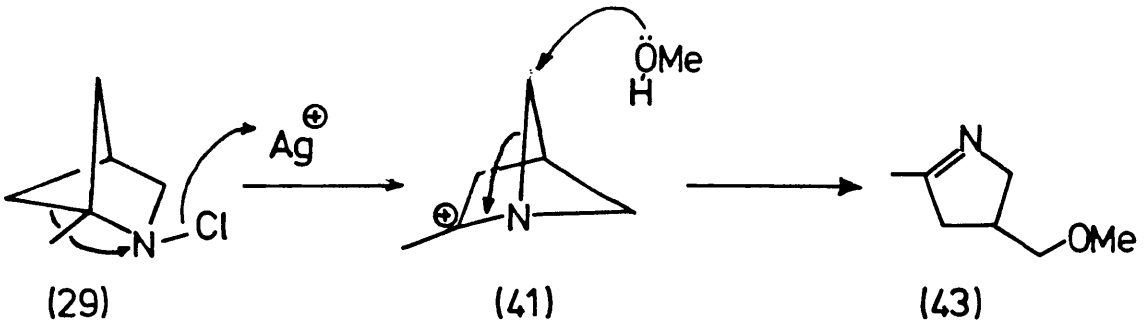


Figure 2:31

Before discussing the evidence leading to the assignment of the structure of (43) it is necessary to describe the further rearrangement chemistry of the C-chloro compound (40). It was found that treatment of (40) with hydrogen chloride gas followed by basification with aqueous potassium hydroxide unexpectedly led to the product (44) which is very similar to (43), (figure 2:32).

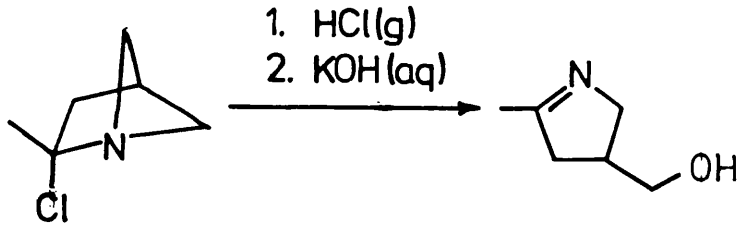


Figure 2:32

Given that the N-chloroamine (40) itself is stable to aqueous base, its N-protonated form (45) must encourage attack at one of the one-carbon bridges with concomitant relief of strain, (figure 2:33).

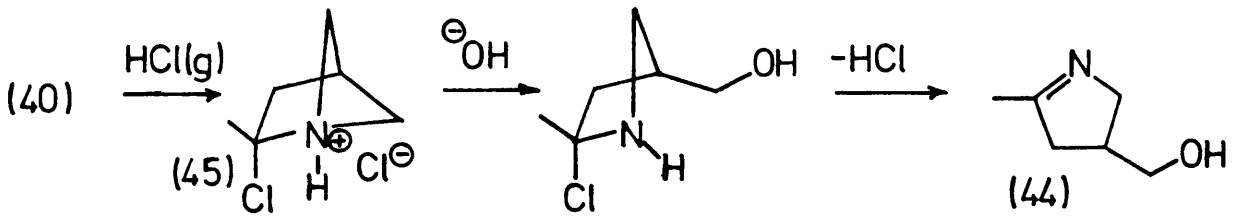


Figure 2:33

When (43) was subjected to the same reaction conditions it was recovered unchanged.

The high field (400 MHz) ^{1}H NMR spectra of (43) and (44), (figure 2:34) were very similar. To help with the assignments of the spectra a COSY experiment was performed on a sample of (44), (figure 2:35). Both compounds (43) and (44) showed characteristic imine stretching absorptions in the IR spectrum at 1650 cm^{-1}. From the ^{1}H NMR spectra it was possible to assign the relative positions of all the protons within the molecules except those of the methyl group. The methyl group for both (43) and (44) showed a small coupling to the protons H_a and H_b. The two possible structures which might fit the data are shown in figure 2:36.

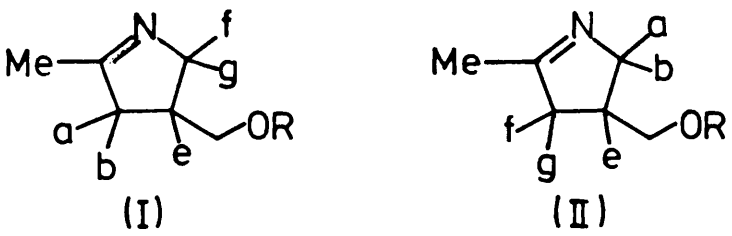


Figure 2:36

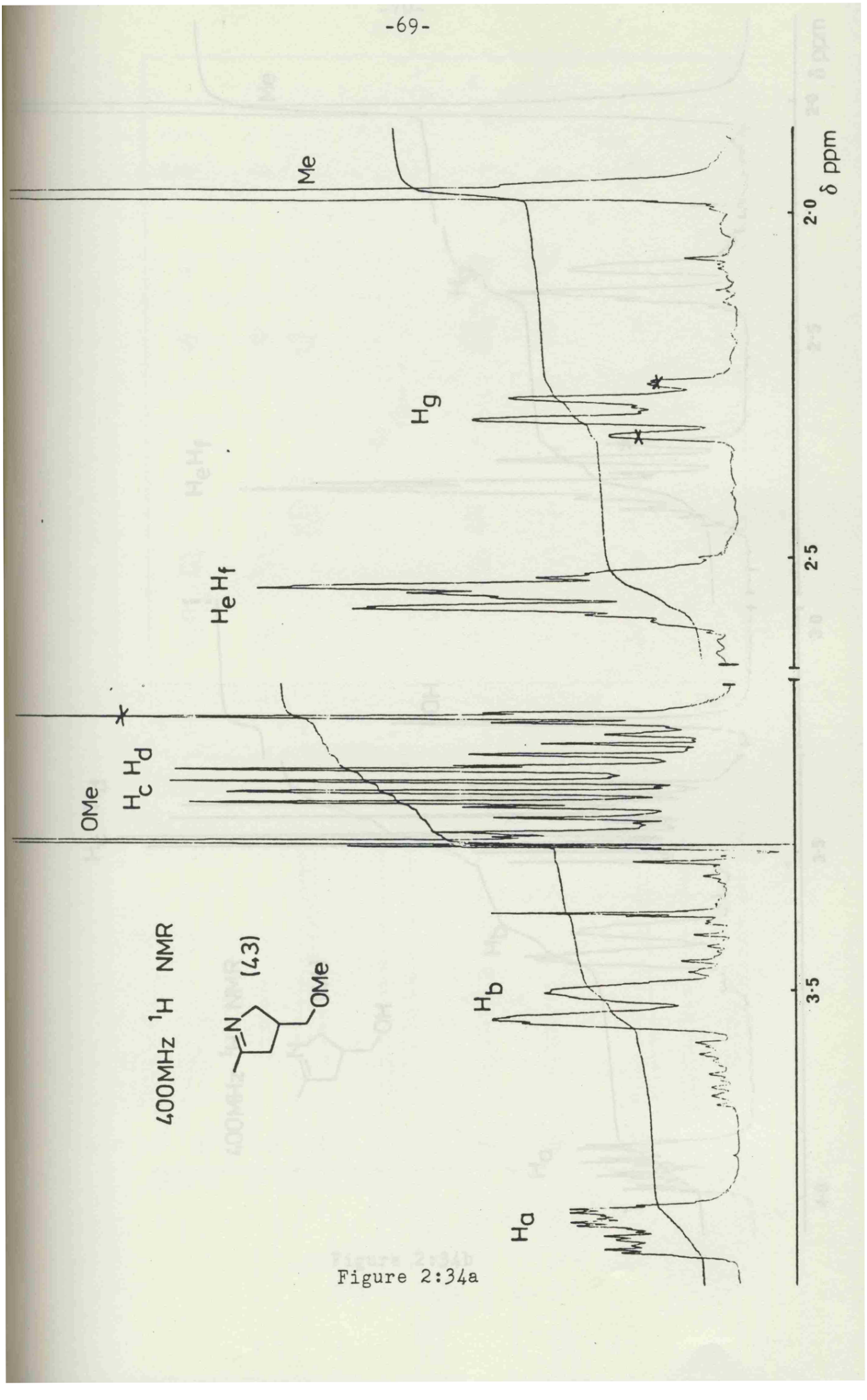


Figure 2:34a

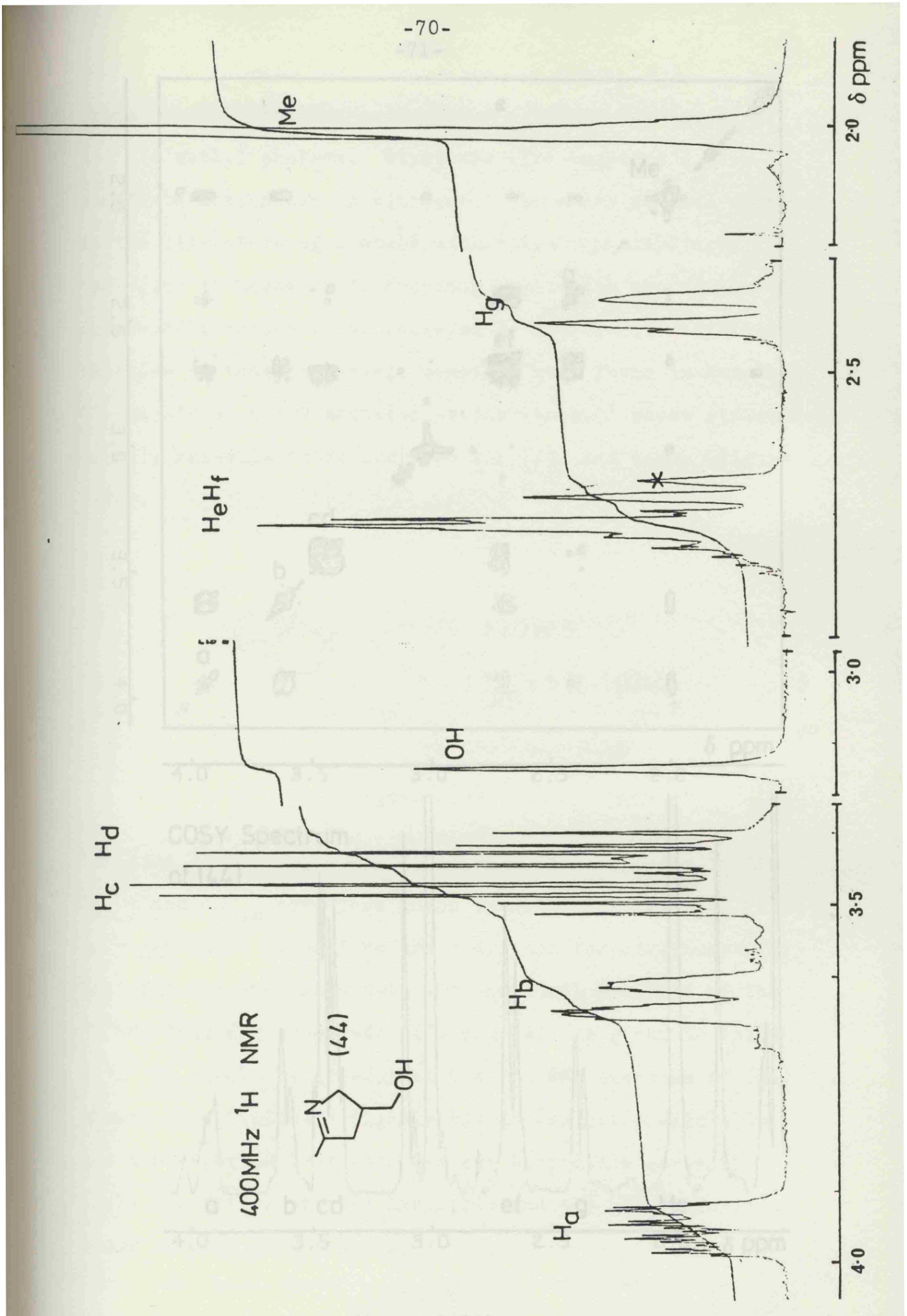


Figure 2:34b

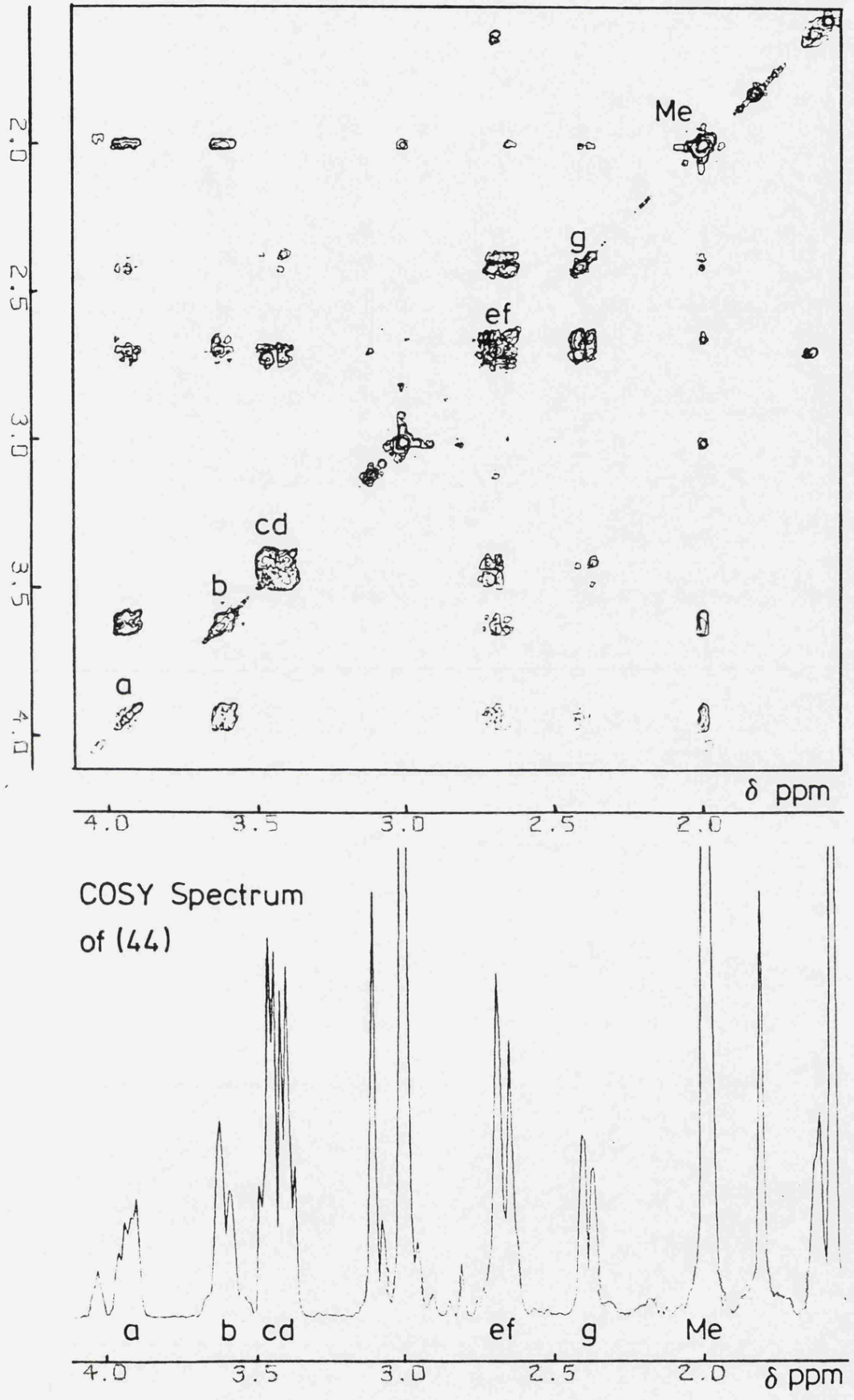
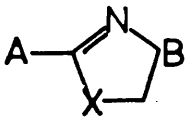

Me
g
ef
cd
b
a
δ ppm
4.0
3.5
3.0
2.5
2.0
COSY Spectrum
of (44)
a
b
cd
ef
g
Me
δ ppm

Figure 2:35

Structure (I) requires a four-bond coupling between H_a/H_b and the methyl protons. Structure (II) requires a five-bond interaction across nitrogen. There are several examples in the literature of systems with long-range couplings, analogous to homoallylic coupling - but with one of the intervening carbon atoms replaced by nitrogen.[61] Particular examples of this long-range coupling were found in 2-methyl-Δ^2-oxazolines and 2-methyl-Δ^2-thiazolines,[62] whose structures closely resemble those proposed for (43) and (44), (figure 2:37).



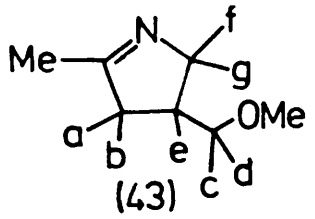
X=O or S

J_{AB} = 1·38-1·60Hz

Figure 2:37

The size of the J_{AB} coupling is of a similar order to the $J_{Me,a}$ and $J_{Me,b}$ couplings found in compounds (43) and (44), (J = ca. 2Hz). Therefore the couplings for structure (II) best fit the available data and the final analysis of the ^1H NMR data for compounds (43) and (44) is given in table 2:9. It should be noted that the ^{13}C NMR spectrum of (44) showed five "upfield" signals but it was not possible to see the expected C=N; this was not surprising given the small quantities of (44) available and the long relaxation times of such carbon atoms.

TABLE 2.9a



(43)

(43) δ_H (400 MHz; $CDCl_3$)

2.02 (3H, brs)

2.41 (1H, brd, J_{fg} 12 Hz, J_{ag}, J_{dg}, J_{eg} small, H_g)

2.57 (1H, brm, H_f)

2.57 (1H, brm, H_e)

3.19 (1H, ddd, J_{cd} 14 Hz, J_{de} 8 Hz, J_{dg} small, H_d)

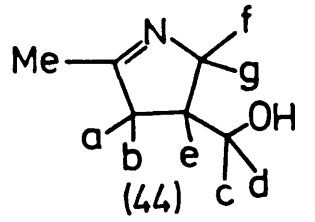
3.21 (1H, dd, J_{cd} 14 Hz, J_{ce} 8.2 Hz, H_c)

3.28 (3H, s, -OMe)

3.52 (1H, brd, J_{ab} 15 Hz, J_{be} small, J_{bMe} small, H_b)

3.84 (1H, brddq, J_{ab} 15 Hz, J_{ae} 8 Hz, J_{aMe} 2 Hz, J_{ag} small, H_a)

TABLE 2.9b



(44)

(44) δ_H (400 MHz; $CDCl_3$)

2.02 (3H, brs)

2.41 (1H, brd, J_{gf} 13 Hz, J_{eg}, J_{dg}, J_{ag}, H_g)

ca. 2.70 (1H, brm, H_f)

ca. 2.70 (1H, brm, H_e)

3.14 (1H, brs, -OH)

3.42 (1H, brdd, J_{cd} 11 Hz, J_{de} 7 Hz, J_{dg} small, H_d)

3.48 (1H, brdd, J_{cd} 11 Hz, J_{ce} 6 Hz, J_{cg} small, H_c)

3.63 (1H, brdq, J_{ab} 16 Hz, J_{bMe} 2 Hz, J_{be} small, H_b)

3.95 (1H, brddq, J_{ab} 16 Hz, J_{ac} 8 Hz, J_{aMe} 2 Hz, J_{ag} small, H_a)

Further consideration of the data gathered for the rearrangement reactions of (29) and (40) has led to the following tentative proposals. Since (40) can be shown to be neither an intermediate nor a product of the silver-catalysed rearrangement of (29), it may be assumed that this reaction proceeds via a carbenium ion intermediate (as described in figure 2:31). This would mean that although (29) is highly strained, the internal return of chloride-ion is not competitive with tertiary carbenium ion formation, during rearrangement under these solvolytic conditions. Therefore the clean production of (40) from (29) under conditions of alumina catalysis cannot be uniquely dependent on the highly-strained structure of (29) and must, to a significant extent, be due to the nature of the alumina catalyst.

It may thus tentatively be predicted that other sufficiently strained N-chloroazabicycles, which would normally rearrange under conditions of silver-ion catalysis via a tertiary carbenium ion intermediate to afford products in which chlorine is absent, could be rearranged in the presence of alumina catalysis to give products in which the chloride is retained.

2.IV Summary

The N-chloroamine (29) has been synthesised and the barrier to nitrogen inversion measured as 71.5 $kJmol^{-1}$ (which is not sufficiently high to confer configurational stability at nitrogen). The rearrangement chemistry of (29) has also been extensively studied; of particular interest was the alumina-catalysed rearrangement which produced the chlorine-retaining compound (40), which is the first reported derivative of the 1-azabicyclo[2.1.1]hexane ring system. In the reaction which produced (40), none of the expected carbenium ion-derived product was observed. It seems that this must be due to the highly-strained nature of (29) and also to the influence of the alumina catalyst. The silver-ion-catalysed methanolysis of (29) and the basic hydrolysis of protonated-(40) were shown to produce similar 1-pyrroline derivatives, whose structures were elucidated with the aid of high-field NMR experiments.

CHAPTER 3

SYNTHESIS AND STUDY OF 9,10-DIHYDRO-ANTHRACEN-9,10-IMINE SYSTEMS AND THE SOLVOLYTIC BEHAVIOUR OF THEIR N-CHLOROAMINE DERIVATIVES

3.I Introduction

a) Inversion barriers in 7-azabicyclo[2.2.1]heptyl derivatives

The previous chapter discussed the raising of inversion barriers at nitrogen in azabicycles by reducing the size of the carbon bridges in such systems, effectively increasing the angle strain at nitrogen (CN̂C). The search for compounds with even higher barriers than those obtained for the 2-azabicyclo[2.1.1]hexyl system would logically lead to the study of the even more strained 2-azabicyclo[1.1.1]pentyl system. At the moment, this would be impractical, as there is no readily available synthesis for such systems; further if they could be prepared they would be difficult to handle due to their high volatility.

In the preceding chapter, mention of a certain azabicycle was deliberately omitted. This was 7-azabicyclo[2.2.1]-heptane, whose derivatives are known to possess anomalously high barriers to nitrogen inversion. The expected CN̂C angle for the 7-azabicyclo[2.2.1]heptyl structure is comparable to that found in azetidines (ca. 95°), yet the inversion barriers for these systems are at least 20 $kJmol^{-1}$ higher, (table 3:1). Therefore in these systems, factors other than ring strain must have a large influence on inversion barriers. The simplest derivative for which an inversion barrier has been reported is 7-methyl-7-azabicyclo[2.2.1]hept-2-ene (45),[63] but many other more elaborate systems have been prepared and studied. Table 3:2 shows a few such examples.

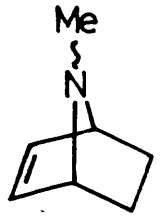
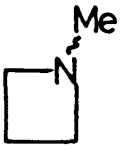
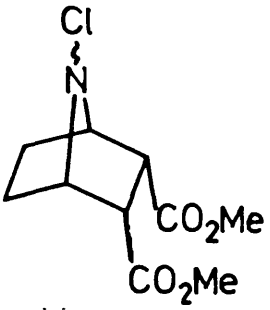
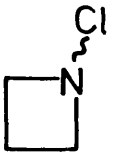
	Barrier to Inversion $\Delta G^{\ddagger}$ (kJ/mol)		Barrier to Inversion $\Delta G^{\ddagger}$ (kJ/mol)
	62·3[11]		42·7[2]
	87·8[1]		56·1[2]

Table 3:1

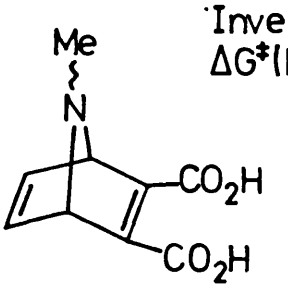
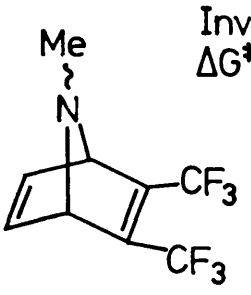
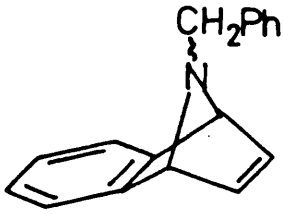
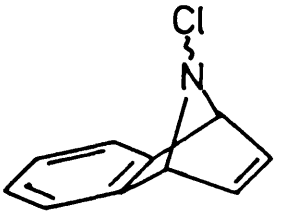
	Barrier to Inversion $\Delta G^{\ddagger}$ (kJ/mol)		Barrier to Inversion $\Delta G^{\ddagger}$ (kJ/mol)
(45) 	81·5[1]		62·3[65]
	52·7[64]		98·2[1]

Table 3:2

Inversion barriers in 7-azabicyclo[2.2.1]heptyl systems have long been studied but relatively few studies have covered structurally comparable systems in a systematic fashion. Gribble et al.[66] reported inversion barriers for the N-methyl derivatives (46-48) and Sutherland[64] performed a similar study on N-benzyl derivatives (49-51), (table 3:3).

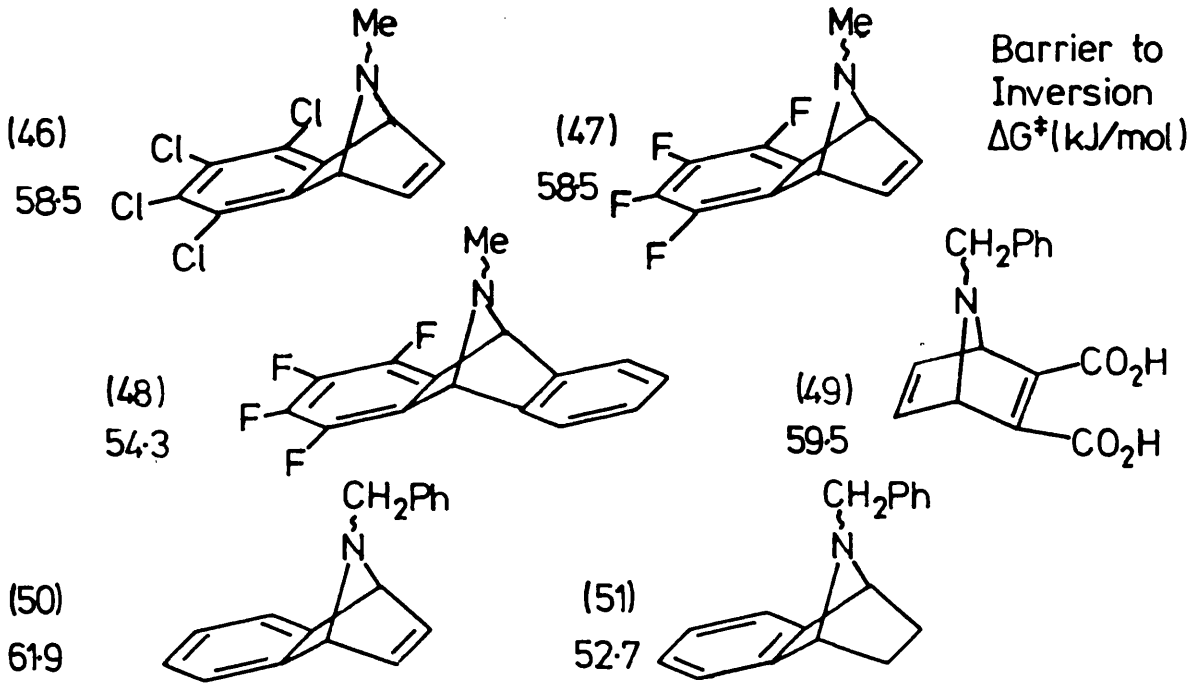


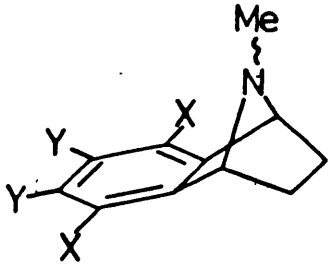
Table 3:3

More recently a qualitative study of the relative inversion barriers of 9-chloro-1,2,3,4-tetrahydronapthalen-1,4-imine derivatives, differing only in benzo-ring substitution, showed that the inversion barrier decreased as the aromatic ring became more electron-deficient.[67] A more detailed study was conducted into a series of 9-methyl-

1,4-dihydronapthalen-1,4-imines (52-56).[68] In these cases the inversion barriers were calculated from ^{1}H NMR coalescence temperature studies, the results of which are given in table 3:4.

Table 3:4

			Inversion Barriers	
	Compound	Tc(±2°C)[a]	$\Delta G^{\ddagger}$(anti→syn)[b]	$\Delta G^{\ddagger}$(syn→anti)[b]
(52)	x=y=Me	44°C	65.7	67.9
(53)	x=y=H	34	63.6	65.9
(54)	x=OMe, y=H	32	64.3	67.8
(55)	x=y=Cl	5	58.6	62.1
(56)	x=y=F	6	58.1	62.7

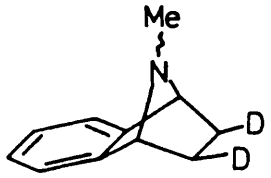


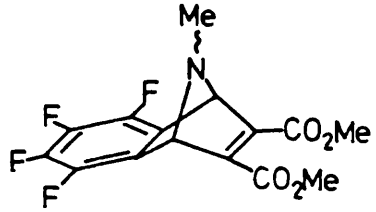
(a) (50-53) For N-methyl signals, (49) for vinyl signals.
(b) With respect to aromatic ring, all values ±0.43 kJmol^{-1}

The results confirm that the inversion barrier decreases as the benzo-ring becomes more electron-deficient. The inductive effect of an electron-withdrawing ring can be discounted as the cause of this trend, since the inductive effect of an unsaturated bridge via the σ-framework in such systems is negligible.[63] If such an effect did operate it would increase the s-character of the nitrogen lone-pair and raise the inversion barrier which is opposite to the effect observed. The rationale which seems to explain the

trend best was proposed by Lehn[1] and is based on the interaction of π-electrons with the nitrogen lone-pair. He explains that repulsions from π-electrons may cause the accumulation or localisation of electron density in the nitrogen lone-pair which would destabilise the transition state more than the ground state, and raise the barrier to inversion. The trend observed in table 3:4 could therefore be explained by the π-electrons of the aromatic rings of the napthalen-1,4-imine systems giving rise to such a repulsive interaction. The effect of electronegative substituents would reduce the electron density of the aromatic ring and therefore reduce the repulsive interactions (described above) and consequently the barrier height.

Inversion barrier measurements from related systems[68] can also be used to further probe Lehn's theory, (table 3:5).

(57) 

(58) 

		Inversion Barriers	
	Tc	$\Delta G^{\neq}$(anti→syn)	$\Delta G^{\neq}$(syn→anti)
(57)	-5°C[a]	55.2 kJ/mol[b]	61.3 kJ/mol[b]
(58)	-3°C[c]	56.2 kJ/mol[d]	57.2 kJ/mol[d]

a) ±4°C b) ±1 kJ/mol

c) ±2°C d) ±0.43 kJ/mol

Table 3:5

It seems that the decrease in barrier of (53) when deuterogenated to give (57) (63.6 → 55.2 $kJmol^{-1}$) would be expected on the basis of Lehn's proposal, as the removal of the π-bond

would reduce replusive interactions with the nitrogen lone-pair. Similarly, when the electron density of the π-bond of (56) is reduced by electron withdrawing subsitiuents, as in (58), the barrier is lowered by a smaller amount (58.1 → 56.2 $kJmol^{-1}$).

Interactions between nitrogen lone-pairs and π-bonds in azabicyclic systems have also been extensively studied by Morishima et al.[23,69,70,71] One aspect of this work has already been covered in Chapter 1). The investigations concerned the influence of homoconjugative effects in determination of lone-pair preferences in such systems. Two possible limiting cases were considered, (figure 3:1).

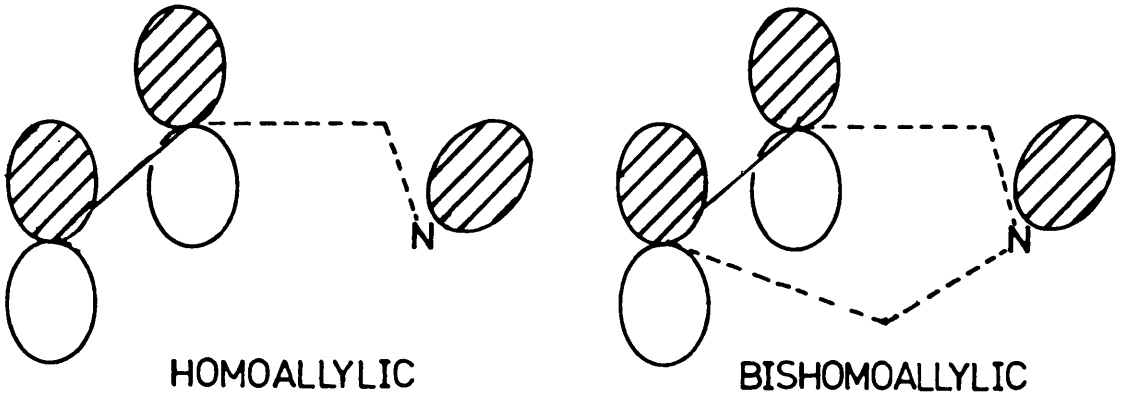


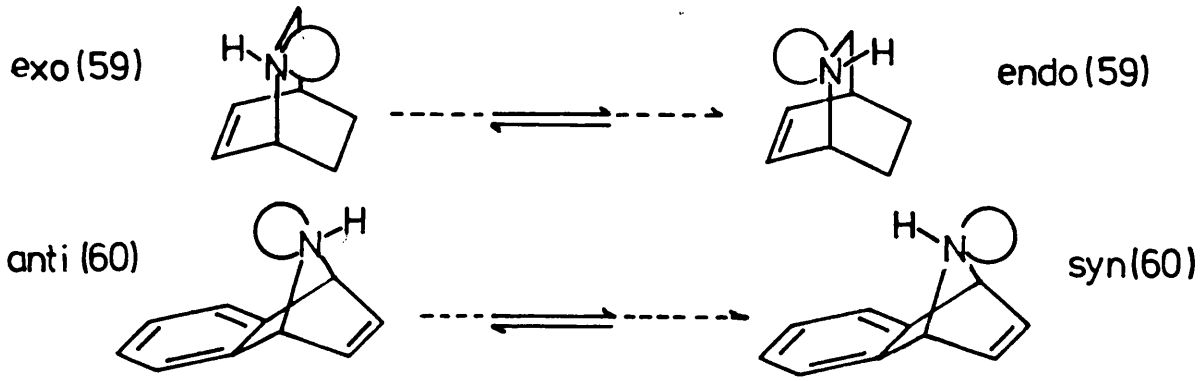
Figure 3:1

The first case, homoallylic interaction, occurs when the nitrogen lone-pair formally overlaps with one of the p-orbitals of a π-bond in a homoconjugative fashion. It is described as homoallylic since normal allylic conjugation is prevented by the presence of an intervening sp^3 hybridised carbon atom. Such an interaction should exert a stabilising influence and therefore determine the lone-pair preference.

In the second case, bishomoallylic interaction, two sp^3 hybridised carbon atoms interrupt the normal allylic

interaction. This type of overlap is considered a repulsive situation and Morishima predicted that, when possible, the lone-pair would prefer that orientation which avoided such an interaction. For 1,4-dihydronapthalen-1,4-imines he predicted that the lone-pair would interact with the less electron-rich double bond.

Grutzner[24] noted that Morishima's own results implied that homoconjugative interactions of this kind cannot be of great energetic consequence. Morishima et al. reported that for compounds (59)[69] and (60)[23], which are typical examples of homoallylic and bishomoallylic interactions respectively, no invertomeric preferences are observed, (figure 3:2).

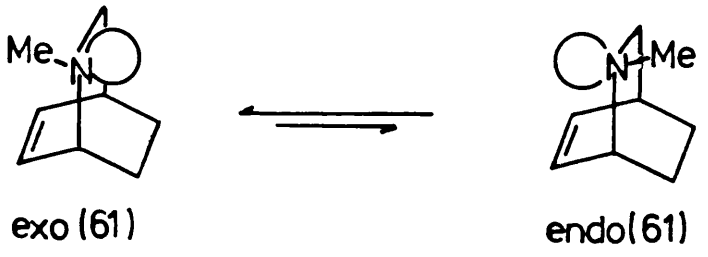


The predicted preferences on the basis of homoconjugative effects are indicated by the dashed lines.

Figure 3:2

Underwood[25] and Grutzner[24] both comment that any homoallylic interaction between the nitrogen lone-pair and the π-bond must be small and that any stabilisation arising

from such delocalisation must also be extremely small in comparison with other factors. From Morishima's work it can be seen that steric factors easily dominate homoallylic interactions: When the N-H bond of (59) was replaced by a $N-CH_3$, as in (61), then the exo-invertomer is strongly preferred due to steric repulsion between the $N-CH_3$ and the ethano-bridge in the endo-invertomer, (figure 3:3).

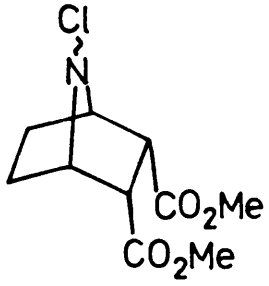


exo (61) endo(61)

Figure 3:3

Thus, having considered interactions between the lone-pair on nitrogen and adjacent π-bonds it has been shown that these interactions can only be of minor energetic signficance. Likewise, it has previously been shown that the contribution of this type of interaction to barrier elevation in 7-azabicyclo[2.2.1]-heptyl systems is small. Therefore these interactions, by themselves, cannot in any way account for the anomalously high barriers found in 7-azabicyclo[2.2.1]heptyl systems. Such interactions would also provide no satisfactory explanation of the high barrier observed for (62) and similar systems in which no π-bonds are present at all, (figure 3:4).

(62)



Barrier to Inversion[1]

$\Delta G^{\ddagger}$ = 87.1 kJ/mol

Figure 3:4

b) <u>The stereospecificity of electrophilic chlorination of 1,4-dihydronapthalen-1,4-imine and its derivatives</u>

It had previously been recongnised that 9-chloro-1,4-dihydronapthalen-1,4-imine (63) possesed a high barrier to nitrogen inversion (98.5 $kJmol^{-1}$).[72] Also when it was prepared in solution at -5°C, by the action of NCS on the parent amine (62), the ratio of invertomers produced was noted to be different to the ratio observed once the solution had been allowed to warm to ambient temperature, (figure 3:5).

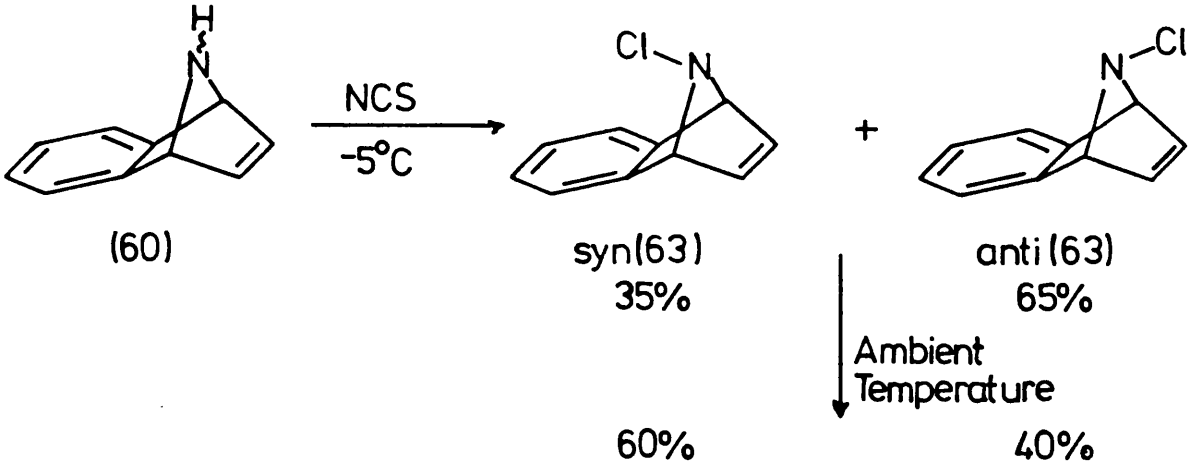


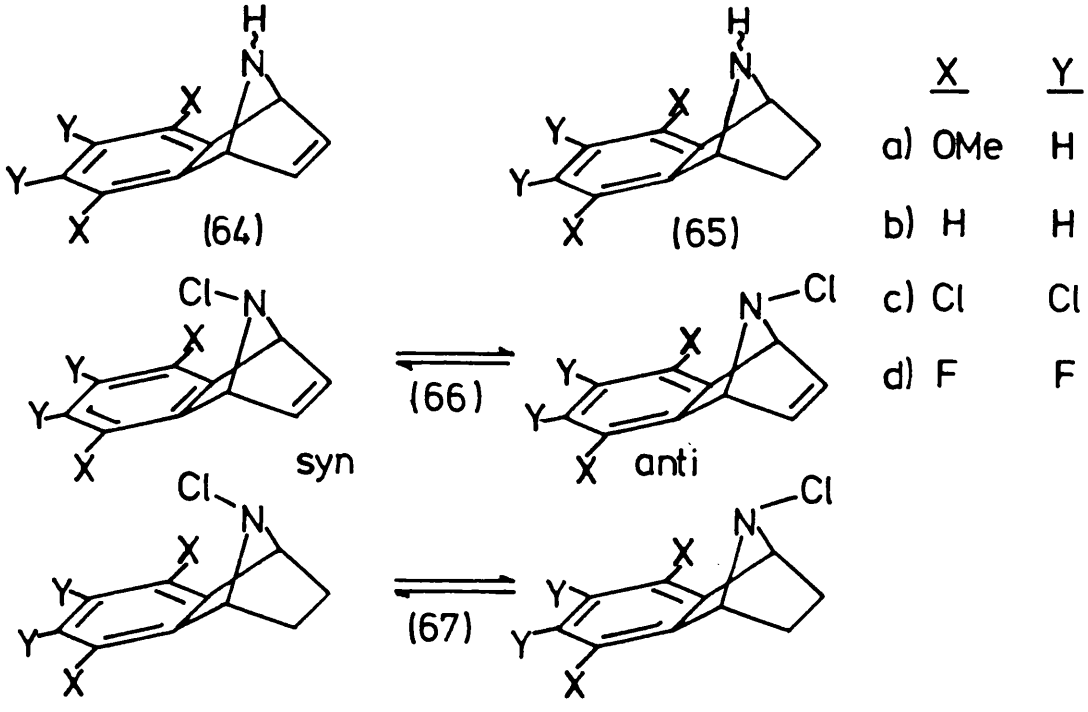
Figure 3:5

The factors giving rise to these varying invertomer ratios were of interest. Further investigations were carried out on a series of 9-chloro-1,4-dihydro- and 9-chloro-1,2,3,4-tetrahydronapthalen-1,4-imines in which subsituents in the aromatic ring were varied to produce a range of compounds

with different electronic enviroments.[73]

The parent secondary amines of these systems were chlorinated in deuterochloroform solution by NCS at -5°C. At this temperature the secondary amine is still inverting rapidly but once the N-chloroamine is formed, inversion is effectively frozen. The ratio of invertomers produced at this temperature reflects the direction of chlorination by NCS. This ratio of invertomers being produced under conditions of kinetic control is known as the kinetic ratio. On warming the solutions to ambient temperatures, where the rate of nitrogen inversion in the N-chloroamines is rapid, thermodynamic equilibrium is reached. The ratio of invertomers is then known as the thermodynamic ratio, reflecting the balance of steric and electronic influences acting on the two diastereoisomeric invertomers. Table 3:6 shows the results of the study of stereoselectivity in the chlorination of 1,4-dihydronapthalen-1,4-imines.

Table 3:6



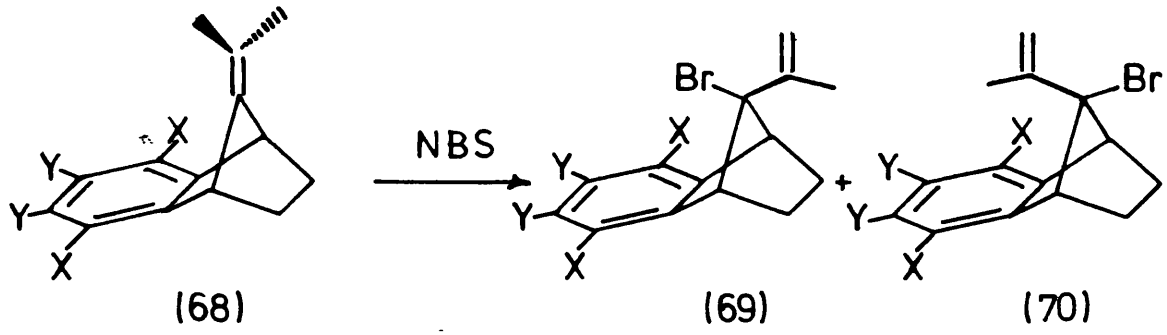
	X	Y
a)	OMe	H
b)	H	H
c)	Cl	Cl
d)	F	F

Substrate	Ratio of Syn:Anti under kinetic control		under thermodynamic control
64a	34:66	66a	67:33
b	28:72	b	60:40
c	41:59	c	82:18
d	68:32	d	84:16
65a	5:95	67a	54:46
b	6:94	b	53:47
c	18:82	c	71:29
d	20:80	d	80:20

Low temperature, kinetic chlorination was found to occur predominantly from the side 'anti' to the aromatic ring, however there was an increased tendency for attack from over the aromatic ring as the substituents on the ring became more electronegative. At ambient temperatures the thermodynamically-controlled ratios were found to be generally opposite to those derived kinetically.

A trend for increased attack over the aromatic ring as the substituents became more electronegative was also noted in an analogous system. Paquette et al.[74] had reported a similar trend in the addition of a variety of electrophiles to several 7-isopropylidene-benzonorbornenes, (table 3:7)

Table 3:7



Substrate(68)	% syn-product	% anti-product
X=OMe, Y=H	14	86
X=Y=H	19	81
X=Y=Cl	55	45
X=Y=F	58	42

Paquette et al. proposed that when the aromatic π-cloud is decreased by electronegative substituents, the aromatic ring becomes better able to stabilise the transition state for 'syn' attack by interaction with the negatively charged succinimide moiety of the brominating agent. Calculations predicted the development of a positive electrostatic potential over the aromatic ring in the tetrafluoro-derivative. (Figure 3:6)

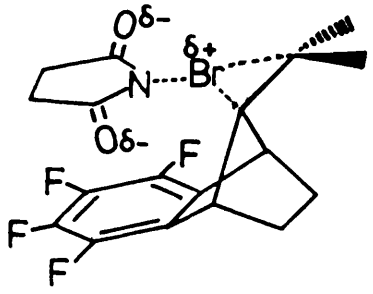


Figure 3:6

In an analogous situation, chlorination of 1,4-dihydro-napthalen-1,4-imines the trend can be explained by invoking a similar transition state, (figure 3:7).

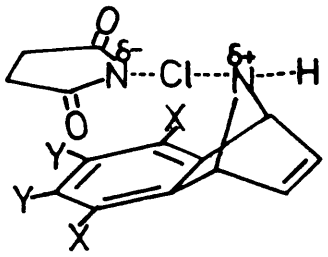


Figure 3:7

In this case, the interaction of the developing negative charge on the trailing-imide nitrogen atom with the aromatic ring would be stabilised as the electron density of such a ring is reduced by electron withdrawing substituents.

c) The solvolytic reactions of 9-chloro-1,4-dihydronapthalen-1,4-imine derivatives and related systems

The first report of solvolytic reactivity in such systems was by Rautenstrauch[72] who showed that 9-chloro-1,4-dihydronapthalen-1,4-imine existed in two invertomeric forms. Under given conditions each invertomer underwent heterolysis reaction at nitrogen with a different rate, via a different route, to give a different product. Although tentative structures were assigned to these products they were subsequently found to be incorrect and were reassigned in a later study,[75] (figure 3:8).

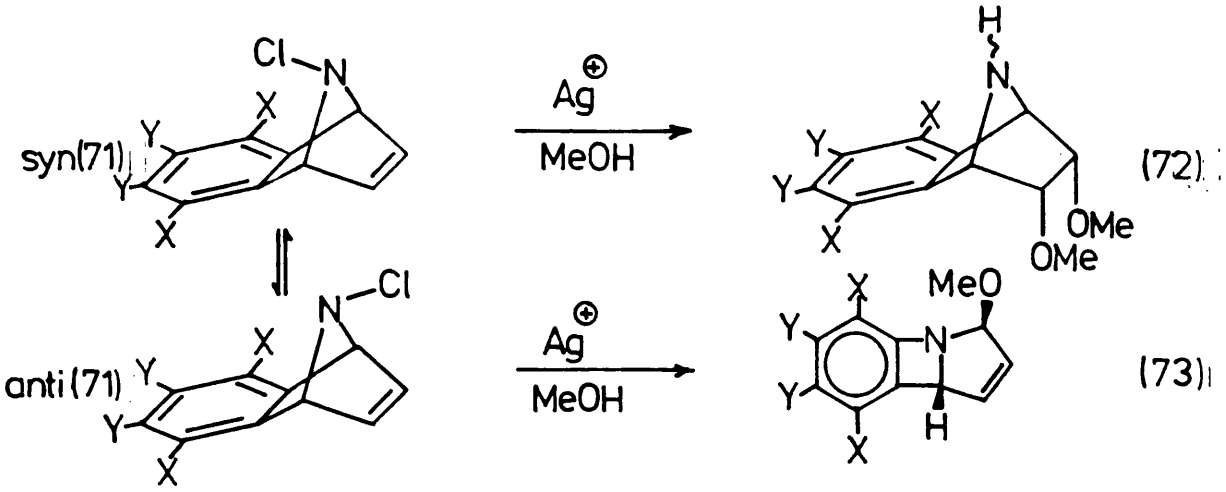


Figure 3:8

This more recent work covered a series of 9-chloro-1,4-dihydronapthalen-1,4-imines in which the character of the aromatic ring was varied by substitution. These N-chloro-amines possessed relatively high barriers to nitrogen inversion (ca.95 $kJmol^{-1}$) which allowed heterolytic rearrangements to be studied under conditions of negligible inversion (ca. $0^{o}C$) and also under conditions of rapid inversion (ca. $25^{o}C$).

Below $0^{o}C$ the invertomers did not interconvert and when treated with silver salts in methanol followed separate reaction pathways. The 'anti' invertomers generally gave products via benzo-participation (73a, 73b), whereas the 'syn' invertomers gave amine products (72a, 72b, 72c), (figure 3:8).

Further studies of these silver-ion promoted reactions showed (71b) to be considerably more reactive than (71a) and anti-(71b) reacted more rapidly than syn-(71b) showing the profound effect of the methoxy-substituents in encouragement of aryl-participation. In contrast (71c) proved unreactive

under any conditions. At ambient temperatures in the presence of methanol only, (71a) and (71c) formed (72a) and (72c). In these reactions the 'anti' invertomer was converted to the 'syn' form before rearrangement could occur via aryl-participation. However for (71b) the aryl-participation route was still competitive under these conditions (of rapid inversion) and both (72b) and (73b) were formed. Subsequent studies of the 1,2,3,4-tetrahydronapthalen-1,4-imines[68] showed that only (74b) reacted under conditions of silver-ion catalysis (with slow or rapid nitrogen inversion), (figure 3:9).

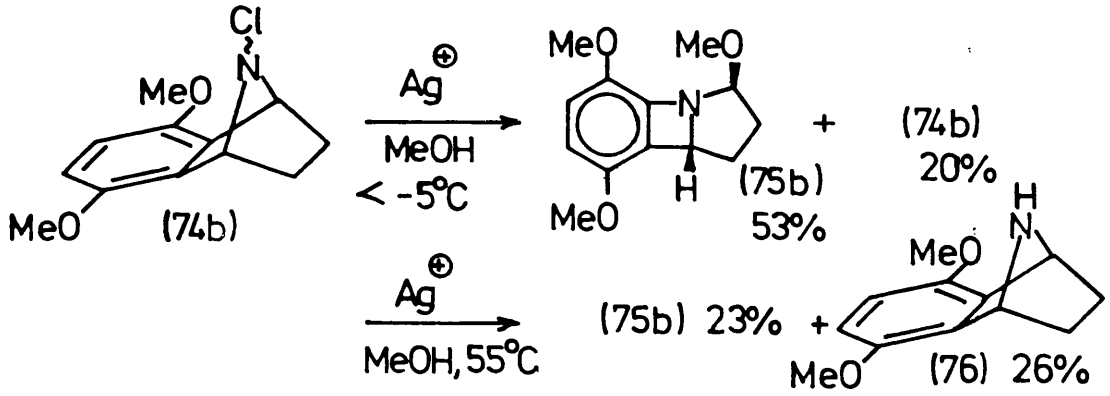


Figure 3:9

The dechlorinated amine in the high temperature reaction probably arises from homolytic fission of the N-Cl bond. The unchanged starting material in the low temperature reaction was probably due to unreacted 'syn' invertomer.

A related system (77) was also found to undergo solvolysis reactions at room temperature to give (78) and (79). In this case it proved possible to separate the 'syn' and 'anti' invertomers due to their different solubilities in trichlorofluoromethane at $0^{o}C$. When pure anti-(77) was solvolysed in the presence of $AgClO_4$ at low temperature, the product from participation of the napthalene π-system

(80) was isolated, (figure 3:10).

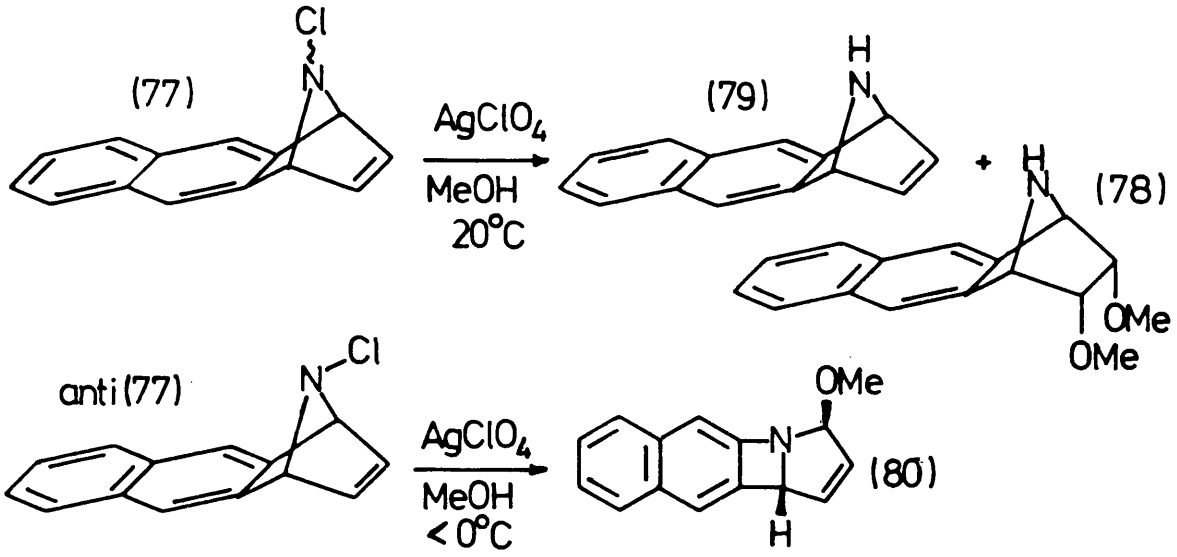


Figure 3:10

d) 11-Substituted-9,10-dihydroanthracen-9,10-imine systems

In the previous parts (a-c) of this introduction, considerable emphasis has been placed on studies of various series of 1,4-dihydronapthalen-1,4-imines with particular attention being paid to the influence of aryl-substitution on both configuration at nitrogen and solvolytic activity. The nature of these systems meant that comparisons of the relative effects of aryl groups could only be made with reference to a carbon-carbon double bond. Recently several syntheses of 9,10-dihydroanthracen-9,10-imine systems have been reported.[76,77] These systems still posses the 7-aza-bicyclo[2.2.1]-heptyl skeleton and thus also posses anomolously high barriers to nitrogen inversion. In such systems it would be possible to compare the effects of two different aryl groups on the configuration at nitrogen, within the same molecule. The advantage of this is that the substituent on nitrogen can be influenced by two environments sterically

very similar and yet electronically dissimilar. The electronic environments could be varied by the choice of substituents on each of the aryl rings. Thus the configuration of the substituent at nitrogen would be determined predominantly by the electronic influences exerted by both aryl rings.

Thus it was hoped that the systems chosen for study would exhibit contrasting behaviour between electron rich and electron deficient aryl groups within the same molecule, (figure 3:11).

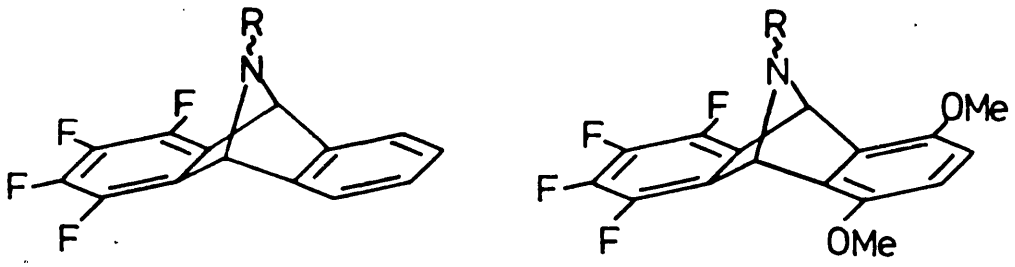


Figure 3:11

3.II Synthesis and Spectroscopic Investigations of 11-Benzyl-1,2,3,4-tetrafluoro-9,10-dihydroanthracen-9,10-imines.

9-Benzyl-5,6,7,8-tetrafluoro-1,4-dihydronapthalen-1,4-imine (81) was prepared by the Diels-Alder reaction of 1-benzylpyrrole[78] with tetrafluorobenzyne.[79,80] This was then treated with 3,6-di-(2-pyridyl)-1,2,4,5-tetrazine[81] to afford an adduct which undergoes a mild fragmentation reaction to produce 2-benzyl-5,6,7,8-tetrafluoroisoindole (82);[82] which had previously been prepared by flash vacuum thermolysis of (81).[80]

The isoindole (82) was converted into the 11-benzyl-1,2,3,4-tetrafluoro-9,10-dihydroanthracen-9,10-imines (83) and (84) by further benzyne cycloadditions. Benzyne, itself, was generated from the Grignard reaction on 2-bromofluorobenzene.[83] When dimethoxybenzyne was prepared by the treatment of 2,5-dimethoxy-chlorobenzene with n-BuLi nucleophilic aromatic substitution by the n-butyl anion on the tetrafluorinated ring of (84) also occurred. This side-reaction was prevented in subsequent reactions by the use of a hindered base, lithium-2,2,6,6,-tetramethylpiperidide,[84] (figure 3:12).

The ^{1}H NMR spectra of (83) and (84) when observed at room temperature implied that nitrogen inversion might be rapid on the ^{1}H NMR timescale. At lower temperatures both ^{1}H and ^{13}C NMR showed that two invertomeric species were present in both compounds.

Before discussion can take place about the invertomer ratios obtained from the above NMR experiments, it is necessary to describe the assignments of the invertomers in each spectrum. These assignments from ^{13}C NMR were facilitated by the application of the γ-effect of carbon substitution.[85]

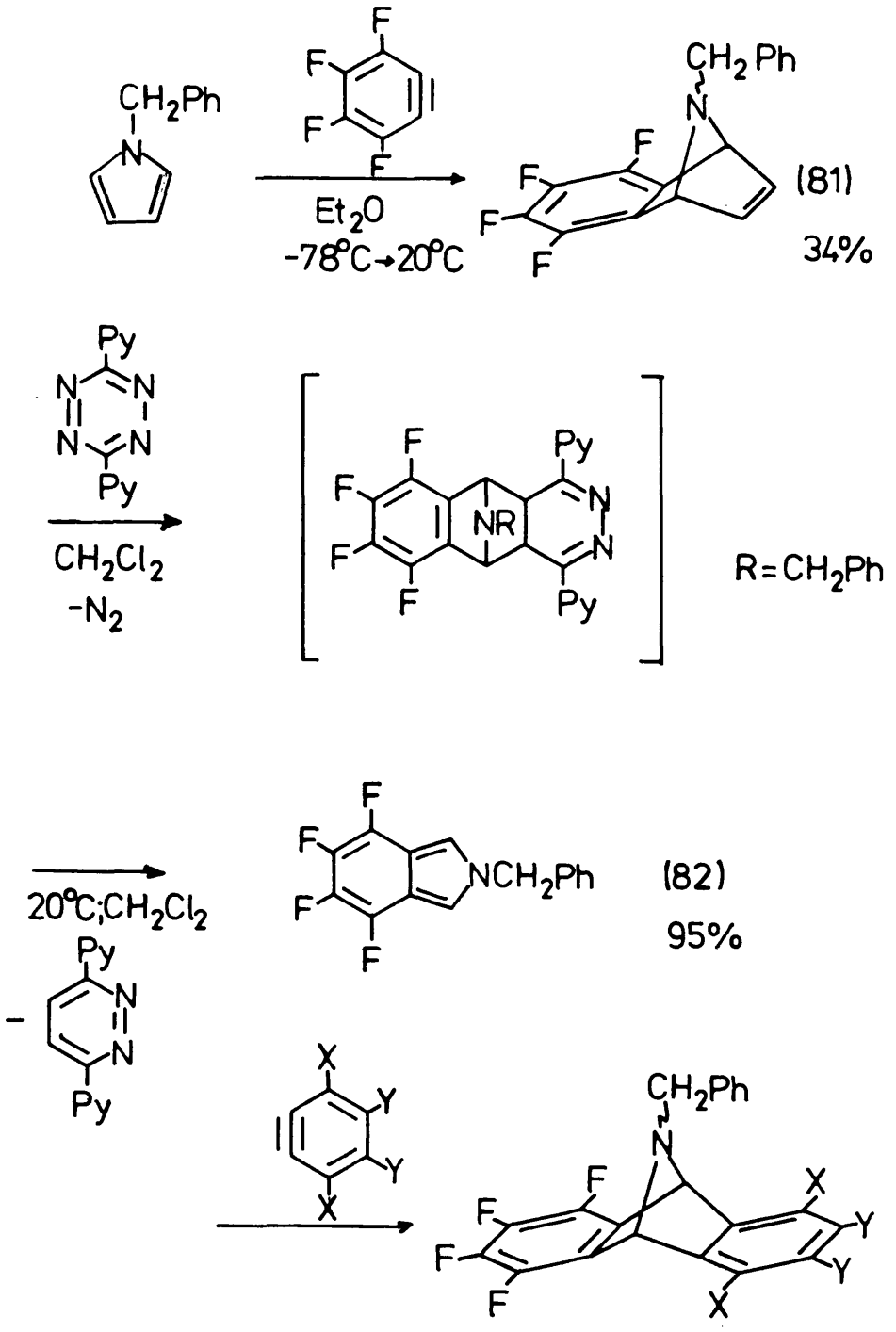

CH2Ph
Et2O
-78°C→20°C
CH2 Ph
(81)
34%
Py
CH2Cl2
-N2
NR
R=CH2Ph
20°C;CH2Cl2
NCH2Ph
(82)
95%
X=Y=H (83) 67%crude yield
X=OMe,Y=H (84) 30%

Figure 3:12

When a carbon atom is eclipsed by another carbon atom in the γ-position, the ^{13}C NMR shift of that carbon is at higher field than the shift of the same carbon trans-to it, (figure 3:13). This is also known as a Compression Shift induced by eclipsing carbon atoms.

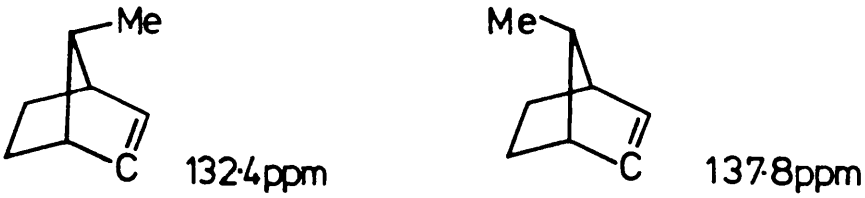
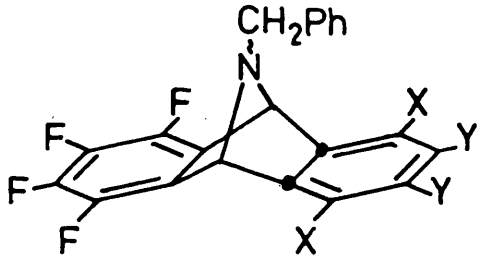


Figure 3:13

When this analysis was applied to the carbon atoms of the bridge opposite to the tetrafluoroaryl ring in (83) and (84), it was observed that in each case the minor invertomer gave rise to the furthest upfield shift. So in both (83) and (84) the major invertomer must be that in which the benzyl group lies to the side of the tetrafluoroaryl ring, (table 3:8).



Chemical Shifts δ ppm (bridgehead C.•)

(83) X=Y=H
major invertomer 134·35
minor " 132·35

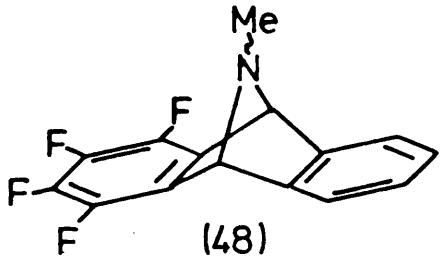
(84) X=OMe, Y=H
major invertomer 145·80
minor " 144·52

Invertomer Ratios	syn:anti
(83)	68 : 32
(84)	60 : 40

a) With respect to tetrafluoroaryl ring, ±2%, values from electronic integration of ^{1}H and ^{13}C NMR.

Table 3:8

The invertomer preference for (83) follows that reported for the N-methyl analogue (48)[68] and the invertomer ratios were very similar, (figure 3:14).



(48)

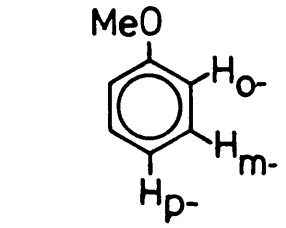
Invertomer Ratio[68]

syn : anti

71 : 29

Figure 3:14

The invertomer ratios in table 3:8 show that, in both compounds (83) and (84), there is a preference for the benzyl group to lie above the electron-withdrawing tetrafluoroaryl ring. From comparison of the ratios obtained for both systems it was evident that the dimethoxy-substituted ring of (84) might be slightly more electron deficient than the unsubstituted ring of (83). Although methoxy groups are normally associated with their (+R) resonance effect, in this case it cannot operate as there is no "electron sink" for the electron density to be "pushed" into. Thus the electron deficiency can be explained in terms of the (-I) inductive effect of the electronegative oxygen atom of the methoxy group. This effect is also thought to be responsible for the upfield shift experienced by protons of an aromatic ring when it is substituted with a methoxy group; indeed the aromatic protons of (84) were also observed to be upfield, (figure 3:15).

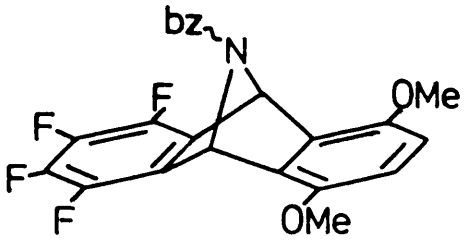


Δδ observed from benzene

H_{o-} = -0·42 ppm

H_{m-} = -0·04 ppm

H_{p-} = -0·37 ppm



(84) Chemical shift δ of $H_{arom.}$ = 6·58 ppm

Figure 3:15

Variable temperature ^1H NMR spectra of (83) and (84) were observed and their barriers to nitrogen inversion were estimated from coalesence temperature measurements. Since invertomer preferences in both (83) and (84) existed it was necessary to use modified calculations in order to take account of the slightly different relative energies of each invertomer (unnecessary in the 2-azabicyclo[2.1.1]hexane systems because the ratio of invertomers in these systems was 50:50 due to their symmetrical nature.) The calculations used provided separate inversion barriers for the syn→anti and anti→syn inversion processes, and were made as follows: from the equations[86]

$$\bar{T} = \frac{T_{anti}\ T_{syn}}{T_{anti}+T_{syn}} \qquad \text{and} \qquad K_{eq} = \frac{T_{anti}}{T_{syn}}$$

where: $\bar{T}$ = population weighted lifetime of the system.

T_{syn}, T_{anti} = lifetimes of the syn and anti invertomers.

K_{eq} = equilibrium constant 'syn' $\rightleftharpoons$ 'anti'

The rate constants for the inversions from 'syn' to 'anti' and vice versa were calculated using the Gutowsky approximation.[87]

$$\bar{T} = \frac{Tsyn.Keq}{1+Keq} = \frac{1}{\pi.\delta v.\sqrt{2}}$$

$$ksyn = \frac{1}{Tsyn} = \frac{Keq.\pi.\delta v.\sqrt{2}}{1 + Keq}$$

where δv = frequency separation.

The inversion barriers were then obtained from the Eyring equation:

$$\Delta G^{\neq} = 19.12\ Tc\ (10.32 + \log_{10}\frac{Tc}{ksyn})$$

The results of these calculations are shown in table 3:9.

Table 3:9

Compound	Tc[a]	$\Delta\nu$[b]	$\Delta G^{\neq}$anti→syn[c]	$\Delta G^{\neq}$syn→anti[c]
(83)	1°C	36.2Hz	56.2 kJmol^{-1}	57.9 kJmol^{-1}
(84)	-7°C	12.2Hz	57.1 kJmol^{-1}	58.0 kJmol^{-1}

a) ±3°C, b) ±2Hz, c) ±0.7 kJmol^{-1} (anti/syn with respect to tetrafluoroaryl ring.)

The values obtained for the inversion barriers of (83) and (84) were very similar, and were also close to the values obtained for 9-methyl-5,6,7,8-tetrahalo-1,4-dihydronapthalen-1,4-imines (see table 3:4). This suggests that in both (83) and (84) the tetrafluoroaryl ring may have the greater influence on the inversion barrier when compared with either the unsubstituted aryl ring or the dimethoxy-substituted ring. The small, but measureable increase in barrier on changing from the unsubstituted ring of (83) to the dimethoxy-substituted ring in (84) had previously been noted in 9-methyl-1,4-dihydronapthalen-1,4-imine systems (see table 3:4). The barrier of the N-benzyl compound (83) was also found to be slightly lower than that of the N-methyl

analogue (48), (~1.9 $kJmol^{-1}$).* This is probably due to the increased steric bulk of the N-benzyl substituent.† A similar decrease in barrier can also be seen on going from N-methyl to N-benzyl derivatives of 1,4-dihydronapthalen-1, 4-imine, compounds (50) → (53), (~1.9 $kJmol^{-1}$).

*Taking the more recent values from reference 68 in preference to those from reference 64.

†See Chapter 1.

3.III Synthesis, Spectroscopic Data and Rearrangement Reactions of 11-Chloro-1,2,3,4-tetrafluoro-9,10-dihydroanthracen-9,10-imines

The debenzylation of 11-benzyl-1,2,3,4-tetrafluoro-9,10-dihydroanthracen-9,10-imines (83) and (84) was accomplished by hydrogenation at atmospheric pressure[76] to afford the amines (85) and (86).

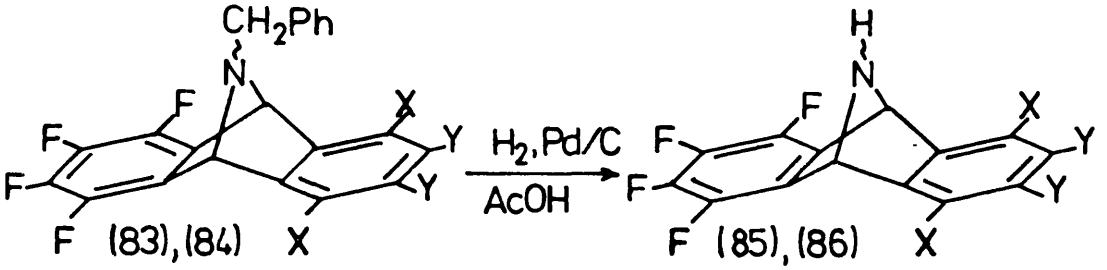


Figure 3:16

Each amine was dissolved in $CDCl_3$ and chlorinated at ca. -50°C with NCS. At this temperature nitrogen inversion is negligible in the N-chloroamines produced. The reaction mixture was quickly transferred to the probe of an NMR spectrometer at the same temperature and the resulting N-chloroamines were observed by ^1H NMR. The ratios of invertomeric N-chloroamines produced under these conditions of "kinetic chlorination" were determined by direct integration of the areas under the respective peaks. These kinetically-derived ratios remained constant below 0°C. The N-chloroamine solutions were warmed to ambient temperature, allowed to equilibrate, then the thermodynamic ratios of invertomers were again determined from the ^1H NMR spectra, (figure 3:17).

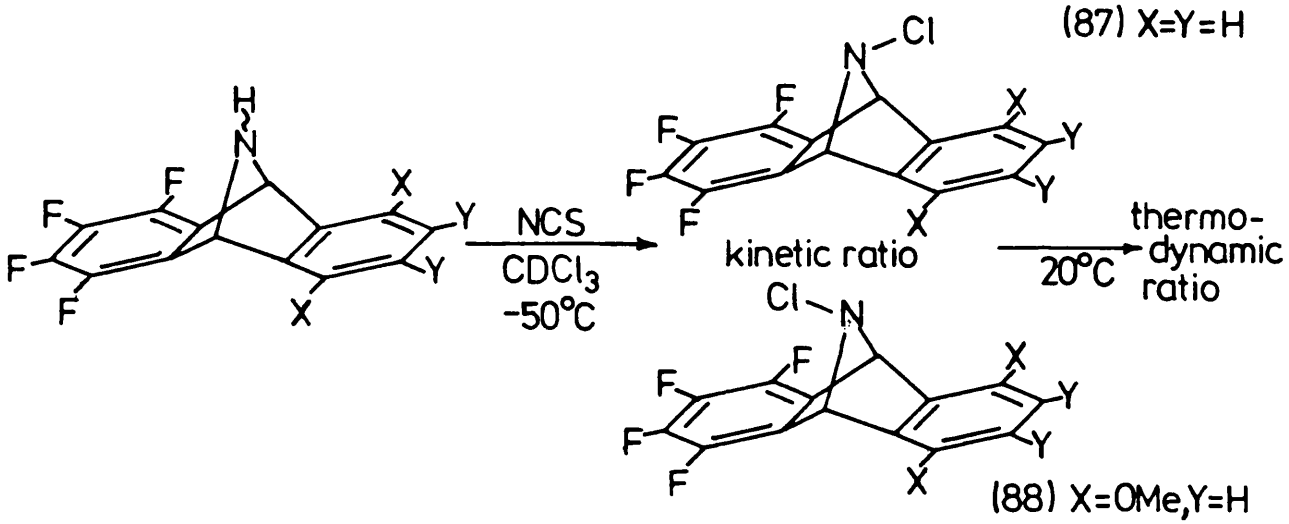
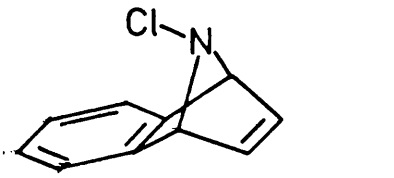


Figure 3:17

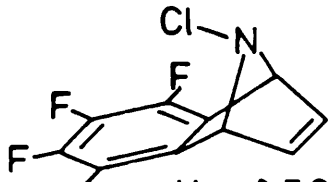
Again, the assignments of the NMR signals corresponding to each invertomer must be discussed before any consideration of the invertomer ratios obtained. In the case of these N-chloroamines it will be easier to consider each compound separately:

a) 11-Chloro-1,2,3,4-tetrafluoro-9,10-dihydroanthracen-9,10-imine (87)

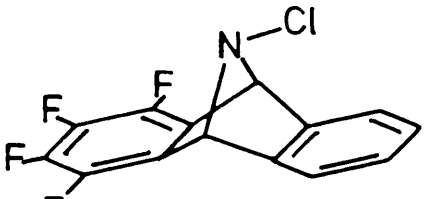
A comparison of the chemical shifts observed in the ^{1}H NMR spectra of the 'syn' invertomers of 9-chloro-1,4-dihydronapthalen-1,4-imines (66b) and (66d)[75] showed that the bridgehead protons for the tetrafluoroaryl compound (66d) were found to be downfield of those observed for the compound with an unsubstituted-aryl ring (66b). Thus the downfield bridgehead signal of (87) was tentatively assigned to the syn-tetrafluoroaryl invertomer (also the major invertomer under both kinetic and thermodynamic conditions), (table 3:10).



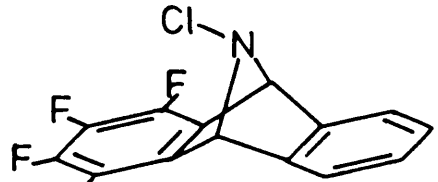
$H_{1,4}$ δ 4·67ppm



$H_{1,4}$ δ 5·27ppm



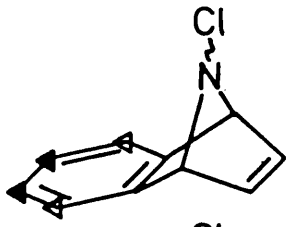
$H_{9,10}$ δ 5·60ppm



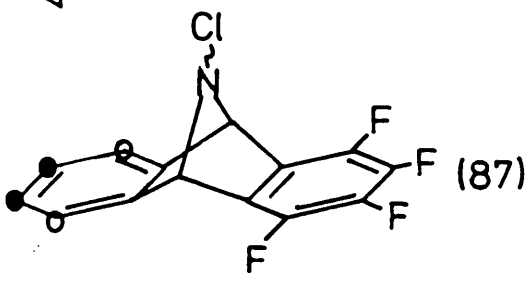
$H_{9,10}$ δ 5·67ppm

Table 3:10

Considering the ^{13}C NMR signals for the outer carbon atoms of the unsubstituted aryl ring (where the influence of the opposite side of the molecule is minimal) in both 9-chloro-1,4-dihydronapthalen-1,4-imine (66b) and 11-chloro-1,2,3,4-tetrafluoro-9,10-dihydroanthracen-9,10-imine (87) it was possible to confirm that the major invertomer was the compound with the chlorine substituent syn- to the tetrafluoroaryl ring, (table 3:11).



(66b)



(87)

^{13}C Chemical Shifts (δ,ppm).

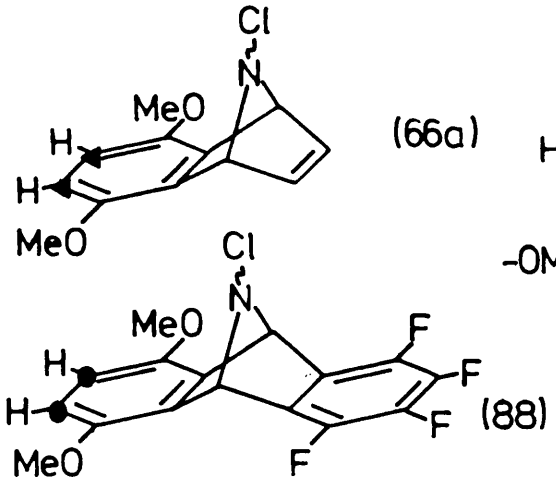
	syn[a]	anti[a]	δΔ
◀	125·64	126·04	(0·40)
●	127·52	127·91	(0·39)
◁	123·37	121·34	(-2·02)
o	124·15	122·07	(-2·08)

a) to the unsubstituted aryl ring, the major invertomer being underlined.

Table 3:11

b) 11-Chloro-1,2,3,4-tetrafluoro-5,8-dimethoxy-9,10-dihydro-anthracen-9,10-imine (88)

When the ^{1}H NMR spectrum of (88) was observed, the bridgehead protons for each invertomer were found to be magnetically equivalent. Fortunately, however, it was possible to determine the invertomeric preferences from the signals due to the protons of the aryl-rings and also from the methoxy groups of the aryl rings by comparisons with the 9-chloro-5,8-dimethoxy-1,4-dihydronapthalen-1,4-imine system (66), (table 3:12). The major invertomer of the N-chloroamine (88) was thus found to have its chlorine substituent 'syn' to the tetrafluoroaryl ring.



^{1}H Chemical Shifts (δ, ppm).

		syn[a]	anti[a]	δΔ
$H_{6,7}$	(66a)	6·60	6·55	-0·05
	(88)	6·64	6·61	-0·03
-OMe	(66a)	3·74	3·71	-0·03
	(88)	3·79	3·77	-0·02

a) to the dimethoxyaryl ring

Table 3:12

The ^{13}C NMR spectra confirm these assignments. In this case the assignments were made using the carbon atoms of the aryl rings to which the methoxy groups were attached, (table 3:13).

See also Table 3:12

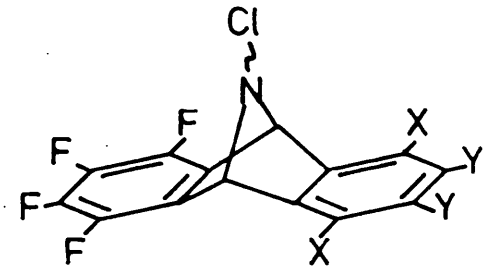
^{13}C Chemical Shifts (δ, ppm)

	syn[a]	anti[a]	$\Delta\delta$
(66a)	149·67	147·23	2·44
(88)	150·57	147·82	2·75

a) to the dimethoxyaryl ring.

Table 3:13

Thus, the kinetic and thermodynamic ratios that were obtained from the integration of both ^{1}H and ^{13}C NMR are presented in table 3:14.



(87) X=Y=H. (88) X=OMe, Y=H.

	Ratios of Invertomers	
	Kinetic syn:anti[a]	Thermodynamic syn:anti[a]
(87)	75 : 25	80 : 20
(88)	61 : 39	77 : 23

a) to the tetrafluoroaryl ring (±2%).

Table 3:14

As it can be assumed that inversion is extremely rapid in the parent secondary amines during the chlorination, even at ca. -50°C, then the kinetic ratios obtained must reflect the preferred modes of approach by the chlorinating agent. In both of the 1,2,3,4-tetrafluoro-9,10-dihydroanthracen-9,10-imines a preference for kinetic chlorination from the side of the tetrafluoroaryl ring was observed. Under conditions of rapid inversion, thermodynamic ratios were observed in each case that indicated a small increase in this preference for the chlorine to remain over the more electron-deficient ring.

From the kinetic ratios, as expected from earlier

studies,[74,75] the preferred mode of approach was from the side of the most electron-deficient tetrafluoroaryl ring. When comparing (87) and (88) there can also be observed a slight preference for chlorination from the side of the dimethoxyaryl ring rather than from the side of the unsubstituted aryl ring, again demonstrating the (-I) inductive effect of the methoxy group acting in a situation where no (+R) resonance effect is possible.

Similarly when considering the thermodynamically preferred ratio little difference in the ratios observed was noted. This was because the chlorine substituent on the nitrogen prefers to remain over the least electron-rich ring and so, in the absence of major steric influences, the factors determining the kinetic ratio of invertomers also substantially effect the thermodynamic ratio produced. The final, significant point to be elucidated from these ratios was that the electronic influences acting on the chlorination reactions and also on the determination of the thermodynamic preferences of invertomers were relatively subtle; in no case was there an overwhelming predominance of one invertomer over the other.

When the silver-ion catalysed methanolyses of (87) and (88) were attempted, the rates of reaction were surprisingly found to be much slower than those previously observed for 9-chloro-1,4-dihydronapthalen-1,4-imines (71a,b).[45] The relative stability of (87) and (88) under these conditions was quite remarkable and for the solvolyses to be successfully completed more forcing conditions were required. Unfortunately, this meant that nitrogen inversion in the N-chloroamines was rapid under these reaction conditions and

the hoped-for kinetic resolution of the less-reactive anti-tetrafluoroaryl invertomers therefore could not be achieved. The reaction of (88) was completed within 2 days whereas the reaction of (87) was almost completed after 6 days under identical conditions. As no products from the solvolyses of either (87) or (88) were observed that could have arisen from participation by the tetrafluoroaryl ring and since nitrogen inversion in the N-chloroamines must be relatively rapid under the reaction conditions then it seems that aryl-participation by a dimethoxyaryl-ring is ca. 3x more effective than aryl participation by a simple aryl ring in these compounds, (figure 3:18).

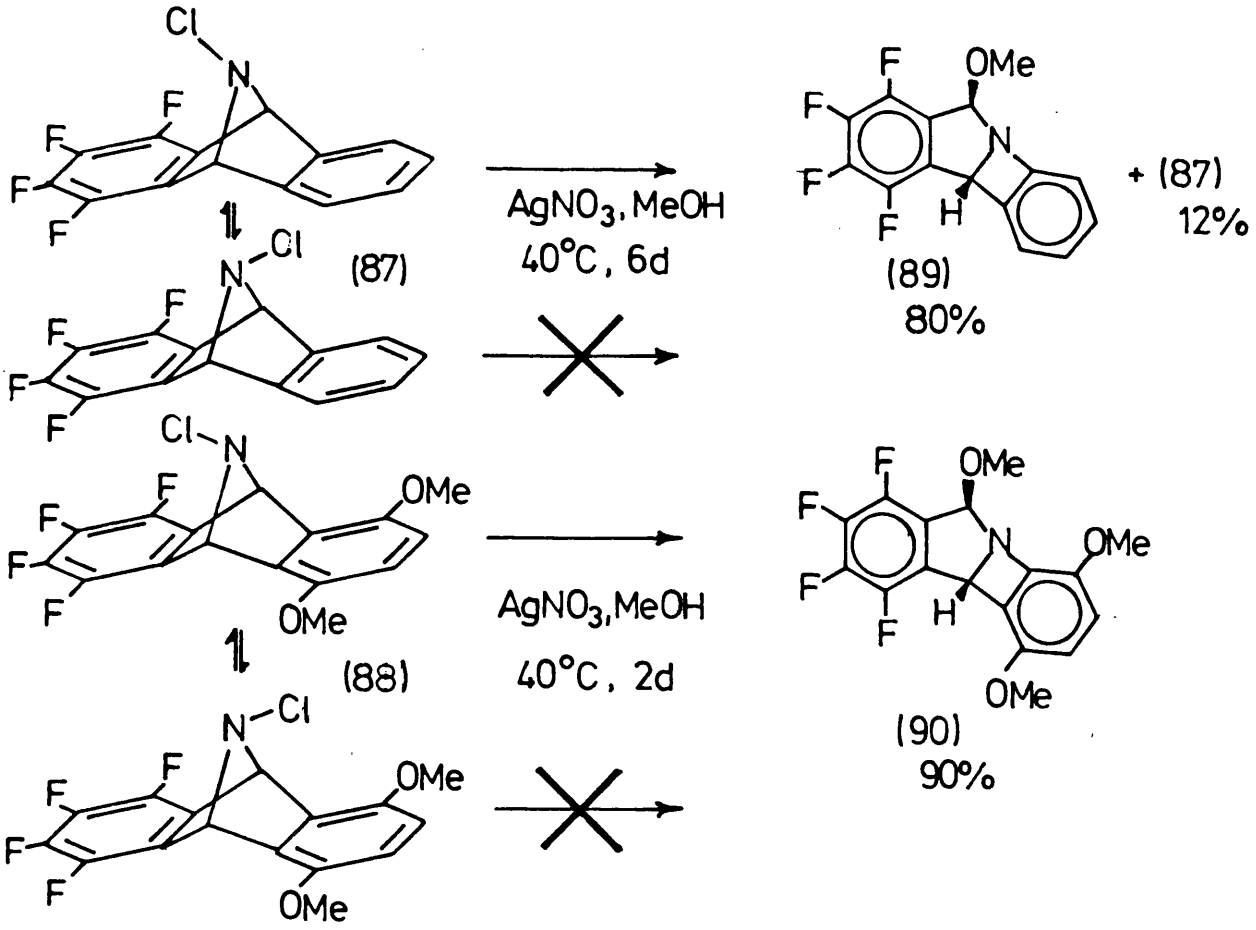


Figure 3:18

In both rearrangement reactions, the amount of products (89) and (90) observed was greater than the original quantities of syn-tetrafluoroaryl invertomer present (so there can be no doubt that the 'anti' invertomer must have been consumed by prior inversion to the 'syn' invertomer before solvolysis). The comparative rates of rearrangement of 'syn' -(87) and -(88), and the absence of any products derived from their 'anti' invertomers gave an order for the relative participatory abilities of aryl rings which is in agreement with results obtained from the solvolyses of 9-chloro-1,4-dihydronapthalen-1,4-imines;[75] this order is shown in figure 3:19.

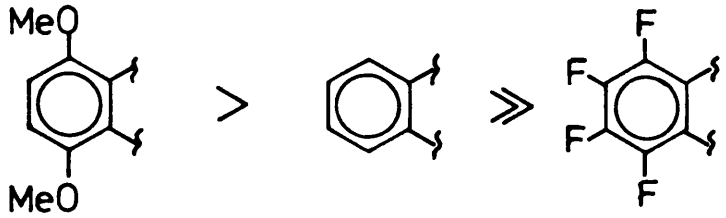


Figure 3:19

CHAPTER 4

THE SYNTHESIS AND STUDY OF SOME 1,4-DIHYDRO-AND 1,2,3,4-TETRAHYDRO-9-CHLORO-1,4-DIMETHYLNAPTHALEN-1,4-IMINE DERIVATIVES[†] AND THEIR REARRANGEMENT REACTIONS

[†]In this chapter and also in the experimental section 1,4-dihydro-1,4-dimethylnapthalen-1,4-imines and 1,2,3,4-tetrahydro-1,4-dimethylnapthalen-1,4-imines have been incorrectly referred to as 1,4-dimethylnapthalen-1,4-imines and 2,3-dihydro-1,4-dimethylnapthalen-1,4-imines respectively.

4.I Introduction

This introduction will be brief as much of the material covered in the introduction to the previous chapter is equally applicable here. The 1,4-dimethylnapthalen-1,4-imines were studied initially as it was thought that the silver-ion-catalysed methanolyses of their N-chloro-derivatives might afford 1-azabicyclo[3.2.0]heptyl systems (91) which were of interest for possible flash vacuum pyrolysis studies (described in Appendix I), (figure 4:1).

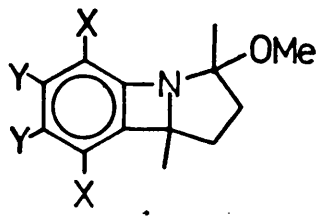
(91) 

Figure 4:1

4.II Synthesis and Spectroscopic Investigations of 9-Chloro-1,4-dimethylnapthalen-1,4-imines

Ths potassium salt of 2,5-dimethyl pyrrole was treated with trimethylsilylchloride to produce N-trimethylsilyl-2,5-dimethyl pyrrole (92).[88,89] The Diels-Alder cycloadditions of this pyrrole derivative with benzyne and with dimethoxy-benzyne (prepared by the action of n-BuLi on 2-bromofluoro-benzene and 1,4-dimethoxy-2-chlorobenzene respectively, afforded the 1,4-dimethylnapthalen-1,4-imines (93) and (94); the trimethylsilyl group was removed easily during aqueous work-up. These amines were readily converted into their 2,3-dihydro-derivatives (95) and (96) by hydrogenation, (figure 4:2).

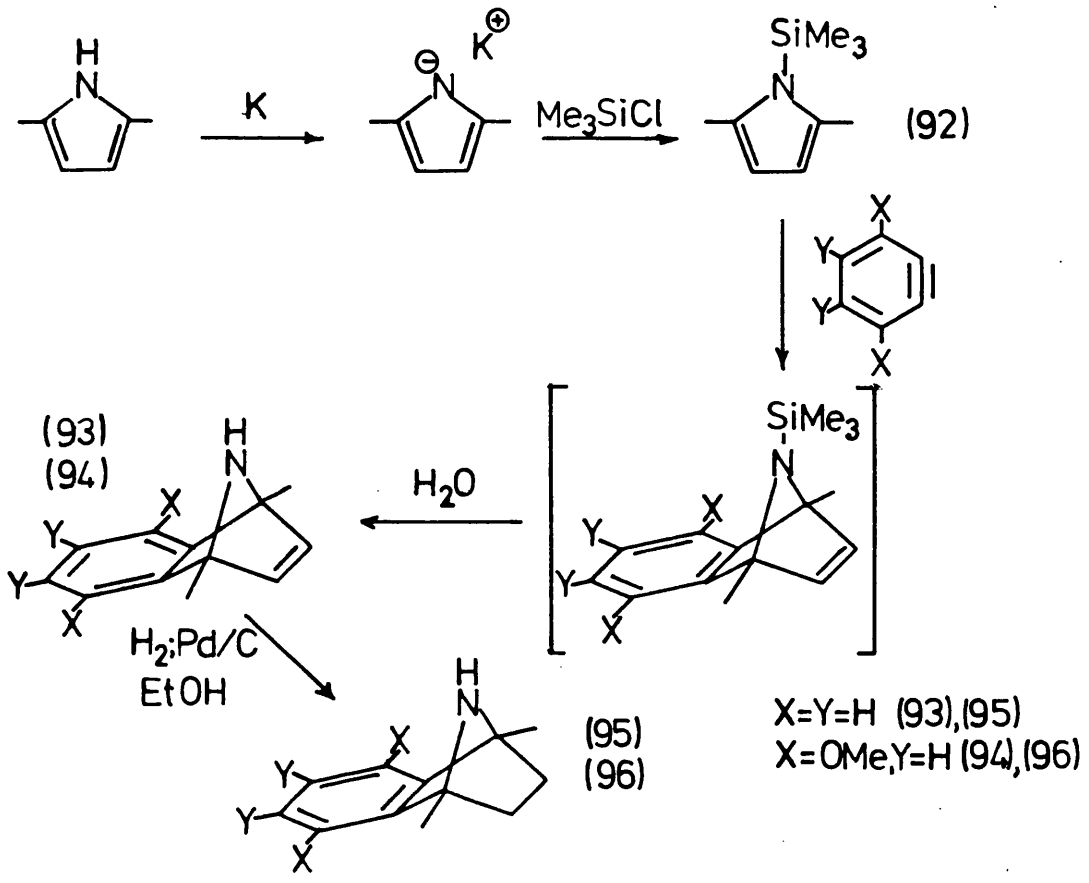


Figure 4:2

Each of the amines (93 - 96) was dissolved in a deuterated solvent at low temperature (-36 to -56°C) and chlorinated with NCS. At such temperatures, nitrogen inversion in the N-chloroamines formed (97 - 100) would be negligible and so the ratio of invertomers observed by ^{1}H NMR at these temperatures (the kinetic ratio) reflects the preferential mode of approach by the chlorinating agent. When the solutions were warmed to room temperature, where inversion was rapid, a thermodynamic equilibrium of invertomers was established, (figure 4:3).

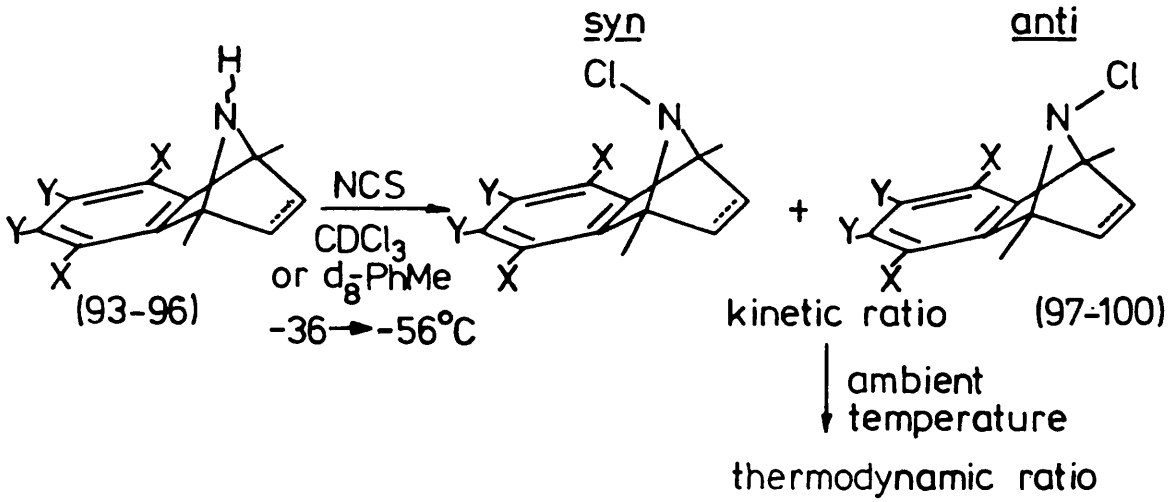
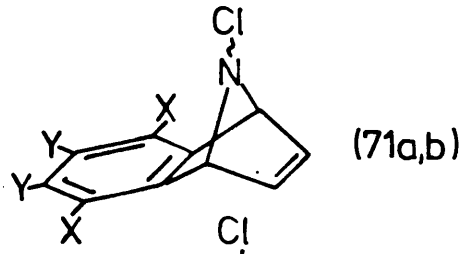


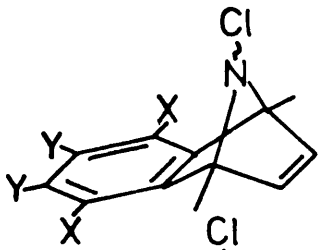
Figure 4:3

The assignment of invertomers from the spectra of (97 - 100) was completed by making comparisons with the analogous compounds having protons at the bridgehead positions (71a,b and 74a,b),[67] (table 4:1).

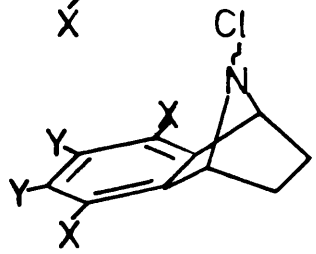
Table 4:1



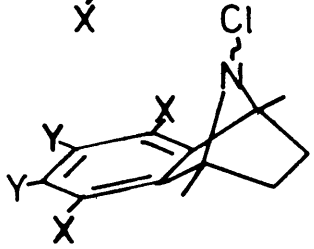
(71a,b)



(97), (98)



(74a,b)



(99), (100)

X=Y=H (71a, 97, 74a, 99)
X=OMe, Y=H (71b, 98, 74b, 100)

Compound	Chemical Shifts[a] Syn:Anti		Invertomer Ratios Kinetic Syn:Anti[b]		Thermodynamic Syn:Anti[b]
(71a)	6.75	6.65[c]	28:72		60:40
(97)	6.75	6.40[c]	33:67	(-56.5°C)	36:64
(71b)	6.60	6.55[d]	34:66		67:33
(98)	6.64	6.57[d]	29:71	(-36°C)	38:62
(74a)	2.17	2.46[e]	6:94		53:47
(99)	2.00	2.24[e]	5:95	(-53.5°C)	52:48[g]
(74b)	6.72	6.50[d]	5:95		54:46
(100)	6.57	6.50[d,f]	21:79	(-36.5°C)	71:29[g]

a) δ, ppm ($CDCl_3$), measured at 100 MHz

b) ±3%, with respect to the aryl ring

c) vinyl proton signals

d) aromatic proton signals

e) exo-protons

f) d_6-toluene

g) confirmed by 100 MHz ^{13}C NMR

Chlorination of the 1,4-dimethyl-5,8-dimethoxynapthalen-1,4-imine (94) and its 2,3-dihydro-derivative (96) was performed at the slightly higher temperature of *ca*. -36°C to overcome the problems caused by insolubility of the N-chloro-amines (98) and (100) at lower temperatures. For (98), the invertomer ratios were obtained from a combination of the vinyl and aromatic protons due to a coincidental overlap of signals. The invertomer ratio for N-chloroamine (99) was determined using the exo-protons of the ethano-bridge (because no separation of other signals was observed); further comparisons were also possible with certain 7-chlorobenzo-norbornene isomers,[90] (figure 4:4)

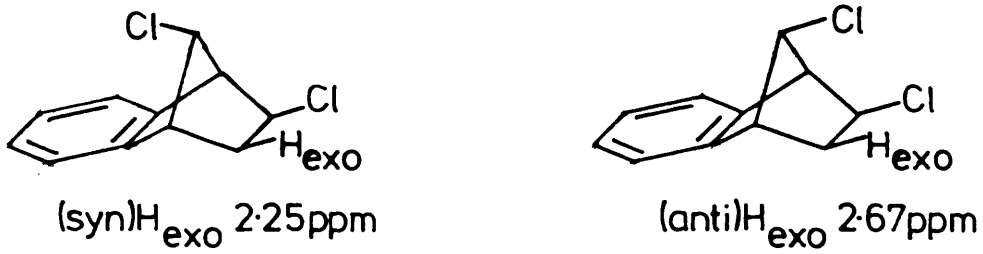


Figure 4:4

The chlorination of (96) was undertaken in d_8 -toluene as no separation of signals from the two invertomers present could be observed in $CDCl_3$; in d_8 -toluene both the aromatic protons and aromatic methoxy groups could be resolved.

Examination of the trends observed in table 4.1 shows that all four amines chlorinate preferentially 'anti' to the aryl ring. The ethano-bridged compounds (99) and (100) exhibit an increased preference for chlorination from the 'anti' side when compared with the etheno-bridged compounds (97) and (98) even though such a trend is contra-steric.

This contra-steric chlorination has also been observed in the case of the 1,4-dihydronapthalen-1,4-imines (71a-c) and (74a-c).[73] There is also an increased thermodynamic preference for syn-chlorine in the dimethoxyaryl compounds (98) and (100) when compared with the benzo-compounds (97) and (99). The explanation of this trend must arise from the (-I) inductive effects of the methoxy groups as also noted in the previous chapter.

The kinetic chlorination behaviour of the 1,4-dimethyl compounds (96-100) follows closely that observed for the 1,4-dihydro analogues (71a,b) and (74a,b). The observed thermodynamic ratios differed substantially from those reported for 1,4-dihydro analogues, especially the etheno-bridged compounds (97) and (98) where the chlorine substituent preferred to be <u>syn</u>- to the etheno-bridge. However it is difficult to understand the relatively subtle effects which result from the replacement of a bridgehead proton with a methyl group in these systems.

High field, 100 MHz, ^{13}C NMR clearly showed the presence of two invertomeric species in both (99) and (100) and the invertomer ratios were confirmed to be as shown in table 4:1. An interesting feature of both ^{13}C NMR spectra was the small frequency separation ($\Delta\nu$) observed between the bridgehead carbon signals arising from each invertomer. This indicated potential for variable temperature coalescence studies, but at 100 MHz these relatively small separations still proved to be too large for coalescence to be observed. Simple calculations suggested that with a lower field (i.e 15 MHz) ^{13}C NMR spectrometer* it might be possible to

*A 60 MHz FT ^{1}H NMR spectrometer.

observe temperature-dependent coalescence for both N-chloroamines (99) and (100) at temperatures which could be realistically attained. The difficulties associated with the move to lower field arose from the significantly lower sensitivity; this required the use of relatively concentrated samples and long acquisition times. The need for concentrated solutions also led to further problems arising from the limited solubility of (100) in high-boiling solvents. Despite these difficulties, temperature-dependent coalescence was observed (using 15 MHz ^{13}C NMR spectroscopy) and the barriers to nitrogen inversion for both (99) and (100) were estimated, (table 4:2)

Table 4:2

Compound	Tc[a]	$\Delta\nu$[b]	$\Delta G^{\neq}$ anti→syn[c]	$\Delta G^{\neq}$ syn→anti[c]
(99)	45°C[d]	0.49Hz	77.6 kJmol^{-1}	77.9 kJmol^{-1}
(100)	88°C[e]	1.34Hz	84.6 kJmol^{-1}	87.2 kJmol^{-1}

a) ±5°C (for bridgend C's) b) ±0.02 Hz, c) ±1.5 kJmol^{-1} (with respect to aryl ring)
d) d_6- DMSO
e) chlorobenzene (using coaxial d_6- DMSO lock).

The inversion barriers observed for (99) and (100) were somewhat lower than might have been expected from comparison of other N-chloroamines possessing the 7-azabicyclo[2.2.1]-heptyl skeleton, (figure 4:5).

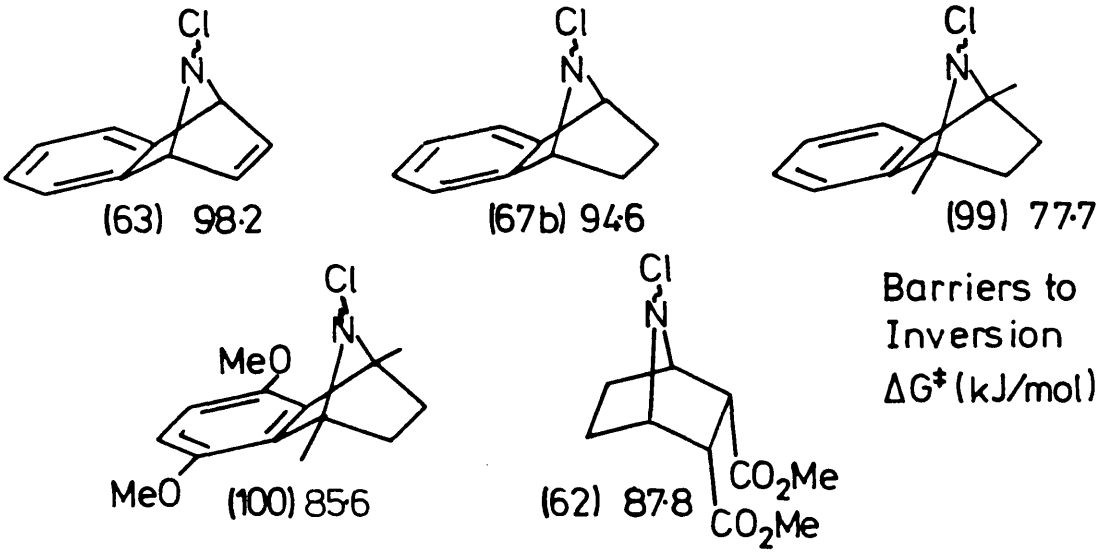


Figure 4:5

The effect of bridgehead methyl-groups in lowering the inversion barrier, from (67b) to (99), was found to be surprisingly large (ca. 17 $kJmol^{-1}$). The reasons behind this phenomenon are difficult to comprehend. Possibly the solvent used for the coalescence temperature measurements (d_6- DMSO) may have had some influence on the inversion barrier, but previous experiments had shown that the use of polar solvents caused slight increases in inversion barrier (ca. 1-5 $kJmol^{-1}$).[68] Another possibility was that there may be some degree of mutual steric repulsion between the two bridgehead methyl-groups causing a widening of the $C\hat{N}C$ angle and consequently a lower barrier to inversion; this will be discussed with the benefit of X-ray crystallographic evidence presented later in Chapter 5.

The higher barrier of the dimethoxyaryl-compound (100) when compared with the unsubstituted aryl-compound (99) was found to be in agreement with qualitative trends noted for 9-chloro-1,2,3,4-tetrahydronapthalen-1,4-imines (67a,b & d).[67] This trend was derived from observation of the temperatures

required for (67a, b and d) as their kinetically-formed invertomeric ratios to reach thermodynamic equilibrium over a period of ca. 1h, (figure 4:6).

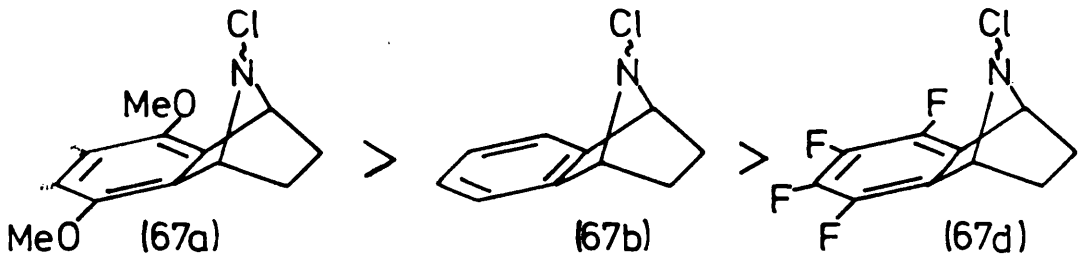


Figure 4:6

Transition-state repulsions between the π-cloud of an aryl ring and a nitrogen lone pair in such systems would be expected to increase as the aryl ring becomes more electron-rich. Therefore as the ring becomes more electron-rich, one would also expect the barrier to nitrogen inversion to increase, (figure 4:7).

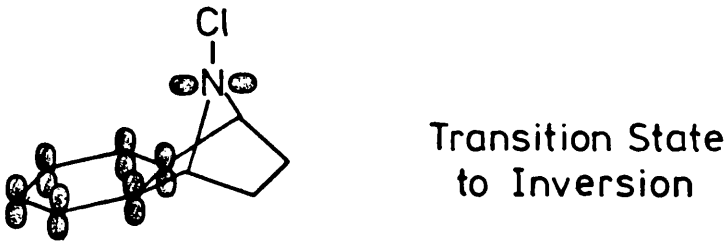


Figure 4:7

Thus from figure 4:5 it would seem that the dimethoxy-aryl ring of (100) was more electron-rich than the aryl ring of (99).

It should be mentioned that a major anomaly exists for the explanation of inversion barriers/invertomer ratios in

napthalen-1,4-imines and related systems. In many cases it seems that invertomer ratio evidence (and also ^{1}H NMR chemical shift evidence) leads to the conclusion that dimethoxyaryl-rings are electron-deficient when compared with unsubstituted aryl rings whereas inversion barrier evidence leads to the opposite conclusion. Both sets of evidence are difficult to dispute and a satisfactory solution which justifies both sets of evidence remains to be postulated. Consequently the transition-state model of figure 4:7 should only be considered as a simple working picture.

4.III Rearrangement Chemistry of 9-Chloro-1,4-dimethyl-5,8-dimethoxynapthalen-1,4-imine (100)

The chlorination of the amine (96) was successfully undertaken on a large scale and the N-chloroamine (100) proved to be sufficiently stable for purification by flash chromatography on silica. When attempts were made to solvolyse (100) using the conditions which had previously been applied successfully to both 9-chloro-1,4-dihydroanthracen-1,4-imines and 11-chloro-1,2,3,4-tetrafluoronapthalen-1,4-imines, no rearrangement products were isolated. The sole product was the dechlorinated amine, presumably formed via a homolytic process, (figure 4:8).

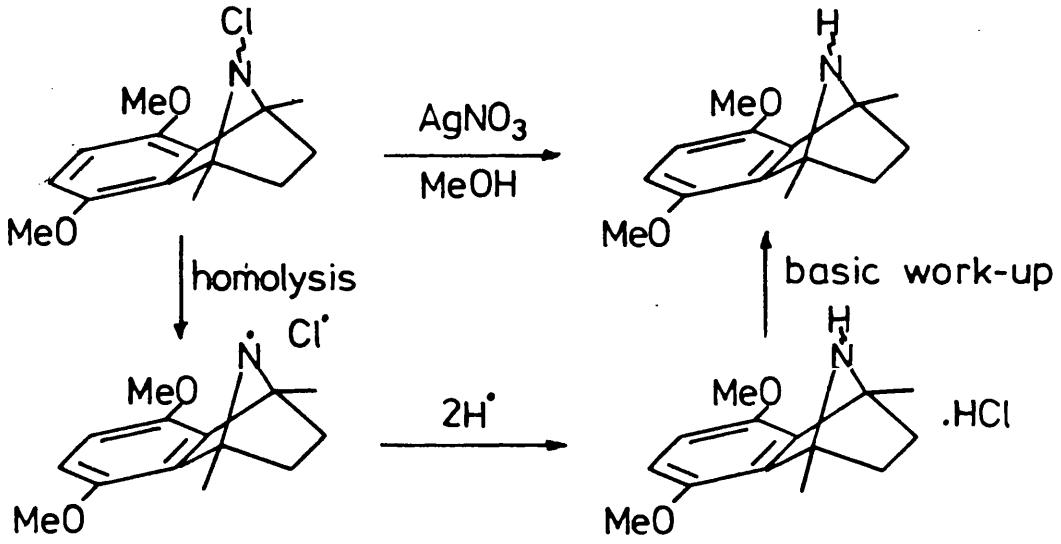


Figure 4:8

The homolytic fission of the N-Cl bond must be followed by the abstraction of two hydrogen radicals from a convenient source (probably the methanol solvent).

Schell et al. had previously circumvented similar

problems encountered during the synthesis of pyrrolizidine ring systems.[48,49] The method used involved the treatment of the N-chloroamines with silver tetrafluoro-borate ($AgBF_4$) in aprotic media, which led to precipitation of the rearrangement product as an iminium salt; in this way the amount of parent secondary amine formed was minimised.[49] This technique was therefore attempted on N-chloroamine (100), but again the only product observed was the dechlorinated parent amine (96), (figure 4:9).

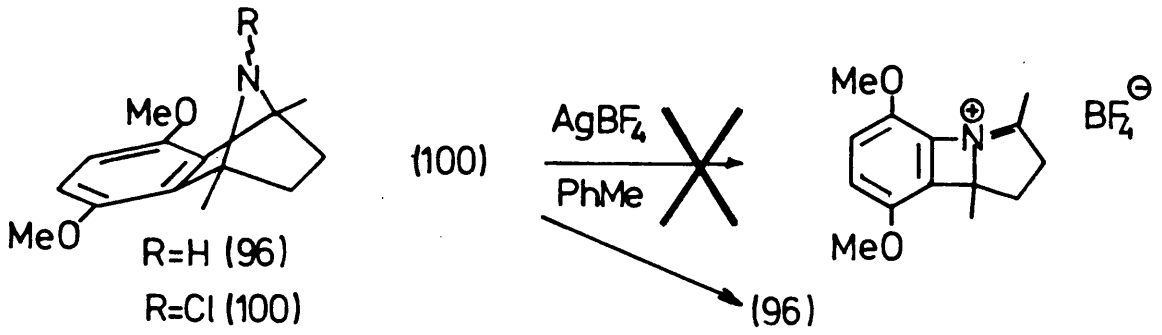


Figure 4:9

However repetition of the reaction in the presence of one molar equivalent of methanol led to the formation of a salt-like precipitate (101). Treatment of this precipitate with sodium borohydride in methanol surprisingly afforded a tetrahydrobenzo(f)-1H-azepine (102), (figure 4:10).

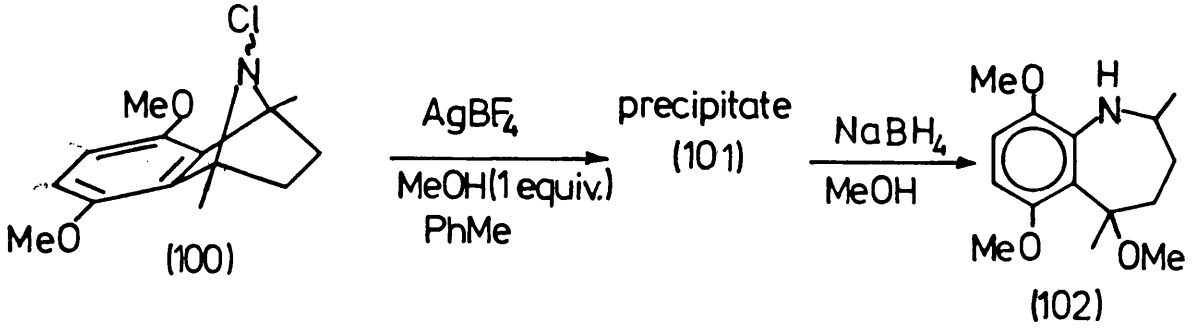
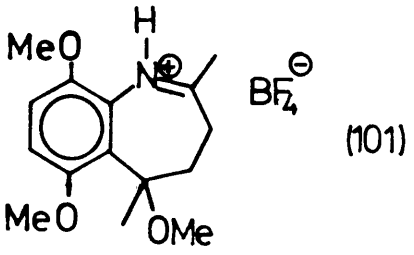


Figure 4:10

This reaction being both unprecedented and a novel route to systems with benzazepine structure merited further study. The structure of the precipitate (101) was determined from its ^{1}H NMR, IR, ^{19}F NMR and consideration of the product of its reduction (102), (figure 4:11).



(101)

Figure 4:11

The ^{1}H NMR showed that three different non-aromatic methyl groups were present, two of which were considerably deshielded (2.88 and 3.88ppm). The IR spectrum was found to include an absorption at 1670 cm^{-1} characteristic of an iminium salt $\nu(C=N^{\oplus})$[91] and a broad band 1150 - 1000 cm^{-1} characteristic of the $BF_4^{\ominus}$ anion.[92] The ^{19}F NMR showed a 4F signal* (150.32ppm)† at a similar chemical shift to HBF_4 (147.5ppm).[93] Finally, it was possible to envisage the reduction of (101) giving the benzazepine (102).

In order to confirm that the non-aromatic methoxy group of (102) originated from the methanol used in the rearrangement reaction and not from the solvent used in the subsequent reduction of the intermediate salt (101); the rearrangement of the N-chloroamine (100) was repeated using d_4-methanol. The product from this reaction was the

*By integration against a known mass of pentafluorobenzene.
†Using $CFCl_3$ as a standard.[93]

tetrahydrobenzo(f)-1H-azepine derivative (102a), whose ^1H NMR exactly matched that of the benzazepine (102) except for the absence of the methoxy signal at 2.88ppm, (figure 4:12).

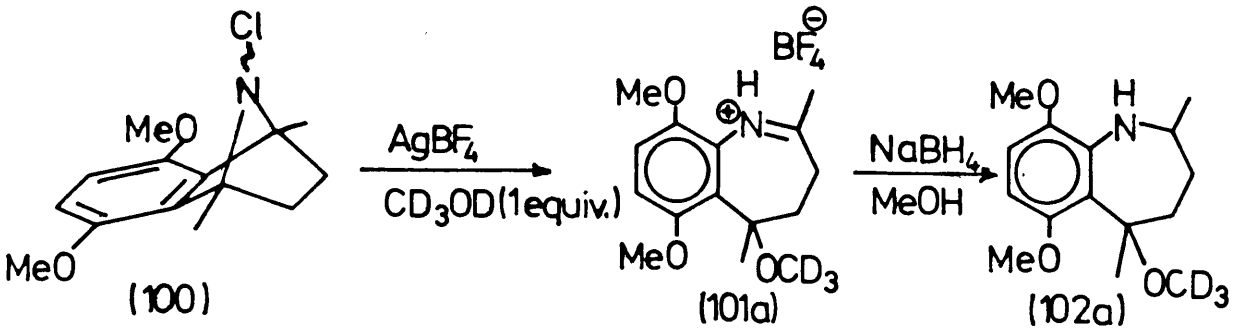


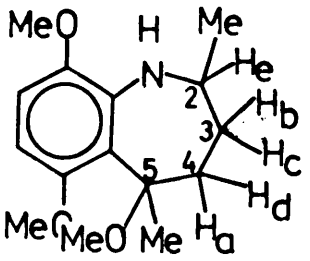
Figure 4:12

The benazepine (102) was characterised from high field ^1H and ^{13}C NMR experiments with the aid of homo-nuclear spin-decoupling in the assignment of ^1H NMR, (table 4:3).

Table 4:3

Decoupling experiments on 5,6,9-trimethoxy-2,5-dimethyl-2,3,5-tetrahydrobenzo(f)-1H,-azepine (102)

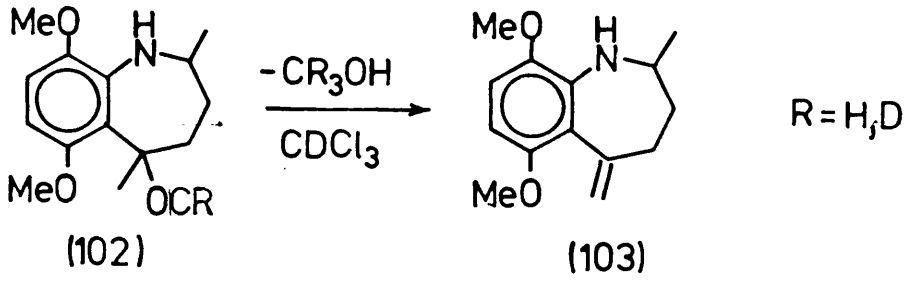
Chemical Shifts (400MHz; $CDCl_3$)	Decoupled at: 1.22ppm	1.85ppm	2.85ppm	3.05ppm
1.22 (3H, d)	*			loses 6.5Hz
1.47 (1Ha, ddd)		loses 5.3Hz	loses 13.1Hz	
1.53 (1Hb, dddd)		loses 13.1Hz	loses 6.2Hz	loses 11.5Hz
1.73 (3H, s)				
1.85 (1Hc, dddd)		*	loses 13.0Hz	loses 5.4Hz
2.85 (1Hd, ddd)		loses 13.0Hz	*	
2.88 (3H, s)				
3.05 (1He, ddq)	loses 6.5Hz	loses 5.5Hz		*
3.78 (3H, s)				
3.79 (3H, s)				
4.40 (1H, brs)				
6.32 (1H, d)				
6.61 (1H, d)				



(102)

It was not possible to identify unambiguously the preferentially-formed diastereomer of (102) from the NMR data because of difficulties in deciding the conformation adopted by the azepine ring† and also the relative stereochemistry at C-5.

When the benzazepine (102) was allowed to stand in solution for several hours a clean elimination occurred with concomitant loss of methanol to form 6,9-dimethoxy-5-methylene-2-methyl-2,3,4,5-tetrahydrobenzo(f)-1H-azepine (103). This rearrangement was similarly observed to occur for the deutero-methoxy analogue (102a), (figure 4:13).



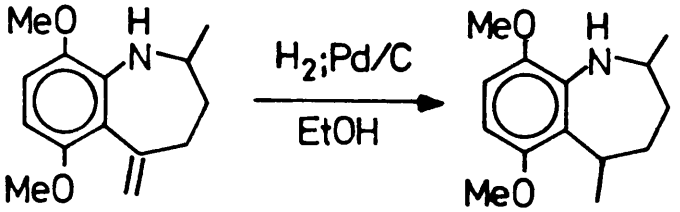
(102) (103)

Figure 4:13

The rearrangement was found to be acid-catalysed and was observed to proceed instantaneously on addition of trifluoroacetic acid. Catalytic hydrogenation of the methylene group of (103) produced two diastereomeric benzazepines (104a) and (104b) in equal proportions. Recrystallisation afforded an advantageous partial separation of the two

† The most stable conformation of an unsubstituted cycloheptane ring is a twist-chair form but it was difficult to predict the conformation for such a complex molecule.[94]

diastereomers which enabled their individual ^{1}H and ^{13}C NMR spectra to be distinguished, (figure 4:14).



(103) (104)

Figure 4:14

The iminium salt (101), when allowed to remain in CD_2Cl_2 solution, underwent rearrangement with loss of methanol. Unlike the rearrangement of (102), which was followed by the appearance of methylene signals in the ^{1}H NMR at ca. 5.30ppm, the production of methanol associated with the rearrangement of (101) coincided with the appearance of upfield signals at 0.74ppm that were characteristic of a cyclopropyl ring. Studies of the rearrangement product by IR and ^{19}F NMR showed the iminium salt function remained, $\nu(\rangle C{=}N\oplus\langle)$ at 1655 cm^{-1} and 4F at 149.43ppm.† The rate of the rearrangement reaction was increased in the presence of d_5-pyridine; however this base proved too weak for the imine to be liberated. From the above information it seemed that the most probable structure for the rearrangement product would be 2,4-dimethyl-3,4-methano-5,8-dimethoxy-3,4-dihydroquinoline hydrogentetrafluoroborate (105), (figure 4:15).

† By integration against a known weight of pentafluorobenzene.

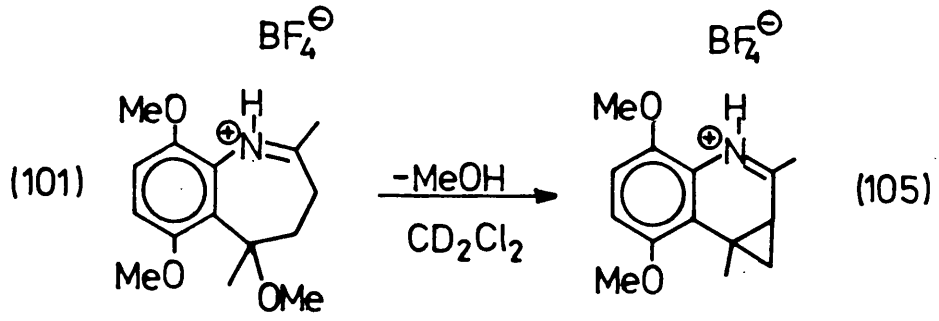


Figure 4:15

The structure of (105) was confirmed by the analysis of the product from its reduction with sodium borohydride in methanol. This product was found from high field ^1H NMR spectra to be 2,4-dimethyl-3,4-methano-5,8-dimethoxy-1,2,3,4-tetrahydroquinoline (106), (figure 4:16).

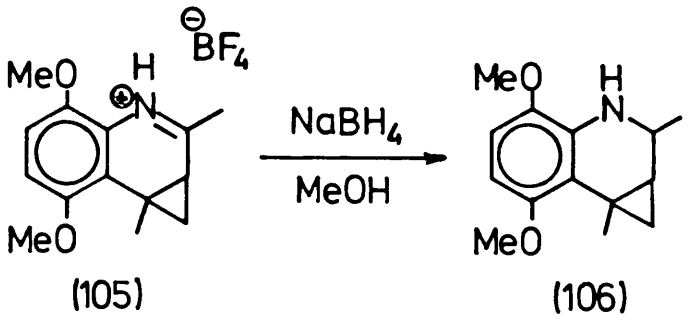


Figure 4:16

The structure of (106) was confirmed from ^{13}C NMR which closely fitted the predicted chemical shift values for this isomer. From the ^1H and ^{13}C NMR spectra of (106), it seems that the reduction of (105) was stereospecific producing a single isomer of (106). Consideration of the coupling constants from the high field ^1H NMR allowed the determination of the relative stereochemistry of (106). This corresponded to reduction of (105) from the less hindered face (opposite to the cyclopropyl group), (figure 4:17).

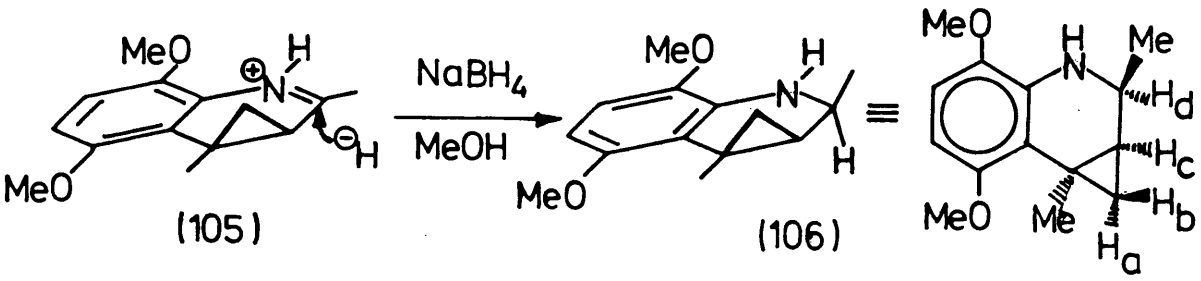


Figure 4:17

The iminium salt (105) when treated with triethylamine could be converted to its "free" imine (107).

4.IV Rearrangement Chemistry of 9-Halo-1,4-dimethylnapthalen-1,4-imines

Chlorination of the amine (95) with NCS afforded the N-chloroamine (99) which was purified by flash chromatography. When attempts were made to rearrange (99) under similar conditions to those used for (100) there was no observed precipitate formation. Therefore, once all the N-chloroamine had been consumed (monitored by tlc), the reaction mixture was reductively worked-up with sodium borohydride and methanol. The amine (95) was the major product, however the rearrangement product 5-methoxy-2,5-dimethyl-2,3,4,5-tetrahydrobenzo(f)-1H-azepine (108b) was isolated in 31% yield, (figure 4:18).

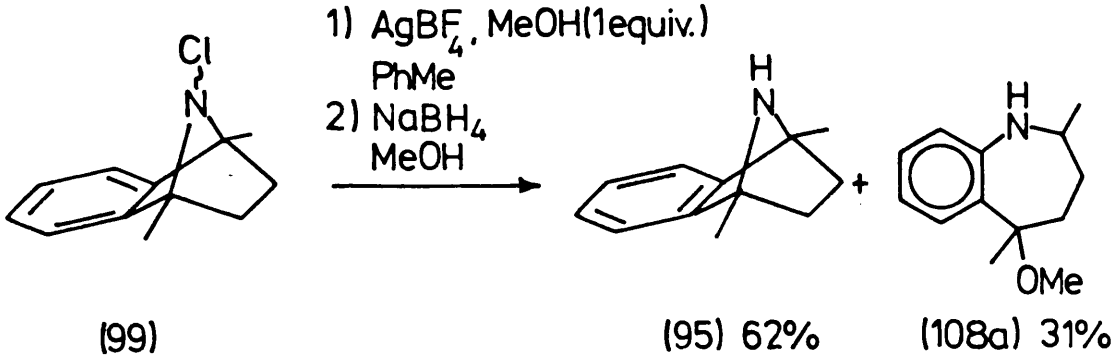


Figure 4:18

High field ^{1}H and ^{13}C NMR confirmed the structure of (108a) and showed that only a single diastereomer was present. The rearrangement of (99) was repeated using the minimum amount of solvent (PhH) and 2.5 equivalents of methanol, this improved the yield of (108a) to (48%). A minor product was also isolated and from its high field ^{1}H NMR spectrum it was assigned the structure diastereomeric to (108a), i.e. (108b) (4%). It proved difficult however to determine the specific stereochemistries of (108a) and (108b) unambiguously.

Further improvements in the yield of rearranged products were obtained from a similar rearrangement of N-bromoamine (109). In this case the primary rearrangement products were allowed to stand overnight before the usual reductive work-up. This was done in order to encourage rearrangement of the initially formed iminium salt, in a manner analogous to that observed for (101). The strategy was successful and the product containing a cyclopropyl ring (110a) was isolated in 17% yield, together with a further 56% of (108a). Thus the total of rearrangement products isolated was 73%, (figure 4:19).

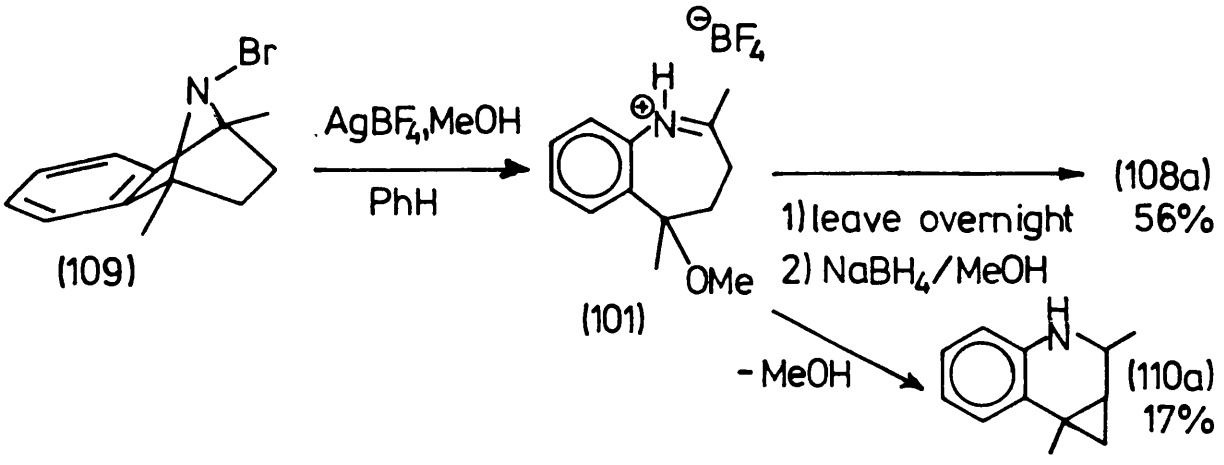


Figure 4:19

The 400 MHz ^{1}H NMR of (110a) was not completely first-order and therefore it was not possible to assign the stereochemistry of the protons in (110a).

Additional rearrangements of N-chloroamine (99) were carried out in which the iminium salt formed was allowed to stand overnight before reductive work-up. After this work-up the crude products were allowed to stand at room temperature for several days before separation was attempted. Following several chromatographic separations five different rearrangement products were identified; these are described in table 4:4.

Table 4:4

5-methoxy-2,5-dimethyl-2,3,4,5-tetrahydrobenzo(f)-1H-azepine (108a)	20%
2,4-dimethyl-3,4-methano-1,2,3,4-tetrahydroquinolines (110a)	6%
(110b)	8%
5-methylene-2-methyl-2,3,4,5-tetrahydrobenzo(f)-1H-azepine (111)	2%
2,5-dimethyl-2,3-dihydrobenzo(f)-1H-azepine (112)	10%

The products summarised in table 4:4 arose from rearrangement of (99) to give the iminium salt, then some further rearrangement of this salt before subsequent reduction and finally from further rearrangements of the reduction products (figure 4:20).

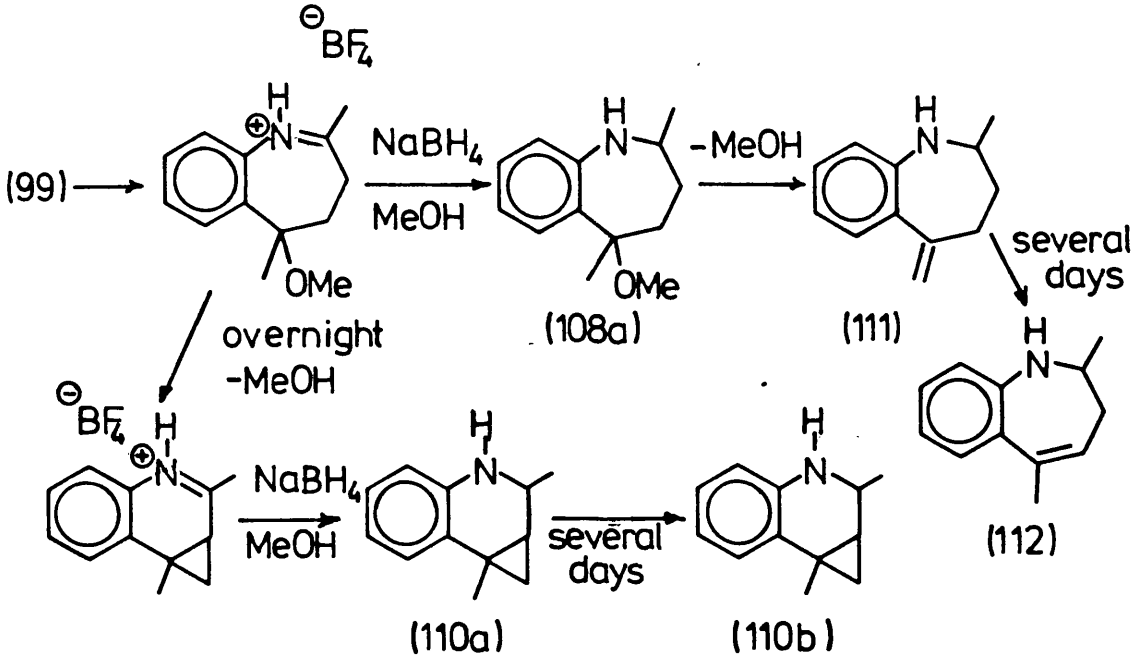


Figure 4:20

The rearrangement of (108a) to afford (111) was analogous to the elimination of (102) to (103). The additional rearrangement of (111) to the more thermodynamically stable product (112) containing an endocyclic double bond could be easily envisaged. The isomerisation of (110a) was not so easy to comprehend, but it may proceed with basic catalysis via an iminium ion.

4.V Production of 6,7-Benzo-1-azabicyclo[3.2.0]heptanes

When the amine (96) was left in the presence of an excess of NBS for several days it was observed that as well as the expected N-bromoamine (113), a small quantity of ring-brominated N-bromoamine (115) was produced. It was discovered that treatment of (113) with bromine in dichloromethane gave the hydrogen bromide salt (114) which possessed a monobrominated aromatic ring. Simple basification of (114)

afforded the amine (118) and not N-bromoamine (115). However treatment of (114) with sodium hypobromite solution led quantitatively to the N-bromoamine (115), (figure 4:21).

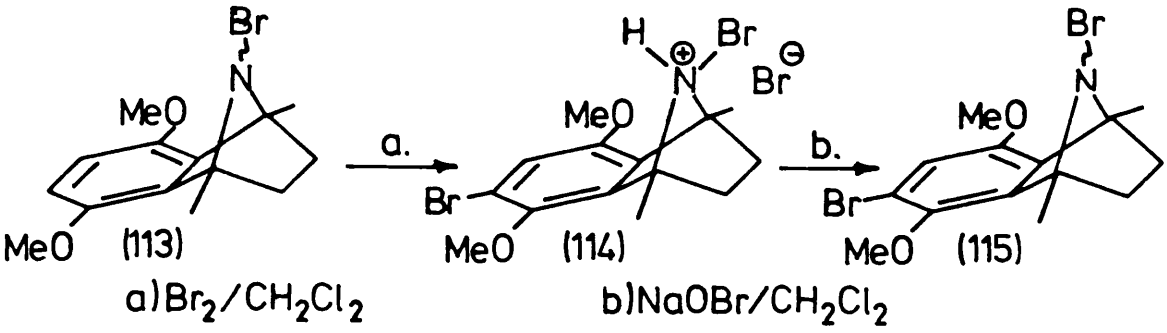


Figure 4:21

The N-bromoamine (115) was treated with $AgBF_4$ in the presence of methanol (1.4 equivalents) and subjected to basic work-up. This afforded mainly the amine (118) together with a small amount of rearranged product which was isolated by chromatography and, when examined by ^1H NMR, was surprisingly found to be 2,5-dimethyl-2-methoxy-6,7-(8,11-dimethoxy-9-bromobenzo)-1-azabicyclo[3.2.0]heptane (116), (figure 4.22).

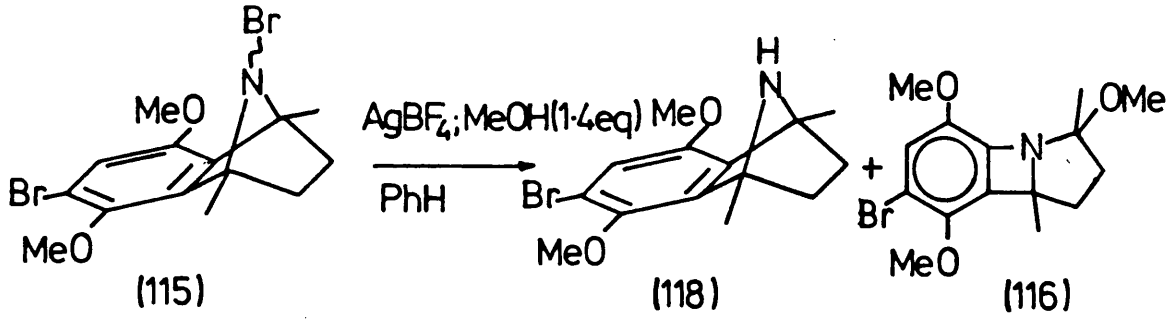


Figure 4:22

During the course of these studies many other rearrangements of N-haloamines (99), (100), (109), (113) and (115) were carried out. The results from these are presented in tables 6:3 and 6:4. These reactions do not constitute a

systematic study and are presented in tabular form for reasons of brevity. As can be seen, due to the number of reaction conditions that could be varied, it was difficult to uncover the precise nature of these rearrangements. Nevertheless, it proved possible to make some general comments. The use of homogeneous reaction conditions led mainly to N-Halogen bond homolysis whereas essentially heterogeneous reaction conditions (achieved by using a large excess of $AgBF_4$ and a minimum volume of solvent) afforded the highest yields of rearranged products. The N-bromoamines (113) and (115) both afforded 2,5-dimethyl-2-methoxy-6,7-(8,11-dimethoxybenzo)-1-azabicyclo[3.2.0]heptane (117) amongst their rearrangement products after the usually reductive work-up. The fact that (115) gave (102) and (117) but not the products with bromine in the aryl ring showed that sodium borohydride and methanol in the presence of silver salts must be sufficient to reductively remove a bromine substituent from a dimethoxyaryl ring, (figure 4:23).

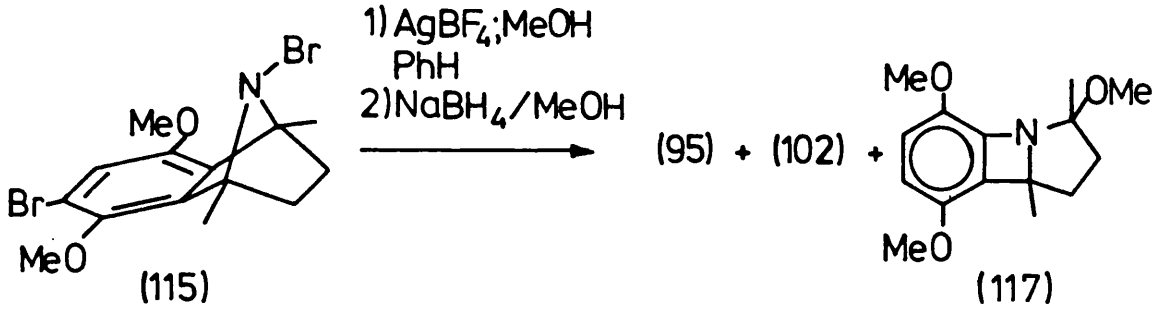
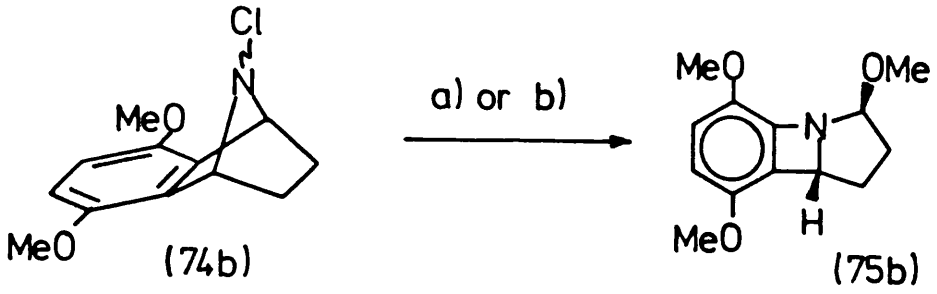


Figure 4:23

The rearrangements of (99). (100) and (109) showed no observable production of 6,7-benzo-1-azabicyclo[3.2.0]-heptane-type compounds and, although the rearrangements of (99) and (109) did give rise to other rearrangement products,

these were found to be secondary products already described, mainly (110a) and (111).

It was also found that the N-chloroamine (74b) underwent clean rearrangement using similar conditions to those used in tables 6:7 and 6:8 to give (75b) in improved yield when compared with previously described preparation,[68] (figure 4:24).



a) i) 0°C; $AgClO_4$ 5.35 eq; MeOH ii) basic work-up (53%)[68]
b) i) $AgBF_4$, 1.28 eq; MeOH, 1.15 eq; PhMe ii) basic work-up (90%).

Figure 4:24

High field ^1H NMR spectra of (75b) obtained via each route were compared and found to be identical; this implied that both products had identical stereochemistry.

4.VI Discussion

The significance of the small quantity of methanol (1.20 eq) being sufficient to suppress N-Halogen bond homolysis in 9-halo-1,4-dimethyl-2,3-dihydronapthalen-1,4-imines was not obvious. It seems that methanol must play a role in the removal of halide by silver-ion, (figure 4:25).

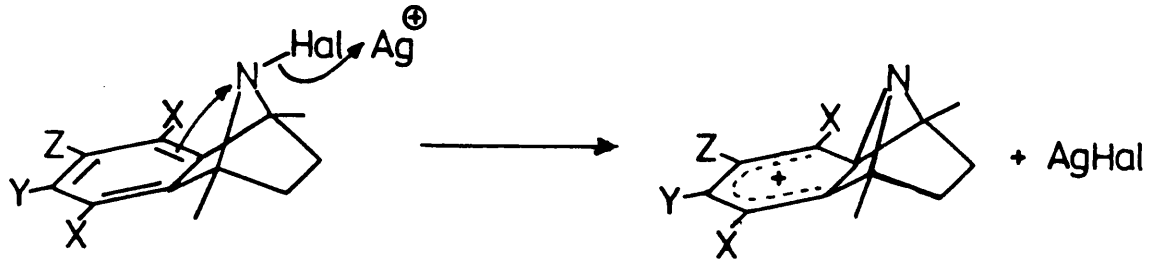


Figure 4:25

A possibility could be that methanol modifies the activity of the silver-ion (whether in solution or on the surface of undissolved $AgBF_4$). Since aromatic solvents are known to complex with silver ion it may be that methanol disrupts these complexes thus increasing the effective ability of silver ion to promote heterolysis of the N-halogen bond.

In general, 9-halo-1,4-dimethyl-2,3-dihydronapthalen-1,4-imines tend to rearrange to give benzazepine-type structures whereas the analogous systems unsubstituted at the 1,4-positions give rise to 6,7-benzo-1-azabicyclo[3.2.0]-heptanes. The different behaviour of the 1,4-dimethyl systems seems to be due to the ability of the inductive effect of the methyl group to increase the stability of an incipient positive charge at the benzylic position in the intermediate (125), (figure 4:26).

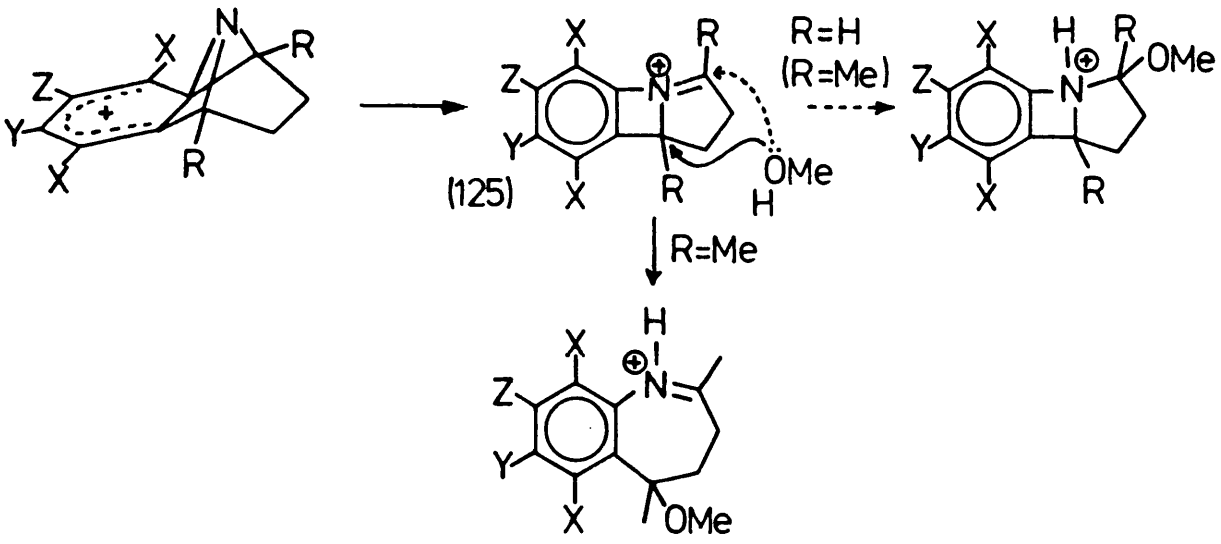


Figure 4:26

However it must be noted that in the rearrangement of N-bromoamines (113) and (115), the intermediate (125) seems to be intercepted competitively by methanol at both positions.

When the rearrangement of (115) was followed by reductive work-up, the products isolated [(95), (102) and (107)] had all lost the bromine from the aromatic ring. It seems that the conditions of sodium borohydride and methanol in the presence of silver-salts or silver metal (produced *in-situ*. by reduction of excess $AgBF_4$ present) caused rapid debromination (within 15 min.). Some similar dehalogenation reactions of aromatic rings have been described although the reaction times are somewhat longer. Egli described dehalogenation of aromatic rings with sodium borohydride in the presence of transition elements,[103] Brown et al. also performed similar reductions with lithium aluminiumhydride in THF.[104]

The rearrangement of 9-halo-1,4-dimethyl-2,3-dihydronapthalen-1,4-imines provided a novel and useful route to benzo(f)azepine systems. These systems are of interest

because of their potential pharmacological properties.[106,107]

Andrieux et al. have prepared similar benzo(f)azepines from tertiary alcohols and trisubstituted olefins of the tetrahydronapthalen series by treatment with HN_3-H_2SO_4 (figure 4:27).

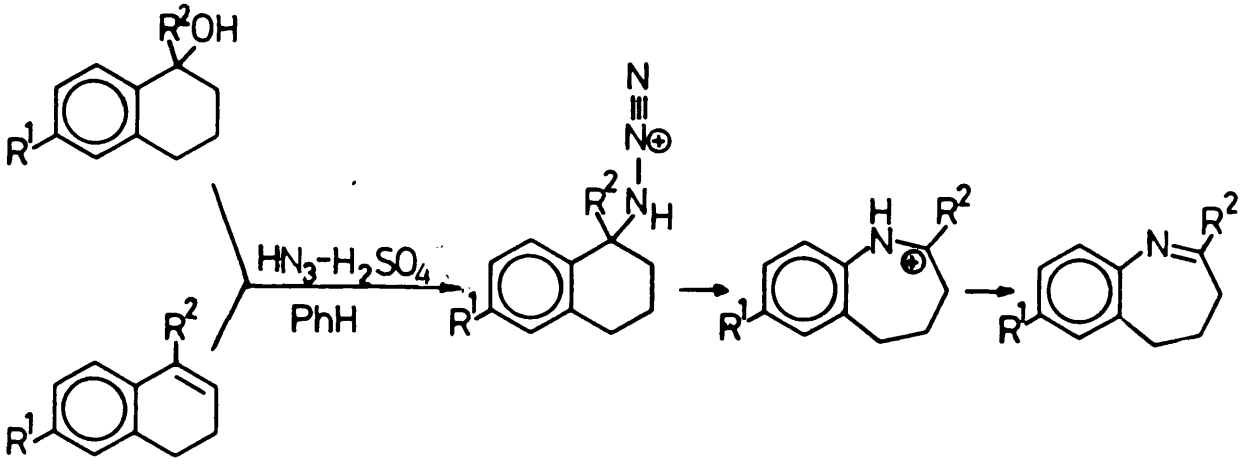


Figure 4:27

Similary the α-tetralones rearrange to lactams, (figure 4:28).[107]

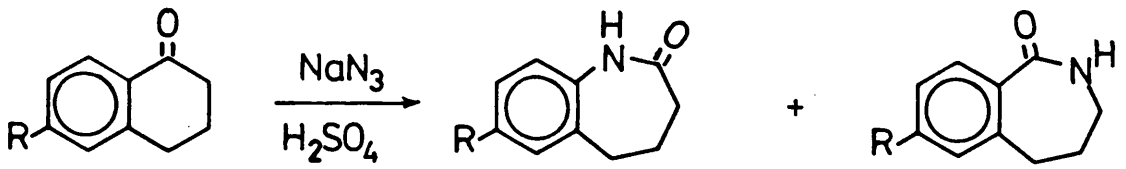


Figure 4:28

2-Ethoxyindoles react with DMAD to give Michael adducts and benzo(f)azepines.[108] and 2-substituted-quinoline-1-oxides undergo 1,3-dipolar cycloadditons to give benzo(f)azepines.[109] Other more complex rearrangements leading to benzo(f)azepines

have also been described,[110] (figure 4:29).

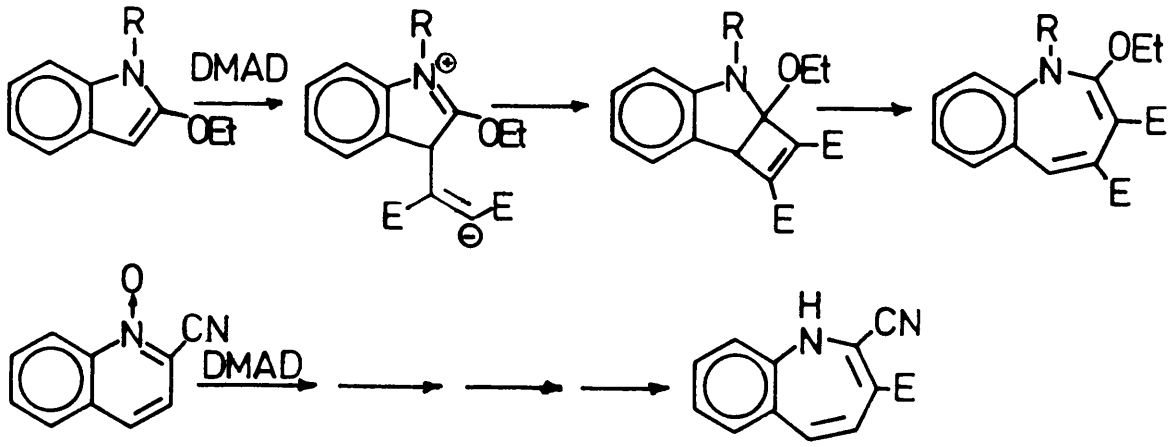


Figure 4:29

Finally the method described in Appendix I may be added to this list.

CHAPTER 5

A STUDY OF 7-AZABICYCLO[2.2.1]-HEPTYL DERIVATIVES AND RELATED SYSTEMS

5.I Introduction

This chapter comprises three sections. The first of these examines the origin of the effect of electronegative substituents on raising the barrier to inversion at nitrogen. The second section studies the ^{15}N NMR of several 7-azabicyclo-[2.2.1]heptyl derivatives and the final section describes features of the X-ray crystal structures of certain 9-chloro-napthalen-1,4-imines.

As indicated in previous chapters, 7-azabicyclo[2.2.1]-heptyl systems have attracted considerable interest due to their anomalously high barriers to nitrogen inversion. The second and third sections of this chapter attempt to probe some basic properties of these systems in order to try to uncover the underlying factors that give rise to these high barriers.

SECTION A

5.II Investigation of the Causes of the Effects of Electronegative Substituents on the Barrier to Nitrogen Inversion

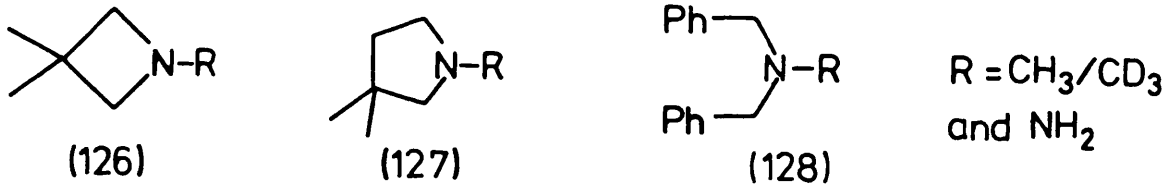
The effect of electronegative substituents on raising the barrier to nitrogen inversion has been comprehensively documented but the origins of this phenomenon are somewhat less certain. As mentioned in Chapter 1, most electronegative atoms possess lone pairs of electrons and thus this gives rise to two possible causes of the barrier raising phenomenon.

a) The inductive effect of the electronegative substituent withdraws electron density from the nitrogen atom. The less-tightly held p-electron density of the nitrogen lone pair would be more easily removed thus increasing the s-character of the lone pair. This would make nitrogen inversion more difficult as the lone pair needs to be in a pure p-orbital at the transition state to inversion and thus the barrier to inversion would be raised.

b) The transition state to nitrogen inversion is destabilised by mutual repulsion of the lone pair of the nitrogen atom and those on the electronegative atom.

It has proved difficult to ascertain convincingly the relative importance of these two influences. Theoretical calculations (LCAO-MO-SCF) completed by Mislow et al.[3] compared the systems NH_2H' and NH_2F', where the nuclear charge of F' was varied to values greater than and less than nine. These studies predicted that electronegative inductive effects would have a much smaller effect on the barrier to nitrogen inversion than the presence of adjacent lone pairs of electrons. Dewar and Jennings[111] suggested that in

compounds (126 - 128) when R = NH_2 the transition states for nitrogen inversion would assume a perpendicular geometry which cancels out the lone pair - lone pair repulsions, (figure 5:1).



(126) (127) (128)

Figure 5:1

The evidence from comparison of the inversion barriers of (128, R = CH_3) with (128, R = NH_2) tends to be in agreement with their proposal as there is only a small rise in barrier when R = CH_3 is replaced by R = NH_2 ($\Delta\Delta G^{\neq}$ 4.2 $kJmol^{-1}$). Similar studies were undertaken by Nelsen et al.[112,115] These involved comparison of nitrogen inversion barriers of 2-methyl-2-azabicyclo[2.2.2]octane (36) and 2-methyl-1,2-diazabicyclo[2.2.2]octane (129), (figure 5:2).

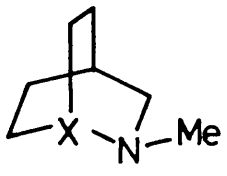
(36) (129)

Figure 5:2

In compound (129) the lone pair - lone pair interaction effects should be eliminated at the transition state to nitrogen inversion as the lone pairs are held in a perpen-

dicular relationship. On going from (36) to (129) the nitrogen inversion barrier increases ($\Delta\Delta G^{\neq}$ 5.9 kJmol^{-1}). Nelsen mentions that the inductive effect of replacing C_1 by the more electronegative N_1 might be invoked as the principal reason for this increase, however further studies on related systems suggested that there was small sensitivity of the size of the inversion barrier ($\Delta G^{\neq}$) to the inductive effect at position 1 and thus implies that the increase in barrier on going from (36) to (129) was not simply due to inductive effects, (table 5:1).

Table 5:1



Compound (X=)	$\Delta G^{\neq}$ (kJmol^{-1}) (-100°C)
(36) CH	26.6
(35) CMe	27.2
(129) N:	32.6
(130) $NMe^{\oplus}$	37.7

As lone pair - lone pair interactions at the transition state are known to raise $\Delta G^{\neq}$ substantially it seems likely that the lone pair - lone pair interaction in (129) is not totally eliminated at the transition state, despite the formal perpendicularity of the N_1 lone pair with the p-hybridised lone pair in a planar N_2 transition state for nitrogen inversion.

In order to overcome these uncertainties in the origins for barrier increase in (129) when compared with (36) it was decided to conduct a similar study of 7-substituted-1,7-diazabicyclo[2.2.1]heptane systems which would be much more rigid than 2-substituted-1,2-diazabicyclo[2.2.2]octane systems. In the transition state for nitrogen inversion, the lone pairs of electrons on the two nitrogen atoms would be rigidly held in an orthogonal relationship. Thus, in this case, any increase in nitrogen inversion barrier would arise only from the inductive effect of the adjacent nitrogen atom (figure 5:3).

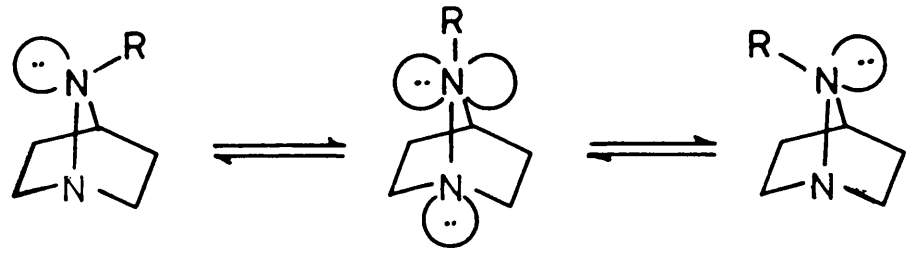


Figure 5:3

5.III Preparation and Spectroscopic Investigation of 7-Substituted-1,7-diazabicyclo[2.2.1]heptane

The preparation of 7-chloro-1,7-diazabicyclo[2.2.1]-heptane (124) was undertaken by modification of procedures used by Oppolzer[99] and Shustov et al.[101] Reaction of 4-bromobut-1-ene with acethydrazide afforded 1-acetyl-2-(but-3-enyl)-hydrazine (119). This was condensed with paraformaldehyde in order to form 7-acetyl-1,7-diazabicyclo[2.2.1]-heptane (120). However, it was found that during this reaction a dimerisation of the intermediate dipole competed with the required cyclisation. It was found that the reaction could be directed to proceed via either pathway by variation

of the dilution of the reactants, (figure 5:4).

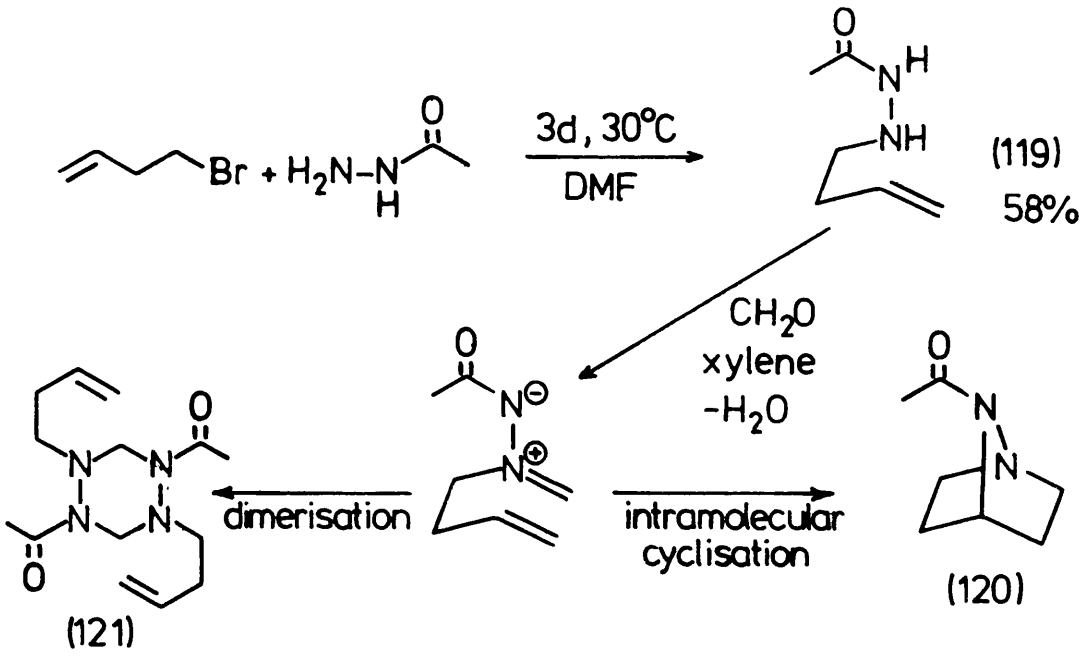


Figure 5:4

Thus in more concentrated solutions the major product was that formed by dimerisation of the intermediate dipolar species and was found to be 1,4-diacetyl-2,5-di(-but-3-enyl)-hexanhydro-1,2,4,5-tetrazine (121). Related compounds have been obtained previously by a variety of methods. The similar 1,4-diacyl-2,5-dimethylhexanhydro-1,2,4,5-tetrazines were prepared by condensing 2-acyl-1-methylhydrazines with formaldehyde;[100] other methods involved either oxidation (with HgO, $Pb(OAc)_4$ or S_2Cl_2)[114] or chlorination (with t-BuOCl) of 2-acyl-1,1-dimethylhydrazines,[115] (figure 5:5).

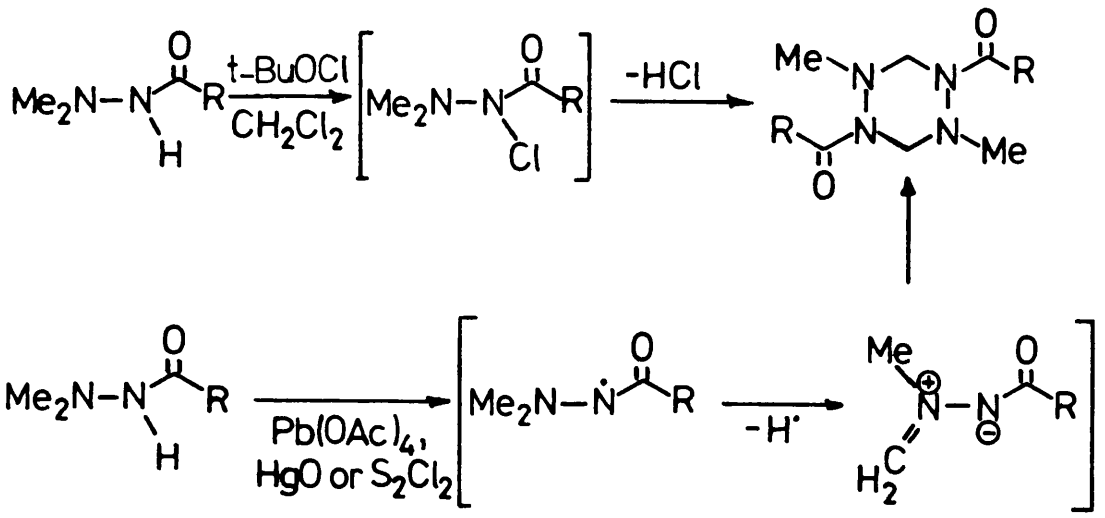


Figure 5:5

When the dipolar intermediate is formed in more dilute conditions the required cyclisation occurs to afford 7-acetyl-1,7-diazabicyclo[2.2.1]heptane (120). This compound was characterised with the aid of high field ^{1}H NMR (table 5:2).

The N-acetylhydrazine was hydrolysed with dilute hydrochloric acid to give the hydrochloride salt (122). Treatment of (122) with sodium hypochlorite solution produced 7-chloro-1,7-diazabicyclo[2.2.1]heptane (124), (figure 5:6).

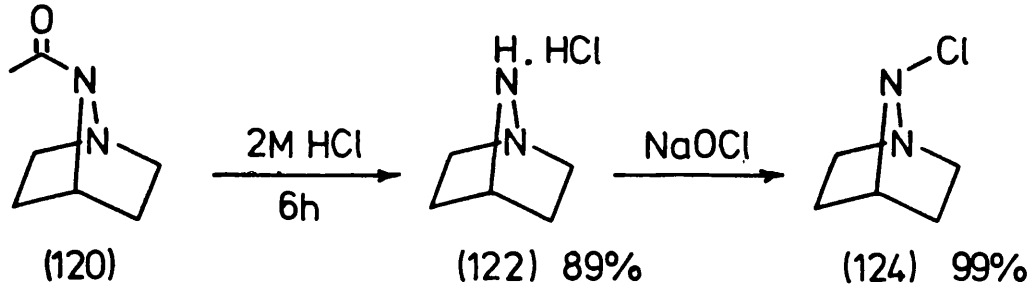
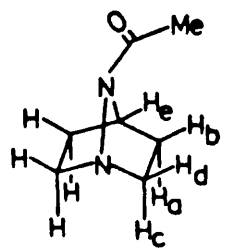


Figure 5:6

a	b	-Me	c	d	e	
1.41	11	-	8.5	4.7	-	a
	1.83	-	4.5	11	4.8	b
		2.07	-	-	-	-Me
			2.64	11	-	c
				2.93	-	d
					4.78	e



(120)

TABLE 5:2*

Chemical shifts (δ, ppm) along diagonal.

Coupling constants (J, Hz) off-diagonal.

δ_H (400 MHz; $CDCl_3$)

Pseudo-first order analysis, some J-values approximate.

The high field ^{1}H NMR spectrum of the N-chlorohydrazine (124) was found to contain nine distinct proton signals, whilst the ^{13}C NMR spectrum displayed five different carbon resonances. This indicated that nitrogen inversion was effectively "frozen" on the NMR timescale in each case. The ^{1}H NMR of (124) was complicated due to extensive coupling interactions, each signal being unusually broad because of this (figure 5:7). The linewidth of these signals prevented satisfactory decoupling experiments because the decoupling frequency bandwidth was insufficiently broad to decouple whole signals totally. Some of these problems were overcome by using 2D COSY experiments. However several signals contained very similar coupling constants and so a contour-plot of the COSY spectrum was obtained to furnish additional data on the relative magnitudes of the coupling constants, (figures 5:8). Utilisation of this information allowed a detailed analysis of the ^{1}H NMR spectrum of (124) to be completed (table 5:3). This was checked against a computer-simulated reconstruction of the spectrum (figure 5:9).

From coalescence temperature measurements using variable-temperature ^{1}H NMR (100MHz) experiments on (124) the barrier for nitrogen inversion was determined, (table 5:4) and (figure 5:10).

Table 5:4

N-Chlorohydrazine (124)	$\Delta\nu(25^{o}C)$	Tc(±5K)	$\Delta G^{\ddagger}$(±1.3kJmol^{-1})
H_g and H_h* (PhCl)†	51 Hz	440K	91.8 kJmol^{-1}

Shustov et al.[102] have also recently conducted coalescence temperature experiments on (124) using ^{13}C NMR ($PhNO_2$

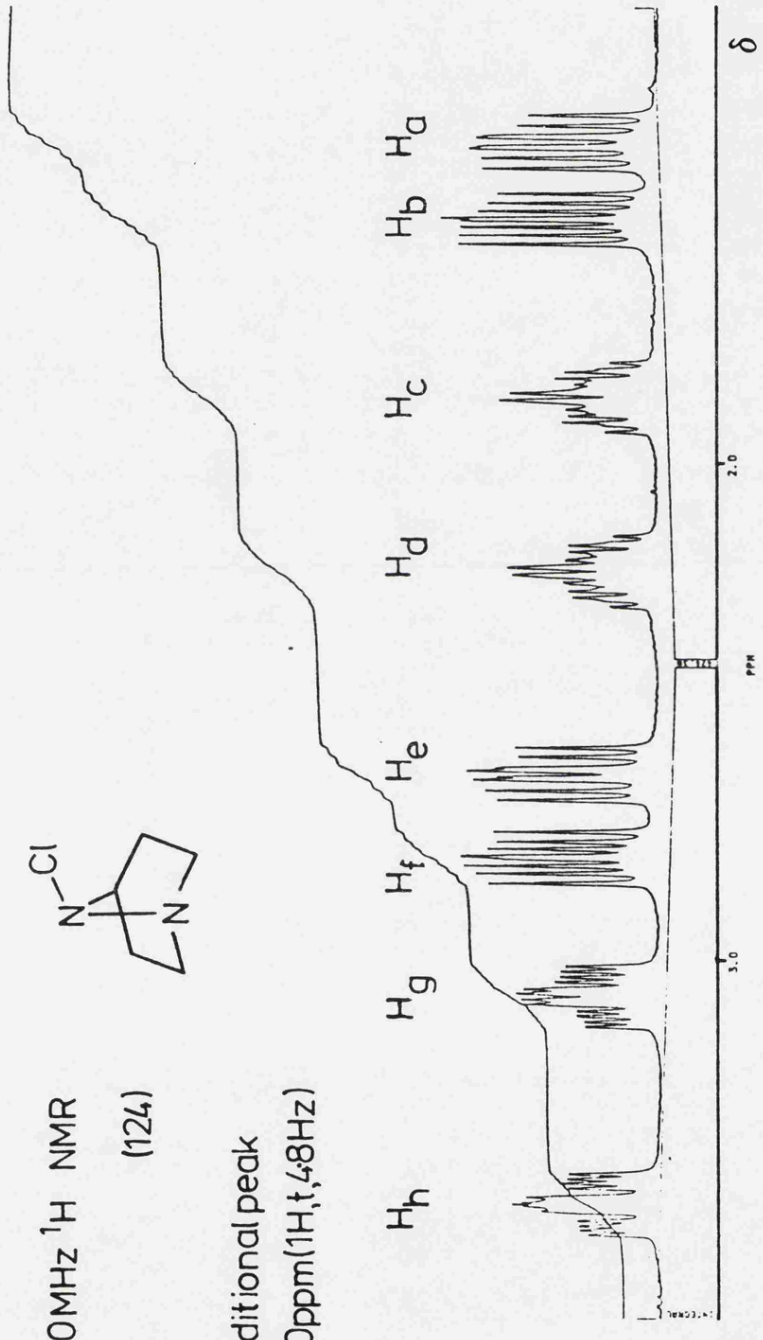
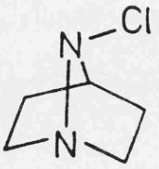

250MHz ¹H NMR
(124)
Additional peak
4·00ppm(1H,t,4·8Hz)
Cl
N
N
Hh
Hg
Hf
He
Hd
Hc
Hb
Ha
δ
PPM
3·0
2·0

Figure 5:7

300MHz COSY Spectrum



(124)

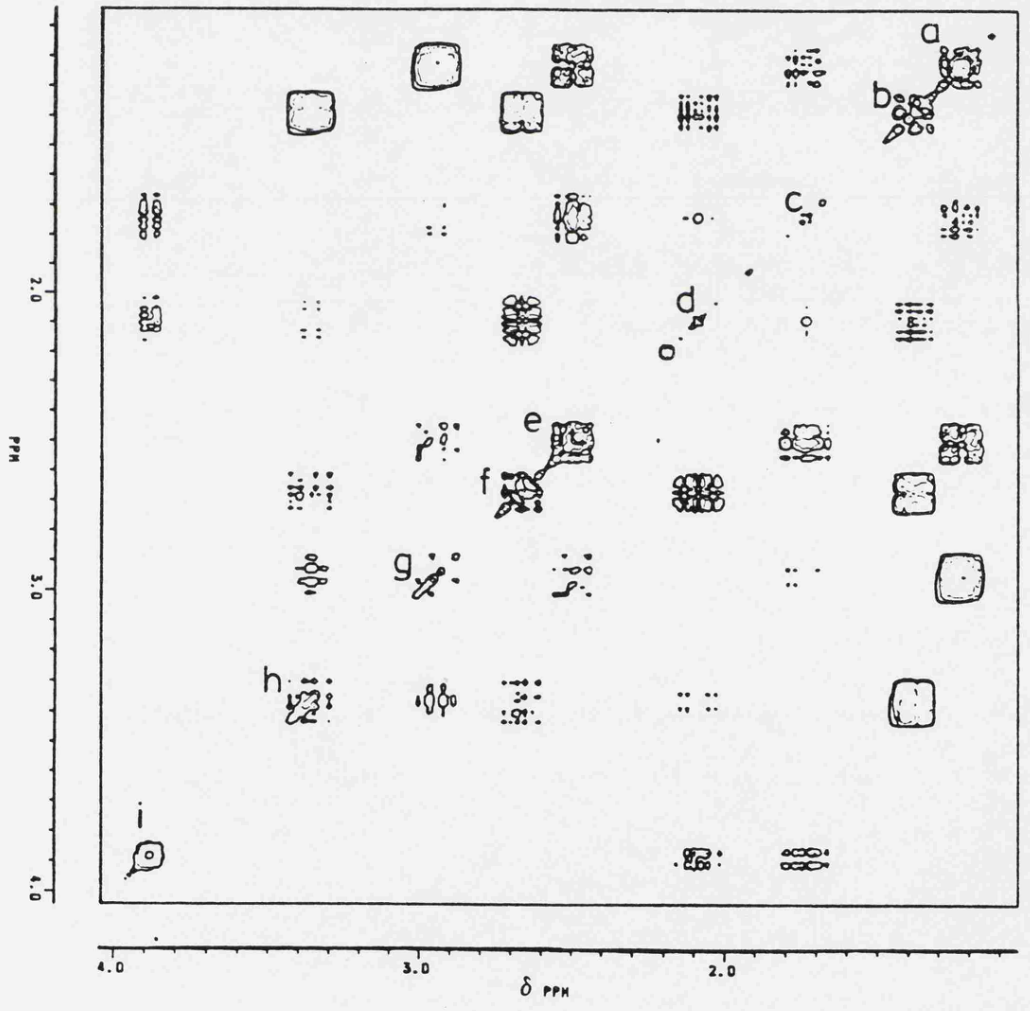


Figure 5:8a

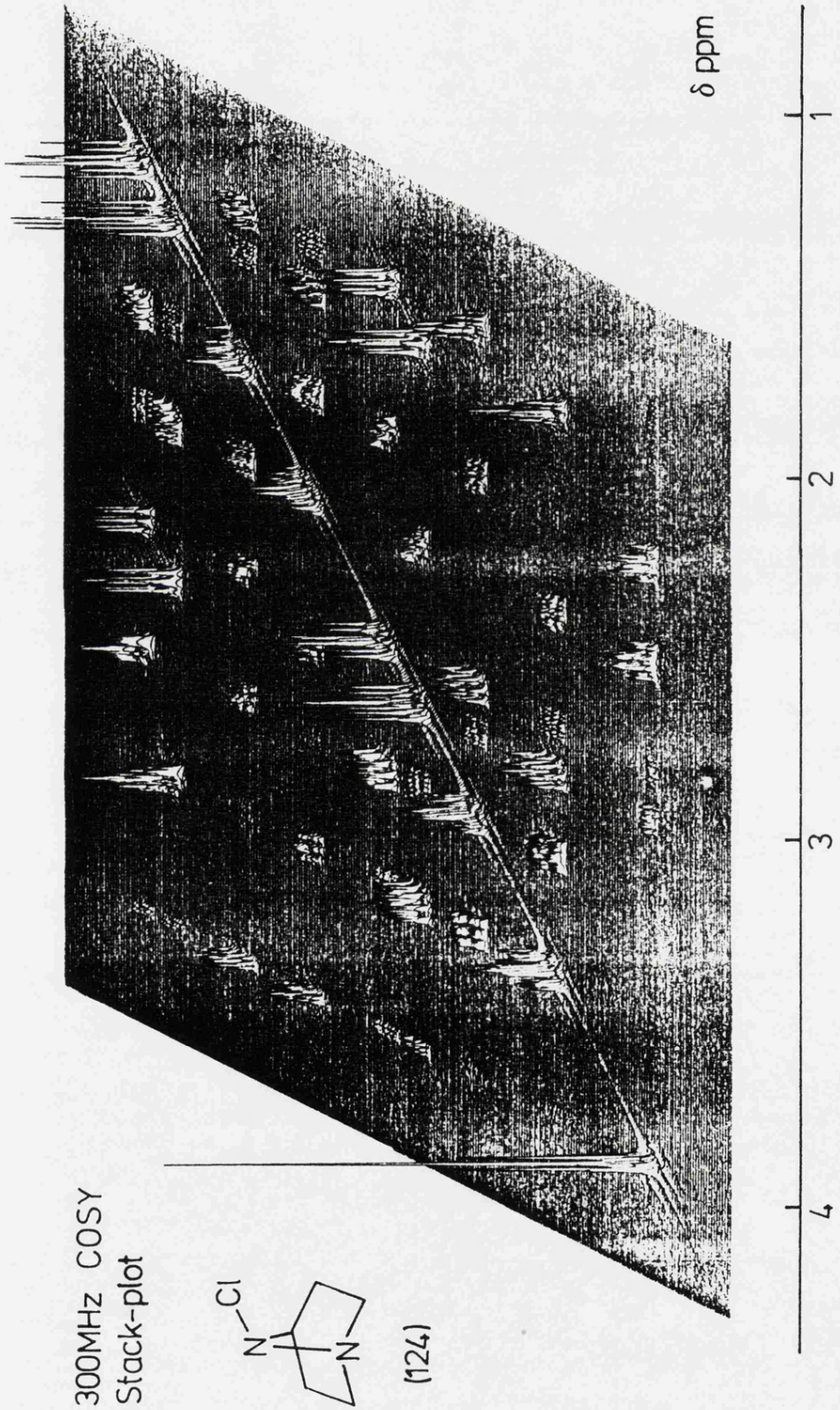
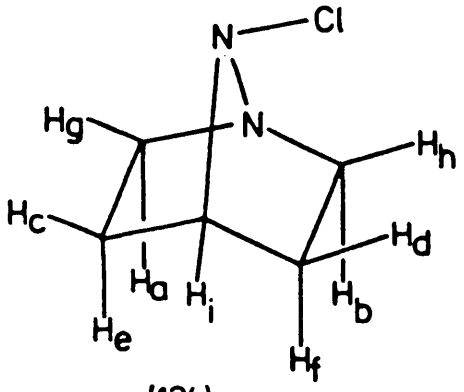


Figure 5:8b

a	b	c	d	e	f	g	h	i	
1.34	-	5.2	-	10.3	-	11.4	-	-	a
	1.50	-	4.7	-	8.8	-	11.9	-	b
		1.87	3.2	11.4	-	10.6	-	4.7	c
			2.22	-	11.9	*	11.1	4.8	d
				2.61	-	4.8	-	-	e
					2.78	-	4.8	-	f
						3.08	2.4	-	g
							3.48	-	h
								4.00	i



(124)

* very small addition coupling

TABLE 5:3

Chemical shifts (δ, ppm) along diagonal.

Coupling constants (J, Hz) off-diagonal.

δ_H (400 MHz; $CDCl_3$)

The position of the chlorine atom was in agreement with data for exo- and endo-protons in both (74b) and (100).

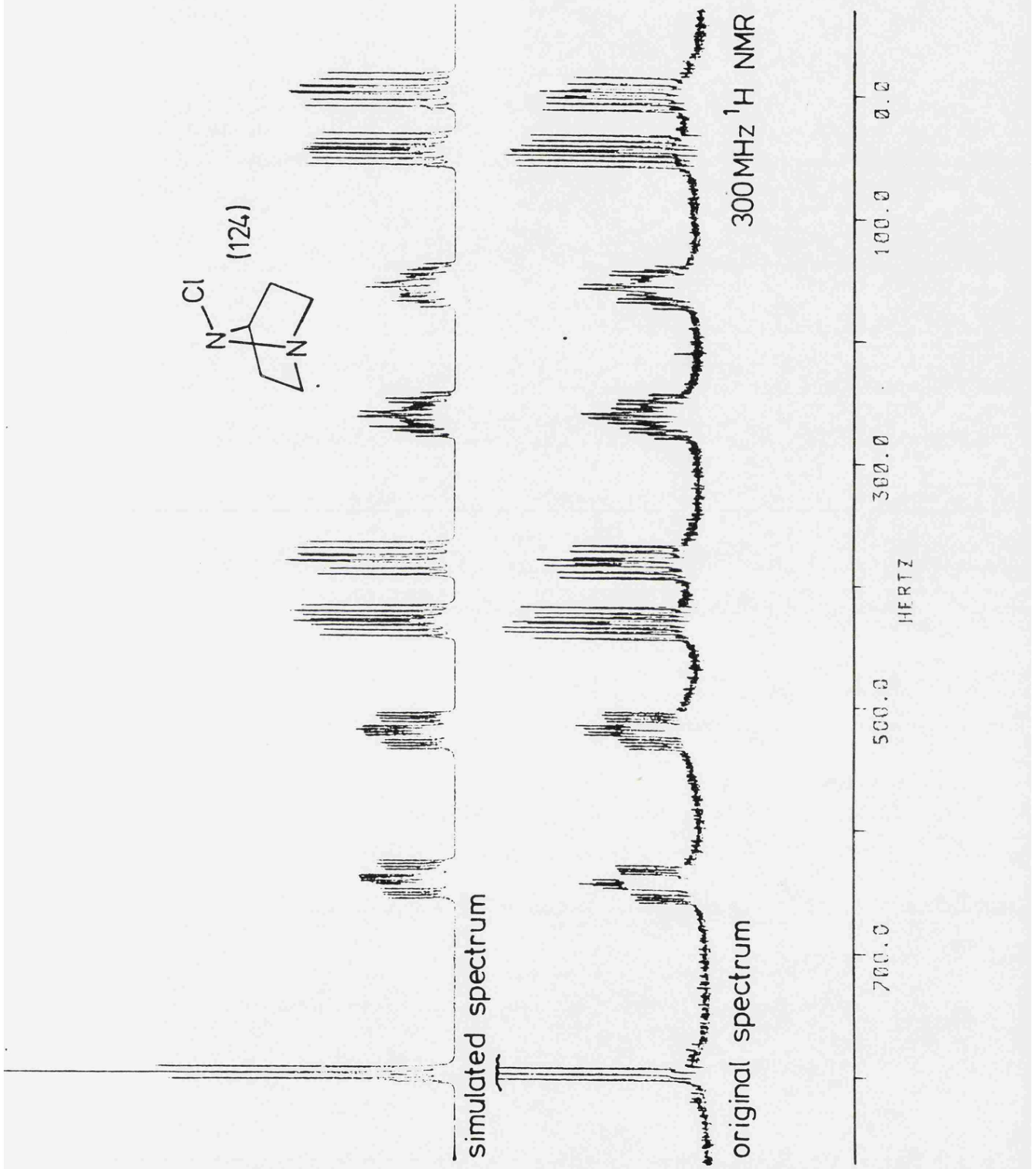
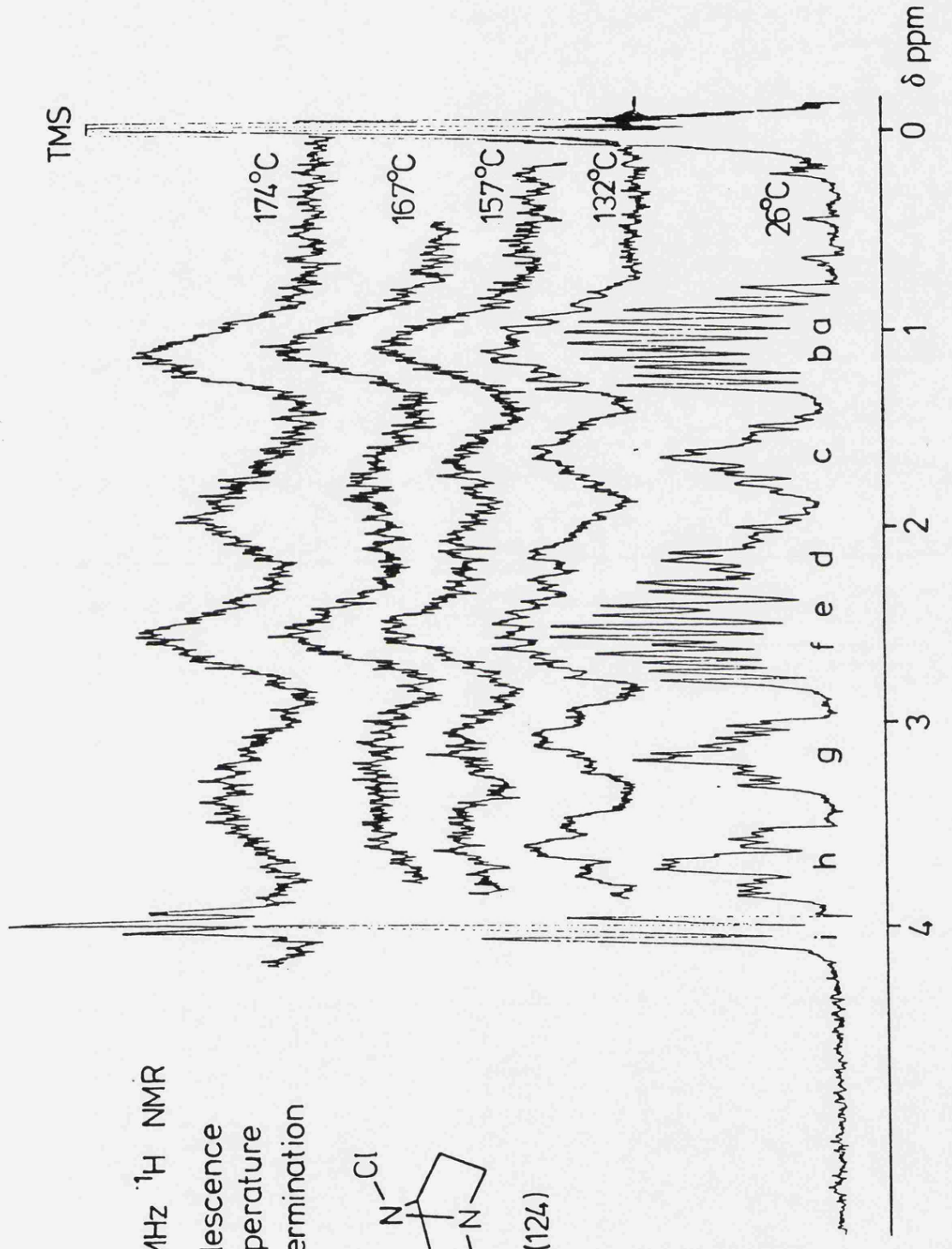

(124)
Cl
N
N
simulated spectrum
original spectrum
300 MHz ^{1}H NMR
700.0
500.0
300.0
100.0
0.0
HERTZ

Figure 5:9



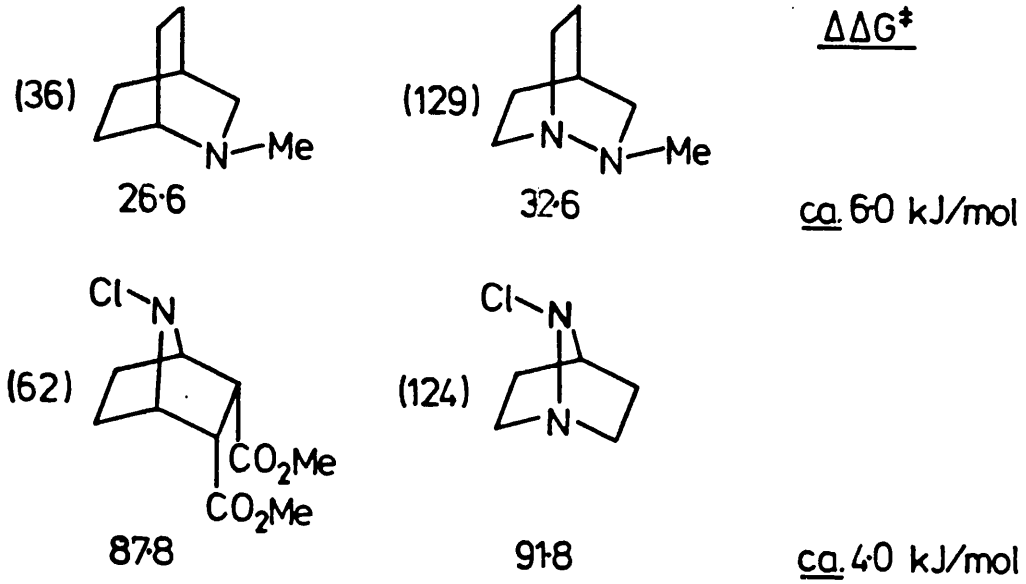
(124)

Figure 5:10

solvent), however they were unable to observe coalescence up to 120°C where they recorded that the sample was "completely decomposed." Shustov did however estimate that the coalescence temperature for (124) was "not lower than 94.5 $kJmol^{-1}$".

During the coalescence studies in this work it should be pointed out that the N-chlorohydrazine (124) was stable at temperatures up to at least 174°C (in $PhCl^{+}$) and that on cooling to ambient temperatures the sample was observed to have remained unchanged.

The barrier to nitrogen inversion for (124) was compared with that of the 7-azabicyclo[2.2.1]heptane derivative (62). The increase in barrier ($\Delta\Delta G^{\neq}$) on going from (62) to (124) was found to be 4.0 $kJmol^{-1}$, which is in good agreement with the figure of 4.2 $kJmol^{-1}$ recorded by Dewar and Jennings for the dibenzylamine derivatives as shown in figure 5:1, (table 5:5).



Barrier to Inversion $\Delta G^{\ddagger}$(kJ/mol)

Table 5:5

*see table 5:3 for assignments.
+in a sealed tube.

The difference in inversion barrier for the bicyclo-[2.2.2]octanes is slightly larger than that for the bicyclo-[2.2.1]heptanes, by *ca.* 2.0 $kJmol^{-1}$. This difference tends to be in agreement with Nelsen's suggestion that in the N-methyl hydrazine (129) there may be a small amount of residual lone pair - lone pair interaction at the transition state to inversion.[113]

In conclusion it seems that increases in inversion barrier caused by electronegative substituents must be predominantly due to lone pair - lone pair interactions and that contributions arising from the inductive effects of electronegative substituents must consequently be small.

The hydrazine (123) was available from basification of the hydrochloride salt (122). Since the inversion barrier of the N-chlorohydrazine (124) was quite high (91.6 $kJmol^{-1}$) it was decided that an attempt to determine the inversion barrier of the parent system (1,7-diazabicyclo[2.2.1]heptane) from coalescence temperature studies would be worthwhile. If possible this would furnish the first inversion barrier for a N-H system by such a method.

It was found that high field low-temperature ^{13}C NMR could provide both the coalescence temperature and frequency separation under conditions of slow inversion for the hydrazine. Therefore it was possible to estimate the coalescence temperature, (table 5:6).

Table 5:6

1,7-diazabicyclo-[2.2.1]heptane (123)	$\Delta\nu(\pm 20Hz)$	$Tc(\pm 5K)$	$\Delta G^{\ddagger}(\pm 1.0 kJmol^{-1})$
C4 ($CFCl_3/CH_2Cl_2/CD_2Cl_2$)	249Hz (133K)	153K	$28.6kJmol^{-1}$

The inversion barrier was very high for N-H inversion, approximately the same order as 2-methyl-2-azabicyclo[2.2.2]-octane (36), (26.6 $kJmol^{-1}$). This shows that the remarkably high barriers associated with the 7-azabicyclo[2.2.1]heptyl skeleton applies also to unsubstituted systems.

Attempts to achieve solvolytic rearrangement of the N-chlorohydrazine (124) in the presence of silver-ion proved unsuccessful. The only species isolated was unchanged N-chlorohydrazine (124). However, the recovery was relatively low which suggested that a substantial amount of volatile hydrazine (123) had formed (via homolytic fission of the N-Cl bond) but that this had been lost during work-up. Later, the solvolysis of (124) was repeated under more severe conditions ($AgBF_4$ in refluxing methanol); the sole product isolated following a more stringent work-up procedure was the hydrazine (123), (figure 5:11).

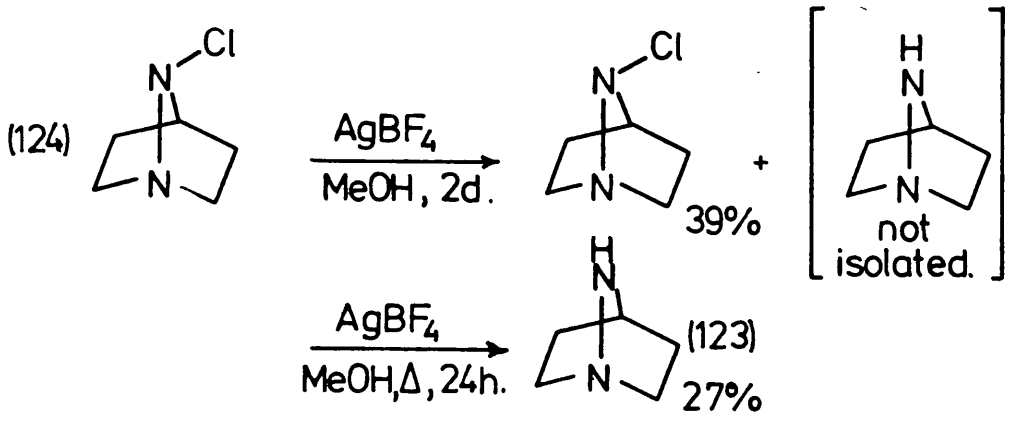


Figure 5:11

The resistance of (124) to rearrangement may be due to the high energy associated with the possible products, (figure 5:12).

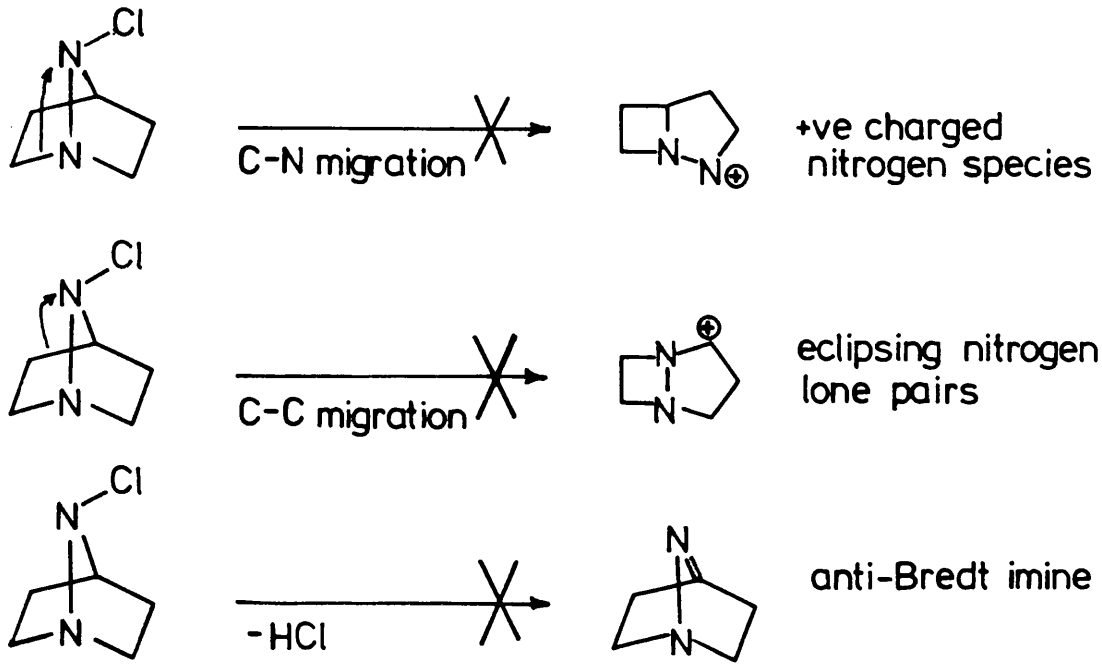


Figure 5:12

Therefore homolytic fission of the N-Cl bond seems to be the only reaction pathway for (124) under such solvolytic conditions.

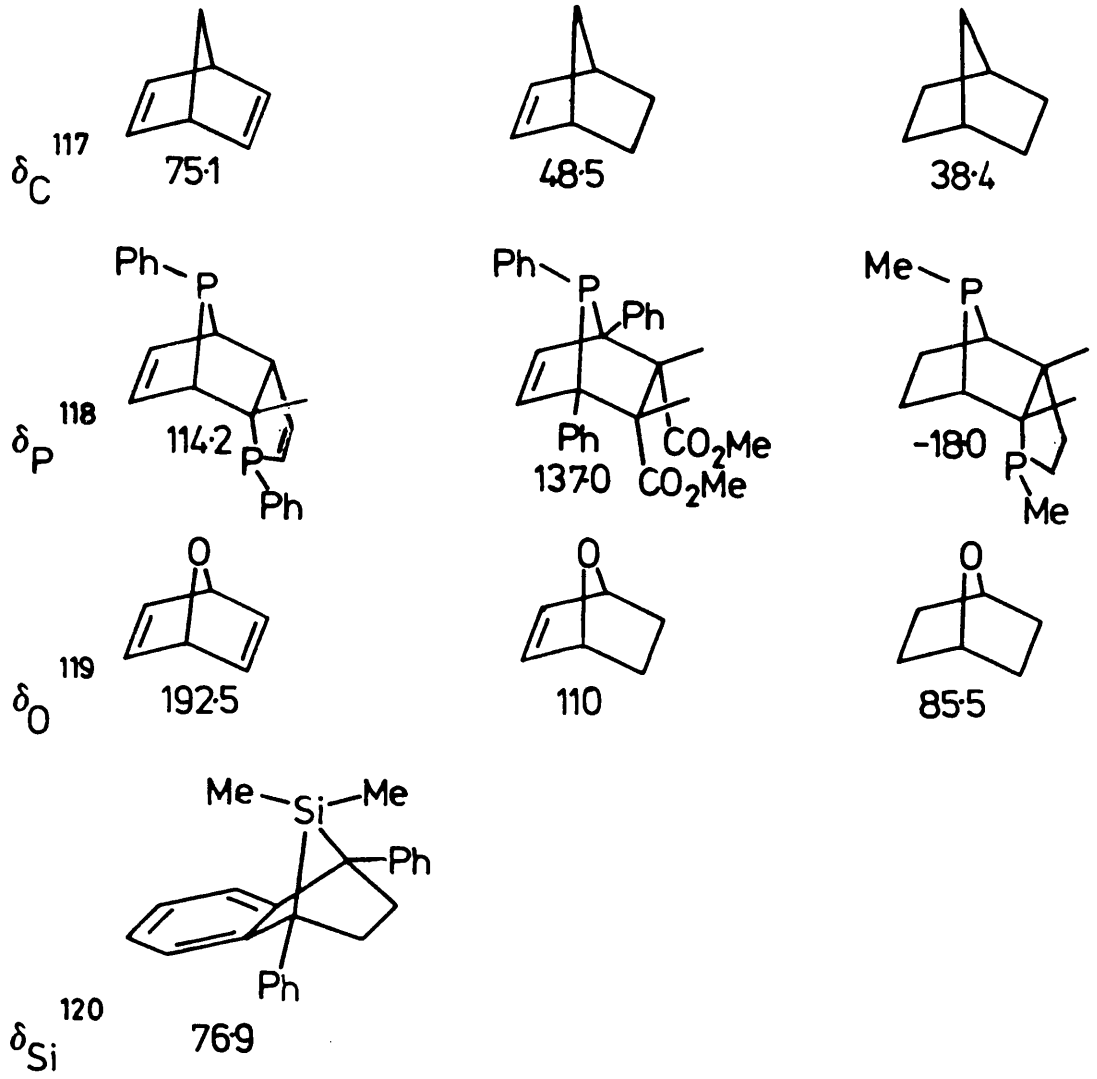
SECTION B

5.IV ^{15}N NMR Spectra of Several 7-Azabicyclo[2.2.1]heptyl Derivatives

The present study has shown that 7-azabicyclo[2.2.1]-heptyl derivatives exhibit unusual solvolytic behaviour and also possess anomalously high barriers to nitrogen inversion. It has been observed that other systems possessing bicyclo -[2.2.1]heptyl skeletons often exhibit an abnormally deshielded signal in their NMR spectra for the atom at the 7-position, (table 5:7).

Table 5:7

Chemical shifts for 7-position atom (ppm)



It seems unlikely that angle strain at the 7-position is the reason for this deshielding phenomenon as atoms found in 3- and 4-membered rings are normally highly shielded. From table 5:7 it can be seen that the degree of deshielding is dependent on the number of unsaturated bonds present at the two-carbon bridges. The greater the unsaturation in the bicyclo[2.2.1]heptyl skeleton, the greater

the downfield shift of the atom at the 7-position. It has been stated that ground-state polarisation arising from σ-π conjugation may provide an explanation for this effect.[118,120,121] Such a conjugative effect would give rise to positive character at the 7-position thus causing the deshielding, (figure 5:13).

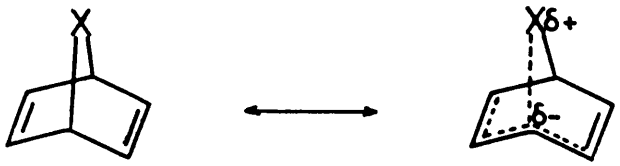


Figure 5:13

It was decided that ^{15}N NMR investigation of certain 7-azabicyclo[2.2.1]heptyl might be advantageous as this would reveal whether such deshielding of the 7-position was also common in these systems. It was hoped that the additional data thus provided might aid the understanding of these strained systems. However to obtain ^{15}N NMR spectra from samples containing ^{15}N at natural abundance was not simple,[122] (table 5:8).

Table 5:8[116]

Isotope	Natural Abundance (%)	Relative Sensitivity	Spin
^{1}H	100	1	$\frac{1}{2}$
^{13}C	1.11	1.59×10^{-2}	$\frac{1}{2}$
^{15}N	0.37	1.04×10^{-3}	$(-)\frac{1}{2}$

Table 5:8 indicates that both the natural abundance and the relative sensitivity of the ^{15}N nucleus are very low. Therefore in order to measure such spectra it is

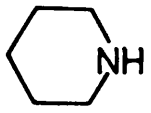
necessary to use a sensitive high-field F.T. NMR instrument together with highly concentrated samples. The slow relaxation of the ^{15}N nucleus requires exceptionally long spectral acquisition times and further problems arise because the NOE factors for the ^{15}N nucleus are negative which means that signals become more negative with proton decoupling.

However proton substituents on nitrogen aid relaxation and thus may shorten spectral acquisition. Further improvements can often be gained by use of $Cr(acac)_3$ as a paramagnetic relaxation agent. Also unwanted NOE's could be removed by gated decoupling or by use of $Cr(acac)_3$.

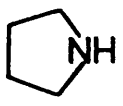
Table 5:9[123] illustrates the reported limits of the chemical shifts attributed to primary, secondary and tertiary amines. Some cyclic amines are included for comparison purposes. Chemical shifts are quoted using nitromethane (CH_3NO_2) as reference.

Table 5:9[123]

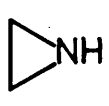
Species	Chemical Shift
NH_2R	-325 ⟶ -380 ppm
NHR_2	-300 ⟶ -370 ppm
NR_3	-325 ⟶ -330 ppm
Hydrazines	-270 ⟶ -330 ppm



-320to-345ppm



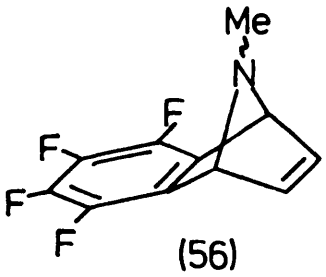
-342/3ppm



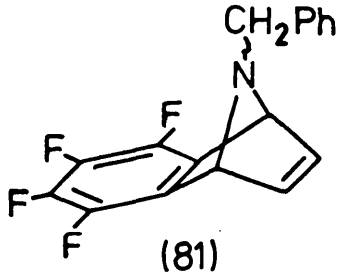
-393ppm

Table 5:10 presents the ^{15}N NMR spectra measured during this study.

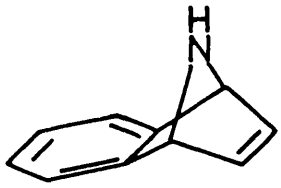
Table 5:10



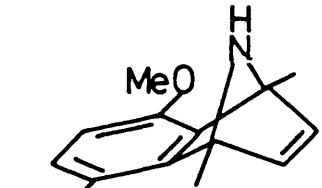
(56)



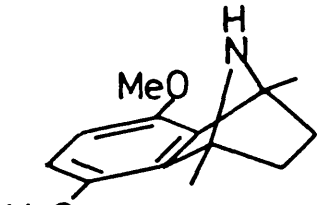
(81)



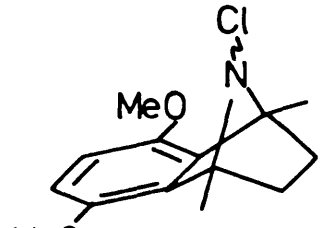
(64)



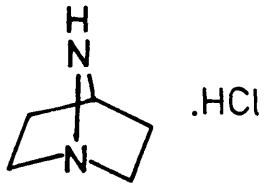
(94)



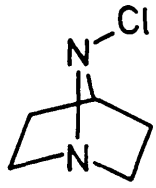
(96)



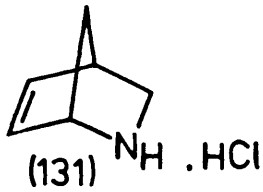
(100)



(122)



(124)



(131)

^{15}N NMR (40·55MHz)

Compound	Chemical Shift (δN, ppm)
(56)	-251.5 $CDCl_2/Cr(acac)_3$
(81)	-243.2 $CDCl_2/Cr(acac)_3$ gated dec.
(64)	-239.6 CD_2Cl_2 no decoupling
(94)	-214.4 CD_2Cl_2/CH_2Cl_2
(96)	-251.7 CD_2Cl_2/CH_2Cl_2

Compound	Chemical Shift (δN, ppm)
(100) "syn" *	-200.1 (65%)† CD_2Cl_2/CH_2Cl_2
(100) "anti" *	-218.3 (35%)†
(122)	-257.2 inverse gated no NOE
	-276.0 D_2O
(124)	-198.0 $CD_2Cl_2/Cr(acac)_3$
	-241.5
(131)	-334.6 H_2O/D_2O

Comparisons between the results of table 5:10 and the data in table 5:9 showed that tertiary amines (56) and (81) exhibit chemical shifts in the ^{15}N NMR that are ca. 75+ ppm downfield of the most deshielded tertiary amines recorded. However it should be mentioned that after completion of this work, Quin et al.[118] reported that 7-azanorbornenes showed the'lowest chemical shifts measured for tertiary amines'but no details of the compounds or the chemical shifts were provided.

Similarly compounds (64), (94) and (96) also showed chemical shifts significantly downfield (ca. 50+ ppm) of the lower limit recorded for secondary amines. The large difference between the chemical shifts of (94) and its hydrogenated form (96) (ca. 37 ppm) parallels similar differences illustrated in table 5:7. That is the presence of endocyclic double bonds leads to a marked downfield shift for the atoms at the 7-position.

The N-chloroamine (100) provided the lowest chemical shifts observed for amines in this study. The spectrum of

*Assignments based on ratio of invertomers derived from ^1H and ^{13}C NMR 71:29 (SYN:ANTI).

†Relative electronic integration of peaks ±15%

this compound was particularly interesting as signals arising from both syn- and anti- invertomers were observed. Although ^{15}N NMR spectra of invertomeric species have previously been measured for several examples, all previously reported examples have involved double inversion at the two nitrogen atoms of bicyclic hydrazine derivatives;[124] in the case of (100) two invertomers were observed in a system containing a single inverting nitrogen atom. It is interesting to note that the electronic integration of the two peaks affords a ratio of 65 : 35 which corresponds, within experimental error, to the invertomer ratio measured for (100) by ^{1}H and ^{13}C NMR, that is 71 : 29 (syn : anti).

The hydrazine (122) and the N-chlorohydrazine (124) were also studied. The signal observed for the nitrogen atom of the 7-position in (122) was downfield of the normal range for hydrazines but only by *ca.* 12 ppm, which was interesting as there are no endocyclic double bonds in this system. The signals observed for both nitrogen atoms in (124) were considerably deshielded, the nitrogen atom at the 1-position being found surprisingly downfield of the normal range of hydrazines (by *ca.* 28 ppm). It seems likely, therefore, that a major factor in the downfield shift of these nitrogen atoms is the inductive effect of the electronegative chlorine substituent at the 7-position.

The chemical shift of the nitrogen atom in 2-azabicyclo-[2.2.1]hept-5-ene hydrochloride (131) showed that the downfield shift was only characteristic of atoms in the 7-position in azabicyclo[2.2.1]heptyl systems.

The deshielding of nitrogen in the 7-azabicyclo[2.2.1]-heptyl derivatives signifies that there exists in such systems

some increased delocalisation of the lone pair of electrons when compared with normal aliphatic and alicyclic amines. In the 7-azabicyclo[2.2.1]heptyl systems which contain endocyclic double bonds the additional deshielding may arise from $n_N \rightarrow \pi^*$ circulations.[123] Finally it should be stated that there seems to be no obvious correlation between inversion barriers and ^{15}N NMR chemical shifts.

SECTION C

5.V X-Ray Crystallographic Studies of 7-Azabicyclo[2.2.1]-heptyl Derivatives

The underlying factors giving rise to the anomalous properties of 7-azabicyclo[2.2.1]heptyl derivatives still remain unclear. Lehn stated[1] that the inversion barriers in such systems were significantly higher than those expected on the basis of angle strain. This assumed that the $C\hat{N}C$ angles in such systems would be similar to that found for the $C1-\hat{C}7-C4$ angle of norbornane (96°), which had been obtained from electron diffraction studies.[125]

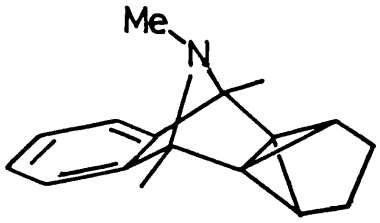
Since the barrier to nitrogen inversion can be dependent to some degree on the $C\hat{N}C$ angle it seemed wise to obtain more accurate data on this and other structural features of these systems. This might also furnish evidence on the possibility of ground state polarisations or other such phenomena occurring in these systems.

Therefore it was decided to undertake X-ray studies on some available crystalline derivatives. Two separate crystal structure determinations on 7-azabicyclo[2.2.1]heptyl systems have been reported in the literature although both of these systems were unsatisfactory for the type of study

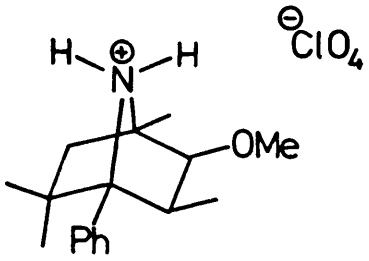
intended.

Dunitz et al.[126] had completed a study of (132) with the goal of gathering evidence on the absence of electron density between inverted carbon atoms. The peculiarity of the ring system fused to the 7-azabicyclo[2.2.1]heptyl skeleton made such a compound unrepresentative. Swanson et al.[127] studied the 7-azabicyclo[2.2.1]heptyl derivative (133) but this, being a perchlorate salt, afforded no data on the relationship of a substituent at nitrogen with the remainder of the bicyclic structure, (table 5:11).

Table 5:11



(132)



(133)

CN̂C	95.8°	97°
N-C1	1.51 Å	1.50 Å
N-C4	1.51 Å	1.54 Å

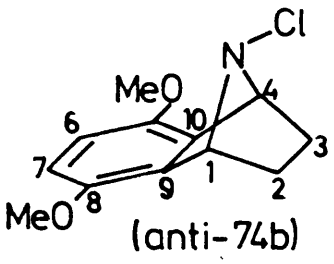
Table 5:11 shows that the CN̂C angles for these compounds were similar to that predicted[1] and that the N-C bonds do not seem significantly longer than usual (1.47 Å).

The N-chloroamines (74b) and (100), when recrystallised from methanol, afforded crystals of sufficient quality for X-ray ananlysis. Several crystals of (74b) were dissolved in $CDCl_3$ at low temperature (-50°C), examined by high field ^1H NMR and found to contain a mixture of diastereomers. However when a single crystal was dissolved at low temperature

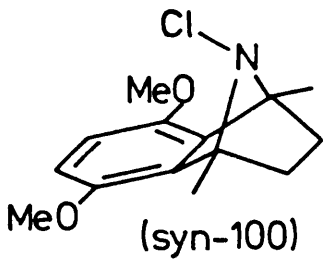
it was found to contain a single diastereomer (anti-74b). Similarly when a single crystal of (100) was dissolved in $CDCl_3$ at low temperature it was found to be the invertomer (syn-100). Later it was discovered that (100) crystallised out of methanol solely as the syn - diastereomer.

X-Ray crystal structures were completed on (anti-74b), (figures 5:14) and also on (syn-100), (figures 5:15). The detailed data from these crystal structure determinations will be given in Chapter 6, however some of the more interesting features are presented in table 5:12.

Table 5:12



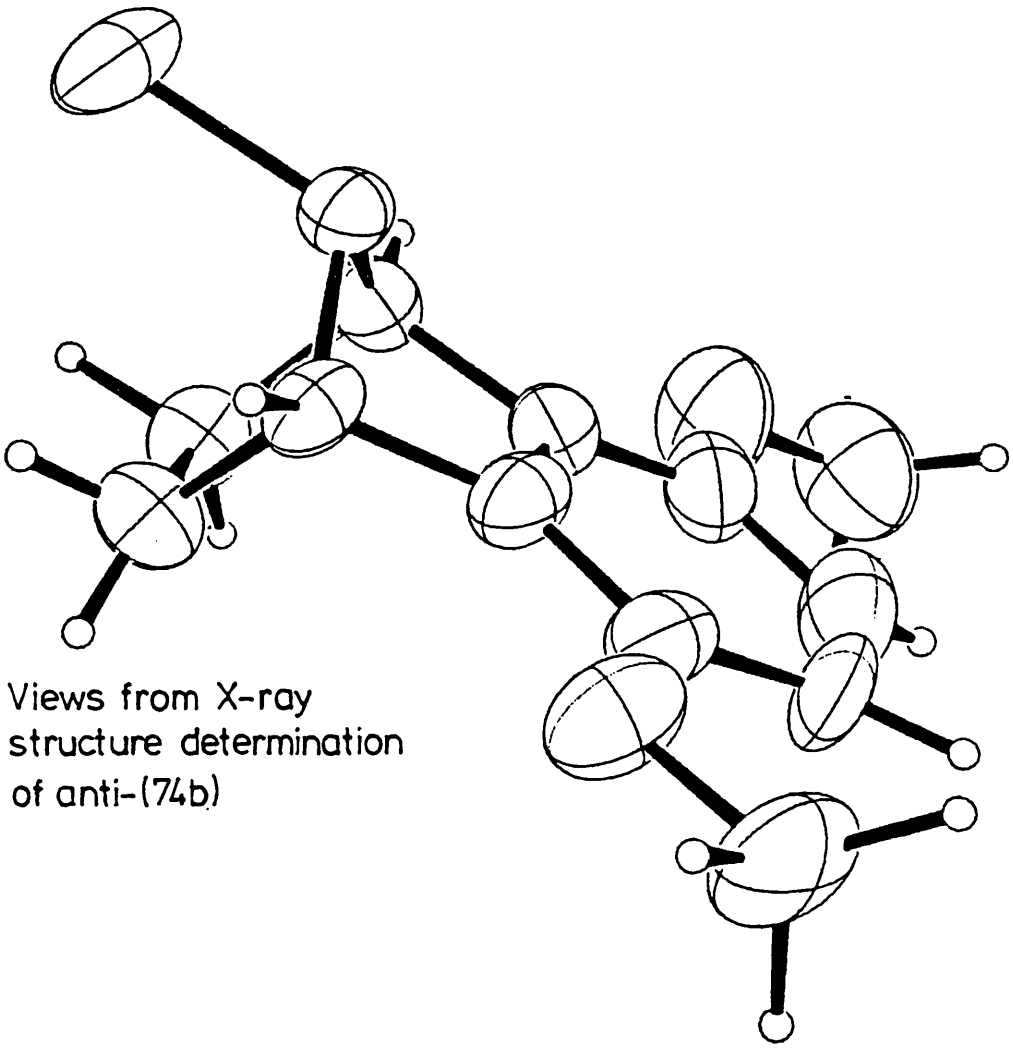
(anti-74b)



(syn-100)

Bond Angles	(anti-74b)	(syn-100)
$C\hat{N}C$	95.7^{o}	97.3^{o}
$N\text{-}\hat{C}(1)\text{-}C(9)$	95.9^{o}	103.7^{o}
$N\text{-}\hat{C}(1)\text{-}C(2)$	104.9^{o}	95.4^{o}
Bond lengths		
N-Cl	1.77Å	1.78Å
N-C(1)	1.48Å	1.50Å

From table 5:12 it can be seen that the $C\hat{N}C$ bond angles are still close to the predicted angle. The N-C bond lengths and N-Cl bond lengths are also close to normal. The bond angles at the bridgehead carbons are somewhat odd. In each



Views from X-ray structure determination of anti-(74b)

Figure 5:14a

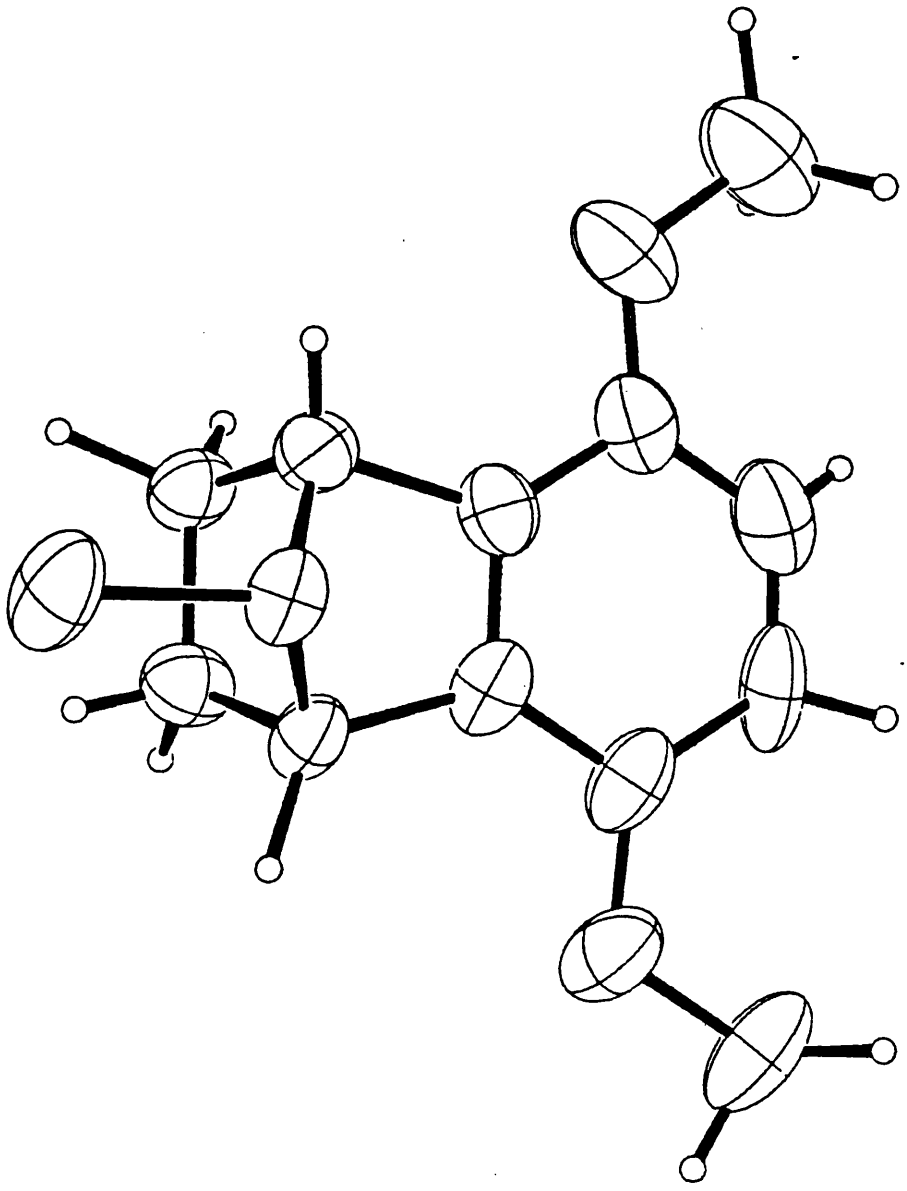
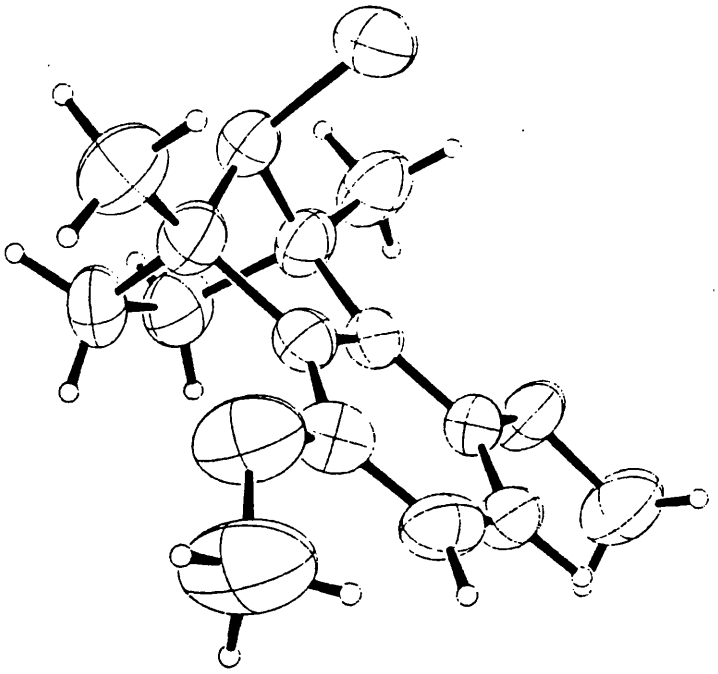


Figure 5:14b



Views from X-ray structure determination of syn(100)

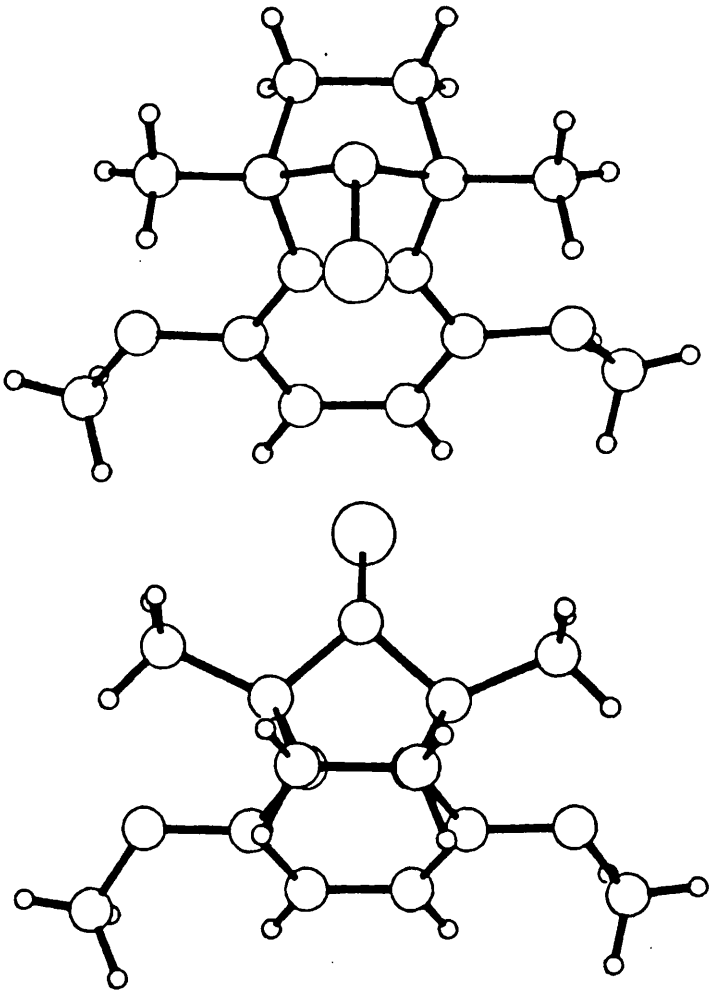
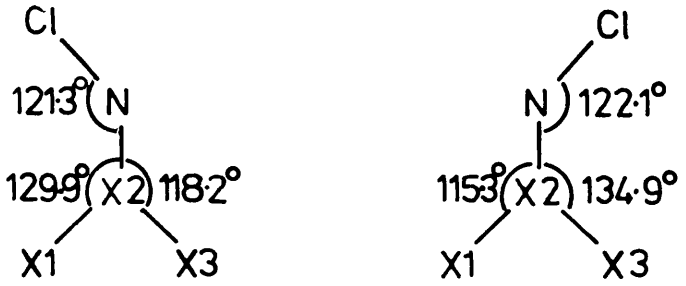


Figure 5:15

case the bond angles $\hat{NCC}$ on the opposite side to the chlorine substituent are compressed. This phenomenon seems to be independent of the configuration at nitrogen. The flap angles for both molecules further illustrate this point (these were measured from the centroids of the bonds C(2)-C(3), C(1)-C(4) and C(9)-C(10) that is (X1), (X2) and (X3) respectively; table 5:13).

Table 5:13



The N-Cl bonds in both cases are close to being anti-periplanar to the planes contained by C(1)-C(4)-C(9)-C(10) for (74b) and C(1)-C(4)-C(2)-C(3) for (100); the angles are 176.9° and 173.2° respectively. This indicates that there could be some interaction between the N-Cl bonds and the bonds to the bridgehead carbon atoms on the opposite side of the molecule to that N-Cl bond, (figure 5:16).

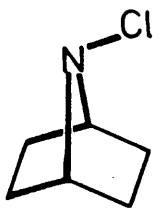


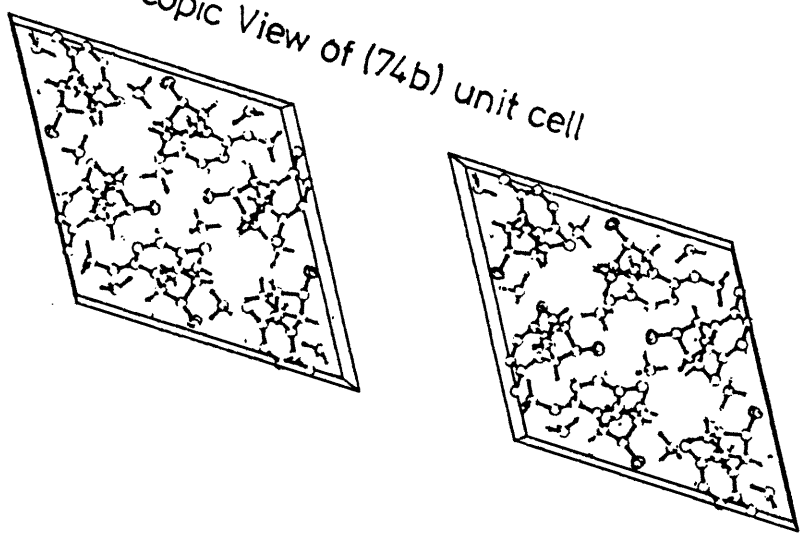
Figure 5:16

The precise nature of such an interaction is difficult to understand, however it may possibly be some form of generalised anomeric effect.

An anomaly was observed in the structure of (anti-74b). The thermal motion of the chlorine substituent on nitrogen had its plane of maximum amplitude askew to the central plane of the molecule (i.e. X1-X2-X3-N), (figure 5:14b). Further investigation revealed that another chlorine atom from a second molecule within the unit cell lay within close proximity of the chlorine atom of the first molecule. In fact the distance separating the chlorine atoms was determined as 3.14 Å which is significantly less than the sum of the Van der Waal's radii for two chlorine atoms (3.60 Å). Furthermore stereoscopic representations of the unit cell show that the two N-Cl bonds appear to point directly at one another, (figure 5:18). Such a situation seems energetically unfavourable when considering steric interactions and electrostatic repulsions. However these factors may be more than compensated by the highly symmetric manner in which the molecules of (anti-74b) pack within the unit cell (trigonal space group $\beta 3$).

It was noted that the $C\hat{N}C$ angle was wider for (syn-100) than that for (anti-74b); the angles being 97.3° and 95.7° respectively. This was similar to the situation reported in a study of 1,3-disubstituted bicyclo[1.1.1]pentanes where the C(1)-C(3) distances were calculated for a number of derivatives, (table 5:14).

Stereoscopic View of (74b) unit cell



Stereoscopic Views of (100) unit cell

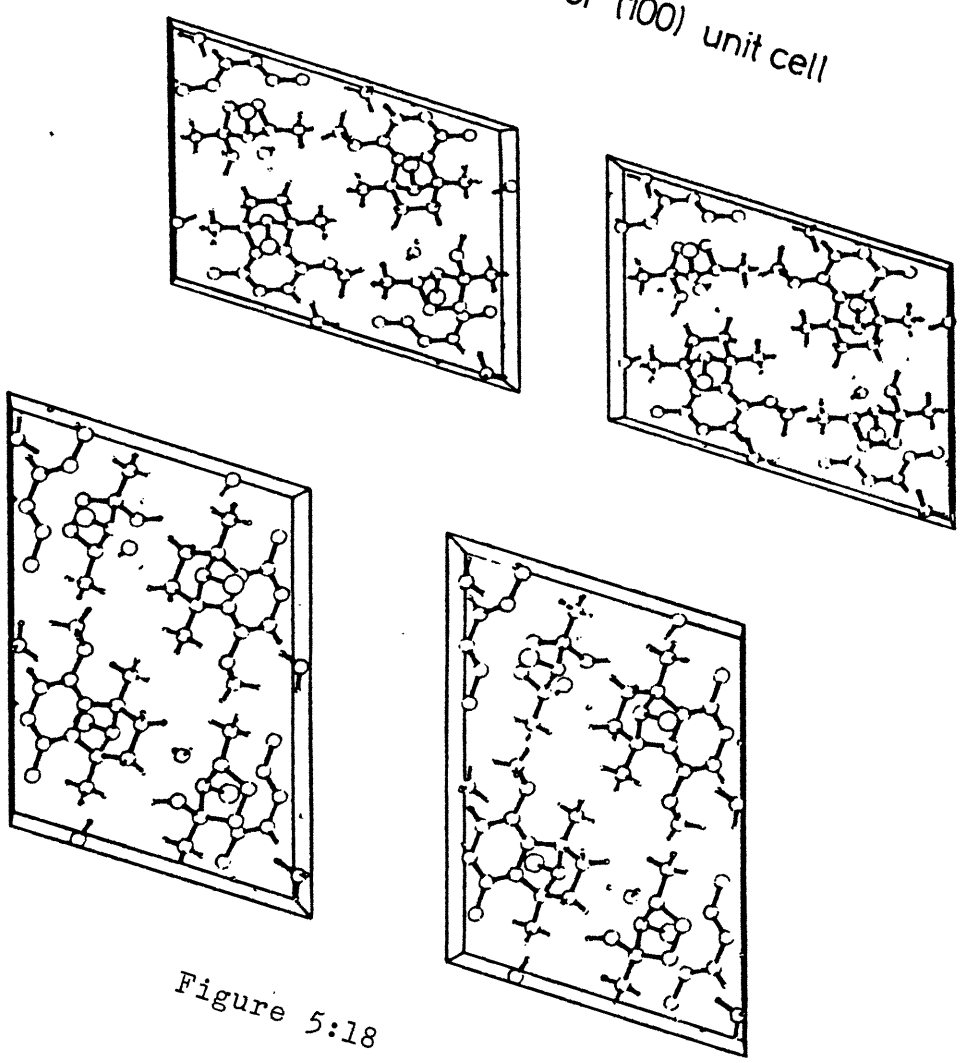


Figure 5:18

Table 5:14

Substituents at positions 1 and 3	distance C1-C3(Å)
H	1.916
Me	1.939

Methyl substituents at the 1 and 3-positions increased the electron density in the carbon bridgehead orbital and therefore increased the non-bonded (C(1)-C(3)) distance with respect to the unsubstituted case.[128]

Finally it seems that there may be some dependence of nitrogen inversion barriers in 7-azabicyclo[2.2.1]heptyl derivatives on the $C\hat{N}C$ angle. The inversion barrier of (100) had been determined in this study (85.6 $kJmol^{-1}$). Although the corresponding barrier for (74b) has not yet been accurately measured, a qualitative study[67] showed that it was in excess of that measured for (74a), (94.6 $kJmol^{-1}$). Therefore as the $C\hat{N}C$ angle widens, on going from (74b) to (100), the inversion barrier decreases as would be expected.

APPENDIX I

THE FLASH VACUUM PYROLYSIS OF 6,7-BENZO-1-AZABICYCLO[3.2.0]-HEPTYL SYSTEMS

A.1 Introduction -Azaxylylenes

There had been considerable interest in azaxylylenes because of their utility as intermediates in organic synthesis. Ito et. al. recently reported a synthesis of the alkaloid Gephyrotoxin[129] in which a key Diels-Alder cyclisation was performed using an azaxylylene intermediate generated *in situ.*, (figure A:1).

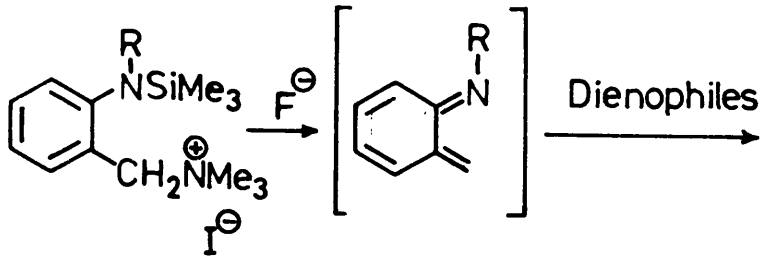


Figure A:1

Azaxylylenes have also been prepared by photochemical methods from benzazetidines,[130] (figure A:2).

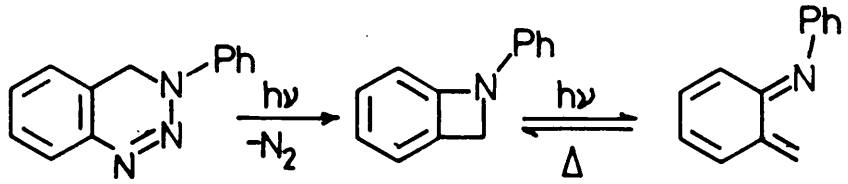


Figure A:2

Storr et.al.[131] have generated azaxylylenes using flash vacuum pyrolytic (FVP) techniques. The intermediates thus formed underwent cyclisation and H-shifts, (figure A:3).

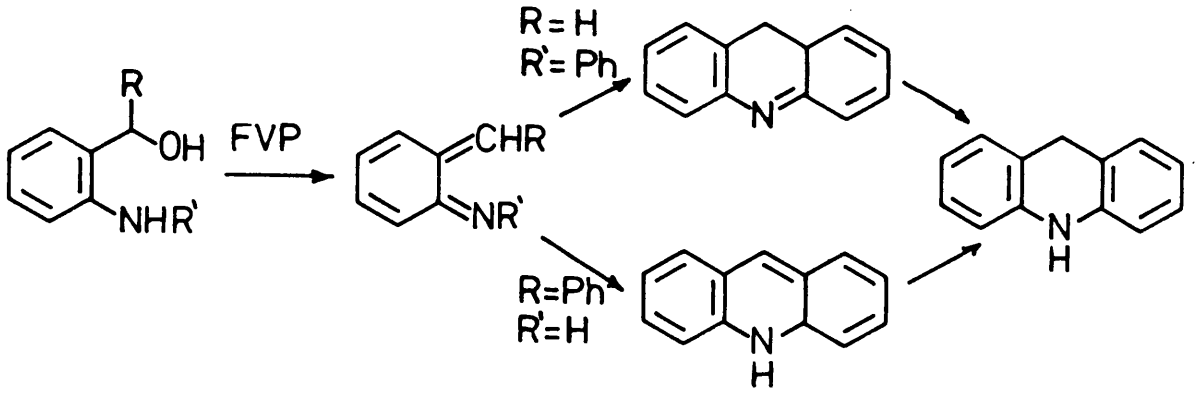


Figure A:3

It was recognised that the solvolytic products of the type (73) might be precursors to azaxylylenes (via pyrolytic or photochemical routes) which might possibly undergo interesting subsequent rearrangements, (figure A:4).

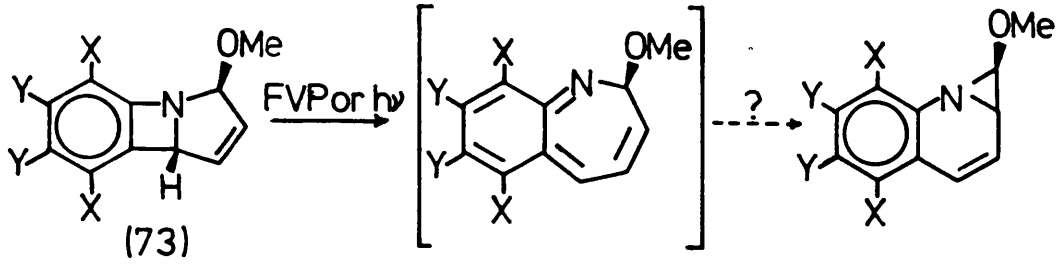


Figure A:4

A.II Flash Vacuum Pyrolysis* of 6,7-Benzo-1-azabicyclo-[3.2.0]heptyl Derivatives

Several attempts were made to photolyse (73b) in the presence of DMAD; these were unsuccessful and it was decided to try a pyrolytic approach. The FVP apparatus utilised is illustrated in figure A:5.

*Reviews are available illustrating the wide applicability of this technique.[132]

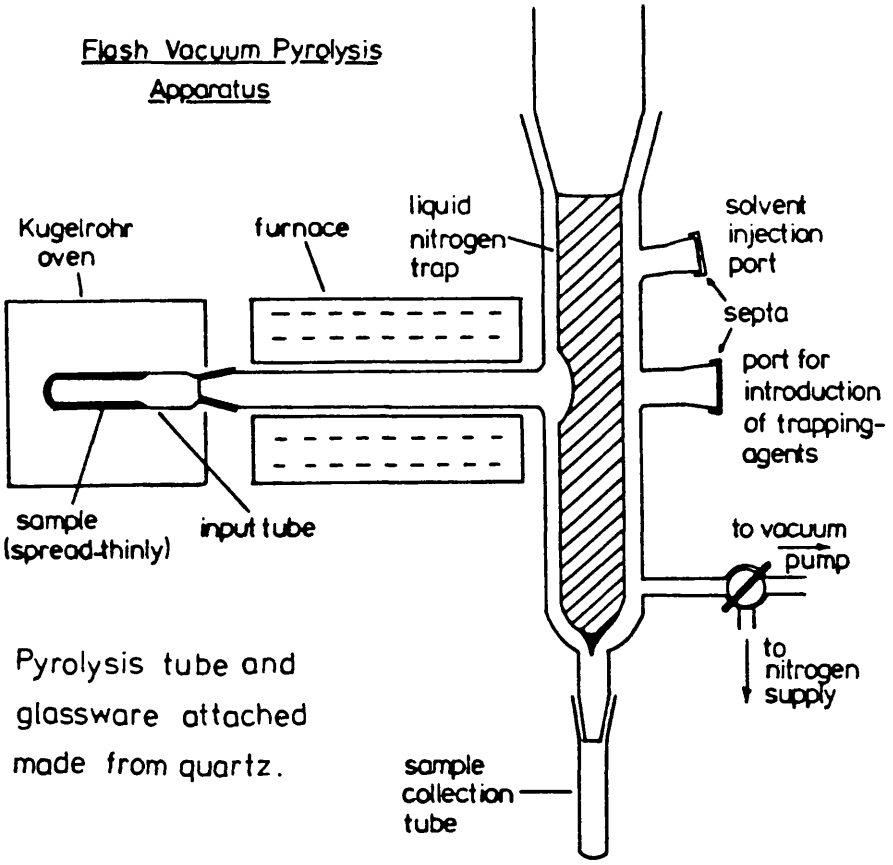
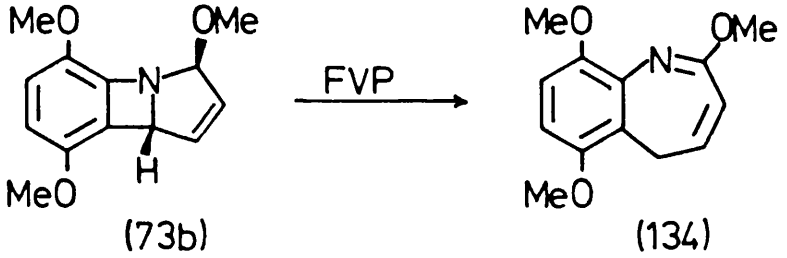


Figure A:5

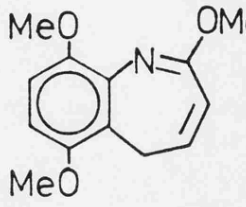
When the solvolysis product (73b) was subjected to FVP, it underwent clean rearrangement to an isomeric compound (134), the two compounds possessing the same molecular ion in the mass spectrum (m^+ = 233). The ^1H NMR spectrum of (134) lacked any aziridine signals and still exhibited olefinic resonances. With the use of simple decoupling experiments (figure A:6) it was shown that rearrangement product (134) was 2,6,9-trimethoxybenzo(f)-5H-azepine, (figure A:7).



(73b) (134)

Figure A:7

90MHz ^{1}H NMR Spectrum of (134)



(134)

including decoupling at ca. 3·1 ppm (3mG)

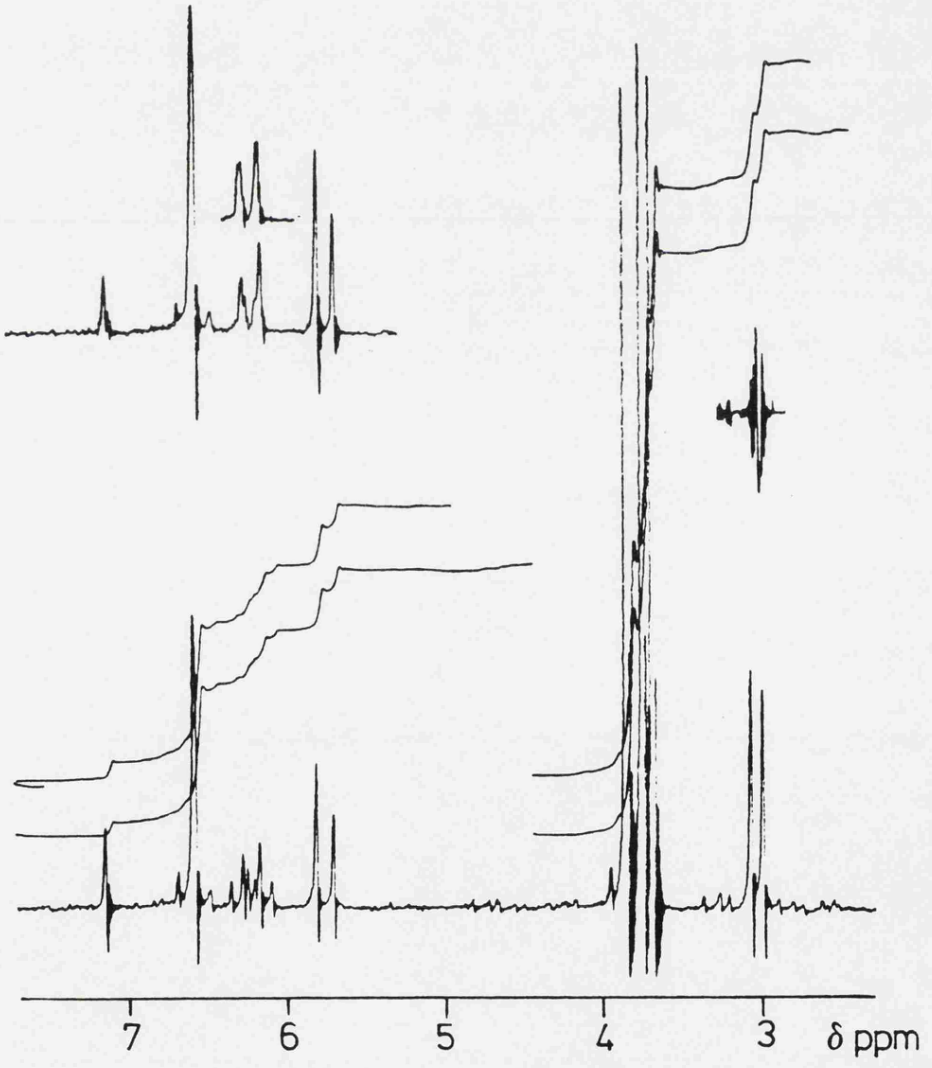


Figure A:6

It seemed likely that the rearrangement proceeded via an azaxylylene intermediate which subsequently underwent a 1,5-sigmatropic hydrogen shift, (figure A:8).

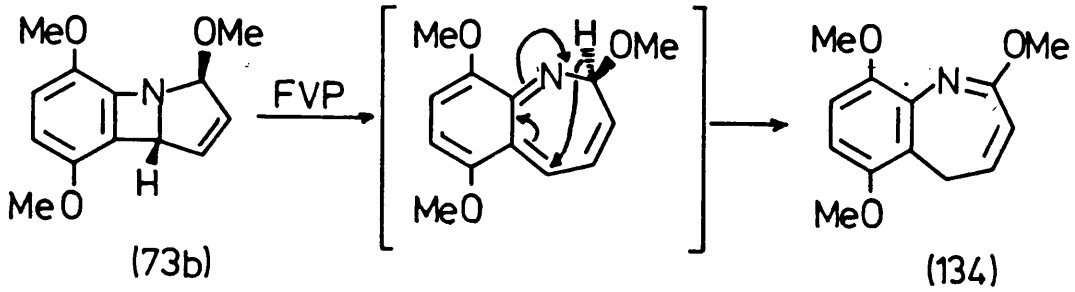


Figure A:8

The pyrolytic rearrangement was found to be common to several similar systems, (figure A:9).

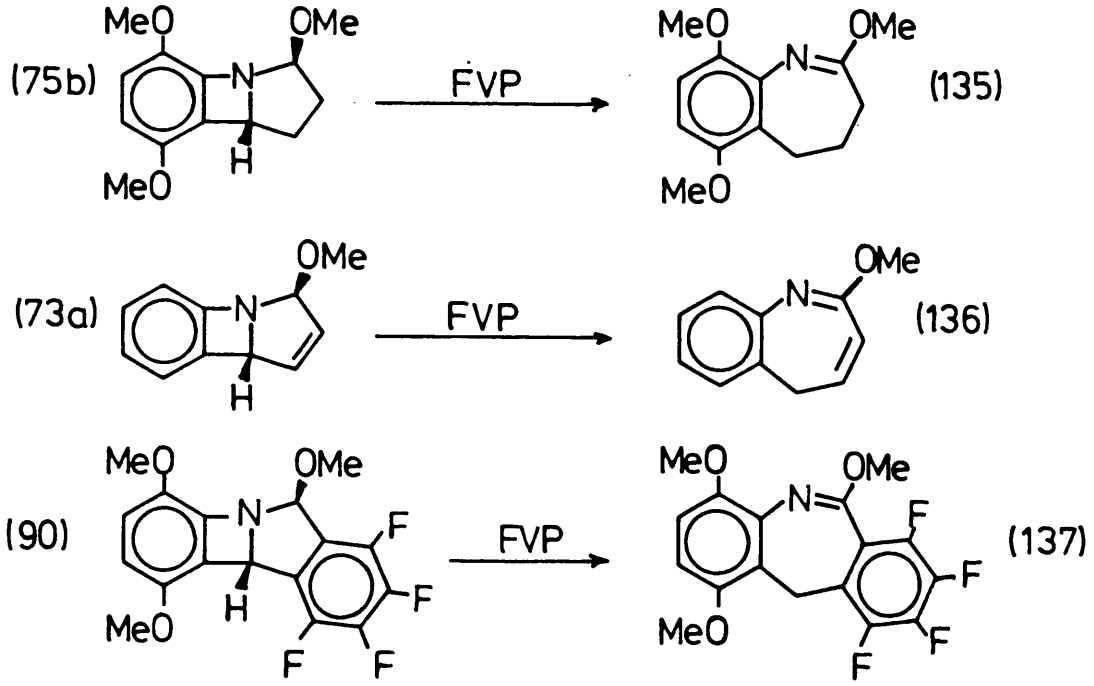


Figure A:9

A slightly higher temperature was necessary to induce compound (90) to undergo rearrangement. It seems likely

that all these rearrangements follow a similar pathway to that described in figure A:8. Attempts were made to intercept the azaxylylene intermediate with various dienophiles (DMAD,PTAD) by sandwiching the pyrolysis product between these on the liquid nitrogen filled cold-trap. These trapping experiments proved unsuccessful. Ito et al. also encountered similar difficulties whilst attempting to trap chemically generated azaxylylenes intermolecularly,[133] although it was possible to isolate dimerised azaxylylene, (figure A:10).

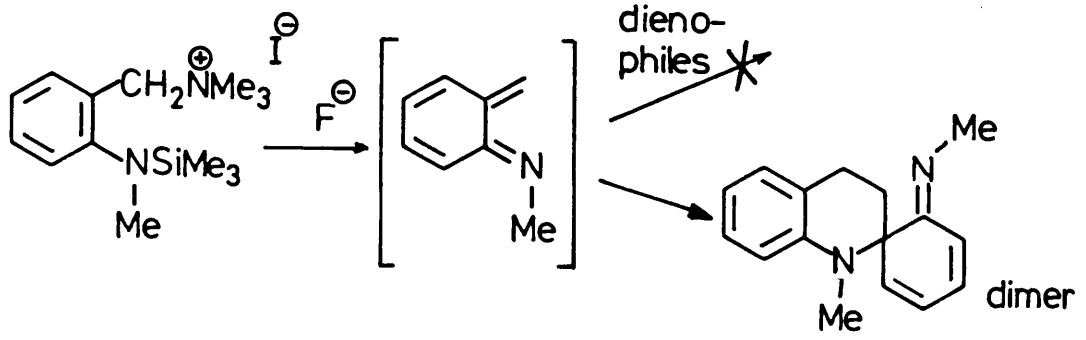


Figure A:10

However it was observed that intramolecular Diels-Alder reactions with azaxylylenes were possible, (figure A:11).

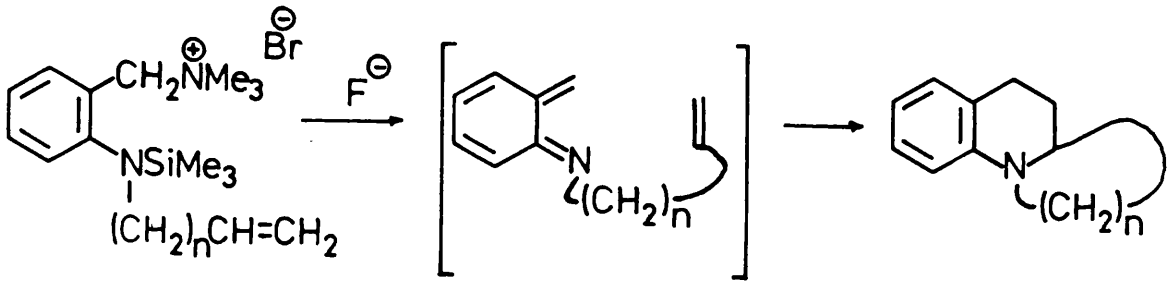
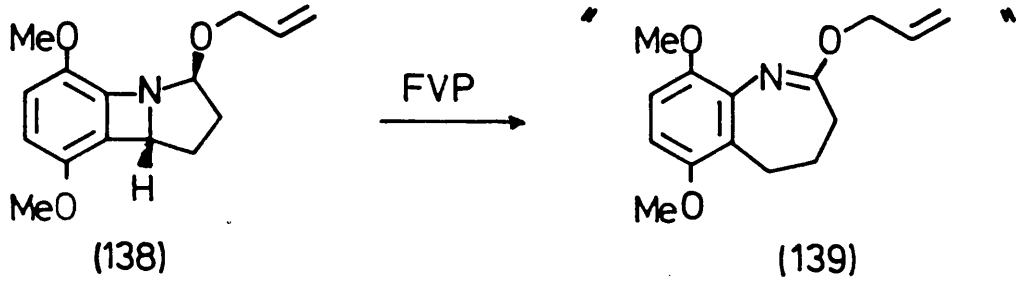


Figure A:11

Therefore a modified rearrangement was designed which incorporated an intermolecular trap for the azaxylylene. The N-chloroamine (74b) was solvolysed in allyl alcohol to afford the desired rearrangement product (138) in low yield. The pyrolytic rearrangement was carried out as before and although a complete analysis of the ^{1}H NMR of the rearrangement product (139) proved impossible, the allylic resonances were still clearly visible. Thus showing that the [1,5] hydrogen shift had occurred and must therefore be energetically preferred to intramolecular Diels-Alder cyclisation under these conditions, (figure A:12).



(138) (139)

Figure A:12

Storr et al.[131] have also observed pyrolytically generated azaxylylenes that preferred to undergo [1,5] hydride shifts rather than intramolecular Diels-Alder cyclisations, although in this case the rapid interconversion of E and Z forms played a part, (figure A:13).

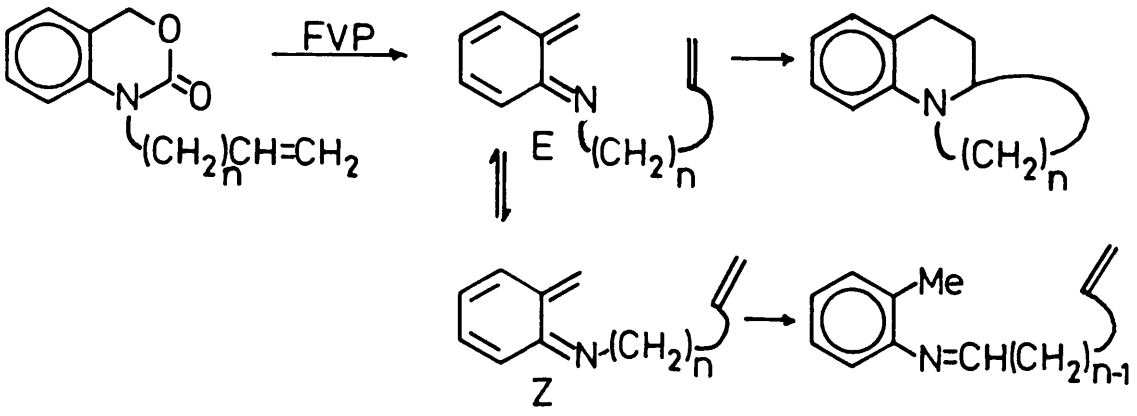


Figure A:13

The next logical step was to try and block the [1,5] hydride shift, however the preparation of the 6,7-benzo-2-methoxy-2,5-dimethyl-1-azabicyclo[3.2.0]heptyl derivatives required to undertake this experiment proved difficult to obtain (see Chapter 4).

CHAPTER 6

EXPERIMENTAL

6.I Instrumentation

Melting points were determined using a Kofler micro heating stage and are uncorrected.

The NMR facilities used included the following instruments:

Varian Associates	T60	- routine 60MHz ^{1}H NMR
Perkin-Elmer	EM390	- routine 90MHz ^{1}H NMR and spin decoupling
Jeol	JNM-PS100	- 100MHz ^{1}H NMR including variable temperature and 94MHz ^{19}F NMR
Bruker	AM-300	- 300MHz ^{1}H NMR and 75MHz ^{13}C NMR*
Bruker	WH-400	- 400MHz ^{1}H NMR, 100MHz ^{13}C NMR and 40MHz ^{15}N NMR. Also including variable temperature COSY, NOE and DEPT studies.†

The positions of all signals are given in ppm (δ) using the appropriate references (tetramethylsilane, $C^{19}FCl_3$ and $CH_3\ ^{15}NO_2$). Signal characteristics are described using the following abbreviations:

(s) - singlet, (d) - doublet, (t) - triplet, (q) - quartet, (m) - multiplet, (br) - broad and combinations of these.

Infrared spectra were recorded on a Perkin-Elmer 580 instrument using sodium chloride plates, 0.1mm sodium chloride cells or KBr discs. Band positions, given in reciprocal centimeters (cm^{-1}), are described by the following abbreviations:

*From Nov'84, University of Leicester

†SERC High Field NMR service, University of Warwick.

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

Routine mass spectra were obtained using a V.G. Micromass 16B instrument and high-resolution mass spectra were obtained via SERC quota from PCMU Harwell.

6.II Technical

Unless specified to the contrary, solvents were not dried except when used for chromatographic purposes in which case all solvents were dried then distilled.

Diethyl ether was dried over sodium wire then distilled from lithium aluminium hydride.

Dichloromethane was distilled from calcium hydride.

Petroleum ether was dried over sodium wire then distilled.

Methanol and ethanol were dried and purified with magnesium and iodine as described by Vogel.[95]

All other solvents were dried and purified as described by D.D. Perrin et al.[96]

Ether, tetrahydrofuran, benzene and toluene were redistilled from sodium-benzophenone for use in certain smaller-scale reactions.

Flash chromatography was always carried out using Keiselgel 60 silica and followed the methodology as described by W. Clark Still.[97]

Solvents for photolysis experiments were degassed with a stream of nitrogen in the presence of ultrasound for 1h prior to use.

B.O.C. (white spot) nitrogen was used directly without further purification.

Evaporation of reaction mixtures was carried out on rotary evaporators using appropriate sources of vacuum.

6.III Preparations

N-Benzoyl-N-allyldehydroalanine ethyl ester (30).[54,55]

Allylamine (14.28g, 0.25mol) was added to a stirred solution of ethyl pyruvate (29.03g, 0.25mol) in toluene (300ml). The resultant solution was stirred at room temperature for 3h, the organic phase was decanted and the aqueous phase extracted with toluene (3 x 300ml). The organic solutions were combined, dried over anhydrous $MgSO_4$ and filtered. Triethylamine (28.31g, 0.28mol) was added to the filtrate and the solution was stirred under N_2 whilst benzoyl chloride (39.36g, 0.28mol) was added dropwise over 15 min. The reaction mixture was stirred for 3h at 65°C and then allowed to cool before removal of the triethylamine hydrochloride by filtration. The solvent was removed under reduced pressure to give a dark oily residue (62.5g). A 12.5g aliquot of this residue was chromatographed on alumina to afford a yellowish oil (30), (5.45g, 43%).*

δH (90 MHz; $CDCl_3$)

1.17 (3H, t, J 7Hz)
4.03 (2H, q, J 7Hz)
4.27 (2H, d, J 6Hz†)
5.10 (1H, brs)
5.25 (1H, d, J 6Hz†)
5.48 (1H, s)
5.70 - 6.20 (1H, m)
6.04 (1H, s)
7.23 - 7.67 (5H, m)

*From allylamine
†Additional small coupling

1-Ethoxycarbonyl-2-benzoyl-2-azabicyclo[2.1.1]hexane (31).[54,55]

A solution of (30) (5.45g, 0.21mol) in benzene (400ml) with 0.2% acetophenone was irradiated in a Rayonet apparatus at 254nm for 30h. The solvent was removed under reduced pressure to afford a semi-crystalline residue, which after several recrystallisations from ether afforded (30) (2.93g, 54%) as white crystals. These were used directly in the following preparation. A small sample recrystallised twice from ether/petrol (bp 40-60°C) afforded an analytical sample, mp 106.5 - 107.0°C.

δH (90 MHz; $CDCl_3$)

1.30 (3H, t, J 7Hz)
1.77 (2H, dd, J 5Hz, 2Hz)
2.10 - 2.28 (2H, m)
2.77 (1H, brm)
3.50 (2H, brs)
4.23 (2H, q, J 7Hz)
7.32 - 7.87 (5H, m)

δC (15 MHz; $CDCl_3$)

14.0 (q, 16)
35.3 (d, 4)
41.8 (t, 5,6)
55.1 (t, 3/15)*
61.0 (t, 3/15)
70.3 (s, 1)
128.3 (d, 10, 11, 13, 14)
131.3 (d, 12)
134.5 (s, 9)
168.4 (s, 7/8)
173.8 (s, 7/8)

*the "/" will be used to indicate "or" in this and subsequent NMR data.

m/z 259 (m^+, 19%), 214(4), 186(2), 154(3), 105(100), 77(17), 51(4).

Found C,69.42; H, 6.65; N, 5.43% $C_{15}H_{17}NO_3$ requires C, 68.48; H, 6.61; N, 5.40%

1-Hydroxymethyl-2-benzyl-2-azabicyclo[2.1.1]hexane (32)

A solution of (31) in dry ether (120ml) was added to a stirred suspension of $LiAlH_4$ (3.24g, 0.09mol) in dry ether (80ml) and heated under reflux for 20h under N_2. The reaction mixture was allowed to cool and the excess $LiAlH_4$ was decomposed by the careful addition of ether saturated with water. The slurry formed was filtered and the solvent removed from the filtrate under reduced pressure to afford (32) (4.09g, 94%) as white crystals. This sample was used directly in the subsequent preparation, however repeated recrystallisation of a small sample of (32) from petrol (40-60°C bp) gave an analytically pure sample as white crystals, mp 58.0 - 58.5°C.

δH (90 MHz; $CDCl_3$)	1.61 (4H, brs, 5-H, 6-H)
	2.06 (1H, brs, exch, OH)
	2.68 (2H, brs, 3-H)*
	(1H, brs, 4-H)*
	3.63 (2H, brs, 7-H/8-H)
	3.75 (2H, brs, 7-H/8-H)
	7.18 - 7.45 (5H, m)

*these signals separate slightly in $CFCl_3$.

δC (15 MHz; $CDCl_3$)	36.6 (d, 4)
	37.5 (t, 5, 6)
	55.9 (t)
	57.5 (t) (3/7/8)
	61.3 (t)
	74.0 (s, 1)
	126.8 (d, 12)
	128.2 (d) (10, 14/11, 13)
	128.6 (d) (10, 14/11, 13)
	139.5 (s, 9)

m/z 203(m^+,33%), 172(10), 112(19), 91(100), 65(10), 55(33).

Found C, 77.06; H, 8.41; N, 6.88%. $C_{13}H_{17}NO$ requires C, 76.81; H, 8.43; N, 6.89%.

p-Toluenesulphonylation of (32)

A solution of (32) (2.03g, 0.10mol) in dry pyridine (50ml) was cooled in an ice-bath and p-toluenesulphonyl chloride (3.81g, 0.20mol) was added portionwise so that the reaction temperature did not exceed 10°C. The reaction mixture was left overnight at 4°C then poured into ice-water (150ml). Basification with conc. aqueous ammonia caused a precipitate to form and this was filtered cold. The yellowish solid obtained was slurried and filtered twice more with 100ml aliquots of ice-water. The solid was dried under reduced pressure to afford the p-toluenesulponate (33) (3.08g, 86%) which was used in the following preparation without further purification.

δH (90 MHz; $CDCl_3$) 1.50 - 1.80 (4H, m, 5-H, 6-H)
2.38 (3H, s)
2.62 (2H, brs, 3-H)
(1H, brs, 4-H)
3.53 (2H, brs, 8-H)
4.13 (2H, s, 7-H)
7.18 - 7.34 (7H, m)
7.69 (2H, brd, J 8Hz)

νmax (CH_2Cl_2) 2980(br), 1598(w), 1360(m), 1185(m), 1171(s), 1090(w), 960(brm) cm^{-1}.

1-Methyl-2-benzyl-2-azabicyclo[2.1.1]hexane (34)

A solution of (33) (3.00g, 8.4mol) in dry THF (80ml) was added dropwise to a stirred suspension of $LiAlH_4$ (1.60g, 40mmol) in dry THF (120ml) under N_2 and heated overnight under reflux. The excess $LiAlH_4$ was decomposed by careful addition of ether saturated with water. The reaction mixture was filtered and the solvents were removed from the filtrate

under reduced pressure to afford a pale yellow oil (34) (1.44g, 91%) which was stored cold under N_2. A small sample of (34) was further purified to provide an analysis sample by column chromatography on UGl alumina using ether eluant. This afforded a colourless oil which was stored cold, under N_2 in the dark.

δH (90 MHz; $CDCl_3$)
1.29 (3H, s, 7-H)
1.41 - 1.62 (4H, m, 5-H, 6-H)
2.55 (1H, brs, 4-H)
2.59 (2H, brs, 3-H)
3.60 (2H, s, 8-H)
7.13 - 7.44 (5H, m)

δC (15 MHz; $CDCl_3$)
17.7 (q, 7)
36.6 (d, 4)
40.8 (t, 5,6)
56.0 (t, 3/8)
57.9 (t, 3/8)
70.1 (s, 1)
126.8 (d, 9)
128.4 (d 10,14/11,13)
128.9 (d 10,14/11,13)
140.6 (s, 9)

m/z 187(m^+22%), 186(16), 172(19), 146(19), 105(9), 104(6), 96(28), 91(100), 65(22), 55(69), 42(13), 41(28), 39(22).

Found C, 83.04; H, 9.17; N, 7.36%. $C_{13}H_{17}N$ requires C, 83.37; H, 9.15; N, 7.48%.

1-Methyl-2-azabicyclo[2.1.1]hexane hydrochloride (38)

A solution of (34) (0.48g, 2.57mmol) in ethanol (15ml) was hydrogenated at 1 Atm over 0.140g of 10% Pd/C for 24h at room temperature. The catalyst was removed by the passage of the reaction mixture through a short, tightly packed column

of Celite. The filtrate was cooled and dry hydrogen chloride was slowly bubbled through the solution for 15 min. The solvent was removed under reduced pressure to leave a dark oil which was dissolved in a minimum of dichloromethane and treated with diethyl ether to precipitate the salt. The salt was filtered and dried under reduced pressure to afford (38) (0.323g, 96%) which was used without further purification.

The hydrochloride salt (38) proved too hygroscopic for the preparation of a satisfactory analytical sample. The picrate salt was therefore prepared as follows. The salt (50mg) was dissolved in water (0.5ml) and basified with 2M (aq) NaOH solution (5ml). The free amine was extracted into diethyl ether (3 x 4ml), the extracts were combined, dried by passage through a short column of anhydrous $MgSO_4$, concentrated to ca. 0.5ml by distilling off the bulk of the ether solvent at atmospheric pressure. The concentrated solution was then treated with a dry saturated solution of picric acid in ether until no further precipitation appeared (the solution was acidic). The supernatant was carefully removed from the precipitate which was then further washed with a small aliquot of cold, dry ether. The precipitate was recrystallised from 80% ethanol/water, filtered and dried under reduced pressure to afford the picrate derivative of (38) as a yellow crystalline solid (10mg, 8%), mp 166-172°C (dec).

(38) δH (90 MHz; $CDCl_3$) 1.70 (3H, s, 7-H)
1.83 (4H, brs, 5-H, 6-H)
2.78 (1H, brs, 4-H)
3.30 - 3.48 (2H, m, 3-H)
9.88 (2H, brs, exch, N-H)

1-Methyl-2-azabicyclo[2.1.1]hexane picrate

Found C, 44.09; H, 4.32; N, 17.02%. $C_{12}H_{14}N_4O_7$ requires C, 44.18; H, 4.33; N, 17.17%.

1-Methyl-2-azabicyclo[2.1.1]hexane

δH (90 MHz; $CDCl_3$)	1.22 (2H, d, J 4Hz†, 5-H_b, 6-H_b)
	1.38 (3H, s, 7-H)
	1.55 (2H, m, J 4Hz, 5-H_a, 6-H_a)
	2.03 (1H, brs, exch, N-H)
	2.64 (1H, m, 4-H)
	2.97 (2H, brs, 3-H)

† additional coupling

1-Methyl-2-chloro-2-azabicyclo[2.1.1]hexane (29)

A solution of (38) (37mg, 0.28mmol) was treated with a commercial aqueous solution of sodium hypochlorite (2ml) followed by $CFCl_3$. The resultant mixture was stirred vigorously at room temperature for 20 min, the $CFCl_3$ solution was separated, and the remaining aqueous solution was extracted further with $CFCl_3$ (3 x 10ml). The $CFCl_3$ extracts were combined and dried by passage through a short column packed with anhydrous $MgSO_4$. The column was eluted with a further 5ml of $CFCl_3$. The dried solution was concentrated to ca. 0.4ml by careful distillation. The concentrated solution was observed by ^1H NMR and found to contain (29) (0.23mmol, 82%†). The N-chloroamine (29) was too volatile for convenient isolation on such small scale and was always handled in solution.*

† ^1H NMR yield by integration against a benzene standard.

* There was some evidence to suggest that (29) was only stable in solution.

δH (400 MHz, $CDCl_3$)	see table 2.5
δC (100 MHz, $CDCl_3$)	16.1 (C7)
	35.7 (C4)
	39.3 (C5/6)
	40.8 (C5/6)
	66.7 (C3)
	76.2 (C1)

Alumina-catalysed rearrangement of (29)

A solution of (29) (0.23mmol) in $CFCl_3/CDCl_3$ (0.4ml) was pipetted onto a short column of UG1 alumina which had previously been eluted with petrol (40-60°C bp) and allowed to run almost dry. The column was further eluted with petrol (40-60°C bp) for 10 min, the flow was halted and the column was allowed to stand for 30 min. The majority of the remaining petrol was run off and then the column was eluted rapidly with dry methanol (50ml). The methanolic solution was basified with 2M (aq) NaOH solution (10ml) and extracted with aliquots of dichloromethane (3 x 15ml). The extracts were dried by passage through a short column of anhydrous $MgSO_4$, then $CDCl_3$ (ca.0.4ml) was added and the bulk of the dichloromethane removed by careful distillation until only ca.0.4ml of solution remained. The solution was then observed by ^{1}H NMR and found to contain 2-chloro-2-methyl-1-azabicyclo-[2.1.1]hexane (40), (0.16mmol, 70%)*

δH (400 MHz; $CDCl_3$) see table 2.8

*Yield by integration of ^{1}H NMR using a known weight of benzene as an internal standard.

δC (100 MHz; $CDCl_3$)[†] 30.7 (C7)
44.9 (C5/6)
45.6 (C5/6)
62.0 (C3/4)
63.6 (C3/4)

m/z 133/131 (m^+, 15/5%), 97(11), 96(92), 95(13), 82(20), 58(13), 56(10), 55(100), 54(16), 45(12), 42(22), 41(23), 39(17)

metastable peaks, M* 70.4 (131→96)
69.3 (133→96)
31.5 (96→55)
30.5 (55→41)

Acid catalysed hydrolysis of (40)

A solution of (40) in dry ether was treated with dry HCl (g) for 5 min, then evaporated to dryness under reduced pressure to give the hydrochloride salt. A solution of this salt in $CDCl_3$ (ca.0.4ml) was made basic with a solution of KOH in D_2O. The organic phase was separated and dried by passage through a short column of anhydrous $MgSO_4$ and the resultant solution was found to contain 4-hydroxymethyl-2-methyl-1-pyrroline (44), 70% ±20%.*

δH (400 MHz; $CDCl_3$) see table 2.9a(includes data from COSY experiment).

[†]C2 - was not observed in ^{13}C NMR, probably due to saturation.
*Approximate ^1H NMR yield relative to dichloromethane standard.

δC (100 MHz; $CDCl_3$)† 38.8
42.3
46.8
63.6
76.1

ν_{max} (CH_2Cl_2) 3660(w), 3050-2800(br), 1650(m), 1415(br)cm^{-1}

† C2 was not observed in ^{13}C NMR due to saturation.

Silver-ion promoted methanolysis of (29)

The N-chloroamine (29) (0.33mmol) in $CFCl_3$ (0.4ml) was carefully warmed by hand until only a small amount of solvent remained. The residue was then taken up into dry methanol (10ml) and silver tetrafluoroborate (0.156g, 0.80mmol) was added. The reaction mixture was stirred overnight in the dark under N_2 and then basified with 2M(aq) NaOH solution (15ml). The basified solution was extracted with aliquots of $CFCl_3$ (3 x 15ml). The $CFCl_3$ extracts were combined and dried by passage through a short column packed with anhydrous $MgSO_4$. The dried solution was reduced in volume to ca.0.4ml by distillation of the excess $CFCl_3$ and subsequently analysed by ^1H NMR and found to contain mainly 4-methoxymethyl-2-methyl-1-pyrroline (43).*

δH (400MHz; $CDCl_3$) see table 2.9b

ν_{max} (CH_2Cl_2) 3100-2800(br), 1650(m), 1430(m), 1380(m)cm^{-1}

m/z 128(13%), 127(m^+,13), 126(52), 111(26), 110(17), 97(39), 96(74), 95(35), 84(17), 83(17), 82(100), 55(61), 44(35).

*Estimated yield by ^1H NMR 60% ± 20%

Attempted methanolysis of (40)

A solution of (40) (0.18mmol) in dry methanol (5ml) was treated with silver tetrafluoroborate (0.089g, 0.457mmol) and stirred in the dark for 18hr. The reaction mixture was made basic with 2M(aq) K_2CO_3 solution (15ml) then extracted with aliquots of $CFCl_3$ (3 x 15ml). The extracts were combined and dried by passage through a short column of anhydrous $MgSO_4$ and concentrated to ca.0.4ml by distilling off the bulk of the solvent at atmospheric pressure. The resulting solution was examined by ^1H NMR and found to contain only unchanged (40) (0.08mmol, 46%)†

†by integration against a CH_2Cl_2 standard.

1-Benzylpyrrole (140)[78]

2,5-Dimethoxytetrahydrofuran* (40ml, 0.31mol) and benzylamine (34ml, 0.31mol) were added simultaneously with stirring to glacial acetic acid (65ml) over 20 min. The addition was slightly exothermic and the reaction took on a red-orange colouration. The reaction mixture was heated under reflux overnight. The solvents were removed under reduced pressure and the dark residue distilled through a 25cm Vigreux column. This afforded (140) as a clear liquid (28.7g, 59%), bp 108-111°C (1mm Hg), lit. 123-125°C (12mm Hg).

δH (90 MHz; $CDCl_3$)	4.72 (2H, s)
	6.05 (2H, s)
	6.40 (2H, s)
	6.90 (5H, m)

*The literature route used 2,5-diethoxytetrahydrofuran, which unlike the dimethoxy derivative was not available in the desired quantities.

9-Benzyl-5,6,7,8-tetrafluoro-1,4-dihydronapthalen-1,4-imine (81)[79]

A solution of n-BuLi (1.1M in hexane; 87ml) was added dropwise over a period of 10 min to a stirred solution of pentafluorobenzene (16.15g, 96mmol) in dry diethyl ether (25ml) under N_2 at -78°C. Subsequently a solution of 1-benzylpyrrole (15.16g, 96mmol) in dry ether (40ml) was added over a further 10 min.

The reaction mixture was allowed to warm to room temperature with continuous stirring and left overnight; it was then poured into water (300ml). The product was extracted into ether (2 x 150ml) and the ether extracts were combined and washed with a further 300ml of water. The organic solution was then extracted with cold 2M hydrochloric acid (2 x 200ml). The acidic extracts were combined and washed with ether (200ml), cooled in a salt-ice bath and carefully basified with 2M(aq) NaOH solution. The basic solution was re-extracted with ether (3 x 300ml), and the ether extracts combined before drying with anhydrous $MgSO_4$. The solvent was removed under reduced pressure to afford a white amorphous solid (81) (9.88g, 34%) which was used without further purification.

δH (90 MHz; $CDCl_3$)	3.40 (2H, s)
	4.86 (2H, s, 2-H, 3-H)
	6.95 (2H, s, 1-H, 4-H)
	7.22 (5H, m)

3,6-Di-(2-pyridyl)-1,2-dihydro-1,2,4,5-tetrazine (141)[81]

2-Cyanopyridine (100g, 0.96mol) was added to hydrazine hydrate (100ml, 2.06mol) and warmed on a steam bath for 3h. The resultant orange solid was filtered and recrystallised from toluene to afford (141), (64.7g, 57%) as orange plates mp 193-6°C, lit. 197-8°C.

3,6-Di(2-pyridyl)-1,2,4,5-tetrazine (142)[81]

Compound (141) (28g, 0.12mol) was dissolved in glacial acetic acid (1.8L) and water (1.0L) and cooled to 2°C with stirring. A solution of sodium nitrite (73.6g, 1.07mol) in water (200ml) was cooled with ice and added dropwise over 2h. The resultant pink solution was stirred overnight, keeping the temperature of the solution below 5°C. The solution was then neutralised by dropwise addition of ammonia (d 0.880), then cooled and filtered to afford a purple solid, which was recrystallised from ethanol giving red-violet plates (14.9g, 53%) mp 226-300°C, lit. 229-300°C.

2-Benzyl-4,5,6,7-tetrafluoroisoindole (82)[82]

A solution of (81) (8.06g, 26.8mmol) in dry dichloromethane (70ml) was added to a stirred solution of (142) (6.30g, 26.8mmol) in dry dichloromethane (60ml), under N_2, over 20min. The addition was slightly exothermic and the progress of the reaction was monitored by observation of evolved N_2 and was found to be complete within 24h. The solvent was removed under reduced pressure to afford an off-white solid (82), (7.15g, 95%) mp 92-95°C, lit. 96-97.5°C.

δH (90MHz; $CDCl_3$)	5.30 (2H, s)
	7.28 (7H, m)

m/z 280(14%), 279(m^+,87), 188(3), 161(5), 140(4), 92(25), 91(100), 65(40), 39(11).

metastable peaks, m^* 46.4 (91→65)
29.7 (279→91)

11-Benzyl-1,2,3,4-tetrafluoro-9,10-dihydroanthracen-9,10-imine (83)[89]

A solution of 2-bromofluorobenzene (1.75g, 0.010mol) in dry THF (7ml) was slowly added to magnesium (0.304g, 0.013g atom) under N_2 whilst the reaction flask was immersed in an ultrasonic bath. The dissolution of magnesium was complete within 30 min. Compound (82) (2.23g, 8mmol) in dry THF (5ml) was slowly added to the reaction mixture with stirring, and the mixture was left stirring overnight.

The reaction mixture was poured into water (200ml) and diethyl ether (200ml). The organic layer was separated and the aqueous layer extracted with a further aliquot of ether (200ml). The organic solutions were combined and dried over anhydrous $MgSO_4$. The solvents were removed under reduced pressure to give a dark oil which after flash chromatography using 9:1 petrol (40-60°C bp): ether eluant afforded a light yellow oil (83), (1.919g, 67% crude yield). Further purification proved difficult and the product was therefore used directly for subsequent reactions.

δH (400MHz; $CDCl_3$) see table 6.1
δC (100MHz; $CDCl_3$) see table 6.2

m/z 355(m^+,89%), 264(84), 251(21), 250(63), 91(100), 65(18).

metastable peak, m^* 46.4 (91→65)

observed m/z: 355.0980

calculated for $C_{21}H_{13}NF_4$: 355.0984

2-Chloro-1,4-dimethoxybenzene (143)[98]

Chlorohydroquinone (102.8g, 0.72mol) was dissolved in dry ethanol (300ml) and stirred with cooling from a salt-ice bath as aqueous NaOH (50g in 150ml water) and dimethylsulphate (125ml) were added alternately in six lots. The reaction was extremely exothermic and care was needed to prevent over-vigorous boiling. On completion of the addition the solution was basified with NaOH (10g in 20ml water) and heated under reflux for 3h. The ethanol was removed by distillation and the remaining liquid extracted with ether (4 x 200ml). The extracts were combined, dried over anhydrous $MgSO_4$ and distilled to afford (143), (103.3g 83%) bp 90°C (1mm Hg), lit. bp 123-124°C (15mm Hg).

δH (90MHz; $CDCl_3$)	3.68 (3H, s)
	3.78 (3H, s)
	6.75 (2H, m)
	6.92 (1H, m)

11-Benzyl-1,2,3,4-tetrafluoro-5,8-dimethoxy-9,0-dihydro-anthracen-9,10-imine (84)[89]

A solution of n-BuLi (1.27m in hexane; 11ml) was added over a period of 15 min to a stirred solution of 2,2,6,6-tetramethylpiperidine (2.40g, 18mmol) in dry ether (25ml) under N_2. After a further 10 minutes this lithium tetramethylpiperidide solution was added to a stirred solution of (82) (4.00g, 14mol) and (143) (2.42g, 14mmol) in dry ether (80ml), under N_2, over 20 min.

The reaction mixture was left stirring overnight, poured into water (300ml) and extracted with ether (2 x 200ml). The organic extracts were washed with water (25ml) and dried over

anhydrous $MgSO_4$. The solvents were removed under reduced pressure and the dark-red residue was purified by flash chromatography using dichloromethane eluant to afford a light yellow oil which on trituration with n-hexane gave (84) as a white crystalline solid (1.70g, 30%) of sufficient purity for use in further preparations.

A small sample was recrystallised several times from n-hexane to provide an analytical sample as white plates, mp 139°C.

δH (90MHz; $CDCl_3$) see table 6.1
δH (100MHz; $CDCl_3$) see table 6.2
m/z 415(m^+,57%), 384(12), 325(15), 324(84), 310(28), 295(44) 280(16), 267(13), 252(17), 224(20), 199(12), 91(100), 65(13), 42(25).
Found C,66.51; H, 4.22; N, 3.37%. $C_{23}H_{17}NO_2F_4$ requires C, 66.51; H, 4.13; N, 3.37%.

1,2,3,4-Tetrafluoro-9,10-dihydroanthracen-9,10-imine hydrochloride (144)[98]

A solution of (83) (1.519g, 4.28mmol) was dissolved in glacial acetic acid (20ml) and hydrogenated at 1 Atm over 10% Pd/C (0.138g) for 48h. The reaction mixture was then filtered through Celite and the solvent removed under reduced pressure. The residual oil was dissolved in dry ether (20ml) and treated with HCl (g) until no further precipitation was observed. The precipitate was filtered and dried under reduced pressure to afford (144) as a white amorphous powder (0.475g, 37%),* mp 183°C (dec).

*Yield from (82).

The amine (85) could be liberated by basification with 2M(aq) NaOH solution and extraction into dichloromethane.

δH (90MHz; $CDCl_3$) see table 6.1

δC (100MHz; $CDCl_3$) see table 6.2

m/z 266(12%), 265(100, M-HCl), 264(8), 250(15), 238(15), 237(38), 219(23).

1,2,3,4-Tetrafluoro-5,8-dimethoxy-9,10-dihydroanthracen-9,10-imine hydrochloride (145)[98]

A solution of (84) (0.408g, 0.98mmol) in glacial acetic acid (15ml) was hydrogenated at 1 Atm over 10% Pd/C (0.101g) for 48h. The reaction mixture was filtered through Celite and the solvent removed under reduced pressure. The residual oil was taken up into dry ether (20ml) and on saturation with HCl(g), the white hydrochloride salt (145) precipitated (0.324g, 92%). A small quantity was recrystallised from methanol/ether to give a fine white powder, mp 173-4°C (dec).

The amine (86) could be liberated by basification with 2M(aq) NaOH solution and extraction into dichloromethane.

δH (90MHz; $CDCl_3$) see table 6.1

δC (100MHz; $CDCl_3$) see table 6.2

m/z 325(61%. M-HCl), 324(31), 310(83), 295(100), 280(28), 267(35), 252(31), 224(39), 163(46), 44(90).

(86) ν_{max} (CH_2Cl_2) 3250(w), 3040-2830(br), 2840(m), 1610(w), 1500(s, br), 1350(m), 1280(w), 1190(m), 1120(m), 1050(br), 820(s) cm^{-1}

11-Chloro-1,2,3,4-tetrafluoro-9,10-dihydroanthracen-9,10-imine (87)

A solution containing (85) (0.193g, 0.73mmol) in dry chloroform (13ml) was treated with NCS (0.097g, 0.73mmol) and stirred in the dark under nitrogen for 1h. The solvent was then removed under reduced pressure. The residue was flash-chromatographed using dichloromethane eluant to afford (87), (0.189g, 86%) as a white solid. An analytical sample was prepared by recrystallisation from n-hexane to give colourless crystals, mp 98-99.5°C.

δH (90MHz; $CDCl_3$) see table 6.1

δC (100MHz; $CDCl_3$) see table 6.2

m/z 301/299 (m^+, 1/3%), 266(38), 265(83), 251(25), 250(100), 244(15), 237(7), 237(25), 219(9), 125(19)

Found C, 56.32; H, 2.16; N, 4.57%. $C_{14}H_6NClF_4$ requires C, 56.12; H, 2.02; N, 4.67%.

11-Chloro-1,2,3,4-tetrafluoro-5,8-dimethoxy-9,10-dihydroanthracen-9,10-imine (88)

A solution of (86) (108mg, 0.33mmol) in dry chloroform (6ml) was treated with NCS (88mg, 0.66mmol) and stirred in the dark under N_2 for 1h. The solvent was removed under reduced pressure and the residual solid was flash-chromatographed using dichloromethane eluant. This afforded (88) (103mg, 87%) as a white solid. Recrystallisation from n-hexane afforded an analytical sample as colourless crystals, mp 151-152.5°C.

δH (90MHz; $CDCl_3$) see table 6.1

δC (100MHz; $CDCl_3$) see table 6.2

TABLE 6:1 ^{1}H NMR Spectra of 1,2,3,4-tetrafluoro-9,10-dihydroanthracen-9,10-imines

$\delta_H(CDCl_3)$[1]	Temperature (°C)	Invertomers	9-H & 10-H	6-H & 7-H	1-H & 4-H	Other Aromatic H's	Benzylic CH_2	-OMe	Exchangeable H's
(83)	25	-	5.27 (s)	7.07 (brs)	7.19 - 7.38 (m)		3.50 (s)		
	-40[2]	syn*	5.34 (s)	7.05 (m)	7.19 - 7.47 (m)		3.53 (s)		
		anti	5.29 (s)				3.44 (s)		
(84)	25	-	5.44 (s)	6.58 (s)		7.25 (m)	3.45 (s)	3.75 (s)	
	-64[3]	syn*	5.52 (s)	6.52 (s)		7.04 - 7.52 (m)	3.50 (s)	3.76 (s)	
		anti		6.66 (s)				3.84 (s)	
(144)	25	-	6.34 (s)	7.12 - 7.61 (m)					3.8 - 8.8 (br)
(145)	25	-	6.37 (s)	6.80 (s)				3.82 (s)	3.5 - 8.6 (br)
(85)	25	-	5.61 (s)	7.14 (m)					2.86 (brs)
(86)	25	-	5.44 (s)	6.58 (s)				3.75 (s)	3.45 (brs)
(87)	25	syn*	5.67 (s)	7.04 - 7.50 (m)					
		anti	5.60 (s)						
(88)	25	syn*	5.80 (brs)	6.61				3.77 (s)	
		anti		6.64				3.79 (s)	

[1] ^{1}H NMR at 90 MHz except [2]400 MHz and [3]100 MHz;
* denotes major invertomer.

TABLE 6:2 ^{13}C NMR of 1,2,3,4-tetrafluoro-9,10-dihydroanthracen-9,10-imines

δ_c[1]	Temperature (°C)	Invertomers	C5 & C8	C6 & C7	C9 & C10	C13 & C14	-OMe	Benzylic Group Carbons				
								CH_2	Aromatic Carbons			
(83)	38	-	126.3	122.1	67.8	146.1	-	53.7	127.5	128.5	129.0	137.0
	-30	syn	126.1	121.2	67.5	145.8	-	53.7	127.51	128.5	129.1	136.3
		anti	126.6	123.9	66.7	144.5	-	52.8	127.50	128.5	129.1	136.6
(84)	90[2]		150.4	114.2	66.7	138.7	58.0	54.9	128.7	129.7	130.2	136.0
	-30	syn	147.0	111.0	64.8	134.4	55.6	53.8	127.44	128.5	129.16	136.3
		anti	150.1	111.3	64.4	134.2	55.7	53.0	127.36	128.5	129.12	136.6
(85)	25	-	126.4	121.4	61.0	147.7	-					
(86)	25	-	148.2	112.1	61.4	136.6	56.4					
(87)	25	syn	127.9	122.1	75.6	142.3	-					
		anti	127.5	124.2	74.4	142.3	-					
(88)	25	syn	150.6	112.5	75.6	130.9	56.2					
		anti	147.8	112.5	71.9	130.9	56.2					

[1] All spectra 100 MHz in $CDCl_3$ except [2] C_2Cl_4.
Several signals were not observed due to extensive ^{13}C-^{19}F coupling.

m/z 361/359 (m^+, 6/2%), 324(32), 310(100), 295(100), 280(21) 267(14), 252(18), 224(21), 198(14), 155(9), 44(21)

Found C, 53.54; H, 2.88; N, 3.92%. $C_{16}H_{16}NClF_4$ requires C, 53.43; H, 2.80; N, 3.89%.

Silver-ion promoted methanolysis of (87)

N-Chloroamine (58mg, 0.19mmol) was dissolved in warm dry methanol (4ml) and transferred to a "Reacti-Vial" containing $AgBF_4$ (93mg, 0.48mmol) under N_2. The reaction mixture was stirred in the dark at 40°C for 6d, after which t.l.c showed that very little N-chloroamine remained. The reaction mixture was filtered through Celite along with a further 6ml of ether washings from the reaction vessel. The filtrate was made up to 20ml with water and basified with 1M(aq) K_2CO_3 solution, then refiltered through Celite. The filtrate was extracted with ether (3 x 15ml) and the combined organic extracts were washed with water then dried over anhydrous $MgSO_4$. Removal of solvent under reduced pressure afforded an off-white solid (53mg).

The solid was examined by ^1H NMR and found to contain 2-methoxy-3,4-tetrafluorobenzo-6,7-benzo-1-azabicyclo[3.2.0]-heptane (89), (46mg, 80%)* and unchanged (87), (7mg, 12%).*

δH (90MHz; $CDCl_3$)	3.58 (3H, s)
	5.66 (1H, brs)
	6.30 (1H, brs)
	7.07 (4H, m)
δC (75MHz; $CDCl_3$)	53.6 (OMe)
	76.6 (C2)
	93.7 (C5)
	111.5
	120.7 (12/13/14/15)
	122.2

128.2
136.4 (C6)
155.2 (C7)

m/z 295(m^+, 43%), 265(100), 264(56), 252(17), 237(23)

observed m/z 295.0615

calculated for $C_{15}H_9NOF_4$ 295.0620

*Yields by ^1H NMR integration against a dichloromethane standard.

Silver-ion promoted methanolysis of (88)

N-Chloroamine (88) (96mg, 0.26mmol) was dissolved with warming in dry methanol (4ml) and transferred by syringe to a Reacti-Vial containing $AgBF_4$ (192mg, 0.98mmol) under N_2. The reaction mixture was stirred in the dark at 40°C for 20h, after which t.l.c. showed no starting N-chloroamine remaining. The contents of the reaction vessel were filtered through Celite with a further 6ml of ether washings. The filtrate was then made up to 20ml with water, basified with 1M(aq) K_2CO_3 solution and filtered again through Celite. The filtrate was made up to 40ml with water and extracted with ether (3 x 20ml). The combined organic layers were dried over anhydrous $MgSO_4$ then evaporated under reduced pressure to afford a white solid (83mg). The solid was examined by ^1H NMR and found to be 2-methoxy-3,4-(8,9,10,11-tetrafluorobenzo)-6,7-(13,15-dimethoxybenzo)-1-azabicyclo-[3.2.0]heptane (90) (82mg, 90%).

A small amount of the solid was recrystallised several times from n-hexane to afford an analytical sample as white needles, mp 149-150°C.

δH (90MHz; $CDCl_3$)

3.59 (3H, s)
3.79 (3H, s)
3.82 (3H, s)
5.85 (1H, brs)
6.33 (1H, brs)
6.44 (1H, J 10Hz)
6.56 (1H, J 10Hz)

δC (15MHz; $CDCl_3$)

54.9 (q, OMe)
56.4 (q, 11,14-OMe)
77.0 (d, 2)
92.3 (d, 5)
109.9 (d) (13/14)
114.2 (d) (13/14)
122.5 (s, 6)
141.2 (s)
142.7 (s) (7/12/15)
147.9 (s)

m/z 355(m^+, 100%), 340(39), 325(31), 324(36), 310(36), 295(19), 294(11), 280(36), 44(14).

Found C, 57.44; H, 3.76; N, 3.97%. $C_{17}H_{13}NO_3F_4$ requires C, 57.47; H, 3.69; N, 3.94%.

1-Trimethylsilyl-2,5-dimethyl pyrrole (92)[88]

A stirred solution of 2,5-dimethylpyrrole (37.56g, 0.40 mol) in dry ether (130ml) and dry benzene (55ml) under N_2 was treated with small pieces of potassium (14.20g, 0.36g atom) over 20min. The reaction mixture was then stirred for 1h and heated under reflux for a further 6h. The potassiopyrrole slurry thus formed was cooled to 0°C and trimethylsilylchloride (39.40g, 0.36mmol) was added dropwise over 20min. The reaction mixture was stirred overnight and filtered.† The solvents were removed from the filtrate under reduced pressure and fractional distillation of the residue afforded (92)

(36.70g, 61%), bp 94-97°C (18mmHg) lit. 95-97 (15mmHg).

δH (90MHz; $CDCl_3$)	0.50 (9H, s)
	2.38 (6H, s)
	5.90 (2H, s)

1,4-Dimethyl-5,8-dimethoxynapthalen-1,4-imine (94)

A solution of n-BuLi (1.57M in hexane, 58.5ml) was added over 20min to a stirred solution of 1,4-dimethoxy-2-chlorobenzene (15.83g, 91.7mmol) in dry ether (40ml) at -78°C under N_2. Compound (92), (15.30g, 91.7mmol) was added over a further 10min and the reaction mixture allowed to warm to room temperature overnight, with stirring. The reaction was quenched by the addition of water (100ml) before extraction into dichloromethane (3 x 60ml). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure to afford a pale yellow oil. The oil when triturated with cold hexane afforded (94) as a crystalline solid (7.22g, 34%), mp 112-117°C (with sublimation) and was used without further purification.

δH (90MHz; $CDCl_3$)	1.90 (6H, s, 1,4-Me)
	2.78 (1H, brs, exch, N-H)
	3.68 (6H, s, 5,8-OMe)
	6.42 (2H, s, 6,7-H)
	6.70 (2H, s, 2,3-H)

δC (74MHz; $CDCl_3$)	17.77 (1,4-Me)
	56.38 (5,8-OMe)
	73.09 (1,4-C)
	111.58 (2,3-C)
	143.09 (5,8/9,10-C)
	146.75 (5,8/9,10-C)
	148.66 (6,7-C)

νmax (CH_2Cl_2) 3240(w), 3100-2850(brs), 2835(s), 1605(m), 1570(w), 1490-1410(brs), 1380(m), 1355(s), 1240(s), 1175(s), 1130(m), 1075-1005(brs), 860(s).

m/z 231(m^+, 47%), 216(37), 205(100), 200(10), 191(14), 176(12), 115(10).

observed m/z 231.1262

calculated for $C_{14}H_{17}NO_2$ 231.1259

1,4-Dimethyl-5,8-dimethoxy-2,3-dihydronapthalen-1,4-imine (96)

A solution of (94), (1.00g, 4.35mmol) in ethanol (20ml) was hydrogenated at 1 Atm over 10% Pd/C (0.104g) for 18h. The reaction mixture was filtered through Celite and the solvent removed from the filtrate under reduced pressure to afford (96), (0.910g, 90%) as a white amorphous solid, mp 144°C (with sublimation).

δH (90MHz; $CDCl_3$) 1.20 - 2.00 (4H, m, 2,3-H)
1.80 (6H, s, 1,4-H)
2.30 (1H, brs, exch, N-H)
3.72 (6H, s, 5,8-OMe)
6.56 (2H, s, 6,7-H)

νmax (CH_2Cl_2) 3270(w), 3090-2850(brm), 2835(m), 1600(w), 1490(s), 1450(brm), 1380(m), 1350(m), 1290-1245(brm), 1210(m), 1175(m), 1120(m), 1090(m), 1050(s), 870(m).

m/z 205(m^+ - CH_2=CH_2, 100%), 190(84), 175(17), 174(4), 118(2), 77(2)

observed m/z (m^+ - CH_2=CH_2) 205.1107

calculated for $C_{12}H_{15}NO_2$ 205.1102

9,Chloro-1,4-dimethyl-2,3-dihydronapthalen-1,4-imine (100)

A stirred solution of (96), (1.515g, 6.50mmol) in dry dichloromethane (20ml) under N_2, was treated with NCS (1.00g, 7.50mmol) and the reaction mixture was stirred for 2.5h. Flash chromatography of the reaction mixture using dichloromethane eluant afforded a pale yellow solid (100), (1.66g, 96%).

A small sample of (100) was recrystallised several times from dry methanol to give an analytical sample,* mp 120-121°C (with sublimation).

δH (400MHz; $CDCl_3$)

syn - (100)	anti - (100)
1.52 (2H, dd, J 12Hz 2,3-H_{endo})	1.48 (2H, dd, J 12Hz, 4.2Hz 2,3-H_{endo})
1.81 (6H, s, 1,4-Me)	1.82 (6H, s, 1,4-Me)
1.91 (2H, dd, J12Hz, 4.2Hz 2,3-H_{exo}	2.13 (2H, dd, J12Hz, 4.2Hz 2,3- H_{exo}
3.76 (6H, s, 5,8-OMe)	3.75 (6H, s, 5,8-OMe)
6.70 (2H, s, 6,7-H)	6.68 (2H, s, 6,7-H)

δC (100MHz; $CDCl_3$†)

syn - (100)	anti - (100)
18.37 (1,4-Me)	16.88 (1,4-Me)
31.47 (2, 3-C)	32.79 (2,3-C)
55.88 (5,8-OMe)	56.01 (5,8-OMe)
75.73 (1,4-C)	75.58 (1,4-C)
111.60 (10,11-C)	111.52 (10,11-C)
134.80 (6,7-C)	132.69 (6,7-C)
149.55(5,8-C)	147.63 (5,8-C)

ν_{max} (CH_2Cl_2) 3100-2850(m), 2840(m), 1610(m), 1500(s), 1460(m), 1440(m), 1285-1250(m), 1090(s), 1010(m), 970(m)

m/z 269/267 (m^+, 1/4%), 241/239(8/31), 240/238 (9/37), 250(27), 204(100), 190(10), 189(8), 175(5), 174(12)

Found C, 62.89; H, 6.75; N, 5.24%. $C_{14}H_{18}NO_2Cl$ requires C, 62.80; H, 6.78; N, 5.23%.

*It was found that each invertomer crystallised out separately.

†At 50°C.

Attempted silver-ion promoted solvolysis of (100) in methanol

A solution of (100), (201mg, 0.75mmol) in dry methanol (25ml) in the dark under N_2 was treated with $AgBF_4$ (257mg, 1.33mmol) and stirred at room temperature for 48h. The reaction mixture was then poured into water (20ml), 2M(aq) NaOH solution (50ml) was added and the resulting mixture extracted with dichloromethane (4 x 20ml). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to afford the amine (96), (170mg, 97%).

Reaction of (100) with $AgBF_4$ in toluene

A solution of $AgBF_4$ (35mg, 0.18mmol) in dry toluene was treated with (100), (40mg, 0.15mmol) and stirred in the dark under N_2 for 5h (when t.l.c. showed no N-chloroamine remained). Methanol (3ml) and an excess of $NaBH_4$ (40mg, 1.05mmol) were then added and the reaction mixture stirred for 15min. The reaction was quenched with water (5ml) and then treated with

2M(aq) NaOH solution (10ml), subsequently extracting with dichloromethane (3 x 15ml). The combined organic extracts were dried over anhydrous $MgSO_4$ and evaporated to dryness under reduced pressure to afford the amine (96), (32mg, 96%).

Silver-ion assisted methanolysis of (100) in toluene

To a stirred mixture of $AgBF_4$ (0.627g, 3.2mmol) dry methanol (87μL, 2.1mmol) in dry toluene (75ml) under N_2 was added (100), (0.500g, 1.87mmol). The mixture was stirred at room temperature for 4h during which a white precipitate formed. The precipitate was allowed to settle and the supernatant was removed carefully. The precipitate was washed with aliquots of toluene (3 x 10ml) and then the remaining solid was dried under reduced pressure. This solid was dissolved in dichloromethane (20ml), rapidly filtered through Celite (to remove silver salt residues) and evaporated to dryness under reduced pressure to afford 5,6,9-trimethoxy-2,5-dimethyl-3,4-dihydrobenzo(f)-5H-azepine hydrogen tetrafluoroborate salt (101), (0.449g,68%) which was stored under N_2.

δH (90MHz; $CDCl_3$)	1.65 (3H, s, 5-Me)
	2.52 (4H, brs, 3,4-H)
	2.88 (3H, s, 5-OMe)
	3.70 (6H, s, 6,9-OMe)
	3.88 (3H, s, 2-Me)
	6.98 (2H, s, 7,8-H)
νmax (CH_2Cl_2)	3200(m), 3060(m), 3000(m), 2940(m), 2840(m), 1670(m), 1590(m), 1502(m), 1460(m), 1430(m), 1370(m), 1300-1250(br, m), 1150-1000(br, s), 810(m)

ν_{max} (KBr) 3600-2500(br,w), 1670(m), 1590(w), 1480-1425(br,w) 1390(w), 1270(s), 1240(w), 1170-990(br,s), 800(m)

δF (94MHz; CH_2Cl_2) 150.32 (4F,† s)

(lit. $BF_4^{\ominus}$ 147.5ppm)

† By integration against a known mass of pentafluorobenzene standard.

Reduction of iminium salt (101)

An excess of $NaBH_4$ (0.250g, 6.76mmol) was added to a solution of (101), (0.449g, 1.28mmol) in dry methanol (10ml) and stirred at room temperature for 1h. The reaction was quenched by the addition of water (10ml) followed by treatment with 2M(aq) NaOH solution (15ml). The resulting solution was extracted with dichloromethane (3 x 10ml), the combined organic extracts were dried over anhydrous $MgSO_4$ and the solution was evaporated to dryness under reduced pressure to yield a colourless oil. Chromatography on alumina using (6:1), petrol (bp 40-60°C): ether eluant gave 5,6,9-trimethoxy-2,5-dimethyl-2,3,4,5-tetrahydrobenzo(f)-1H-azepine (102), (0.282g, 83%). Recrystallisation, three times from petrol (bp 40-60°C) gave an analytically pure sample, mp 74.5-76.5°C.

δH (400MHz; $CDCl_3$)

1.22 (3H, d, J_{Mee} 6.5Hz, 2-Me)
1.47 (1H, ddd, J_{ab} 2.0Hz, J_{ac} 5.3Hz, J_{ad} 13.1Hz, 2-Ha)
1.53 (1H, dddd, J_{ab} 2.0Hz, J_{bc} 13.1Hz, J_{bd} 6.2Hz, J_{be} 11.5Hz, 3-H_b)
1.73 (3H, s, 5-Me)
1.85 (1H, dddd, J_{ca} 5.3Hz, J_{cb} 13.1Hz, J_{cd} 13.0Hz, J_{ce} 5.5Hz, 3-H_c)
2.85 (1H, ddd, J_{da} 13.1Hz, J_{db} 6.2Hz, J_{dc} 13.0Hz, 4-Hd)
2.88 (1H, s, 5-OMe)

3.05 (1H, ddq, J_{eb} 11.5Hz, J_{ec} 5.4Hz, J_{eMe} 6.5Hz, 2-Me)
3.78 (3H, s, 6/9-OMe)
3.79 (3H, s, 6/9-OMe)
4.40 (1H, brs, exch, N-H)
6.32 (1H, d, J 8.8Hz, 7/8-H)
6.61 (1H, d, J 8.8Mz, 7/8-H)

δC (100MHz; $CDCl_3$)		
	22.60 (q, 2/5-Me)	
	27.02 (q, 2/5-Me)	
	33.42 (t, 3/4)	
	39.06 (t, 3/4)	
	49.53 (q, 5-OMe)	
	52.30 (d, 2)	
	55.99 (q, 6/9-OMe)	
	56.06 (q, 6/9-OMe)	
	79.62 (s, 5)	Predicted Values[134]
	101.54 (d, 7)	101.6
	108.08 (d, 8)	112.1
	118.29 (s, 11)	120.5
	142.31 (s, 9/10)	133.1 (10)
	142.75 (s, 9/10)	134.8 (9)
	154.78 (s, 6)	148.8

νmax (CH_2Cl_2) 3390(m), 3010-2810(s), 1600(s), 1490(s), 1460-1410(s), 1365(m), 1345(m), 1230(s), 1175(m), 1165(m), 1100-1050(s), 920(m), 865(m)cm^{-1}.

m/z 265 (m^+, 0.5%), 264(5), 234(18), 233(95), 219(9), 218(100), 204(23), 203(14), 202(9), 191(59), 190(18), 188(27), 176(41), 174(9).

Found C, 67.74; H, 8.66; N, 5.25%. $C_{15}H_{23}O_3N$ requires C, 67.90; H, 8.74; N, 5.28%.

Acid catalysed rearrangement of (101)

A solution of (101), (278mg, 1.05mmol) in dichloromethane (6ml) was treated with trifluoroacetic acid (100μL, 1.3mmol) and stirred at room temperature for 1h. The reaction mixture was then basified with 2M(aq) NaOH solution (15ml) and extracted with dichloromethane (3 x 10ml). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure to afford a yellow oil. This oil was chromatographed over alumina using petrol (bp 40-60°C): ether, (7:1) as eluant to give (103), 6,9-dimethoxy-5-methylene-2-methyl-2,3,4,5-tetrahydrobenzo(f)-1H-azepine as a colourless oil (249mg, 71%) which was stored in the dark under N_2.

δH (400MHz; $CDCl_3$)

1.23 (3H, d, J_{Mee}6.5Hz, 2-Me)

1.68 (1H, dddd, J_{ab}11.6Hz, J_{ac}5.9Hz, J_{ad}6.2Hz, J_{ae}12.7Hz, 3-Ha)

1.88 (1H, dddd, J_{bd}11.6Hz, J_{bc}6.4Hz, J_{bd}8.5Hz, J_{be}3.4Hz, 3-H_b)

2.37 (1H, ddd, J_{ca}5.9Hz, J_{cb}6.4Hz, J_{cd}12.6Hz, 4-H_c)

2.65 (1H, ddd, J_{da}6.2Hz, J_{db}8.5Hz, J_{dc}12.6Hz, 4-H_d)

3.48 (1H, ddq, J_{ea}12.7Hz, J_{eb}3.4Hz, J_{eMe}6.5Hz, 2-H_e)

3.72 (3H, s, 6/9-OMe)

3.79 (3H, s, 6/9-OMe)

4.38 (1H, brs, exch, N-H)

5.28 (1H, d, J 2.4Hz)

5.32 (1H, d, J 2.4Hz)

6.29 (1H, d, J 8.7Hz, 7/8-H)

6.59 (1H, d, J 8.7Hz, 7/8-H)

m/z 233(m^+, 78%), 218(100), 205(13), 204(33), 203(27), 202(13), 191(38), 190(29), 189(11), 188(33), 187(8), 177(36), 176(13), 175(17)

ν_{max} (CH_2Cl_2) 3400(w), 3100-2860(brm), 2835(m), 1595(m), 1495(s). 1460(s), 1375(w), 1360(w), 1240(s), 1175(m), 1090(s), 1060(s), 895(m) cm^{-1}

Found C, 72.00; H, 8.28; N, 5.78%. $C_{14}H_{19}NO_2$ requires C, 72.07; H, 8.21; N, 6.00%.

Silver-ion promoted rearrangement of (100) with d_4-methanol in toluene and subsequent reduction of the rearrangement product

The N-chloroamine (100), (80mg, 0.30mmol) was added to a mixture of $AgBF_4$ (111mg, 0.47mmol), d_4-methanol (14µl, 0.35mmol) and dry toluene (15ml) under N_2. The reaction mixture was stirred for 3h. The precipitated salt was allowed to settle and the supernatant solution removed. The solid residue was washed with further aliquots of dry toluene (3 x 10ml) before drying under reduced pressure. Separation from insoluble silver residues was accomplished by dissolution in dry dichloromethane (10ml), rapid filtration through Celite and then removal of solvent under reduced pressure. The sample of iminium salt produced was examined by ^1H NMR then re-evaporated. The sample was taken up into methanol (5ml) and reduced with $NaBH_4$ (30mg, 0.8mmol) with vigorous stirring over 15 min. The reaction mixture was treated with water (5ml) followed by 2M(aq) NaOH solution (15ml) then extracted with dichloromethane (3x25ml). The extracts were combined, dried over anhydrous $MgSO_4$ and evaporated to dryness to afford 5-(d_3-methoxy)-6,9-dimethoxy-2,5-dimethyl-2,3,4,5-tetrahydro-

benzo(f)-1H-azepine (102a), (53mg, 66%).

A sample of (102a) was dissolved in $CDCl_3$ and treated with a trace of trifluoroacetic acid. Basification followed by the usual work-up afforded a sample which had identical ^1H NMR characteristics to (103).

Iminium salt	δH (90MHz; CD_2Cl_2)	1.65 (3H, s)
		2.52 (4H, brs)
		3.70 (6H, s)
		3.88 (3H, s)
		6.98 (2H, s)
(102a)	δH (90MHz; $CDCl_3$)	1.22 (3H, d, J6.5Hz)
		1.47 (1H, m)
		1.53 (1H, m)
		1.73 (3H, s)
		1.85 (1H, m)
		3.05 (1H, m)
		3.79 (6H, s)
		4.40 (1H, brs, exch)
		6.32 (1H, d, J8.8Hz)
		6.61 (1H, d, J8.8Hz)

Catalytic hydrogenation of (103)

A solution of (103), (131mg, 0.56mmol) in ethanol (10ml) was hydrogenated at 1 Atm over 10% Pd/C (50mg) for 18h. The reaction mixture was filtered through Celite and the solvent removed under reduced pressure to afford 6,9-dimethoxy-2,5-dimethyl-2,3,4,5-tetrahydrobenzo(f)-1H-azepine (104), (126mg, 95%) as a (1:1) mixture of diastereomers.

The product was recrystallised twice from petrol (bp 40-60°C) to provide a sample which was analysed as a mixture of diastereomers. Further recrystallisation afforded samples in which some separation of diastereomeric forms had occurred.

(104a) δ_H (400MHz;$CDCl_3$)*

1.19 (3H, d, $J_{Me\ e}$ 6.5Hz, 2-Me)
1.31 (3H, d, J_{Mef} 7.2Hz, 5-Me)
1.49 (1H, dddd, J_{ab} 2.0Hz, Jac 12.9Hz, Jad 6.0Hz, J_{ae} 10.4Hz, 3-Ha)
1.66 (1H, dddd, J_{ba} 2.0Hz, J_{bc} 5.6Hz, J_{bd} 13.9Hz, J_{bf} 5.7Hz, 4-H_b)
1.93 (1H, dddd, J_{ca} 12.9Hz, J_{cb} 5.6Hz, J_{cd} 12.6Hz, J_{ce} 5.3Hz, 3-Hc)
2.18 (1H, dddd, J_{da} 6.0Hz, J_{db} 13.9Hz, J_{dc} 12.6Hz, J_{de} 2.5Hz, 4-H_d)
3.47 (2H, m, 2-He and 5-Hf)
3.75 (3H, s, 6/9-OMe)
3.77 (3H, s, 6/9-OMe)
4.36 (1H, brs, exch, N-H)
6.23 (1H, d, 8.7Hz, 7/8-H)
6.56 (1H, d, 8.7Hz, 7/8-H)

(104a) δ_C (100MHz;$CDCl_3$)*

20.6	(2/5-Me)	
24.3	(2/5-Me)	
27.7	(3/4)	
30.1	(3/4)	
32.9	(5)	
51.8	(2)	
55.5	(6/9-OMe)	
56.0	(6/9-OMe)	Predicted Values
99.4	(7)	102.4
107.0	(8)	113.1
122.1	(11)	119.0
139.9	(10)	135.0
142.8	(9)	143.4
157.6	(6)	150.7

(104b) δ_H (400MHz;$CDCl_3$)*

1.18 (3H d, 7.2Hz, 2-Me)
1.29 (3H, d, 6.4Hz, 5-Me)
1.59 (2H, m)
1.83 (2H, m)

2.71 (1H, ddq, J10.7Hz, J6.4Hz, J1.8Hz, 5-Hf)
3.75 (3H, s, 6/9-OMe)
3.77 (3H, s, 6/9-OMe)
3.89 (1H, ddq, J7.2Hz, J5.2Hz, J2.8Hz, 2-He)
4.26 (1H, brs, exch, N-H)
6.35 (1H, J8.8Hz, 7/8-H)
6.59 (1H, J8.8Hz, 7/8-H)

(104b) δC (100MHz;$CDCl_3$)* 15.9 (2/5-Me)
22.1 (2/5-Me)
28.5 (3/4)
32.0 (3/4)
33.5 (5)
54.6 (2)
56.2 (6/9-OMe)
56.5 (6/9-OMe)

		Predicted Values
102.4	(7)	102.4
107.6	(8)	113.1
127.0	(11)	119.0
139.6	(10)	135.0
144.4	(9)	143.4
151.5	(6)	150.7

Found C, 71.46; H, 9.03; N, 5.87%. $C_{14}H_{21}NO_2$ requires C, 71.46; H, 8.99; N, 5.95%.†

Rearrangement of (101) in solution

A solution of (101), (17mg, 0.05mmol) in CD_2Cl_2 (0.3ml) was observed by ^{1}H NMR to rearrange to 2,4-dimethyl-3,4-methano-5,8-dimethoxy-3,4-dihydroquinoline hydrogen tetrafluoroborate salt (105) with the production of an equivalent of methanol. The solvent was then removed under reduced

*From the NMR spectra of the mixture of diastereomers.
†As a mixture of diastereomers.

pressure to give (105) as a yellow solid. This was dissolved in methanol (5ml) and stirred with $NaBH_4$ (26mg, 0.6mmol) for 20 min. The reaction was quenched with water (5ml), treated with 2M(aq) NaOH solution (5ml) and extracted into dichloromethane (3x10ml). The organic extracts were dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure to afford 2,4-dimethyl-3,4-methano-5,8-dimethoxy-1,2,3,4-tetrahydroquinoline (106), (12mg, 96%) as a white solid.

(105) δH (90MHz; $CDCl_3$) 0.74 (1H, dd, J4Hz, 7Hz, 11-Ha)
1.68 (3H, s, 4-Me)
2.25 (2H, m, 11-H_b, 3-Hc)
2.88 (3H, s, 2-Me)
3.79 (3H, s, 5/8-OMe)
3.88 (3H, s, 5/8-OMe)
6.93 (2H, s, 6,7-H)

δF (94MHz; $CDCl_2$) 149.43 (4F*)

ν_{max} (CH_2Cl_2) 3300-2840 (brm), 1655(m), 1602(m), 1490(s), 1450(m), 1430(m), 1370(m), 1240(m), 1130-980(brs), 805(m) cm^{-1}

(106) δH (400MHz; $CDCl_3$) 0.68 (1H, dd, Jac 8.3Hz, Jab 4.2Hz, 11-Ha)
0.98 (1H, dd, J_{bc} 5.8Hz, J_{ab} 4.2Hz, 11-H_b)
1.07 (1H, ddd, J_{ca} 8.3Hz, J_{cb}5.8Hz, J_{cd} 3.3Hz, 3-H_c)
1.13 (3H, d, J_{Med} 6.1Hz, 2-Me)
1.50 (3H, s, 4-Me)
3.44 (1H, dq, J_{Med} 6.1Hz, J_{cd} 3.3Hz, 2-H_d)
3.69 (6H, s, 5,8-OMe)

*By integration against a known weight of pentafluorobenzene.

4.15 (1H, brs, exch, N-H)
6.11 (1H, d, J8.8Hz, 6/7-H)
6.46 (1H, d, J8.8Hz, 6/7-H)

(106) δC (100MHz;$CDCl_3$) 15.15 (t, 11)
15.52 (s, 4)
22.19 (q, 2/4-Me)
26.27 (q, 2/4-Me)
32.68 (d, 3)
41.84 (d, 2)
55.82 (q, 5/8-OMe)
56.14 (q, 5/8-OMe)

	Predicted Values
100.01 (d, 6)	101.9
106.78 (d, 7)	112.1
115.64 (s, 10)	113.8
133.33 (s, 8)	135.1
140.74 (s, 5)	149.4
154.22 (s, 9)	152.1

Basification Study of (101)

A solution of (101) (17mg, 0.048mmol) in CD_2Cl_2 (0.15ml) was treated with d_5-pyridine and was observed to have undergone immediate rearrangement of (105). The solvent was removed under reduced pressure to afford a red oil which contained (105) (0.045mmol, 94%). The oil was dissolved in a minimum of dichloromethane and the salt precipitated by the addition of dry ether. The supernatant was removed and the remaining solid evaporated to dryness under reduced pressure. The salt was then redissolved in CD_2Cl_2 (0.2ml), treated with triethylamine (0.4ml) and a precipitation was observed. The supernatant was carefully drawn off and the precipitate was further washed with dry ether (2x10ml). The organic solutions were combined and evaporated to dryness

under reduced pressure to afford 2,4-dimethyl-3,4-methano-5,8-dimethoxy-3,4-dihydroquinoline (107) quantitatively from (105).

δH (90MHz; $CDCl_3$) 0.90 - 1.63 (3H, brm)
1.55 (3H, s, 4-Me)
2.40 (3H, s, 2-Me)
3.78 (3H, s, 5/8-OMe)
3.81 (3H, s, 5/8-OMe)
6.70 (2H, s, 6,7-H)

ν_{max} (CH_2Cl_2) 3020cm^{-1}(m), 3010 - 2840(br, m), 2840(m), 1660(m), 1580(m), 1500(m), 1485(s), 1465(s), 1445(m), 1240(s), 1140 - 1010(br, s)

m/z (232, 16%), 231(66, m^+), 230(22), 218(28), 217(100), 206(22), 202(44), 201(44), 190(31), 188(28), 186(25), 84(38)

1,4-Dimethylnapthalen-1,4-imine (93)

A solution of bromofluorobenzene (6.28g, 0.036mol) in dry ether (25ml) was stirred vigorously under N_2 and cooled to -78^{o}C then n-BuLi (0.9M in hexane, 40ml) was added over 20 min. The reaction mixture was then treated with (92) (6.96g, 0.042mol) and allowed to warm slowly to ambient temperature overnight with stirring. The reaction mixture was poured into water (50ml) and extracted with dichloromethane (3x50ml). The organic extracts were combined and dried over anhydrous $MgSO_4$ and evaporated under reduced pressure to afford (93) (3.23g, 53%) as a pale yellow oil.

δH (90MHz; $CDCl_3$) 1.80 (6H, s)
3.02 (1H, brs, exch)
6.78 (2H, s)
6.90 - 7.25 (4H, brm)

1,4-Dimethyl-2,3-dihydronapthalen-1,4-imine (95)

A solution of (93), (2.66g, 0.0156mol) in ethanol (40ml) was hydrogenated at 1Atm for 24h over 10% Pd/C (79mg). The reaction mixture was filtered through Celite and the solvent removed under reduced pressure to afford (95), (2.44g, 91%) as a yellow oil. This was used in the subsequent preparation without further purification.

δH (90MHz; $CDCl_3$) 1.16 - 1.49 (2H, brm, 2,3-H_{endo})
1.58 - 2.16 (2H, brm, 2,3-H_{exo})
1.94 (6H, s)
2.50 (1H, brs, exch)
7.19 (4H, s)

m/z 145(m^+-CH_2=CH_2, 100%), 144(48), 132(26), 128(9), 115(13), 94(28), 91(12), 77(12), 57(10), 55(9), 51(8)
observed m/z 145.0894

(m^+-CH_2=CH_2) $C_{10}H_{11}N$ calculated 145.0892

9-Chloro-1,4-dimethyl-2,3-dihydronapthalen-1,4-imine (99)

A solution of (95), (1.92g, 11mmol) was dissolved in dichloromethane (25ml) and treated with NCS (1.78g, 13.4mmol) then stirred under N_2 for 1.5h. The reaction mixture was flash chromatographed using dichloromethane eluant and (99), (1.928g, 85%) was isolated as a yellow oil.

δH (100MHz; $CDCl_3$)

syn - (99)	anti - (99)
1.50 (2H, brm,† 2,3-Hexo	1.44 (2H, dd, J 12Hz, 4Hz, 2,3-H_{endo})
1.78 (6H, s)	1.78 (6H, s)
2.02 (2H, dd, J11.3Hz, 4.9Hz, 2,3-H_{exo})	2.24 (2H, dd, J12Hz, 4Hz, 2,3-H_{exo})

7.29 (4H, brs) 7.29 (4H, brs)

†obscured by anti-signal

δC (100MHz; $CDCl_3$)

syn - (99)	anti - (99)
16.2 (1,4-Me)	15.2 (1,4-Me)
31.3 (2,3)	32.6 (2,3)
75.2 (1,4)	75.2 (1,4)
118.2 (6,7)	119.9 (6,7)
126.6 (5,8)	127.1 (5,8)
146.9 (10,11)	144.3 (10,11)

m/z 181/179(m^+ - CH_2=CH_2, 9/30%), 144(100), 143(4), 115(6), 103(10), 102(4), 77(6), 51(4)

observed m/z 181.0476
Calculated for (m^+ - CH_2=CH_2) $C_{10}H_{10}N^{37}Cl$ 181.0472

Reaction of (99) silver ion in toluene in the presence of 1.2 equivalents of methanol

A solution of (99) (60mg, 0.29mmol) in dry toluene (3ml) was added to a stirred solution of $AgBF_4$ (217mg, 1.09mmol) and dry methanol (15µL, 0.36mmol) in dry toluene (20ml) and stirred in the dark under N_2 for 4h. Dry methanol was added, followed by the addition of $NaBH_4$ (110mg, 2.89mmol) in small portions. When the addition was complete the reaction mixture was stirred for a further 10min, then treated with water (5ml) followed by 2M(aq) NaOH solution (20ml). The resultant mixture was extracted with dichloromethane (3x15ml). The extracts were combined, dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure to afford a yellow

oil (47mg). When examined by ^{1}H NMR the oil was found to contain the amine (95) (0.18mmol, 62%)* and 5-methoxy-2,5-dimethyl-2,3,4,5-tetrahydrobenzo(f)-1H-azepine (108a) as a single diastereomer (0.09mmol, 31%).*

(108a) δH (400MHz; $CDCl_3$)

1.22 (3H, d, J_{Mee} 6.4Hz, 2-Me)
1.58 (3H, s, 5-Me)
1.66 (1H, ddd, J_{ab} 4.4Hz, J_{ac} 5.0Hz, J_{ad} 13.0Hz, 4-H_a)
1.71 (1H, dddd, J_{ab} 4.4Hz, J_{bc} 13.5Hz, J_{bd} 10.8Hz, J_{be} 5.2Hz, 3-H_b)
1.86 (1H, dddd, J_{ca} 5.0Hz, J_{cb} 13.5Hz, J_{cd} 5.4Hz, J_{ce} 11.1Hz, 3-H_c)
2.56 (1H, ddd, J_{da} 13.0Hz, J_{db} 10.8Hz, J_{dc} 5.4Hz, 4-H_d)
2.94 (3H, s, 5-OMe)
3.22 (1H, ddq, J_{eb} 5.2Hz, J_{ec} 11.1Hz, J_{eMe} 6.4Hz, 2-He)
6.61 (1H, dd, J7.9Hz, J1.3Hz)
6.86 (1H, dd, J7.9Hz, J7.2Hz, J1.3Hz)
7.03 (1H, dd, J7.9Hz, J7.2Hz, J1.6Hz)
7.43 (1H, dd, J7.9Hz; J1.6Hz)

δC ($CDCl_3$)		
	22.8 (2-Me)	
	29.9 (5-Me)	
	33.2 (3/4-C)	
	33.5 (3/4-C)	
	49.7 (2-C)	
	52.4 (5-OMe)	
	78.7 (5-C)	Predicted Values
	119.4	111.2 (9)
	120.1 (6/7/8/9-C)	115.0 (7)
	127.3	125.2 (6)
	129.2	125.5 (8)
	131.2 (11)	133.9
	148.9 (10)	146.8

*By integration against a known weight of dichloromethane

m/z 205(m^+, 35%), 175(25), 174(68), 173(14), 162(24), 158(100), 146(29), 145(36), 144(28), 143(31), 131(9), 130(25), 91(12), 77(14).

observed m/z 205.1467
Calculated for $C_{13}H_{19}NO$ 205.1466

Silver ion assisted methanolysis of (99)

A portion of $AgBF_4$ (212mg, 1.09mmol) was added to a solution of (99) (92mg, 0.44mmol) in dry benzene (2.5ml) with dry methanol (110µL, 2.72mmol). The reaction mixture was stirred in the dark under N_2 for 4h then treated with dry methanol (5ml) followed by the addition of $NaBH_4$ (167mg, 4.39mmol) in small portions. After stirring for 20min, water (5ml) was added then 2M(aq) NaOH solution (20ml) and the resulting mixture was extracted with dichloromethane (3x15ml). The organic extracts were combined, dried over anhydrous $MgSO_4$ and evaporated to dryness under reduced pressure to afford a dark oil which, when observed by ^1H NMR, was found to contain the amine (95) (0.14mmol, 32%)*, (108a) (0.21mmol, 48%)* and some other minor products. The mixture of products were chromatographed on alumina using dichloromethane eluant to give (108a), (22mg, 25%) and 5-methoxy-2,5-diemthyl-2,3,4,5-tetrahydrobenzo(f)-1H-azepine (108b), diastereomeric with (108a), (4mg, 4%).

(108b) δH (400MHz; $CDCl_3$)

1.24 (3H, d, J_{Mee} 6.5Hz)
1.47 (3H, s, 5-Me)
1.65 (1H, dddd, J_{ad} 4.0Hz, J_{ae} 10.4Hz, J_{ac} 10.8Hz, J_{ab} 14.0Hz, 3-Ha)
1.78 (1H, dddd, J_{ba} 14.0Hz, J_{bc} 3.8Hz, J_{bd} 5.8Hz, J_{be} 2.4Hz, 3-H_b)

1.93 (1H, ddd, J_{ca} 10.8Hz, J_{cb} 3.8Hz, J_{cd} 13.6Hz, 4-Hc)
1.96 (1H, ddd, J_{da} 4.0Hz, J_{db} 5.8Hz, J_{dc} 13.6Hz, 4-Hd)
3.02 (1H, ddq, J_{ea} 10.4Hz, J_{eb} 2.4Hz, J_{eMe} 6.5Hz, 2-He)
3.33 (3H, s, 5-OMe)
6.66 (1H, dd, J1.3Hz, J7.7Hz, 6-H)
6.89 (1H, ddd, J1.3Hz, J7.3Hz, J7.9Hz, 8-H)
7.04 (1H, ddd, J1.6Hz, J7.3Hz, J7.7Hz, 7-H)
7.46 (1H, dd, J1.6Hz, J7.9Hz, 9-H)

Preparation and subsequent rearrangements of 9-bromo-1,4-dimethyl-2,3-dihydronapthalen-1,4-imine (109)

Several drops of bromine were added to a rapidly stirred 10ml aliquot of 2M(aq) NaOH solution. The solution was allowed to stand for 30 min then added to a solution of the amine (95) (105mg, 0.61mmol) in dichloromethane (5ml) and stirred for 1h. The organic layer was separated and the aqueous layer washed with dichloromethane (2x5ml). The organic solutions were combined, dried over anhydrous $MgSO_4$ and evaporated to afford the N-bromoamine (109),* (150mg, 98%). This N-bromoamine was dissolved in benzene (3ml) and dry methanol (120µL, 2.97mmol), then treated with $AgBF_4$ (379mg, 0.61mmol). The reaction mixture was stirred overnight before methanol (5ml) was added followed by $NaBH_4$ (50mg, 1.32mmol) in small portions with stirring. After 20 min water (5ml) was added, then 2M(aq) NaOH solution (10ml) and the resulting mixture was extracted with dichloromethane (3x15ml). The organic extracts were combined, dried over anhydrous $MgSO_4$ and evaporated to afford a dark oil. This was examined by ^{1}H NMR† and found to contain (108a) (0.33mmol, 56%), (95) (0.06mmol, 10%) and (0.12mmol, 20%) of other products (based on aromatic protons). Column chromatography on alumina using (3:1) carbon tetrachloride:dichloromethane

afforded 2,4-dimethyl-3,4-methano-1,2,3,4-tetrahydroquinoline (110a) (17mg, 17%) as a pale yellow oil. Further elution with (4:1) petroleum (40 - 60°C bp):ether gave (108a) (43mg, 35%).

(110a) δH (400MHz; $CDCl_3$)

0.56 (1H, dd, J7.9Hz, J4.0Hz, 11-H_a)
1.22 (3H, d, J6.1Hz, 2-Me)
1.30-1.38 (2H, m, H_b & H_c)
1.44 (3H, s)
2.45 (1H, brs, N-H)
3.41 (1H, dq, J2.1Hz, J6.1Hz, 2-H_d)
6.46 (1H, dd, J7.8Hz, J1.3Hz)
6.72 (1H, dt, J1.3Hz, J7.7Hz)
6.95 (1H, dt, J1.5Hz, J7.7Hz)
7.28 (1H, dd, J7.6Hz, J1.5Hz)

*The ^{1}H NMR (90MHz; $CDCl_3$) was identical to N-chloroamine (99)
†By integration against a known weight of dichloromethane standard

(110) δC (100MHz; $CDCl_3$)

		Predicted Values
12.6	(t, 11)	
16.9	(s, 4)	
22.0	(q, 2/4-Me)	
22.9	(q, 2/4-Me)	
33.2	(d, 3)	
43.2	(d, 2)	
113.7	(d, 6/8)	111.5 (8)
118.1	(d, 6/8)	115.3 (6)
125.4	(d, 5/7)	125.5 (7)
125.5	(d, 5/7)	125.8 (5)
128.5	(s, 10)	127.2 (10)
142.5	(s, 9)	147.1 (9)

m/z 173(m^+, 45%), 172(20), 171(32), 170(80), 169(13), 158(100), 157(24), 156(22), 144(24), 143(36), 131(51), 130(35), 128(19), 115(20), 91(10), 77(15), 51(10).

observed m/z 173.1195
Calculated for $C_{12}H_{15}N$ 173.1204

Further rearrangement products from the silver ion assisted methanolysis of (99) in toluene

Two further reactions were completed following methodology used in previous rearrangements and the following quantities of reactants (in total); (99) (280mg, 1.35mmol), $AgBF_4$ (759mg, 3.90mmol) and dry methanol (267µL, 6.61mmol). In each case the rearrangement products were allowed to stand overnight before reduction with a large excess of $NaBH_4$ in methanol, followed by basic work-up. The crude products thus obtained were stored at room temperature for several days then combined and column chromatographed on alumina using dichloromethane eluant to separate the rearrangement products from amine (95), which was not isolated. The rearrangement products thus obtained (173mg) were shown by ^1H NMR to be free of amine (95) and it was obvious that the major components were the previously isolated benzazepine derivative (108a) and quinoline derivative (110a). A sample of this mixture (150mg) was chromatographed on a silica preparative t.l.c. plate using (3:1) petroleum (bp 40 - 60°C): ether eluant. The two product-containing bands were removed and placed in 20ml aliquots of methanol and allowed to remain as such overnight (i.e. still in the presence of silica) before the organic solutions were separated and evaporated under reduced pressure. Each of the two bands still contained mixtures of products. The products mixture from the

higher Rf band (40mg) was flash chromatographed using (20:1) petroleum (bp 40 - 60°C):ether. Unfortunately the three components of the mixture possessed very similar Rf values and therefore only a partial separation was possible. Two fractions were isolated. The first fraction (8mg) contained all three components (one of which was (110a); however high field ^{1}H NMR showed the predominant component was 5-methylene-2-methyl-2,3,4,5-tetrahydrobenzo(f)-1H-azepine (111).

(111) δH (400MHz; $CDCl_3$)[a]

1.22 (3H, d, $J_{Me,e}$ 2-Me)
1.70 (1H, m[b], J_{ae} 3.0Hz, J_{ac} 6.0Hz + other J's, 3-H_a)
1.88 (1H, dddd, J_{bc} 3.8Hz, J_{bd} 6.4Hz, J_{be} 10.4Hz, J_{ba} 12.8Hz[c], 3-Hb)
2.44 (1H, ddd, J_{cb} 3.8Hz, J_{ca} 6.0Hz, J_{cd} 12.4Hz, 4-H_c)
2.69 (1H, ddd, J_{db} 6.4Hz, J_{da} 9.6Hz[c], J_{dc} 12.4Hz, 4-H_d)
3.51 (1H, ddq, J_{ea} 3.0Hz, J_{eMe} 6.4Hz, J_{eb} 10.4Hz, 2-H_e)
4.94 (1H, d, J2Hz)
5.17 (1H, d, J2Hz)
6.57 (1H, dd, J7.7Hz, J1.3Hz)
6.74 (1H, dt, J1.6Hz, J7.8Hz)
7.03 (1H, dt, J1.6Hz, J7.8Hz)
7.25 (1H, dd, J7.9Hz, J1.6Hz)

The second fraction (27mg) contained two components. High field ^{1}H NMR showed that one was (110a) but the second component had not been previously observed. This component was tentatively assigned as the other diastereoisomer of (110a).

(110b) δH (400MHz; $CDCl_3$)[d]

0.95 (1H, dd, J_{bc} 5.7Hz, J1.0Hz, H_b)
1.40 (3H, d, J_{dMe} 5.9Hz, 2-Me)
1.68 (3H, s, 4-Me)
1.95 (1H, d, J_{cb} 5.7Hz, additional small J, 3-H_c)

3.46 (1H, q, J_{dMe} 5.9Hz, additional small J, 2-H_d)
6.48 (1H, dd, J1.3Hz, J8.0Hz)
6.77 (1H, dt, J1.3Hz, J7.8Hz)
7.01 (1H, dt, J1.4Hz, J7.8Hz)
7.30 (1H, dd, J1.4Hz, J7.7Hz)

a) From a mixture, (111) ca. 50%, (110a) ca. 25%, (110b) ca. 25%.
b) Partially obscured by coincident peaks of other compounds.
c) Assigned by deduction.
d) From a mixture, (110a) ca. 42%, (110b) ca. 58%. H_a not observed as probably considerably shielded and obscured by TMS peak.

The lower Rf band from the preparative t.l.c. (87mg) consisted mainly of (108a) however an interesting minor product was visible. Therefore this fraction was flash chromatographed using dichloromethane eluant. This afforded (108a) (54mg, 20%) and 2,5-dimethyl-2,3-dihydrobenzo(f)-1H-azepine (112) (23mg, 10%).

(112) δH (400MHz; $CDCl_3$)

1.25 (3H, d, J_{eMe} 6.4Hz, 2-Me)
2.10 (1H, m, 3-H_a)
2.14 (3H, d, J_{dMe} 1.6Hz, 5-Me)
2.27 (1H, m, 3-H_b)
3.69 (1H, ddq, J3.8Hz, J9.4Hz, J_{cMe} 6.4Hz, 2-H_c)
5.99 (1H, ddd, J_{dMe} 1.6Hz, J5.9Hz, J7.2Hz, 4-H_d)
6.73 (1H, dd, J1.8Hz, J8.0Hz)
6.90 (1H, dt, J1.6Hz, J8.0Hz)
7.06 (1H, dt, J1.8Hz, J8.0Hz)
7.31 (1H, dd, J1.6Hz, J7.9Hz)

(112) δC (100MHz; $CDCl_3$)*

22.9 (q, 2/5-Me)

*Sample with added $Cr(acac)_3$ and relaxation delay. Assignments were made using DEPT.

24.3 (q, 2/5-Me)
36.8 (t, 3)
57.7 (d, 2)
119.9 (d)
120.1 (d)
126.4 (d)
127.0 (d)
128.0 (d)
129.2 (s, 5/11)
133.9 (s, 5/11)
146.0 (s, 10)

m/z 173(m^+, 30%), 172(17), 158(100), 157(20), 156(13), 144(61), 143(48), 142(24), 131(47), 130(56), 118(13), 115(24), 91(17), 77(16), 63(10), 57(9), 51(15).

observed m/z 173.1190
Calculated for $C_{12}H_{15}N$ 173.1204

Thus, the rearrangement products observed for this rearrangement are as follows: (108a) 20%, (112) 10%, (110b) 8%, (110a) 6% and (111) 2%.

9-Bromo-1,4-dimethyl-5,8-dimethoxynapthalen-1,4-imine (113)

A solution of (95) (0.303g, 1.30mmol) in dichloromethane (10ml) was treated with NBS (0.278g, 1.56mmol) and stirred in the dark under N_2 for 3h. The solvent was removed under reduced pressure and the residue was flash chromatographed on silica using dichloromethane eluant to give (113) 0.359g (88%).

(113) δH (90MHz; $CDCl_3$)

1.31 - 1.64 (2H, m)
1.78 (6H, s)
1.78 - 2.25 (2H, m)
3.70 (6H, s)
6.63 (2H, s)

m/z 313/311(m^+, 6/6%), 285/283(3/3), 231(6), 206(9), 205(94), 204(100), 203(34), 202(6), 201(6), 191(6), 190(63), 189(9), 188(20), 175(17), 174(20), 173(11)

6,9-Dibromo-1,4-dimethyl-5,8-dimethoxynapthalen-1,4-imine (115)

The N-bromoamine (113) (0.168g, 0.54mmol) was added to a solution of bromine (0.129g, 0.81mmol) in dichloromethane (10ml) and stirred overnight. The resultant solution was evaporated under reduced pressure. The residue was re-dissolved in carbon tetrachloride:dichloromethane and re-evaporated several times until the excess bromine was removed, this afforded 6-bromo-1,4-dimethyl-5,8-dimethoxynapthalen-1,4-imine hydrogen bromide (114). This was dissolved in dichloromethane (5ml) and treated with 2M(aq) NaOH solution (10ml) containing bromine (0.2ml) and vigorously stirred for 10 min. The organic layer was separated and the aqueous layer was further extracted with aliquots of dichloromethane (2x10ml). The combined organic solutions were washed with 2M(aq) NaOH solution (20ml) and dried over anhydrous $MgSO_4$. Removal of solvent under reduced pressure afforded (115) 207mg (98%) as a pale yellow solid.*

Basification of (114) with 2M(aq) NaOH solution, extraction into dichloromethane, drying over anhydrous $MgSO_4$ and removal of solvent under reduced pressure afforded the amine (118) quantitatively.

(114) δH (90MHz; $CDCl_3$)

1.42 - 2.72 (4H, m)
2.10 (6H, brs)

*(115) can also be produced from exposure of (95) to 2 equivalents of NBS in $CDCl_3$ for prolonged periods (ca. 3d).

3.75 (3H, s)
3.79 (3H, s)
6.92 (1H, s)
8.90 (1H, brs)

(118) δ_H (90MHz; $CDCl_3$)

1.27 - 1.58 (2H, m)
1.78 - 2.08 (2H, m)
1.78 (3H, s)
1.81 (3H, s)
2.26 (1H, brs, exch)
3.74 (3H, s)
3.75 (3H, s)
6.83 (1H, s)

(118) m/z 314/312(0.5/0.5%). 313/311(m^+, 0.5/0.5), 297/295(6/6), 286/284(15/15), 285/283(85/85), 281(10), 279(9), 171/169(15/15), 170/168(100/100), 265/263 (23/23), 264(9), 174(20), 44(25), 42(20), 40(30).

(115) δ_H (90MHz; $CDCl_3$)

1.41 - 1.69 (2H, m)
1.73 - 2.16 (2H, m)
1.78 (3H, s)
1.82 (3H, s)
3.74 (3H, s)
3.75 (3H, s)
6.89 (1H, s)

(115) m/z 393/391/389 (m^+, 3/6/3%), 365/363/361(3/6/3), 311/309(5/5), 296/294(16/16), 285(63), 284(69), 283 (100), 282(65), 281(33), 270(44), 268(63), 266(25), 255(12), 254(16), 253(20), 252(16), 251(9), 81(50), 79(50), 44(100)

2,5-Dimethyl-2-methoxy-6,7-(8,11-dimethoxy-9-bromobenzo)-1-azabicyclo[3.2.0]heptane (117)

A solution of (115) (100mg, 0.26mmol) in dry benzene (5ml) was added to a mixture of $AgBF_4$ (213mg, 1.1mmol), dry

benzene (5ml) and dry methanol (15μL, 0.37mmol). The reaction mixture was stirred in the dark under N_2 for 2h then poured into water (15ml) and basified with 2M(aq) NaOH solution (25ml). The aqueous solution was extracted with dichloromethane (4x25ml). The organic extracts were combined, filtered through Celite, dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure to afford a yellow solid (78mg).* The sample was chromatographed on alumina using petroleum (bp 40 - 60°C):ether (3:1) and afforded (117), 15mg (17%) as a pale yellow oil.

(117) δ_H (90MHz;$CDCl_3$)

	1.45	(3H, s)
	1.69	(3H, s)
1.82 -	2.30	(4H, m)
	3.35	(3H, s)
	3.70	(3H, s)
	3.85	(3H, s)
	6.86	(1H, s)

(117) m/z 343/341(m^+, 11/11%), 328/326(5/5), 313(23), 312(100), 311(53), 310(100), 309(30), 297/295(91/91), 283(16), 282(33), 281(32), 280(37), 279(19), etc.

Reactions Summarised in Tables 6.3 and 6.4

The reactions shown in tables 6.3 and 6.4 were conducted using the following procedure: The haloamine was added to a mixture of $AgBF_4$, dry methanol and solvent, then stirred in the dark under N_2 for ca. 4h. An excess of $NaBH_4$ (ca. 10 fold) was added followed (cautiously) by methanol (ca. 10ml), after the vigorous reaction had subsided the reaction mixture

*By ^1H NMR this was mainly (118), which was not isolated.

Table 6:3 Various Silver Ion Promoted Rearrangements of (100) and Derivative Systems

Substrate	Solvent	MeOH (eqivalents)	$AgBF_4$ (eqivalents)	Products[†]
(100) 1.87mmol	PhMe 45ml	1.2	1.7	(95) *, (102)68%
(100) 0.30mmol	PhMe 15ml	1.2	1.6	(95) *, (102)66%
(100) 2.02mmol	PhMe 65ml	1.1	1.2	(95) *, (102)63%
(100) 0.27mmol	PhMe 15ml	1.1	1.8	(95) *, (102)53%
(100) 0.39mmol	PhH 12.5ml	1.2	2.6	(95) 53%, (102)44%
(100) 0.19mmol	PhH 2.5ml	1.2	2.5	(95) 20%, (102)78%
(113) 0.16mmol	PhMe 15ml	1.1	6.4	(95) 61%, (102)29%
(113) 0.16mmol	PhH 10ml	1.2	7.1	(95) 60%, (102)20%, (117)10%
(113) 0.32mmol	PhH 10ml	1.2	2.6	(95) 51%, (102)34%, (117)11%
(113) 0.14mmol	PhH 2.5ml	13.3	2.5	(95) 56%, (102)37%, (117)7%
(115) 0.26mmol	PhH 18ml	1.2	2.5	(95) 74%, (102)22%
(115) 0.13mmol	PhH 2.5ml	1.2	4.5	(95) 56%, (102)20%, (117)20%
(115) 0.12mmol	PhH 2.8ml	10.3	9.7	(95) 17%, (102)52%, (117)26%
(115) 0.065mmol	PhH 1.3ml	19	8.0	(95) 17%, (102)56%, (117)23%

*Present, but yield not recorded

†Yields approximate (±7%)

Table 6:4 Various Silver Ion Promoted Rearrangements of (99) and Derivative Systems

Substrate	Solvent	MeOH (equivalents)	$AgBF_4$ (equivalents)	Products[†]
(99) 0.29mmol	PhMe 23ml	1.2	3.8	(95) 62%, (108a) 31%
(99) 0.31mmol	PhH 2.5ml	6.1	3.3	(95) 41%, (108a) 27%, (*) 22%
(99) 0.44mmol	PhH 2.5ml	6.2	2.5	(95) 32%, (108a) 48%, (*) 20%
(99) 0.67mmol	PhH 3.8ml	5.9	2.6	(95) 42%, (108a) 25%, (*) 30%
(109) 0.6 mmol	PhH 3ml	4.9	3.2	(95) 10%, (108a) 56%, (*) 20%

*Combinations of other rearrangement products

†Yields approximate (±7%)

was stirred for 20 min. Water (ca. 5ml) was added followed by 2M(aq) NaOH solution (ca. 15ml) and the resultant mixture extracted with dichloromethane (3x10ml). The organic extracts were combined, dried over anhydrous $MgSO_4$, evaporated under reduced pressure and the resultant residue examined by ^1H NMR (90MHz). Approximate yields (±7%) were determined by integration against a known weight of either dichloromethane or benzene.

(117) δH (90MHz; $CDCl_3$)*

	1.26	(3H, s)
	1.49	(3H, s)
ca.	1.80 - 2.20	(4H, m)
	3.36	(3H, s)
	3.70	(3H, s)
	3.72	(3H, s)
	6.40	(1H, d, J8.8Hz)
	6.62	(1H, d, J8.8Hz)

1,4-Dihydro-5,8-dimethoxynapthalen-1,4-imine (64a)[67]

This was prepared in 25% yield following the procedure described in ref. 67.

δH (90MHz; $CDCl_3$) 2.70 (1H, brs, exch, N-H)
3.70 (6H, s)
5.12 (2H, m, 1&4-H)
6.40 (2H, s, 6&7-H)
6.90 (2H, m, 2&3-H)

1,2,3,4-Tetrahydro-5,8-dimethoxynapthalen-1,4-imine (65a)[67]

This was prepared in 90% yield (mp 82 - 84°C, lit. 84 - 85°C) as described in ref. 67.

δH (90MHz; $CDCl_3$) 1.20 - 2.10 (4H, m)
2.43 (1H, brs, exch, N-H)
3.70 (6H, s)
4.68 (2H, m)
6.50 (2H, s)

9-Chloro-1,2,3,4-tetrahydro-5,8-dimethoxynapthalen-1,4-imine (74b)

A solution of (65a) (904mg, 4.41mmol) in dichloromethane (10ml) was treated with NCS (660mg, 4.9mmol) and stirred in the dark under N_2 for 2.5h. The reaction mixture was flash chromatographed using dichloromethane eluant and afforded (74b) 733mg (73%) as an off-white crystalline solid.

A small amount of (74b) was recrystallised for analytical purposes to give colourless needles from methanol mp 122.5 - 123.5°C (with sublimation).

δH (400MHz; $CDCl_3$)

syn - (74b)	anti - (74b)
6.72 (2H, s)	6.65 (2H, s)
4.76 (2H, dd, J1.6Hz, J2.7Hz)	4.72 (2H, dd J1.7Hz, J2.7Hz)
3.80 (6H, s)	3.76 (6H, s)
2.17 (2H, m)	2.44 (2H, m)
1.32 (2H, dd, J3.9Hz, J11.3Hz)	1.41 (2H, dd, J4.4Hz, J12.6Hz)

Found C, 60.13; H, 5.92; N, 5.83%. $C_{12}H_{14}NO_2Cl$, requires C, 60.13; H, 5.89; N, 5.84%.

2-Methoxy-6,7-(8,11-dimethoxybenzo)-1-azabicyclo[3.2.0]-heptane (75b)[68]

The N-chloroamine (74b) (92mg, 0.39mmol) was added to a stirred mixture of $AgBF_4$ (97mg, 0.50mmol), dry methanol (18µL, 0.45mmol) and toluene (15ml). The reaction mixture was stirred in the dark under N_2 for 3h. The formation of a white precipitate was observed. The supernatant was removed and the precipitate dried under reduced pressure, treated with 2M(aq) NaOH solution (20ml) then extracted with dichloromethane (3x20ml). The organic extracts were combined,

dried over anhydrous $MgSO_4$ and evaporated under reduced pressure to afford (75b), 86mg (90%) as a pale yellow solid.

δH (400MHz; $CDCl_3$)	1.93 - 2.18	(4H, m)
	3.47	(3H, s)
	3.76	(3H, s)
	3.79	(3H, s)
	4.63	(1H, d, J4.6Hz)
	5.27	(1H, brd, J7.6Hz)
	6.39	(1H, d, J9.0Hz)
	6.64	(1H, dd, J9.0Hz, 0.5Hz)

1-Acetyl-2-but-3-enyl hydrazine (119)[99]

4-Bromobut-1-ene (17.29g, 0.13mol) was added to a solution of acethydrazine (31.6g, 0.43mmol) in dry DMF (800ml) and maintained at 30°C for 5d. The solvent was removed under reduced pressure and the residual oil added to water (120ml) and extracted with ether (4x100ml). The organic extracts were combined, dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure to afford (119) (9.71g, 58%) as a yellow oil which was used without further purification.

δH (90MHz; $CDCl_3$)	1.89	(3H, s)
	2.23	(2H, brt, J7Hz, small addition J)
	2.85	(2H, dt, J7Hz, J2.5Hz)
	4.02	(1H, brs, exch)
	4.86 - 5.08	(2H, m)
	5.46 - 5.97	(1H, m)
	7.47	(1H, brs, exch)

Attempted preparation of 7-acetyl-1,7-diazabicyclo[2.2.1]-heptane (120)[99,100]

Paraformaldehyde (1.03g, 34mmol) was added to a solution of (119) (2.02g, 16mmol) in dry xylene (160ml) and the

resulting mixture refluxed in a Dean-Stark apparatus for 9h. The solvent was removed under reduced pressure to afford a yellow oil. A rapid chromatographic separation on alumina using (1:9) methanol:ether afforded a mixed fraction and 1,4-diacyl-2,5-(but-3-enyl)-hexahydro-1,2,4,5-tetrazine (121) as a white crystalline solid (0.546g). The mixed fraction was flash chromatographed using ether eluant to afford (120) (0.328g, 15%) as a pale yellow oil (121) (85mg). The total yield of (121) was 0.631g (28%). A small sample of (121) was recrystallised from ether to give colourless plates, mp 94.5 - 95°C.

δ_H (90MHz; $CDCl_3$)

1.95	(6H, s)
2.04 - 2.45	(4H, s)
2.80 - 3.02	(4H, m)
4.35	(2H, d, J13Hz)
4.92 - 5.15	(4H, m)
5.08	(2H, d, J13Hz)
5.56 - 5.97	(2H, m)

m/z 280(m^+, 3%), 239(8), 156(5), 141(10), 140(16), 139(24), 111(37), 99(100), 84(11), 70(15), 84(11), 70(15), 57(13), 55(40), 43(36), 42(30).

Metastable peak, m^* 204.0 (280 → 239)

Found C, 59.91; H, 8.57; N, 19.89%. $C_{14}H_{24}N_4O_2$ requires C, 59.98; H, 8.63; N, 19.98%.

7-Acetyl-1,7-diazabicyclo[2.2.1]heptane (120)[99,100]

A solution of 1-acetyl-2-but-3-enyl hydrazine (2.40g, 19mmol) in xylene (730ml) was refluxed with p-formaldehyde (7.50g, 250mmol) in an apparatus fitted with a Dean-Stark trap for 9h. The solvent was then removed under reduced pressure leaving a yellow oil which was chromatographed on

silica using ether as eluant to afford (120) as a yellow oil (0.977g, 37%).

δ_H (400MHz; $CDCl_3$) see table 5.2

m/z 140(m^+, 24%), 112(5), 99(13), 83(3), 70(100), 69(35), 57(6), 43(33).

metastable peak : m^* 89.6 (140 → 112).

1,7-Diazabicyclo[2.2.1]heptane hydrochloride (122)[101,102]

The hydrazide (120) (0.977g, 7.0mmol) was dissolved in 2M hydrochloric acid (100ml) and heated under reflux for 6h. The reaction mixture was allowed to cool and the solvent was removed under reduced pressure to afford a yellow oil. This was dissolved in a minimum of dichloromethane and the hydrochloride salt precipitated by the dropwise addition of dry ether. The supernatant was removed and the precipitated salt was washed with a small amount of ether then dried under reduced pressure leaving (122) as a yellowish powder (0.842g, 89%).

The free hydrazine (123) could be isolated quantitatively by basification of the salt with 2M(aq) sodium hydroxide solution, extraction into dichloromethane, drying and removal of the solvent by distillation at atmospheric pressure (due to the volatility of the hydrazine).

(122) δ_H (90MHz; $CDCl_3$) 1.80 (2H, brs)
2.30 (2H, brs)
3.13 (2H, brs)
3.54 (2H, brs)
4.47 (1H, brs)
4.74 (2H, brs, exch)

(122) δH (90MHz; D_2O) 1.81 - 2.35 (4H, m)
3.30 (4H, brt, J8Hz)
4.46 (1H, t, J5Hz)

(123) δH (90MHz; $CFCl_3$) 1.17 (2H, m)
1.49 (2H, m)
2.16 - 2.80 (4H, m)
2.85 (1H, brs, exch)
3.67 (1H, t, J5Hz)

7-Chloro-1,7-diazabicyclo[2.2.1]heptane (124)[101,102]

A solution of (122) (0.491g, 3.65mmol) in water (0.5ml) was treated with 5% (aq) sodium hypochlorite (6ml) followed by dichloromethane (5ml) and stirred vigorously for 20 min. The dichloromethane layer was separated and the aqueous layer extracted with dichloromethane (3x15ml). The combined organic solutions were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure (ca. 18mmHg) to give a yellow oil (124) (0.480g, 99%).

δH (400MHz; $CDCl_3$) see table 5.3

δC (67.8MHz; $CDCl_3$) 28.9 (t, 3/5)
29.7 (t, 3/5)
52.8 (t, 2/6)
53.3 (t, 2/6)
69.7 (d, 4)

m/z 134/132(m^+, 7/21%), 106/104(4/12), 98(14), 97(64), 83 (36), 70(36), 69(64), 55(71), 43(36), 42(79), 41(100)

Attempted silver ion assisted methanolysis of (124)

A solution of (124) (66mg, 0.50mmol) in dry methanol (0.5ml) was treated with $AgBF_4$ (233mg, 1.2mmol) and allowed to stir in the dark for 48h. The reaction mixture was then made basic with 2M(aq) NaOH solution (15ml) and extracted

with dichloromethane (3x15ml). The organic extracts were dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure (ca. 18mmHg). This afforded a yellow oil (30mg) which was taken up in $CDCl_3$ (ca. 0.4ml) and when examined by ^1H NMR† was found to be unchanged (124) (0.19mmol, 39%).

Further attempted methanolysis of (124)

A solution of (124) (40mg, 0.32mmol) in dry methanol (5ml) was treated with $AgBF_4$ (196mg, 1.01mmol) and heated under reflux for 24h under N_2. The reaction mixture was basified with 2M(aq) NaOH solution (25ml) and extracted with aliquots of $CFCl_3$ (3x25ml). The combined extracts were passed through a short column of anhydrous $MgSO_4$. The resultant solution was concentrated to ca. 0.3ml by distillation of excess $CFCl_3$ at atmospheric pressure. The residual solution was examined by ^1H NMR and found to contain (123) (ca. 0.09mmol, 27%).†

Typical Procedure for small-scale flash vacuum pyrolysis* of 6,7-Benzo-5-methoxy-1-azabicyclo[3.2.0]heptane derivatives††

The azabicyclic compound (ca. 30mg) was introduced into the input tube of the pyrolysis apparatus. The apparatus was evacuated below 10^{-4} mbar (typically 10^{-5} to 10^{-6}mbar) then the cold trap was filled with liquid nitrogen. A Kugelrohr oven was placed around the input tube and its

†By integration against a benzene standard (±10%).

*Appendix I includes a diagram of the apparatus used.

††The 6,7-benzo-5-methoxy-1-azabicyclo[3.2.0]heptane derivatives were prepared either as described in this work or as in ref 68.

contents distilled into the pyrolysis tube (which had been pre-heated to ca. 510°C). The rearrangement product was collected by condensation onto the cold-finger at the exit of the pyrolysis tube.

When the input tube was empty, the cold finger was allowed to warm to room temperature. The apparatus was filled with N_2. The sample was washed from the cold-finger with a minimum of $CDCl_3$ and the solution was collected for subsequent ^1H NMR analysis. (See table 6.5).

Attempted Trapping of Azaxylylene Intermediates Produced During the Flash Vacuum Pyrolysis

The reciever-cup of the cold-finger, whilst cold and under vacuum, was coated with various combinations of di-eneophiles and solvents. This was accomplished by rotation of the cold-finger through 180°, so that the reciever-cup faced an inlet port on the opposite side of the apparatus to the pyrolysis tube, then by use of a tap small quantities of compounds were allowed through, distilled through or sublimed through onto the cold-finger where they were immediately frozen. The cold-finger was then rotated back through 180° and the pyrolysis carried out as previously described. After the pyrolysate had deposited on the cold-finger, the cold-finger was again rotated through 180° and coated with more trapping agents/solvents then allowed to warm to ambient temperature and the pyrolysis product collected and analysed by ^1H NMR as before. Table 6.12 shows the combinations of trapping agents employed.

Table 6.6

	Coating Before Pyrolysis*	Coating After Pyrolysis
(a)	DMAD	DMAD
(b)	PTAD	-
(c)	PTAD	PTAD
(d)	$CDCl_3$/PTAD	PTAD/$CDCl_3$
(e)	Me_2CO/PTAD/Me_2CO	PTAD

In all cases (a-d) the sole product observed was identical to that observed in the absence of trapping agent.

*These pyrolyses were performed at ca. 460°C. At temperatures <ca. 400°C mixtures of starting material and product were obtained.

Table 6.5

(134) δH (90MHz;$CDCl_3$)	(135) δH (90MHz;$CDCl_3$)
3.09 (2H, d, J7Hz)	2.20 (2H, m)
3.75 (3H, s)	2.60 (2H, t, J7Hz)
3.80 (3H, s)	3.74 (3H, s)
3.90 (3H, s)	3.77 (3H, s)
5.81 (1H, d, J10Hz)	3.89 (3H, s)
6.30 (1H, dt, J10Hz, J7Hz)	6.45 (1H, d, J9Hz)
6.65 (2H, s)	6.66 (1H, d, J9Hz)

(136) δH (90MHz;$CDCl_3$)	(137) δH (300MHz;$CDCl_3$)†
3.02 (2H, d, J7Hz)	2.88 (1H, d, J12Hz)
3.80 (3H, s)	3.82 (3H, s)
5.75 (1H, d, J9Hz)	3.83 (3H, s)

*As these reactions only formed part of a preliminary study, accurate yields were not assessed. However they were all in excess of 60%.

†This compound was produced by FVP at 610°

6.28 (1H, dt, J9Hz, J7Hz)
6.90-7.20 (4H, m)
4.11 (3H, s)
4.74 (1H, d, J12Hz)
6.65 (1H, d, J8Hz)
6.74 (1H, d, J8Hz)

(134) m/z 233(m^+, 100%), 218(75)

(136) m/z 173(m^+, 100%), 172(44), 158(26), 144(28), 143(51), 130(38), 129(90), 128(38).

(137) m/z 355(m^+, 100%), 340(78), 325(33).

2-Allyloxy-6,7-(8,11-dimethoxybenzo)-1-azabicyclo[3.2.0]-heptane (138)

This was prepared in 3% yield following the method used to prepare (75b) described in reference 68 but with allyl alcohol instead of methanol as solvent.

δH (300MHz; $CDCl_3$) 1.97 - 2.29 (4H, m)
3.79 (3H, s)
3.80 (3H, s)
4.11 (1H, ddt, J12.6Hz, J6.2Hz, J1.3Hz)
4.42 (1H, ddt, J12.6Hz, J5.1Hz, J1.4Hz)
4.81 (1H, brm)
5.20 (1H, ddt, J10.2Hz, J1.3Hz, J.17Hz)
5.29 (1H, brm)
5.33 (1H, ddt, J17.1Hz, J1.8Hz, J1.7Hz)
5.98 (1H, dddd, J17.1Hz, J5.1Hz, J6.2Hz, J10.2Hz)
6.41 (1H, d, J9.1Hz)
6.64 (1H, d, J9.1Hz)

(138) m/z 261(m^+, 36%), 205(50), 204(100), 203(50), 57(86), 41(71).

Typical Low Temperature Chlorination Experiments

A solution of amine (ca. 50mg) in $CDCl_3$ (ca. 0.35ml) in a NMR tube was cooled to -50°C. Finely powdered NCS (ca. 1.lequivs) was slowly added. A finely drawn glass rod was slowly introduced to the solution which was subsequently agitated to ensure homogeneity. The glass rod was removed and the NMR tube introduced, without warming, into the probe of an NMR spectrometer precooled to ca. -50°C. After 15min the kinetic ratio of invertomers was determined. The probe temperature was raised to ca. 25°C and after 20 min the thermodynamic invertomer ratio was obtained.

Additional Information

Compounds (56), (64), (73a), (73b) were prepared as described in reference 68. Compound (131) was prepared as described in reference 67.

Crystal Sturcture Data (74b)

$C_{12}H_{14}ClNO_2$, m = 239.70 Trigonal,
space group $P\bar{3}$, a = 16.094 (1), c = 7.80 (1) Å,
U = 1745.06 Å^3, z = 6. λ(Mo - K α) 0.7107 Å

The intensities of 1447 unique reflections with $2\theta < 45^\circ$ were measured using a Stoe STADI-2 Weissenberg diffractometer, of these 1172 reflections had $|F_o| > 2.5\sigma(|F_o|)$. The structure was solved by direct methods and refined to R = 0.0845, R_w = 0.0770. The hydrogen atoms of the methoxy group were included in calculated positions (d_{C-H} = 1.08 Å) the remaining hydrogen atoms were located and refined.

Crystal Structure Data (100)

$C_{14}H_{18}ClNO_2$, m = 267.76, Monoclinic,
space group $P2_1/a$, a = 17.010(2), b = 6.859(2),
c = 12.490(1) Å, β = 107.8(1)°, u = 1387.47 Å^3, z = 4.

The intensities of 1713 unique reflections with $2\theta < 45^\circ$ were measured using a Stoe STADI-2 Weissenberg diffractometer, of these 1241 reflections had $|F_o| > 3\sigma(|F_o|)$. The structure was solved by direct methods and refined to R = 0.037, R_w = 0.0385.
All hydrogen atoms were located and refined as normal atoms.

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Abstract

A Study of some Strained Azabicyclic Compounds and their Rearrangement Reactions by J.W.Davies

The barriers to nitrogen inversion were determined for several 1-methyl-2-azabicyclo[2.1.1]heptyl systems. The rearrangement chemistry of the N-chloro derivative was investigated. This underwent silver-ion catalysed solvolysis to afford 4-methoxymethyl-2-methyl-1-pyrroline and also rearranged in the presence of alumina with retention of chlorine to give 2-methyl-2-chloro-1-azabicyclo[2.1.1]-hexane, a novel ring system. The hydrochloride salt of this chlorine-retaining product rearranged with aqueous base to afford 4-hydroxymethyl-2-methyl-1-pyrroline.

A study of 1,2,3,4-tetrafluoro-9,10-dihydroanthracen-9,10-imines showed that electronic influences exhibit subtle effects on the mode of kinetically-controlled chlorination at the 11-position and on the preferred orientation of the chlorine substituent under conditions of thermodynamic control. The influence of aryl substituents on the rate of aryl participation during silver-ion catalysed solvolysis was also investigated.

The heterolytic rearrangement of 9-chloro-1,4-dimethyl-2,3-dihydronapthalen-1,4-imines required the use of novel solvolytic conditions. Unlike their 1,4-dihydro analogues, these preferred rearrangement to benzo(f)-5H-azepines which themselves underwent an extensive series of rearrangements.

Investigation of 7-chloro-1,7-diazabicyclo[2.2.1]heptane provided evidence that the effect of raising the barrier to nitrogen inversion by electronegative substituents arose predominantly from lone pair - lone pair repulsions. The ^{15}N NMR signals of a variety of systems containing the 7-azabicyclo[2.2.1]heptyl skeleton were observed downfield of the most shielded examples reported for several classes of amine. X-ray crystallographic studies of two 9-chloro-2,3-dihydronapthalen-1,4-imines, each possessing a different stereochemistry at nitrogen, showed that the position of the chlorine atoms exerts influence on the structure of the remainder of the 7-azabicyclo[2.2.1]heptyl skeleton.