Syntheses & Reactions of Azabicycles

by

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A Thesis submitted for the Degree of

Doctor of Philosophy

in the

Faculty of Science

of the

Department of Chemistry

at the

University of Leicester

1988

UMI Number: U012920

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ABSTRACT

Syntheses and Reactions of Azabicycles by A. Bathgate

Several novel nitrogen containing bicyclic systems have been synthesised and their chemistry investigated.

The kinetic and thermodynamic invertomer ratios of N-chloro-1,2,3,4-tetrahydro-2-keto-1,4-iminonaphthalene derivatives were determined. The results suggested that a repulsive interaction existed between the positive end of the carbonyl dipole and the incoming electrophilic chlorine. Despite reaction under favourable solvolytic conditions, it appeared that homolysis of the N-chloroamines was favoured over heterolysis.

Under conditions of negligible inversion, N-chloro-1,4-dihydro-1-methyl-1,4-iminonaphthalenes underwent heterolytic rearrangement to form 4-methylquinolines. From these experiments it was deduced that the quinoline products must be derived from the anti-N-chloroamines with loss of a bridgehead carbon atom. A mechanism for the formation of these products was proposed.

Nortropane was synthesised in high overall yield and the first synthesis of a simple derivative of nortrop-6-ene which has been achieved in significant yield was also accomplished. The procedure demonstrated the viability of an intramolecular cyclisation approach given an appropriately nucleophilic nitrogen.

Investigation of the reactions of chlorosulphonyl isocyanate with 7-substituted cycloheptatrienes provided evidence that choice of solvent and reaction time along with careful monitoring exerts control over the addition of either the C=O or C=N moiety across the termini of the triene unit.

STATEMENT

The experimental work described in this thesis has been carried out by the author in the Department of Chemistry of the University of Leicester, between October 1984 and September 1987, under the supervision of Dr. J.R. Malpass. The work has not been, and is not concurrently being presented for any other degree.

Date: ...*A. Bathgate*......   Signed: .12th April 1988........

ACKNOWLEDGEMENTS

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CONTENTS (continued)

ADDITIONAL EXPERIMENTAL DATA

Additional experimental and analytical data are appended inside
the back cover of the thesis.

ABBREVIATIONS

atm	atmosphere
bp	boiling point
$^\circ$C	centigrade
cm^{-1}	wavenumber
CSI	chlorosulphonyl isocyanate
dba	dibenzylideneacetone
h	hour
HMPA	hexamethylphosphoric triamide
Hz	hertz
i.r.	infra-red
$kJmol^{-1}$	kilojoule per mole
lit.	literature
MHz	megahertz
min.	minute
mp	melting point
mm Hg	millimetres of mercury
mmol	millimole
M	$mol\ dm^{-3}$
M^+	molecular ion
NCS	N-chlorosuccinimide
NMR	nuclear magnetic resonance
ppm	parts per million
THF	tetrahydrofuran
t.l.c.	thin layer chromatography

Chapter 1

Introduction

1. I.   PYRAMIDAL INVERSION AT NITROGEN

In the ground state, amines exist in an approximately pyramidal sp^3 hybridised state (1) and they may undergo spontaneous inversion via an sp^2 coplanar transition state (2) to form the invertomer (3).[1,2,3,4]   The energy required to effect rehybridisation is called the inversion barrier, (figure 1.1).

$\triangle G^{\ddagger}$ = free energy of activation for inversion
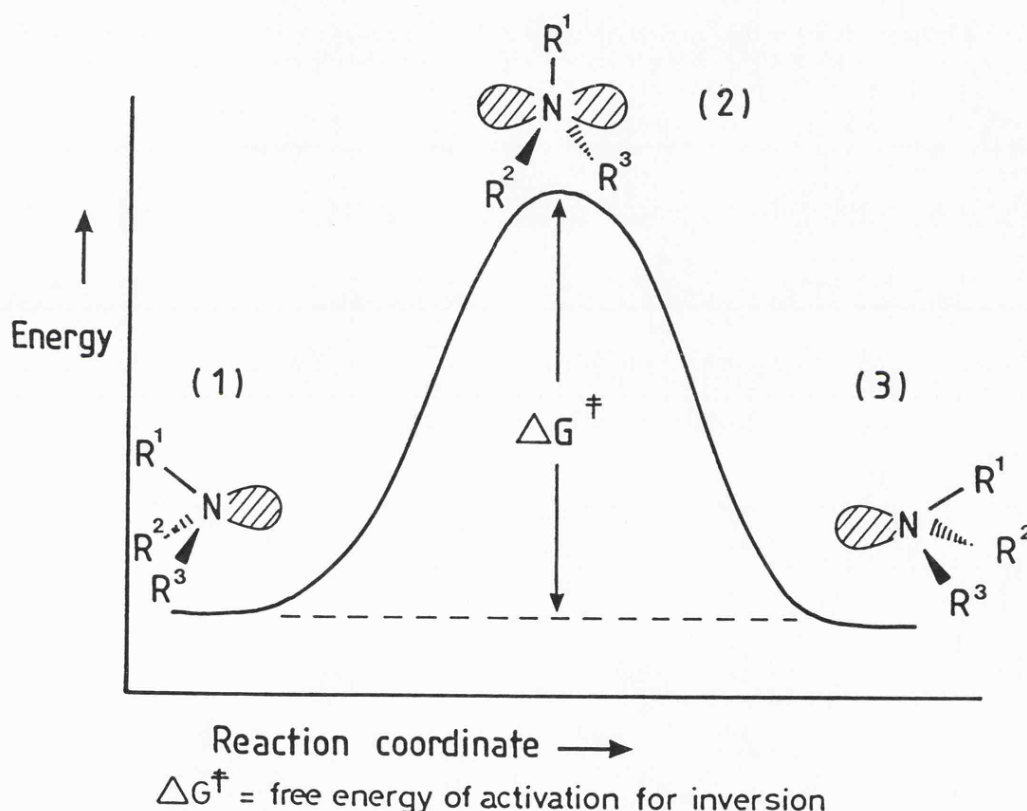
Figure 1·1

Several alternatives to the pyramidal mechanism for nitrogen inversion have been proposed;[2] of these only quantum-mechanical tunnelling is thought to be of any importance. This mode of inter-conversion is operative in ammonia and amines with very light substituent atoms such as hydrogen, or where the inversion barrier is very low.

A chiral centre is created if the three ligands attached to nitrogen are different, the lone pair of electrons being considered as a fourth group. The two invertomers do not necessarily have an enantiomeric relationship, however; the equilibrating forms (1) and (3) may also be diastereoisomers. In carbon chemistry, diastereoisomers frequently possess different physical and chemical properties which allow their separation.[5] Due to the dynamic process occurring at nitrogen, separation of diastereoisomeric invertomers is impossible in the majority of cases. Nevertheless, there are several classes of three coordinate nitrogen compounds that possess high inversion barriers, some sufficiently high to attain configurational stability at nitrogen at normal temperatures, thus allowing their physical separation.

Amines with such high inversion barriers are of particular interest. It is important to determine which structural features raise the inversion barrier in order to increase our understanding of nitrogen inversion generally. With most amines, rapid inversion at nitrogen precludes meaningful discussion of stereochemistry and their reactions. However, compounds with sufficiently high inversion barriers may allow the study of the stereochemical consequences of reactions at nitrogen.

Several factors influence either the energy of the ground state or the transition state, and hence the magnitude of the barrier to inversion at nitrogen. These structural effects fall broadly into electronic and steric categories.
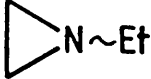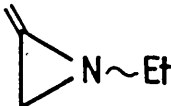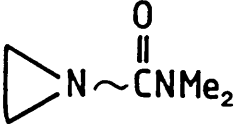
Electronic Effects

a)   Conjugative Interactions

Conjugation of the nitrogen lone pair of electrons with an adjacent π-system is greater in the planar transition state, where the lone pair is in a p-orbital, than in the pyramidal ground state where it

possesses a higher degree of s-character. Overlap and subsequent delocalisation lower the barrier to nitrogen inversion by stabilisation of the transition state. The presence of such conjugative interactions also leads to a geometric change: the nitrogen site becomes less pyramidal. However, in the case of aziridines, the angle strain of the cyclic system opposes the tendency of conjugative groups to render the nitrogen site less pyramidal. This class of compound illustrates the effect of (p-p) π-overlap in the transition state, (table 1.1).

Table 1.1. Inversion Barrier $(\Delta G^{\ddagger}/\text{kJmol}^{-1})$[1]

b)   Heteroatom Effect
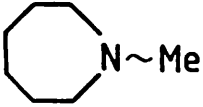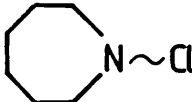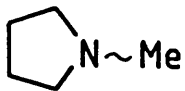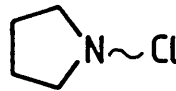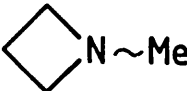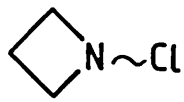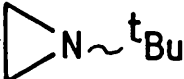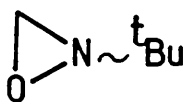
If the inverting centre bears a sufficiently electronegative substituent, the displacement of electron density away from nitrogen increases the pull of the nitrogen nucleus on the lone pair. Electronegative substituents on nitrogen are thus expected to increase the s-character of the lone pair. As the lone pair is in a p-orbital in the transition state, such substituents therefore increase the barrier to inversion.

c)   Electron Repulsion Effects

If the substituent on nitrogen possesses a lone pair of electrons, the inversion barrier may increase. As the lone pair on nitrogen passes from approximate sp^3 hybridisation in the ground state to p in the transition state, repulsion with lone pairs on adjacent atoms will increase.

The effects of substituent electronegativity and electron repulsion interactions are very difficult to distinguish as electronegative substituents are also likely to bear lone pairs which lead to repulsive interactions. The combined effect of these variables on the inversion barrier is illustrated in table 1.2 by comparing alkyl-substituted azacycles with those containing a heteroatom substituent.

Table 1.2.   Inversion Barrier ($\Delta G^{\ddagger}$/kJmol^{-1})[1]

N~Me	28·5		N~Cl	38·5
N~Me	35·2		N~Cl	43·1
N~Me	42·7		N~Cl	56·1
N~^{t}Bu	71·1		N~^{t}Bu	138·1

Steric Effects

a)   Ring Strain

At the transition state for inversion, the R-N-R bond angle must attain 120°. The amount of energy required to dilate the ground state R-N-R angle as it approaches the transition state for inversion increases as this angle is reduced from 109° to smaller R-N-R bond angles as in azetidines (ca. 96°) and aziridines (ca. 60°). The very high nitrogen inversion barriers of aziridine derivatives were predicted[6] almost thirty years before the first configurationally stable invertomers were isolated.[7]

Table 1.3 illustrates the increase in inversion barrier as the ring size (and hence the R-N-R angle) contracts. The exocyclic lone pair of electrons in aziridines has more s-character than that of a normal sp^3 lone pair and thus requires more energy to assume pure p-character in the transition state.

Table 1.3.   Inversion Barrier $(\Delta G^{\ddagger}/kJmol^{-1})$[1,2]

⬡N~Me	28·4
⬠N~Me	33·9
◇N~Me	42·6
△N~Me	81·1
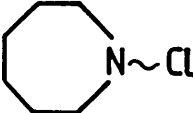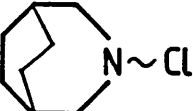
b)   Non-bonded Interactions

As the steric requirement of a substituent attached to nitrogen increases, appreciable non-bonded repulsions occur which are stronger in the pyramidal ground state than in the planar transition state.[1,2] Replacement of a small alkyl group, such as methyl on nitrogen by a large group, such as t-butyl, will lead to a lower inversion barrier since on going to the transition state, the R-N-R bond angle increases from ca. 109° to 120°. Thus, any strain present in the ground state can be relieved to some extent at the transition state.

c)   The Bicyclic Effect
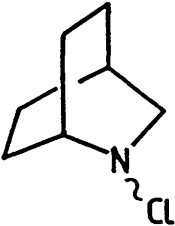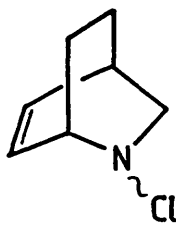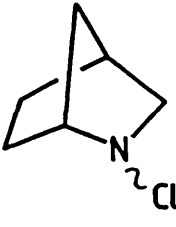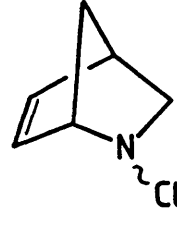
An increase in the inversion barrier is incurred if an azamono-cycle is bridged by one or more carbon atoms. The bicyclic effect may be partially due to the increased molecular rigidity imparted by the bridging carbon atoms consequently raising the angle strain at nitrogen, (table 1.4).

Table 1.4.   Inversion Barrier $(\Delta G^{\ddagger}/kJmol^{-1})$[2]

⬡N~Cl	38·5
⬡N~Cl	42·3
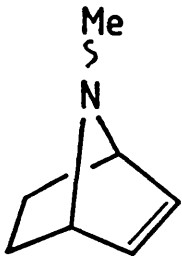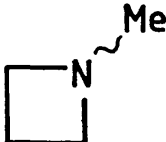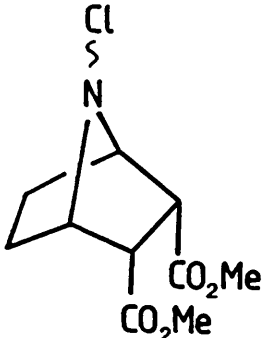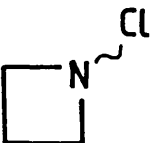
The inversion barriers of the 2-azabicycles in table 1.5 can be rationalised in terms of the degree of flexibility of the carbon bridges and hence of each molecule as a whole.[8] Replacement of the $-CH_2-CH_2-$ bridge in (4) by the shorter $-CH=CH-$ bridge in (5) raises the inversion barrier as does replacement by a $-CH_2-$ bridge (6). A combination of both as in (7) leads to a free energy of activation greater than in azetidines.

Table 1.5. Inversion Barrier ($\Delta G^{\ddagger}$/kJmol^{-1})[8]

(4) 44·3   (5) 48·5

(6) 51·0   (7) 64·0

The most remarkable effect is found in 7-azabicyclo[2.2.1]-heptane derivatives where barriers are comparable with those of aziridines. The C-N-C bond angle in these azabicycles is ca. 96°,[9] similar to that in azetidines but the inversion barriers are considerably higher, (table 1.6).

Table 1.6. Inversion Barrier $(\Delta G^{\ddagger}/\text{kJmol}^{-1})$

This extraordinary effect on the nitrogen inversion barrier remains unexplained. Tentative suggestions have been made[1,11] which will be explored later in the present work.

I. II. THE DETERMINATION OF INVERSION BARRIERS AND INVERTOMER RATIOS

a) Inversion Barriers

Any meaningful discussion of pyramidal inversion at nitrogen requires a knowledge of the amount of energy that must be put into a molecule to cause it to undergo an inversion. Various methods have been employed to determine barriers to pyramidal inversion. The choice of technique depends largely on the structure of the molecule and the magnitude of the barrier.

Barriers in the range $0-20kJmol^{-1}$ are usually measured by microwave spectroscopy and, to a lesser extent, infra-red spectroscopy. These techniques have enabled the barriers of low molecular weight amines such as ammonia and methylamine to be determined.

Amines with very high barriers ($>96kJmol^{-1}$) have very low rates of inversion and the isolation of invertomers becomes feasible. The free energy of activation may be determined by using classical kinetic techniques. A measurement of the rate of conversion of one invertomer into another under necessarily non-equilibrium conditions is determined using an appropriate spectroscopic means:- nuclear magnetic resonance, ultraviolet or infra-red absorbance or decay, or polarimetry if the invertomer is chiral.

The bulk of the barrier data to date has been determined using NMR spectroscopy. This wide application results not only from instrumental and analytical simplicity, but also because the barriers that are susceptible to NMR are in the common range $20-100kJmol^{-1}$. Measurements are made with the sample at thermodynamic equilibrium. The inversion process must bring about exchange between two magnetically non-equivalent sites at a rate which is slow on the NMR timescale.[4] The NMR signals due to these sites must be sufficiently separated for temperature-coalescence to be observed.

Two distinct signals may be observed when nitrogen inversion is slow on the NMR timescale. As the temperature is raised and the rate of inversion increases, the two peaks broaden and eventually merge. Peak coalescence is observed when the rate of inversion is comparable to the frequency difference at slow exchange. A further increase in temperature results in the inversion becoming 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 average of the slow exchange frequencies, (figure 1.2).
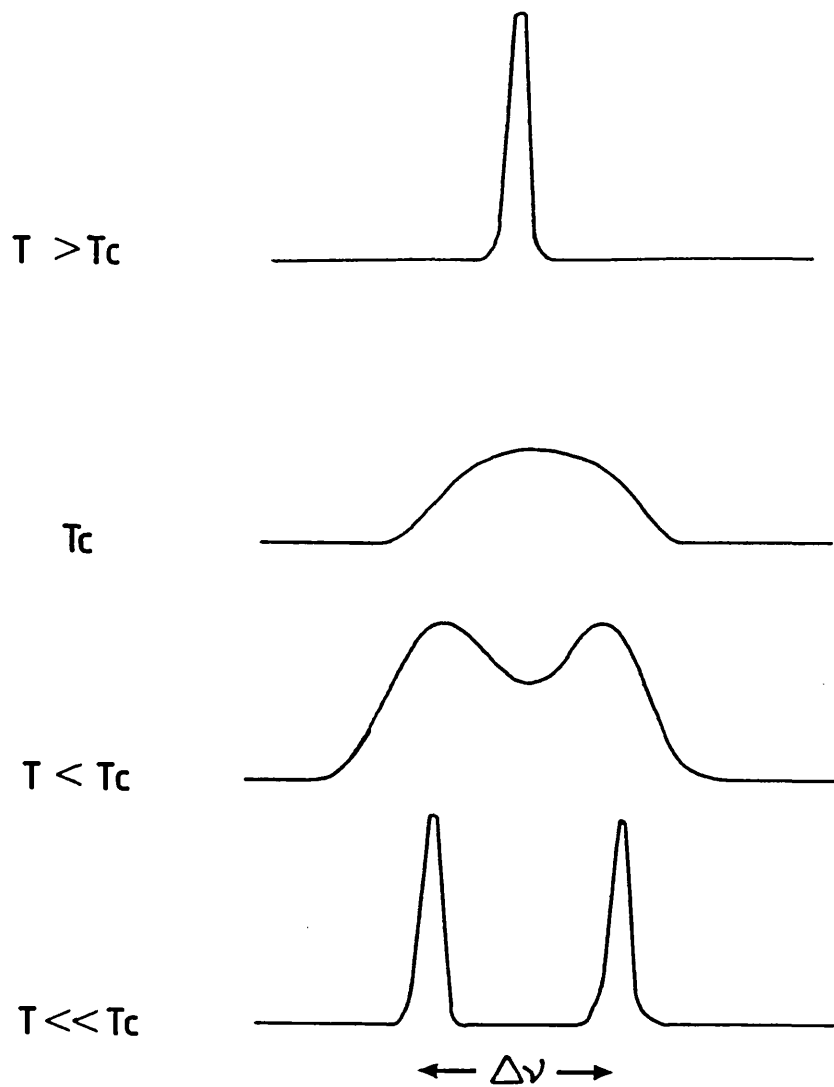
Figure 1·2

The temperature at which the two signals just become incoherent is known as the coalescence temperature, T_c. The rate constant for inversion at this temperature, k_c, may be determined from the expression (1:1).

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

where $\Delta \nu$ is the frequency separation at slow exchange.

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

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

where k_B = Boltzmann's constant

h = Planck's constant

R = gas constant

T = absolute temperature

This equation may be re-expressed, (1:3).

$$\Delta G^{\ddagger} = 19.12 \ T_C \left(10.32 + \log_{10} \frac{T_C}{k_C} \right) \qquad (1:3)$$

This method is only strictly applicable to systems with an equal population of invertomers at equilibrium.[12] However, with modifications, its use can be extended to include evaluation of $\Delta G^{\ddagger}$ for unequally populated sites.[13]

The coalescence method does not provide a measure of the free enthalpy ($\Delta H^{\ddagger}$) or entropy ($\Delta S^{\ddagger}$) for inversion. It only allows the determination of $\Delta G^{\ddagger}$ but it does so to a high degree of accuracy.[4] Recently, it has become possible to obtain accurate values for all the activation parameters associated with inversion using computer-based lineshape analysis of spectra.

As well as nitrogen inversion, other temperature-dependent phenomena may occur, and it may become difficult to decide which process is being observed. One of the more frequently encountered processes is hindered rotation about bonds which can occur in amides,[4,14] hydroxyl-amines,[15] sulphenamides,[16] hydrazines[17] and even some simple amines.[18]

Another conformational process to be considered is ring inversion. Nitrogen-substituted piperidines, for example, have similar energies of activation for six-membered ring inversion and nitrogen inversion.

When such ambiguities exist, it may be possible to distinguish nitrogen inversion by application of one of the structural effects mentioned earlier. For example, if the barrier decreases by conjugating the nitrogen with a carbonyl group, or by increasing the bulk of the substituents on nitrogen, then the process observed is nitrogen inversion. However, in the study of N-t-butyl-N-haloamines, Bushweller et al. reported the existence of coupled nitrogen inversion and t-butyl rotation and proposed a dynamic model for the rotation-inversion dichotomy in all alkylamines.[19]

Problems may occur if the signals of the exchanging site coincide. This may be overcome by the use of paramagnetic shift reagents although this approach neglects any effect of the shift reagent on the invertomer ratio. The use of a different solvent may also remove the coincidence of shifts. However, change of solvent has an important influence on the magnitude of the inversion barrier;[20] thus identical solvents must be used in order to make direct comparisons of barriers.

However, more recently, with the development of sensitive FT NMR spectrometers, other nuclei have been increasingly used to study nitrogen inversion. [13]C, ^{15}N and, where applicable, ^{19}F NMR have become increasingly important. ^{13}C NMR[21-26] is particularly useful as the resulting spectra are often far less complex than ^{1}H NMR due to the wider range of chemical shifts and the lack of coupling. They also show larger values of $\Delta\nu$ which increases the accuracy of the coalescence method. However, one drawback is that the slow relaxation of the ^{13}C nuclei decreases the accuracy of integration of absorptions. The use of
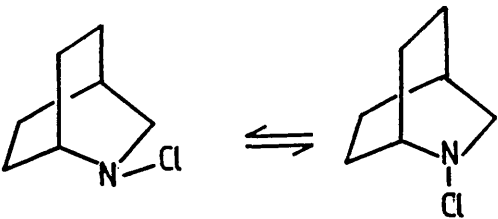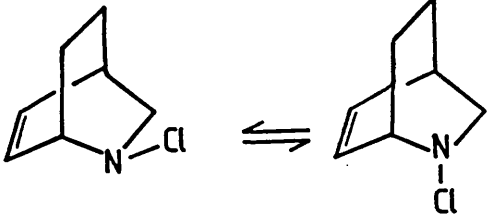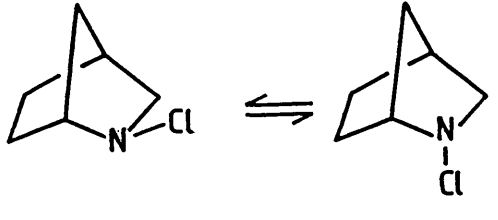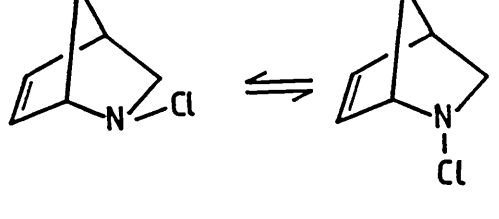
^{15}N NMR[27] has been minimal until recently due to its low natural abundance and low sensitivity. The study of this nucleus at natural abundance has become possible due to the advent of more sensitive, high-field NMR spectrometers. Improved results are obtained after modest ^{15}N enrichment.[28]

b)   Invertomer Ratios

The relative invertomer populations can be obtained simply by direct integration of the signals due to the group exchanged by slow inversion below the coalescence temperature. The degree of accuracy of such measurements depends largely on the separation of the signals due to an atom at one exchanging site. Problems due to signal overlap are usually confined to ^{1}H NMR and are frequently alleviated by measurements at high field. Signal overlap is less likely in ^{13}C NMR, and invertomer ratios are often directly measurable. Unfortunately, integrations are not always reliable due to variations in the relaxation rates of ^{13}C nuclei.

Asymmetric amines tend to have unequal invertomer populations due to steric and/or electronic influences. In the series of azabicycles shown in table 1.7,[8] steric influences appear to be the predominant factor for determining the invertomer preferences. The azabicycle (4), being symmetrical, has an equal population of invertomers. However, there is a clear preference for exo-Cl over endo-Cl in (6) which must be steric in origin. The N-chloroamines (5) and (7) show a preference for an exo-orientation of the nitrogen lone pair and the vinyl bridge which is thought to be due to the diminished steric congestion between the chlorine and the exo-hydrogens.

Table 1.7

		% exo-chlorine at equilibrium		% endo-chlorine at equilibrium
(4)		50	:	50
(5)		9	:	91
(6)		75	:	25
(7)		12	:	88

The question of interaction between the π-system and the nitrogen lone pair has been examined by Morishima. He attempted to construct a model upon which it is possible to predict the preferred orientation of the lone pair based on ^{1}H and ^{13}C NMR,[29,30] photo-electron[31] and ultraviolet[32] spectra of a range of mono- and bicyclic amines. Two limiting forms were defined, (figure 1.3).
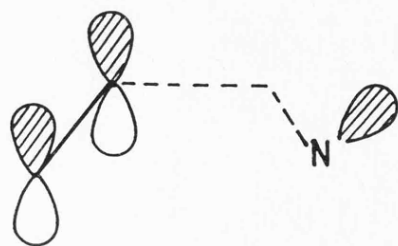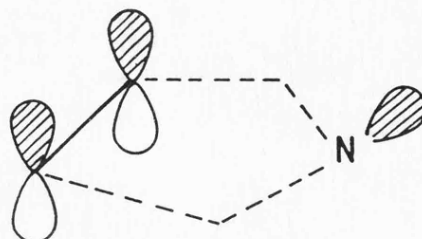
Homoallylic Interaction   Bishomoallylic Interaction

Figure 1·3

In the first case, the nitrogen lone pair overlaps formally with one of the p-orbitals of a π-bond in a monohomoconjugative fashion. This is described as a homoallylic interaction since orthodox allylic conjugation is not possible due to an intervening sp³ hybridised carbon atom. Nevertheless, the geometry of the molecule sustains overlap of the lone pair and p-orbitals. Such an interaction should exert a stabilising influence and therefore determine the lone-pair preference.

The second limiting form is the symmetrical bishomoallylic interaction. In this case, two sp³ hybridised carbon atoms interrupt the normal interaction. This type of overlap is considered to be a repulsive one and Morishima predicted that, when possible, the lone pair will prefer that orientation which avoids such an interaction. When the lone pair is faced with interaction with two double bonds as in 1,4-dihydro-1,4-imine derivatives, Morishima predicted that it would prefer to interact with the less electron-rich double bond.

However, it has been noted by Grutzner[33] and Underwood[34] that Morishima's results (as well as their own) imply that homoconjugative reactions of this kind cannot be of great energetic consequence. Morishima stated that no invertomeric preferences are observed for (8)

or (9), (figure 1.4), two compounds that typify homo- and bishomoallylic interactions respectively. The predicted preferences based on homo-conjugative effects are indicated by the dashed continuation of the arrows.

exo-(8)   endo-(8)

syn -(9)   anti -(9)
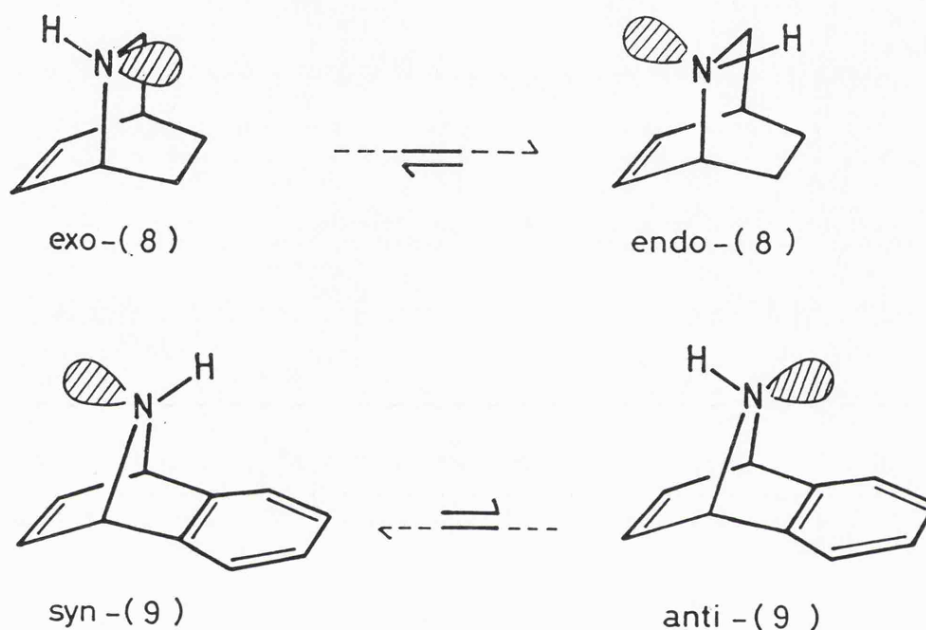
Figure 1·4

It has also been shown that interactions between the nitrogen lone pair and adjacent π-bonds can only be of minor importance compared to steric factors. With substituents larger than hydrogen on nitrogen, the congestion of neighbouring parts of the molecule and the inverting group will dominate the invertomer preferences. This is illustrated by (10), where the major invertomer is exo,[30,35] (figure 1.5). The observed preference is thought to be due to diminished steric repulsion between the methyl group and the exo-hydrogens, H_x, of the ethano-bridge.

endo-(10)   exo - (10)
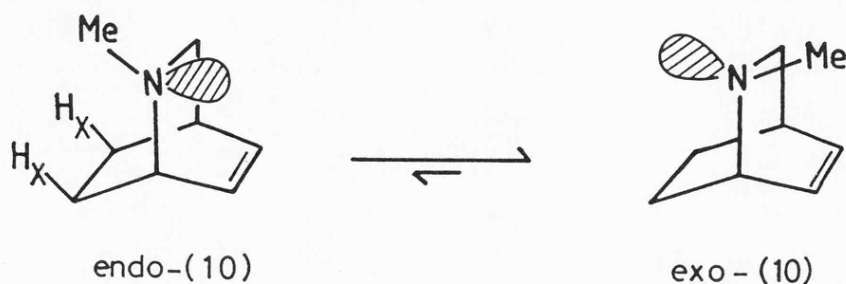
Figure 1·5

Homoconjugative interactions have therefore been shown to be of only minor energetic signifance. Similarly, it has been elucidated that contributions from this type of interaction to barrier elevation in 7-azabicyclo[2.2.1]heptyl systems is small. Hence, these interactions, by themselves, cannot account for the anomalously high barriers found in such systems. Interactions of this type would not provide any satisfactory explanation for the high barriers observed in (11) and similar systems which have no π-bonds at all, (figure 1.6).

(11)

Barrier to inversion[1]
$$\Delta G^{\ddagger} = 87\cdot1 \ kJ\,mol^{-1}$$
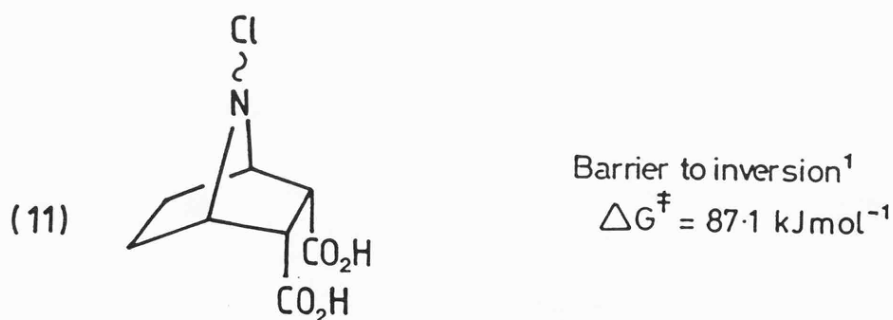
Figure 1·6

These concepts of nitrogen inversion barriers and invertomer ratios are important requisites for discussion of the results in subsequent chapters.

1.III. SOLVOLYTIC REACTIONS OF N-CHLOROAMINES

The rearrangement reactions of N-chloroamines are of interest for both theoretical and synthetic reasons. In the past, theoretical discussions have focused on the intermediacy of nitrenium ions in the solvolytic rearrangements of N-chloroamines.

Trivalent electron-deficient carbon species i.e. carbenium ions are widely accepted in modern organic chemistry. Gassman[36] felt that a nitrogen analogue i.e. a nitrenium ion should exist, having six electrons in its valence shell and bearing a positive charge on nitrogen. He speculated that the species should resemble a carbenium ion in its chemical behaviour, but that it should be much more reactive.

One of the compounds extensively studied by Gassman was N-chloroisoquinuclidine (4).[37,38] A solvolysis reaction carried out in a refluxing methanolic solution of silver nitrate afforded 2-methoxy-1-azabicyclo[3.2.1]octane (12) in 60% yield. Gassman proposed that the formation of (12) from (4) could occur by either of two routes, (figure 1.7).
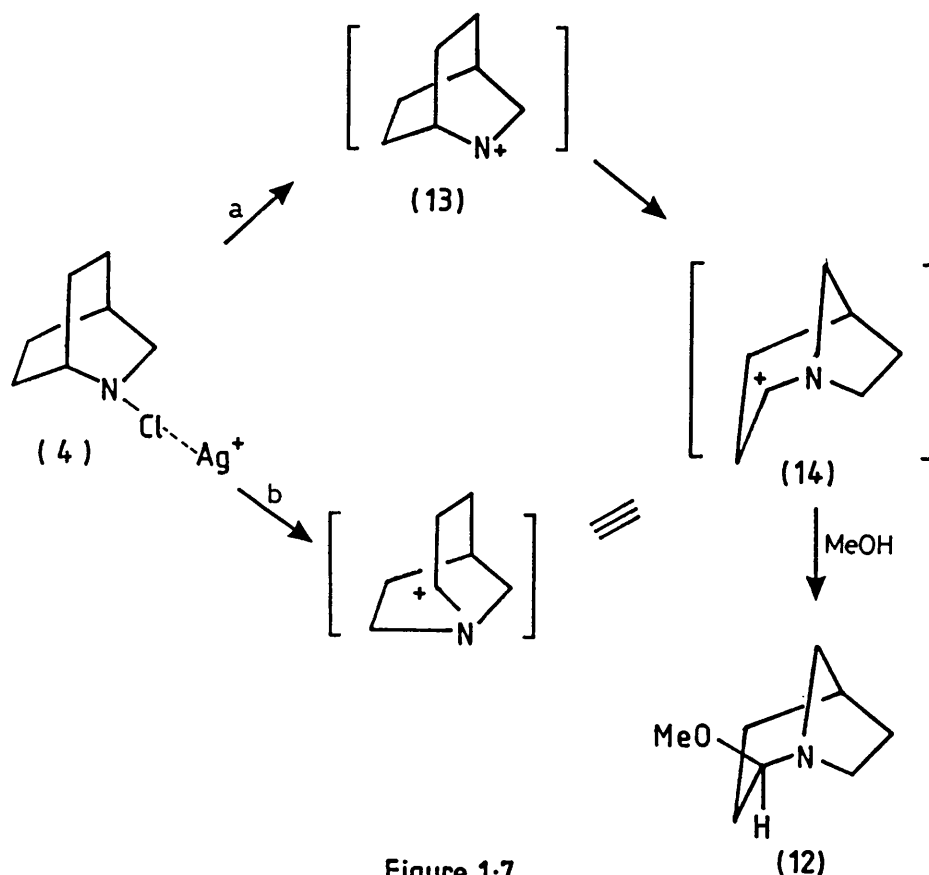
Figure 1·7

Path a involves the removal of chloride ion by cationic silver to yield (13) as a discrete nitrenium ion intermediate. Alkyl migration to produce the carbenium ion (14) followed by nucleophilic addition of solvent would give (12). The alternative route (path b) would involve a concerted loss of chloride and migration of the alkyl group with its pair of bonding electrons to give (12) directly. On the basis of this reaction, Gassman could not establish whether or not a discrete nitrenium ion intermediate was formed. However, he considered that regardless of which path was followed, the alkyl group must have migrated with its electron pair and so an electron-deficient nitrogen species must have been involved. This observation provided the foundation for his theory of the existence of divalent electron-deficient nitrogen.

Further product studies and kinetic data left Gassman in little doubt that the cleavage of the N-Cl bond under solvolytic conditions was a heterolytic process which produced a chloride anion and a nitrenium ion.

However, it is now believed that nitrenium ions do not exist as discrete species but such heterolysis reactions involve only a partial positively charged nitrogen species. The idea of σ-participation is preferable to a discrete nitrenium species, (figure 1.8).

(4)

Figure 1·8

(12)
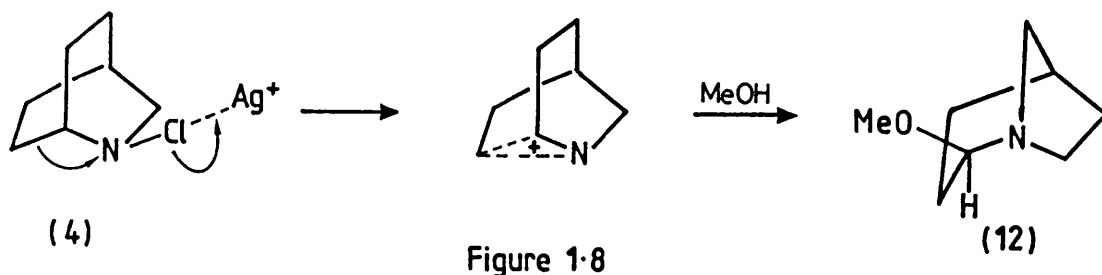
Intramolecular participation of π-electrons has been shown to control silver ion-assisted heterolysis of unsaturated N-chloroamines.[39] The cyclic N-chloroamine (5) exists predominantly as the endo-invertomer, but at ambient temperatures, this is in rapid equilibrium with the exo-invertomer, (figure 1.9). Competition between the two possible reaction pathways can thus be readily assessed by product studies.
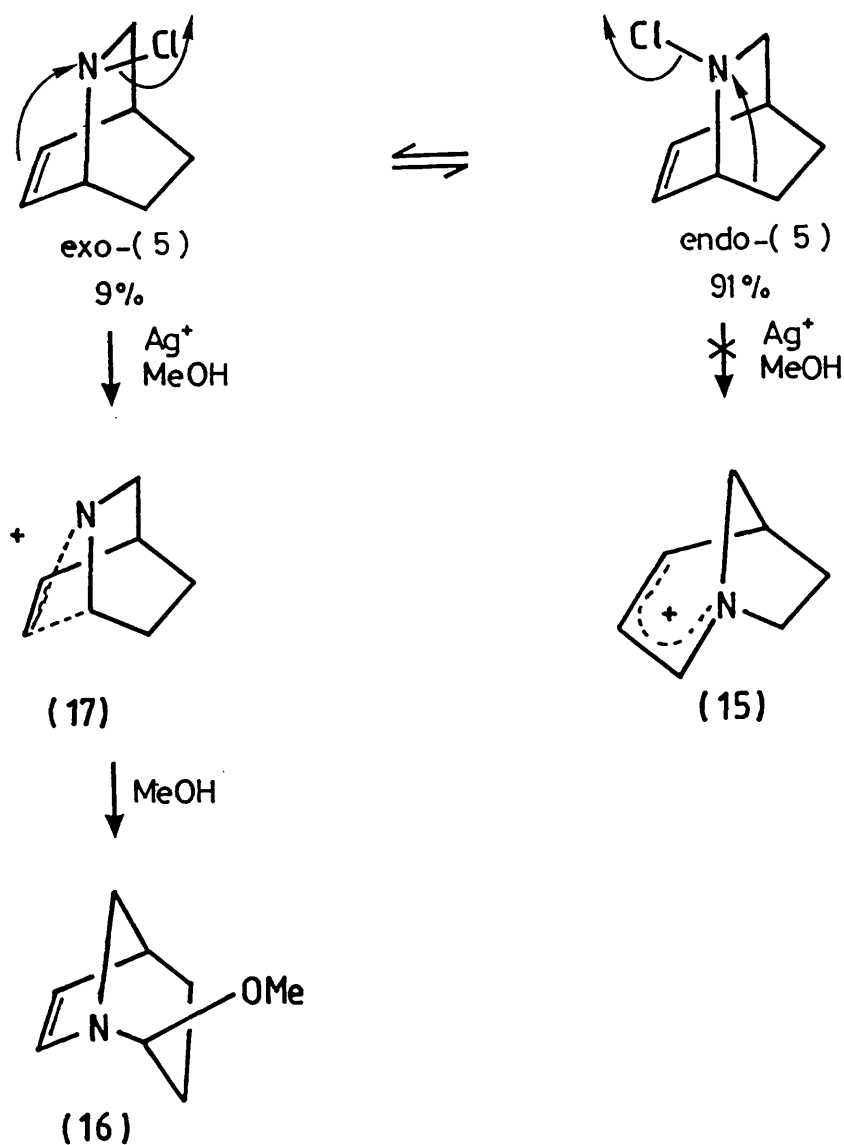
Figure 1·9

Participation of the σ-bond would parallel the observed behaviour of (4). It would be expected to lead even more readily to the formation of methyl ethers via the allylic carbenium ion (15). However, π-participation would lead to (16) via the intermediate represented as (17). In fact, treatment of the N-chloroamine (5) with AgClO$_4$ in methanol afforded (16) as the sole product in 94% yield. The chloride ion has therefore been removed specifically from the minor exo-invertomer. This degree of discrimination argues against heterolysis of the N-Cl bond to give a discrete nitrenium ion and in favour of participation of the π-electrons and hence delocalisation of the developing positive charge.

Solvolyses of various azabicycles will be examined during the course of the present work and the mechanisms of the formation of the products will be discussed. In addition, observations concerning the relationship between the structure of each of the N-chloroamines and its relative reactivity will be examined.

Chapter 2

Synthesis and Spectroscopic Investigations of

N-Chloro-1,2,3,4-tetrahydro-2-keto-1,4-

iminonaphthalenes

2. I. INTRODUCTION

a)   Inversion Barriers of 7-Azabicyclo[2.2.1]heptyl Derivatives

Derivatives of 7-azabicyclo[2.2.1]heptane are known to possess anomalously high nitrogen inversion barriers. The C-N-C bond angle in these azabicycles is comparable to that in azetidines ($\underline{ca.}$ 96°)[9], yet the inversion barriers are at least 20kJmol^{-1} higher, (table 1.6). Consequently, factors other than ring strain must be exerting a considerable influence on the inversion barriers.
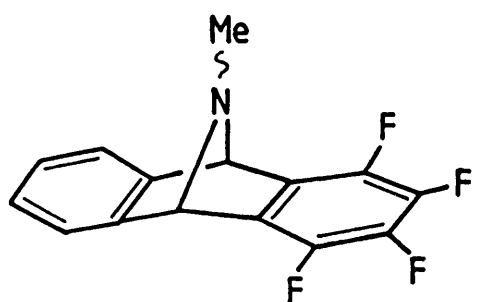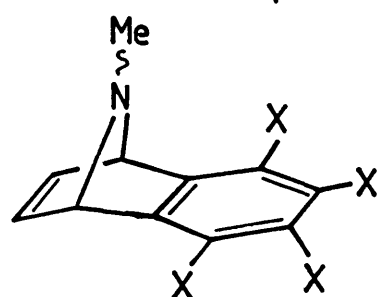
The sole reported measurement of an inversion barrier for a simple derivative is that of 7-methyl-7-azabicyclo[2.2.1]hept-2-ene (18) but many other more elaborate derivatives have been prepared and studied. Table 2.1 shows a few such examples.

Table 2.1.   Inversion Barrier ($\Delta G^{\ddagger}$/kJmol^{-1})

(18)
$62 \cdot 3^{10}$

$62 \cdot 3^{40}$

$81 \cdot 5^{1}$

$98 \cdot 2^{1}$
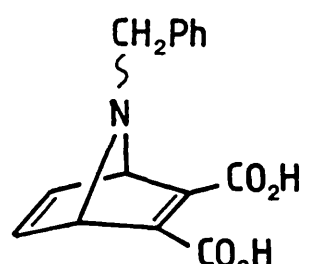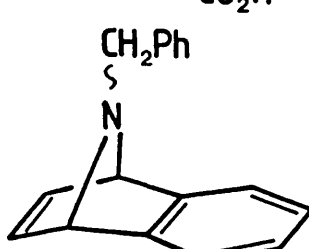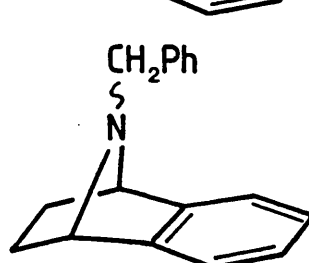
Relatively few systematic studies have been carried out on structurally comparable systems. Gribble[41] determined the inversion barriers of several N-methyl derivatives, (table 2.2).

Table 2.2. Inversion Barrier ($\Delta G^{\dagger}$/kJmol^{-1})[41]

54·3

X = Cl ; 58·5

X = F ; 58·5

Sutherland[14] carried out a similar study on N-benzyl derivatives, (table 2.3).

Table 2.3. Inversion Barrier ($\Delta G^{\dagger}$/kJmol^{-1})[14]

59·8

61·9

52·7

A more recent study of 9-methyl-1,4-dihydronaphthalene-1,4-imine derivatives, differing only in the benzo-ring substitution showed that the inversion barrier decreased as the aromatic ring became more electron-deficient,[42] (table 2.4).

Table 2.4. Inversion Barrier ($\Delta G^{\ddagger}$/kJmol^{-1})[42]

Compound	$\Delta G^{\ddagger}$(anti→syn)	$\Delta G^{\ddagger}$(syn→anti)
X = Y = Me	65·7	67·9
X = OMe, Y = H	64·3	67·8
X = Y = H	63·6	65·9
X = Y = Cl	58·6	62·1
X = Y = F	58·1	62·7
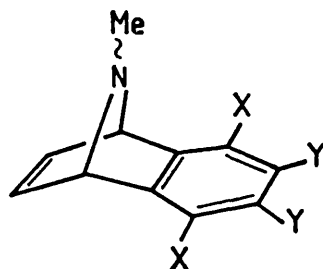
An explanation to this trend was proposed by Lehn[1] and is based on the interaction of the nitrogen lone pair with the π-electrons. He suggested that repulsion between the nitrogen lone pair and the flanking π-electrons at the transition state may play an important role in raising the energy of the transition state. Electronegative substituents would decrease the electron density of the benzo-ring, thus decreasing the repulsive interaction and consequently the barrier height. However, Lehn's idea cannot account for the high barrier observed for (19) where each two carbon bridge is a σ-bond, (figure 2.1).

Cl
ζ
N

(19)

$\Delta G^{\ddagger} = 87 \cdot 8 \text{ kJmol}^{-1}$

CO$_2$Me
CO$_2$Me
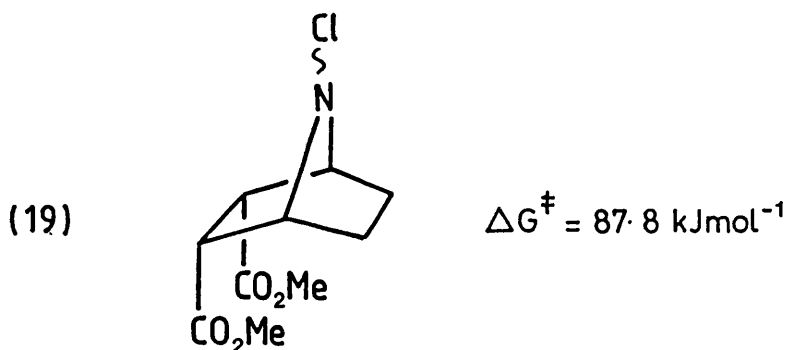
Figure 2·1

Obviously, there must be other significant factors operating in such systems for the inversion barrier to be so high. However, the exact nature of such factors remains obscure.

b)   The Stereospecificity of Electrophilic Chlorination of

1,4-Dihydro-1,4-iminonaphthalene Derivatives

In 1969, Rautenstrauch[43] noted that the preparation of N-chloro-1,4-dihydro-1,4-iminonaphthalene (20) by the action of NCS on the parent amine (9) in solution at low temperatures produced a ratio of invertomers which was different to the ratio observed once the solution had been allowed to warm to ambient temperature.

Repetition of this experiment at -50°C showed that once the N-chloroamines have been formed, inversion is effectively frozen.[44] (Rautenstrauch's experiment was conducted at 5°C and partial equilibration had occurred). The ratio of invertomers recorded at -50°C 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 to ambient temperature, nitrogen inversion is rapid and thermodynamic equilibrium is established. 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, (figure 2.2).
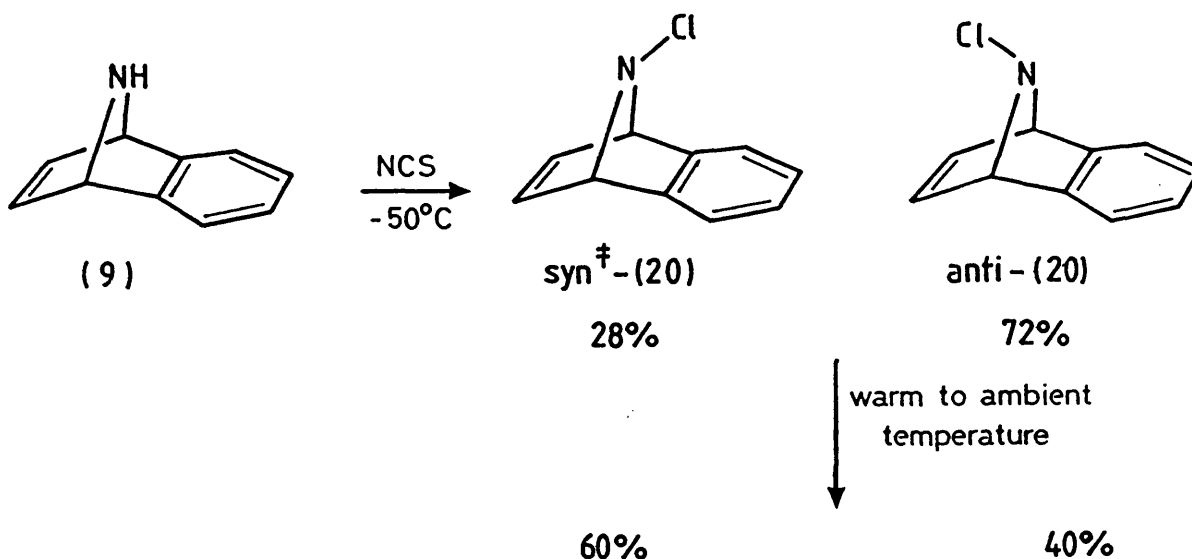
Figure 2·2

†syn- refers to the invertomer with the chlorine on the same side as the aromatic ring.

c)   Solvolytic Reactions of N-Chloroamines

Rautenstrauch[43] noted that N-chloro-1,4-dihydro-1,4-imino-naphthalene (20) existed as two invertomers and was the first to report solvolytic reactivity in such systems. Under given conditions, each invertomer underwent a heterolysis reaction at nitrogen via a different route, to give a different product. Although tentative structures were assigned to these products, they were subsequently proved to be incorrect and were reassigned in a later study.[45]

A series of N-chloro-1,4-dihydro-1,4-iminonaphthalenes was prepared varying only in the electronic character of the benzo-ring. The high inversion barriers of such compounds (ca. 95kJmol⁻¹) allowed heterolytic rearrangements to be studied under conditions of slow or rapid inversion,[45] (figure 2.3).
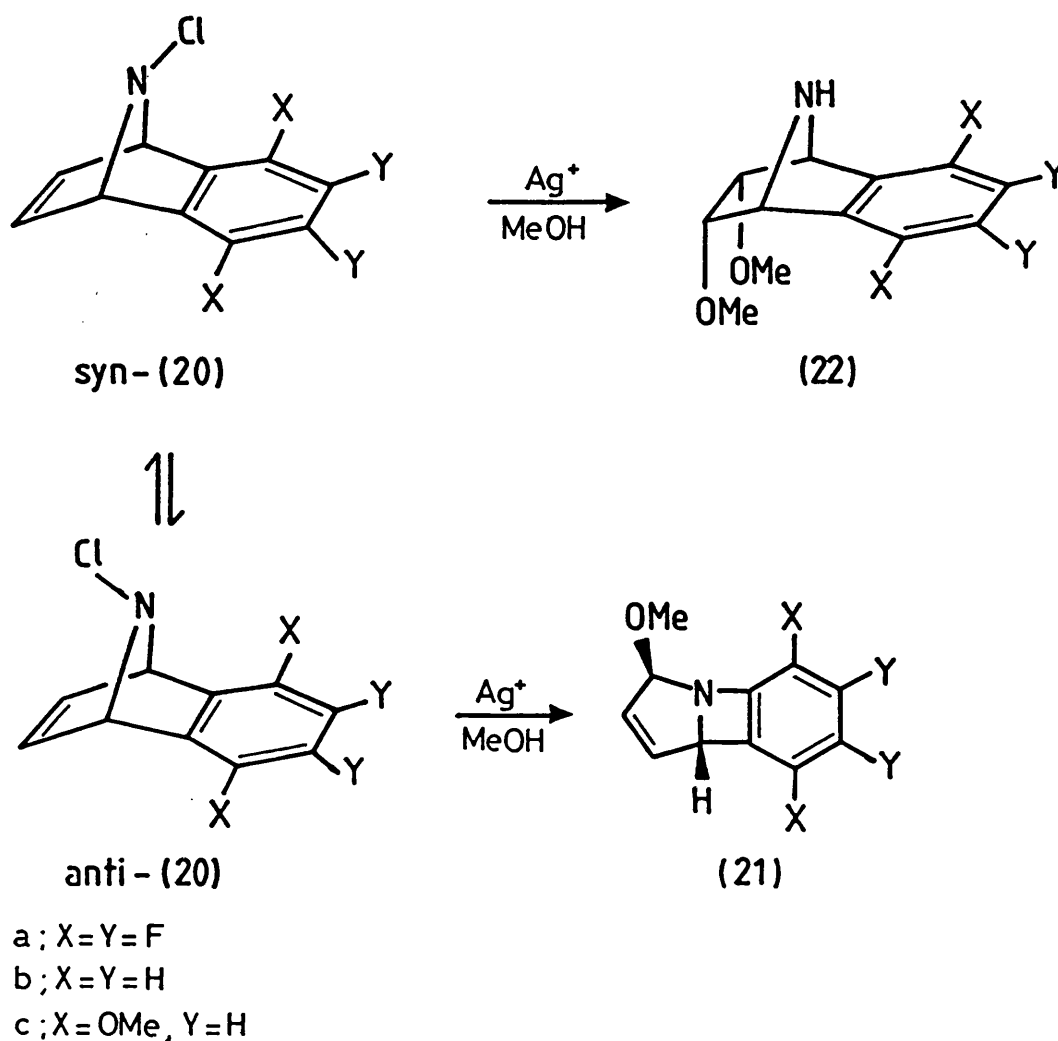
Figure 2·3

Below 0°C, the diastereoisomeric chloroamines (20) did not interconvert and followed different reaction pathways when treated with silver salts in methanol. The anti-invertomers generally afforded products via participation of the aryl group (21b, 21c) whereas the syn-invertomers yielded the amines (22a, 22b, 22c) via participation of the π-electrons of the etheno-bridge.

The rates of reaction of the anti-N-chloroamines were shown to vary according to the ability of the substituents in the benzo-ring to encourage benzo-participation. When silver ion promoted reactions were followed by NMR spectroscopy in CD_3OD at low temperatures (20c) was found to be considerably more reactive than (20b). In fact, anti-(20c) disappeared much more rapidly than the syn-invertomer, showing the profound effect of the methoxy groups in encouraging benzo-participation. In contrast, anti- (20a) was unreactive at low temperatures and no (21a) was observed under any conditions, (22a) and the parent amine being the sole products.

The syn-invertomers of (20a) and (20b) were found to be more reactive than the anti-invertomers. This was confirmed by solvolysis experiments in methanol at ambient temperature (without silver salt) which led to the formation of (22a) and (22b), with no observable (21). In these reactions, the anti-invertomer reacted via prior inversion to the syn-form. However, in the case of (20c), the aryl-participation route was competitive even under conditions of rapid inversion, affording both (21c) and (22c).

· 1,2-Migration of a neighbouring carbon during solvolytic loss of a nucleofuge from carbon has been studied intensely, typically in the norbornyl system.[46] The corresponding reaction involving loss of a nucleofuge from nitrogen and 1,2-migration to nitrogen has been observed in the silver ion-assisted methanolysis of bicyclic N-chloroamines in which the skeletally rearranged carbenium ion is generally intercepted by methanol. However, a few examples exist in which chlorine is retained in the major product. Gassman[47] first noted the large proportion of internal return of chlorine in the rearrangements of 2-azabicyclo[2.2.1]heptane derivatives, (figure 2.4).
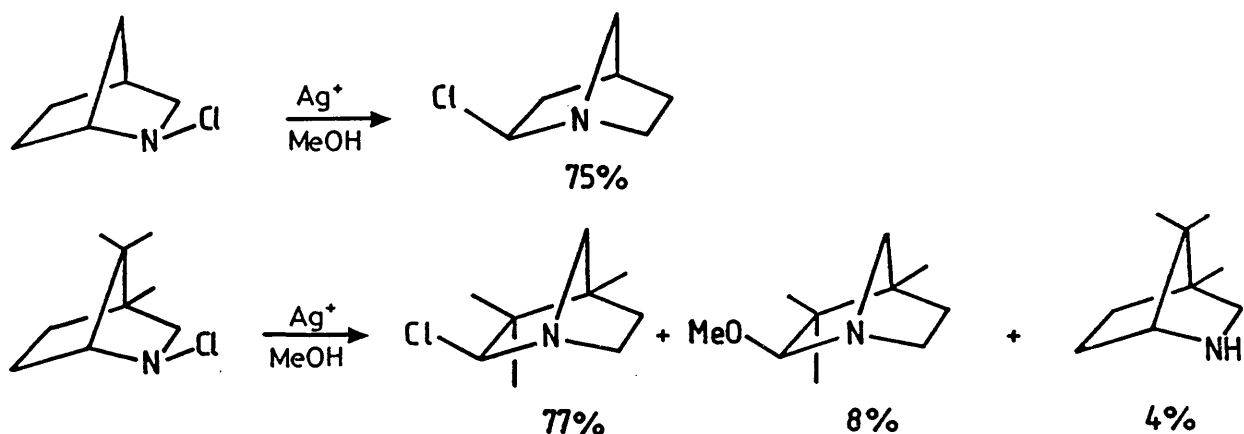
Figure 2·4

This type of reaction may be viewed formally as a dyatropic shift; there is an effective σ-bond participation in the reaction together with a retention of chlorine in the product.

Such rearrangements have been found to occur more cleanly and efficiently using chromatographic alumina as a mild catalyst.[48] The reaction of 2-chloro-2-azabicyclo[2.2.1]hept-5-ene (7) with silver nitrate and methanol is complex.[39] In contrast, treatment of (7) with alumina yielded only the rearrangement product (23) with retention of chlorine, (figure 2.5).

(7)   (23)
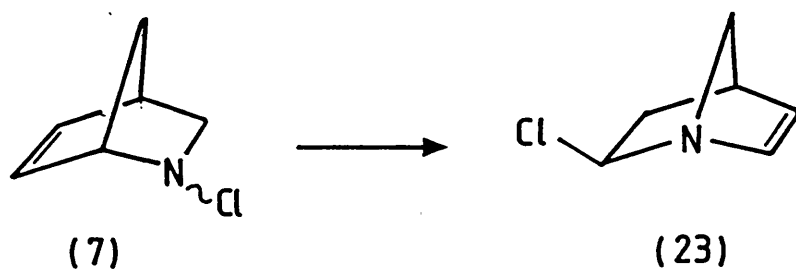
Figure 2·5

The observation of migration of an sp^2 carbon to an incipient electron-deficient nitrogen is of interest in view of a report by Shustov et al.[49] of an unusual 1,2-migration of an acyl group in the rearrangement of a N-chlorodiaziridine. N-chlorination of the bicyclic diaziridines (24a,b) was noted to proceed with the unexpected formation of the rearrangement products (25a,b) via 1,2-acyl migration to an electron-deficient nitrogen atom, (figure 2.6).

a: R = OMe
b: R = NHMe
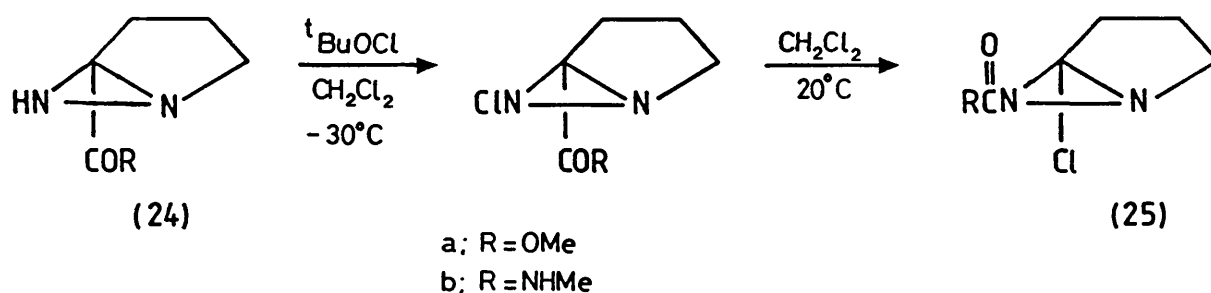
Figure 2·6

1,2-Acyl migrations to electron-deficient carbon atoms are well documented and several experimental[50-53] and theoretical[54] papers have been published on the subject. Thus, the idea of an acyl group migrating to an electron-deficient nitrogen atom in 7-azabicyclo[2.2.1]-heptane-derived systems was proposed. Silver ion-assisted solvolysis of N-chloro-1,2,3,4-tetrahydro-2-keto-1,4-iminonaphthalenes might reasonably be expected to involve acyl migration and lead to the rearrangement product (26), for example, (27) in which the tetrafluorinated ring would discourage benzo-participation, (figure 2.7).
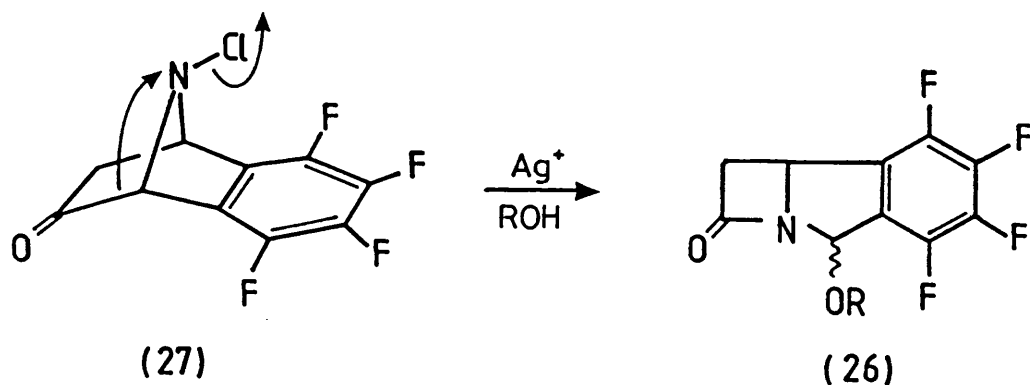
Figure 2·7

This would be interesting if it occurred and would provide a totally novel route to β-lactam derivatives.

Thus, the synthesis of derivatives of the N-chloro-1,2,3,4-tetrahydro-2-keto-1,4-iminonaphthalene system was attempted.

2. II   SYNTHESES AND SPECTROSCOPIC INVESTIGATIONS

The Diels-Alder cycloaddition of N-trimethylsilyl pyrrole (28) and tetrafluorobenzyne (generated by the action of n-butyllithium on pentafluorobenzene) afforded 5,6,7,8-tetrafluoro-1,4-dihydro-1,4-imino-naphthalene (9a),[42] (figure 2.8), the trimethylsilyl protecting group being removed in the aqueous work-up. Initially, protection of the nitrogen atom of the cycloadduct was achieved using a trifluoroacetyl group but this proved to be unsatisfactory since it was readily cleaved during the basic work-up of the subsequent hydroboration reaction. However, reaction of the parent amine (9a) with sodium hydride and methyl chloroformate afforded the protected amine (29a) cleanly and efficiently. Hydroxylation of the double bond was accomplished by hydroboration, followed by oxidation of the resultant trialkylborane with alkaline hydrogen peroxide. Initially, oxidation of the resulting alcohol (30a) proved to be difficult, attempts using pyridinium

chlorochromate,[55] N-bromosuccinimide[56] and chromic acid were unsuccessful. A further method devised by Brown[57] involving a direct conversion of olefins to ketones via organoboranes was utilised but to no avail. However, a Swern oxidation,[58] using dimethyl sulphoxide and trifluoroacetic anhydride afforded the required ketone (31a) in 60% yield. Removal of the carbomethoxy protecting group using trimethyl-silyl iodide and methanol[59] yielded 5,6,7,8-tetrafluoro-1,2,3,4-tetra-hydro-2-keto-1,4-iminonaphthalene (32a).
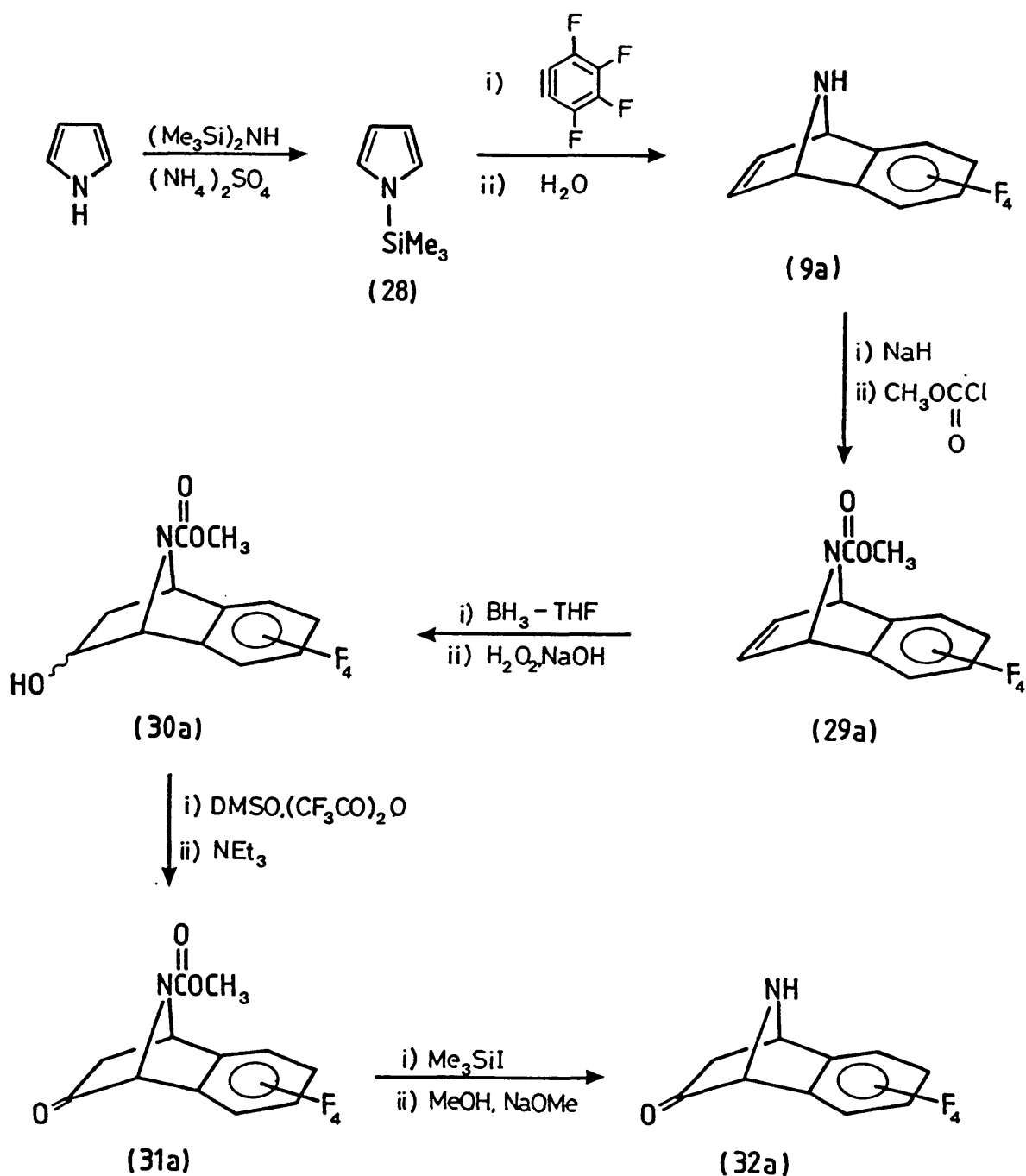
Figure 2·8

The amine (32a) was dissolved in deuterochloroform at -50°C and chlorinated with NCS to yield syn- and anti-chloroamines (33a), (figure 2.9).

| Ratio at -50°C | 75 | 25 |
| Ratio at 25°C | 72 | 28 |
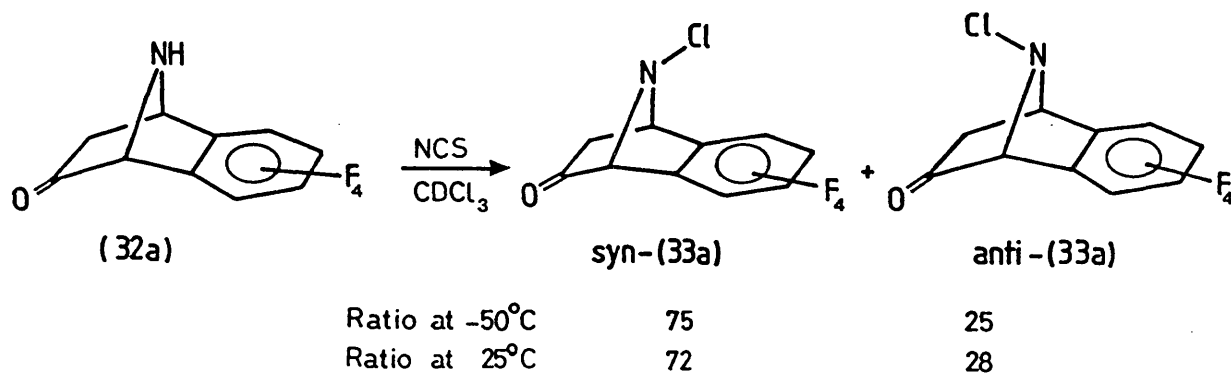
Figure 2·9

The ratio of chloroamines recorded at -50°C where inversion is negligible reflects the relative favouring of the two possible modes of approach of the chlorinating agent to the amine, i.e. the kinetic ratio.

High field ^{13}C off-resonance NMR confirmed the presence of two distinct invertomeric species, (figure 2.10).
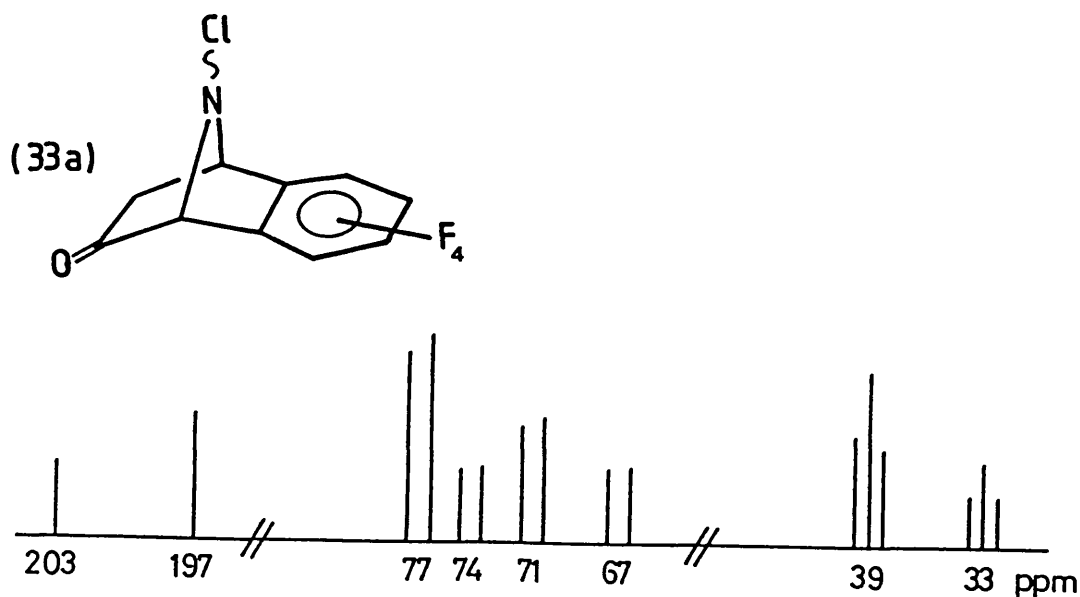
Figure 2·10

The assignment of the invertomers using the ^{13}C NMR data was facilitated by the application of the γ-effect of carbon substitution.[60] When a carbon atom is eclipsed by another carbon atom in the γ-position, the ^{13}C NMR shift of that carbon is at a higher field than the shift of the same carbon trans- to it, (figure 2.11). This is known as a compression shift induced by eclipsing carbon atoms.

132·4 ppm   137·8 ppm
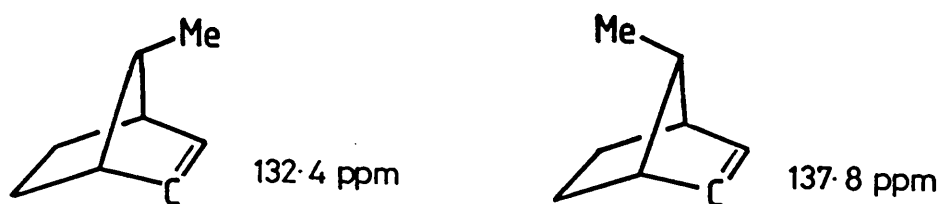
Figure 2·11

When this analysis was applied to the $-CH_2-$ carbon atom of the ethano-bridge in (33a), it was observed that the minor invertomer gave rise to the furthest upfield shift. This implies that the minor invertomer has the $-CH_2-$ eclipsed by the chlorine atom, i.e. it is the anti-invertomer.

The kinetic ratio of invertomers was determined by direct integration of the ^1H NMR spectrum; the result was 75% syn:25% anti. When the solution of N-chloroamines was warmed to room temperature, inversion was rapid and a thermodynamic equilibrium of invertomers was established, the ratio being 72% syn:28% anti. The kinetic and thermodynamic ratios are very similar. This implies that either the ratios are almost coincident or that the nitrogen inversion barrier is low and so an equilibrated system is being observed even at low temperature. However, equilibration is unlikely due to the observation of kinetic invertomers in a comparable system in subsequent studies.

Attempted solvolysis of (33a) with a methanolic solution of silver nitrate afforded only the dechlorinated amine (32a) which was presumably formed <u>via</u> a homolytic process, (figure 2.12).
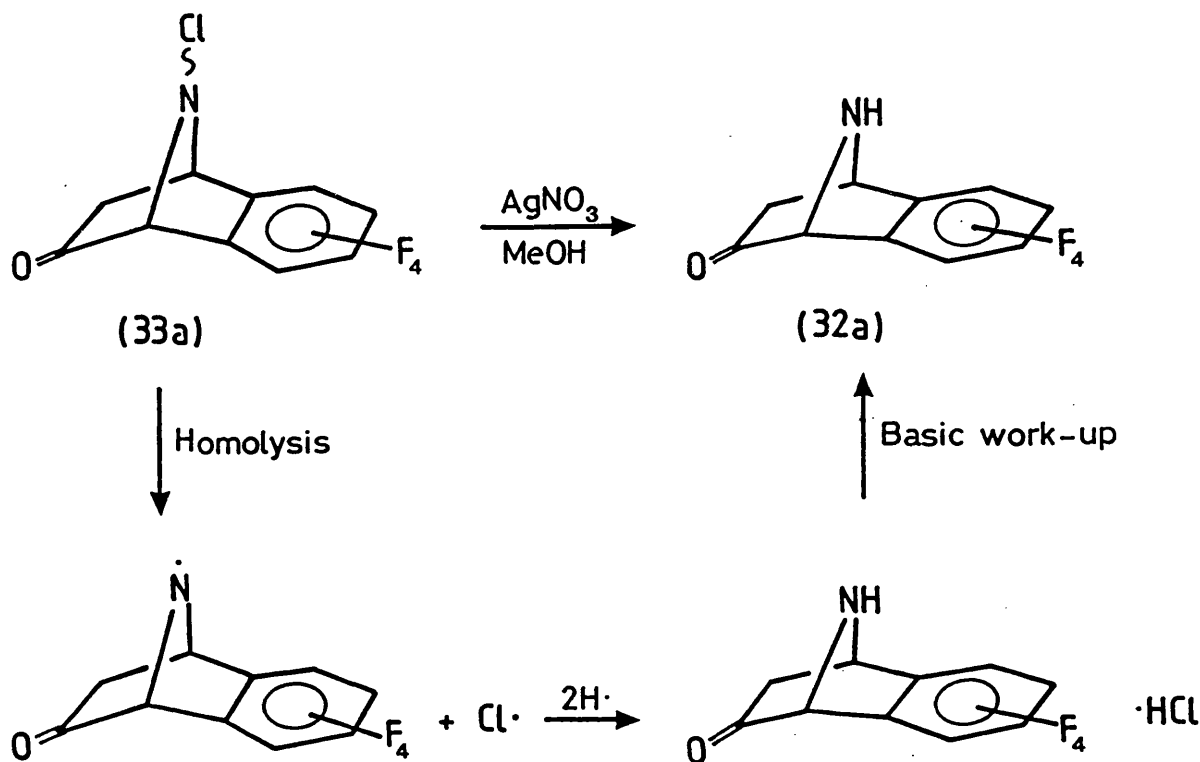
Figure 2·12

This mechanism presumably proceeds <u>via</u> homolytic fission of the N–Cl bond to produce an aminyl radical and a chlorine radical. This is followed by the abstraction of two hydrogen radicals from a suitable source, probably the methanol solvent.

In the past, homolysis has consistently hindered attempts to heterolyse N–chloroamines. More recently Schell[61,62] encountered similar difficulties during the synthesis of pyrrolizidine ring systems and overcame the problem by treating the N–chloroamines with silver tetrafluoroborate in an aprotic medium. This technique was therefore applied to N–chloroamine (33a) but, again, the sole product was the dechlorinated parent amine (32a).

The failure of heterolytic cleavage to compete with homolysis prevented any investigation of acyl migration. Hence, a more promising candidate to rearrange might be N-chloro-1,2,3,4-tetrahydro-2-keto-5,8-dimethoxy-1,4-dimethyl-1,4-iminonaphthalene (34c), (figure 2.13). The benzylic position of (34c) is activated by the bridgehead methyl group which might reasonably be expected to stabilise the incipient carbenium ion. However, solvolysis at room temperature would almost certainly lead to rearrangement entirely via aryl-participation due to the high reactivity of the dimethoxy-substituted benzo-ring. Nevertheless, rearrangement via this route would lead to compounds such as (35) which are of interest in their own right.
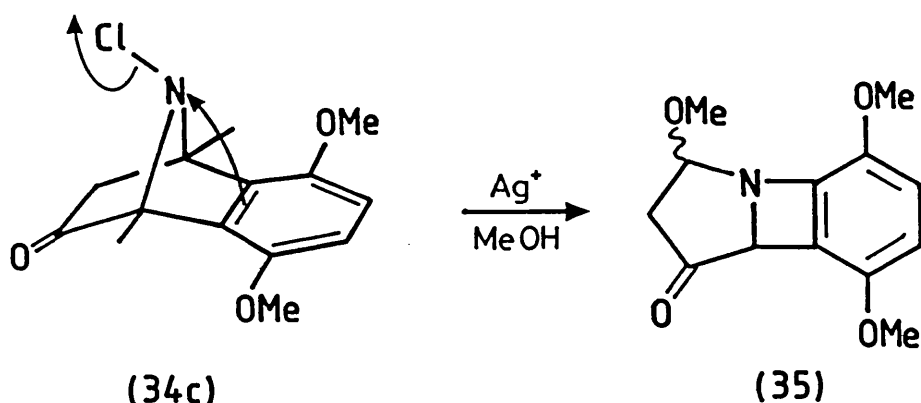
Figure 2·13

However, solvolysis at low temperature would define the chlorine stereochemistry and hence allow an opportunity for acyl migration.

An attempt was made to synthesise (34c) via a Diels-Alder cyclo-addition of 1-trimethylsilyl-2,5-dimethyl pyrrole (36) and 1,4-di-methoxybenzyne (generated by the action of n-butyllithium on 1,4-di-methoxy-2-chlorobenzene) to yield 1,4-dihydro-5,8-dimethoxy-1,4-imino-naphthalene (37c),[63] (figure 2.14). A carbomethoxy amine protecting

group was employed due to its success in the synthesis of (33a).
Hydroboration of (38c) afforded the alcohol (39c). However, a Swern
oxidation[58] proceeded in very poor yield (7%) and so an alternative
oxidising agent was sought. This was accomplished using chromium
trioxide and pyridine[64] to give (40c), the reaction proceeding cleanly
and fairly efficiently. Deprotection using the previously employed
method, i.e. trimethylsilyl iodide and methanol,[59] proved to be
impossible. Despite careful monitoring by NMR and IR spectroscopy, no
clean deprotection could be induced nor the reaction pathway
understood. Deprotection using ethanolic potassium hydroxide was also
attempted but did not yield the desired product (41c).

b; X = H
c; X = OMe
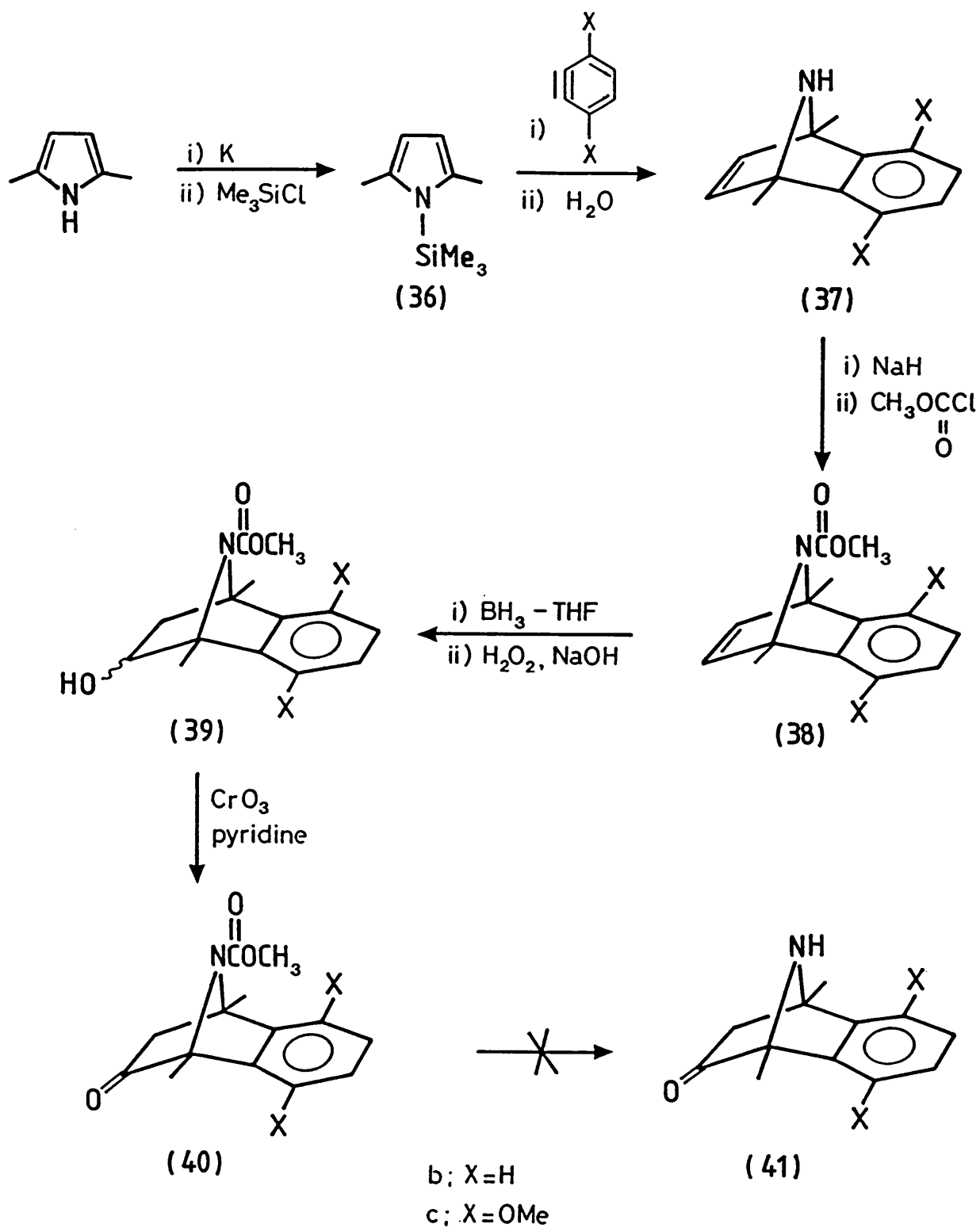
Figure 2·14

Thus, the synthesis of a comparable compound, N-chloro-1,2,3,4-tetrahydro-2-keto-1,4-dimethyl-1,4-iminonaphthalene (34b), was undertaken. Once again the benzylic position is activated by the bridgehead methyl group in order to encourage acyl migration. However, this compound has one advantage over (34c) in that the anti-N-chloroamine would be less reactive via benzo-participation.

The synthesis of (37b) was accomplished via a Diels-Alder cycloaddition of 1-trimethylsilyl-2,5-dimethyl pyrrole (36) and benzyne (generated by the action of n-butyllithium on 2-bromofluorobenzene),[63] (figure 2.14). Amine protection to give (38b), followed by hydroboration afforded the required alcohol (39b), and, unexpectedly, 1,4-dimethylnaphthalene (42). A possible mechanism for the formation of (42) may involve attack of the intermediate trialkylborane (43) by hydroxide ions during the basic work-up, resulting in subsequent ring opening of the bicyclic system to produce (44) and ultimate elimination of the carbamate, (figure 2.15).
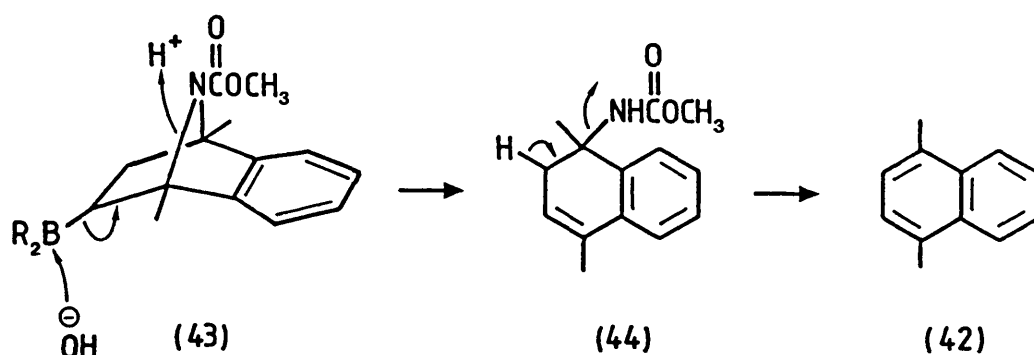
Figure 2·15

Treatment of the alcohol (39b) with chromium trioxide and pyridine yielded the desired ketone (40b). However, as with (40c), the amine protecting group could not be cleaved. Thus, an alternative

protecting group was sought. The syntheses of t-butyloxycarbonyl[65] and carbobenzoxy[66] protected amines were accomplished, the latter protecting group being selected for further work. Unfortunately, after hydroboration, oxidation proved unproductive.

Thus, the presence of the bridgehead methyl groups appeared to complicate matters considerably. Consequently N-chloro-1,2,3,4-tetra-hydro-2-keto-1,4-iminonaphthalene (33b) was synthesised, (figure 2.16).
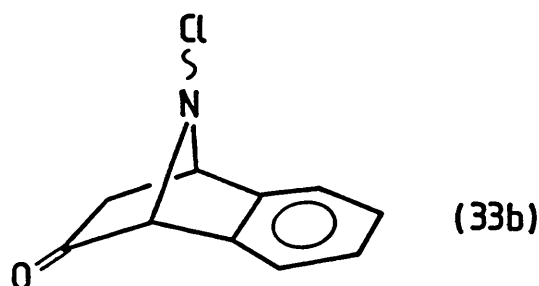
Figure 2·16

The Diels-Alder cycloaddition of N-trimethylsilyl pyrrole (28) and benzyne afforded 1,4-dihydro-1,4-iminonaphthalene (9b),[42] (figure 2.17). Reaction of (9b) with sodium hydride and benzyl chloroformate gave the protected amine (45) as its sole product. Hydroboration to give the alcohol (46) and subsequent oxidation using chromium trioxide and pyridine[64] yielded the ketone (47). The amine protecting group was removed cleanly and efficiently to afford (32b) using the methodology previously devised by Berger et al.[67], i.e. treatment with hydrogen bromide in glacial acetic acid.
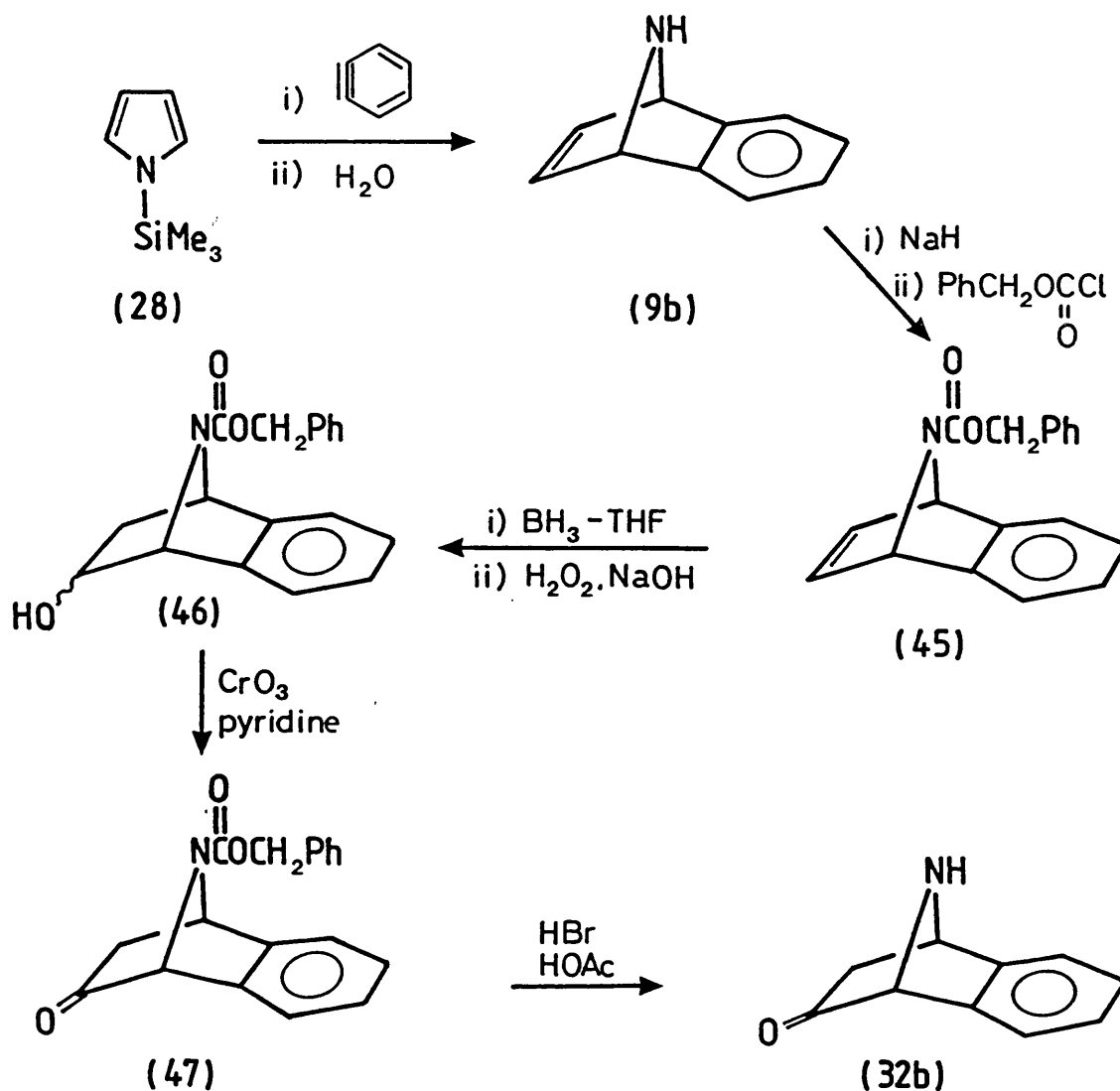
Figure 2·17

The amine (32b) was dissolved in deuterochloroform, chlorinated with NCS at -50°C, and transferred quickly to the probe of an NMR spectrometer at the same temperature. The kinetic invertomer ratio was determined by direct integration of the ^1H NMR spectrum. The solution of N-chloroamine (33b) was warmed to ambient temperature allowing the invertomers to equilibrate and subsequently determining the thermo-dynamic ratio, (figure 2.18).
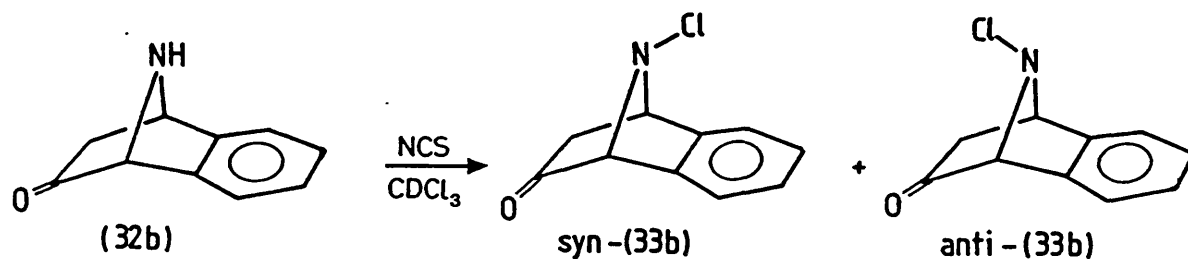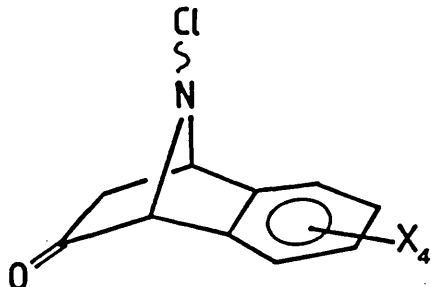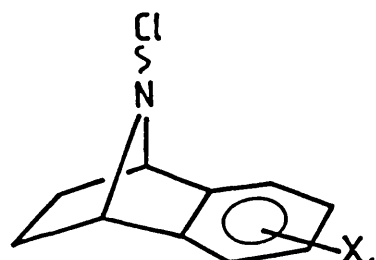
| Ratio at $-50°C$ | 9 | : | 91 |
| Ratio at $25°C$ | 39 | : | 61 |

Figure 2·18

Comparison of the kinetic invertomer ratios of (33a,b) with the corresponding 1,2,3,4-tetrahydro-1,4-iminonaphthalene systems (48a,b),[44] (table 2.5) shows that there is a decreased tendency for anti-attack in the keto-compounds.

Table 2.5

| Compound | | Invertomer Ratios | |
| | | kinetic | thermodynamic |
		syn : anti	syn : anti
(33)	a; X=F	75 : 25	72 : 28
	b; X=H	9 : 91	39 : 61
(48)	a; X=F	20 : 81	80 : 20
	b; X=H	6 : 94	53 : 47

The trend is unexpected on steric grounds but may be due to a repulsive interaction between the positive end of the carbonyl dipole and the incoming electrophilic chlorine, (figure 2.19).
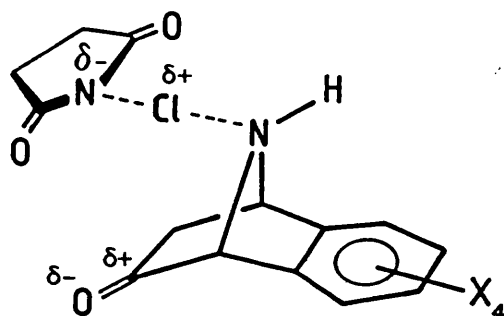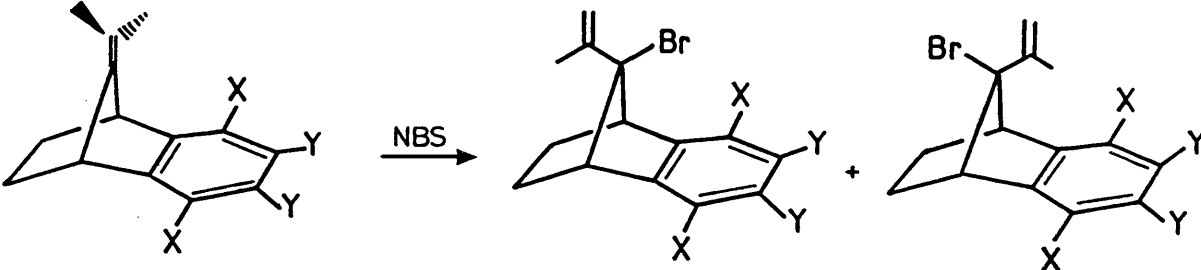
Figure 2·19

The ratios of invertomers of N-chloroamines (33a,b) vary substantially depending on the pattern of substitution in the benzenoid ring, (table 2.5). In view of the minimal steric differences between (33a) and (33b), the variation in kinetic stereoselectivity must be a result of electronic control. There is a relative favouring of the syn approach to nitrogen as the aromatic ring becomes less electron rich. This compares well with similar results obtained from a series of 1,4-dihydro-1,4-iminonaphthalene derivatives.[44] This may be rationalised by considering a transition state in which there is an interaction between the developing negative charge on the trailing imide nitrogen and the aromatic ring which would be expected to exert a greater stabilising influence as the electron density above the ring is reduced by electron withdrawal by fluorine.

Such observations are not confined to nitrogen chemistry. A parallel is provided by Paquette et al. in his report of stereoselective additions to 7-isopropylidenenorbornene derivatives (49),[68] (table 2.6).

Table 2.6

Substrate (49)	% 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

The thermodynamic ratios of N-chloroamines (33) and (48), (table 2.5) show a clear preference for the syn-invertomer as the benzenoid ring becomes more electron deficient. This preference is consistent with that expected of the negative end of a N-Cl dipole.

Attempted solvolyses employing a variety of conditions all failed to initiate acyl migration. No products from aryl participation in the heterolysis of the anti-chloroamine were observed either. The sole product in each case was the dechlorinated amine.

To verify that these solvolytic conditions can favour heterolysis, a rearrangement reaction was carried out on N-chloro-1,2,3,4-tetrahydro-1,4-iminonaphthalene (48b). Previous experiments in these laboratories showed that treatment with silver nitrate in methanol afforded the parent amine only, the low reactivity of the benzo-ring allowing the balance of reactivity to shift in favour of homolysis. However, in the present work, treatment of a 6% syn:94% anti ratio of (48b) (prepared by chlorination with NCS in dichloromethane at -50°C)

with silver tetrafluoroborate and toluene in the presence of one molar

equivalent of methanol at -50°C [without allowing thermal equilibration

of (48b)] gave rise to the rearrangement product (50) in 81% isolated

yield and with no significant intrusion from the homolysis reaction,

(figure 2.20).
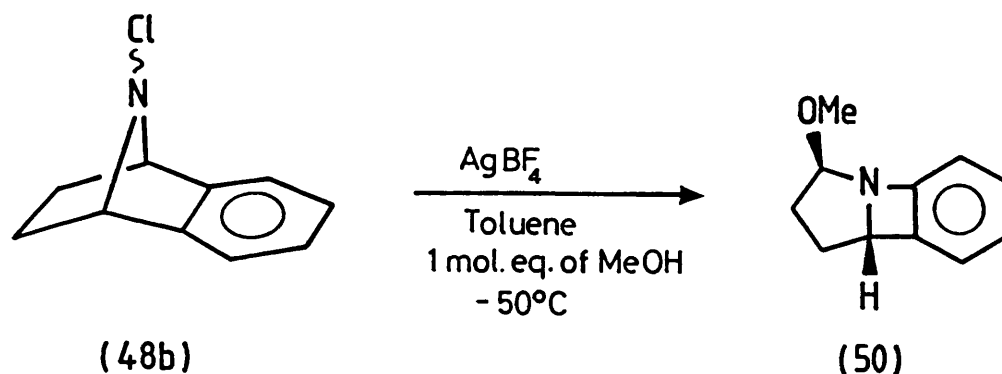
Figure 2·20

It seems that homolysis is favoured over heterolysis in the

keto-compounds (33a,b) contrary to results in etheno- and ethano-

bridged systems.[45] This could possibly be due to a stabilising

interaction between the nitrogen lone pair of electrons and the carbonyl

oxygen. Such interactions have been observed in other azabicycles

bearing a ketone functionality by helium (I) photoelectron spectro-

scopy.[69,70] Thus, in the systems (33a,b), there was no opportunity to

ascertain whether or not acyl migration was able to occur.

At this point, Shustov et al. published a correction to their

previous paper.[71] On further investigation, they found that the

originally proposed 1,2-acyl shift to the electron deficient nitrogen of

the N-chlorodiaziridines (51a,b) to yield (25a,b) did not, in fact,

occur. They were simply observing slow nitrogen inversion of the endo-

chloroamine to the exo-chloroamine, (figure 2.21).
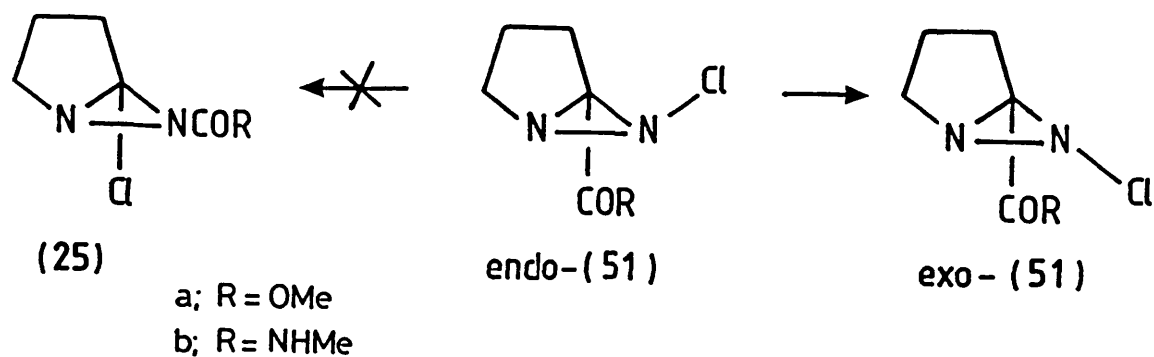
Figure 2·21

Summary

The N-chloroamines (33a,b) were successfully synthesised and their kinetic and thermodynamic invertomer ratios were determined. The amines (32a,b) demonstrated a relative favouring of syn-approach of NCS towards nitrogen as the aromatic ring became less electron rich, this being consistent with previous results.[44] Also, compared to analogous ethano-bridged systems (48a,b), the keto-compounds were found to exhibit a decreased tendency for anti-attack suggesting a repulsive interaction between the positive end of the carbonyl dipole and the incoming electrophilic chlorine. Unfortunately, despite reaction under favourable solvolytic conditions, it appeared that homolysis of the N-chloroamines was favoured over heterolysis, thus allowing no opportunities to observe acyl migration.

Chapter 3

The Synthesis and Study of Some 1,4-Dihydro- and

1,2,3,4-Tetrahydro-9-chloro-1-methyl-1,4-

iminonaphthalene Derivatives and their

Rearrangement Reactions

3. I.   INTRODUCTION

The silver ion promoted methanolysis of N-chloro-1,2,3,4-tetra-hydro-1,4-iminonaphthalene derivatives (48b,c) has been shown to lead to rearrangement entirely via the anti-Cl invertomer to yield the benz-azetidine derivatives (50b,c),[45] (figure 3.1).

anti-(48)

↓↑

syn-(48)

$\xrightarrow[\substack{MeOH(1mol.equiv.) \\ Toluene}]{AgBF_4}$

(50)

b; X = H
c; X = OMe

Figure 3·1
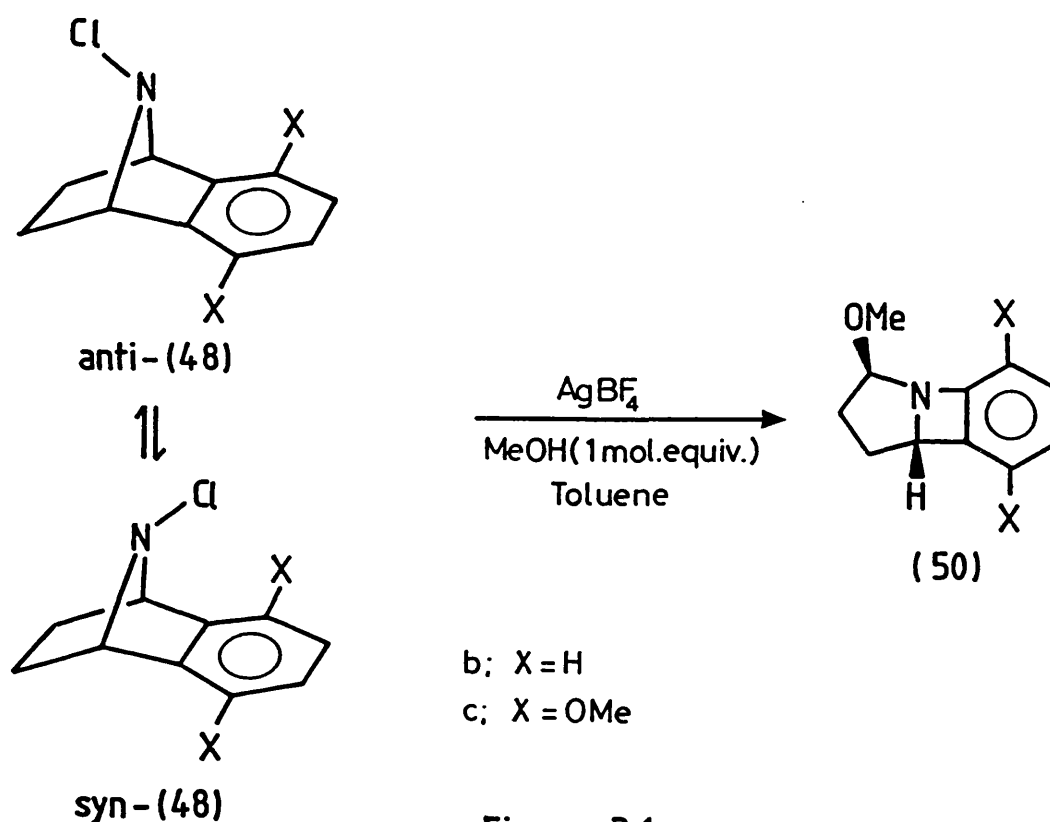
However, replacement of hydrogen by methyl at the 1,4-positions substantially modified the silver ion-catalysed solvolytic behaviour of the system.[72] Reaction of the N-chloroamines (52b,c) with silver tetra-fluoroborate and one molar equivalent of methanol in toluene lead to a precipitate of an iminium salt (53) which on treatment with sodium borohydride in methanol gave the tetrahydrobenzazepine derivative (54), (figure 3.2).

anti - (52)

syn - (52)

AgBF$_4$

MeOH (1 mol. equiv.)
Toluene

(53)

NaBH$_4$
MeOH

(54)

b ; X = H
c ; X = OMe
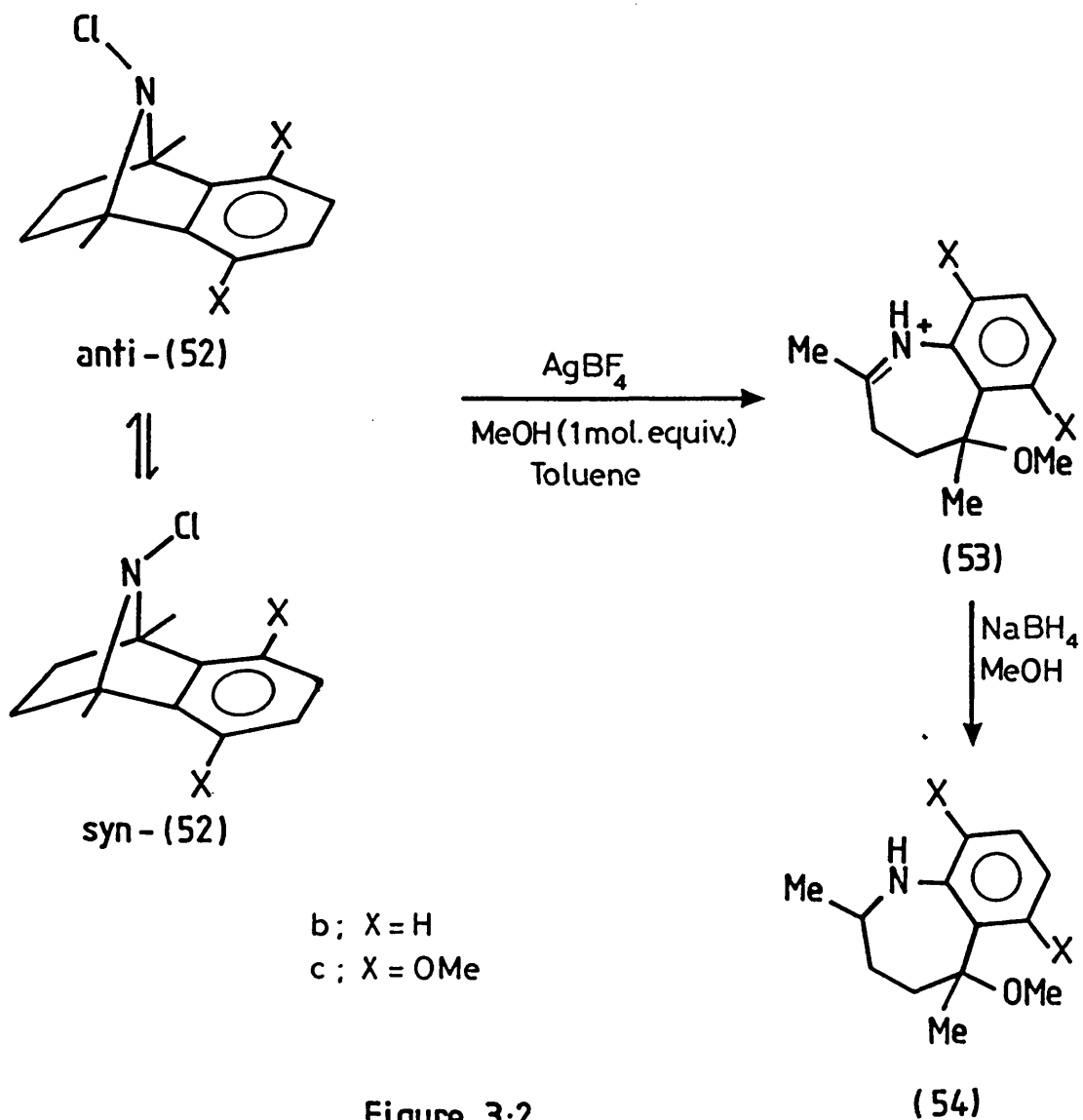
Figure 3·2

Alternatively, on standing in CD$_2$Cl$_2$, the iminium salt (53) underwent rearrangement with loss of methanol. The liberation of methanol coincided with the appearance of upfield signals in the ^{1}H NMR spectrum at δ0.74 indicating the presence of the cyclopropyl ring (55), (figure 3.3). Reduction of (55) with sodium borohydride in methanol afforded the amine (56).
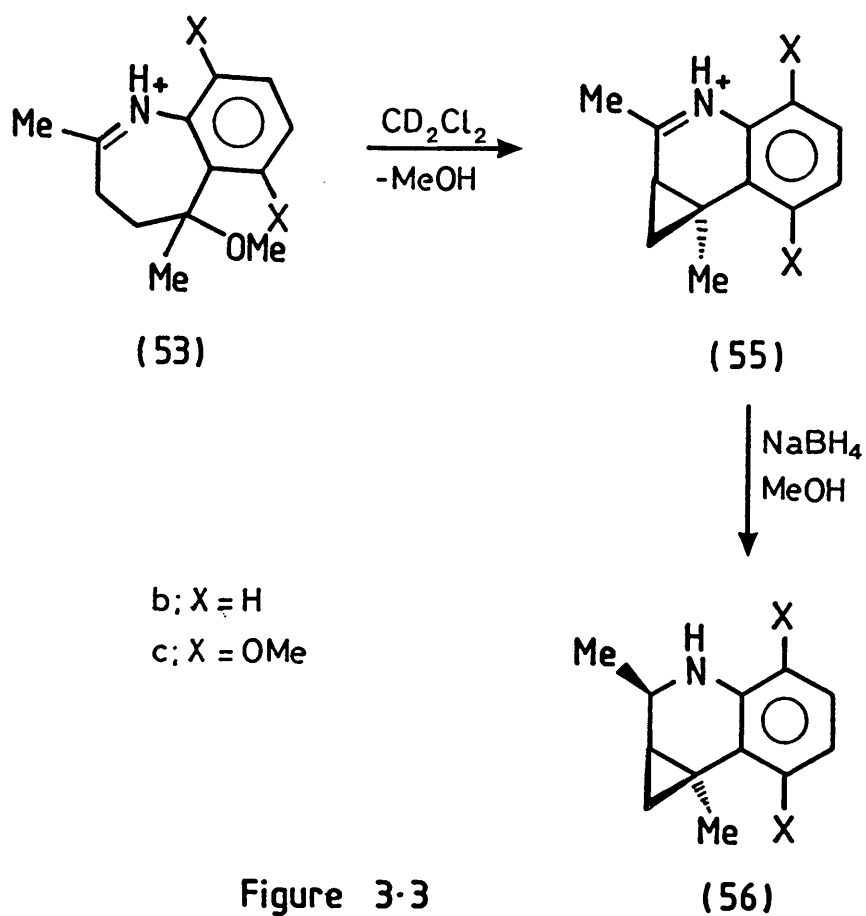
Figure 3·3

Thus, the bridgehead methyl groups have been shown to alter the balance of reactivity substantially, leading to the 7-ring iminium salt (53) rather than the isomeric salt of the more highly strained amine (57), (figure 3.4).

b : X = H

c : X = OMe
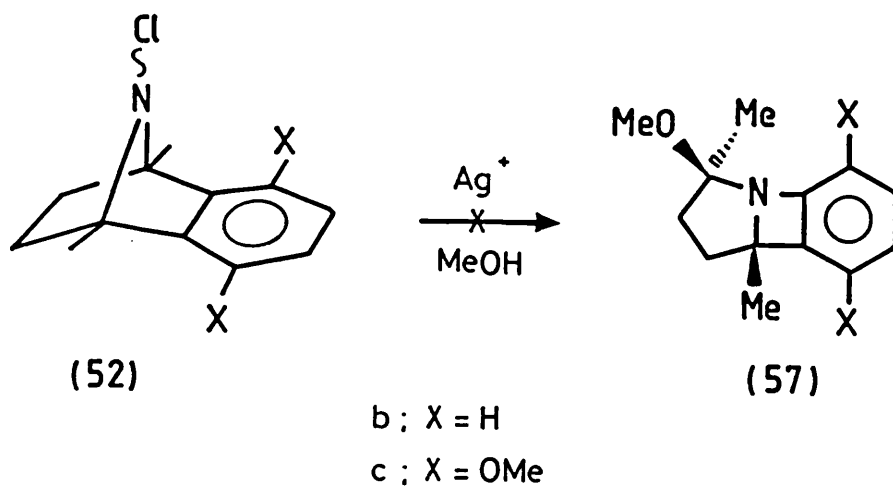
Figure 3·4

The reactivity of the corresponding etheno-bridged N-chloro-amines diverge similarly.[45,72] Below 0°C, the N-chloroamines (20b,c) did not interconvert and followed different reaction pathways when treated with silver salts in methanol, (figure 3.5). For example, the 6,7-benzo-1-azabicyclo[3.2.0]hept-3-ene system (21c) resulted from anti-(20c) via participation of the aryl ring. The syn-invertomer (20c) afforded the amine (22c), this compound presumably being formed by participation of the π-electrons of the etheno-bridge.

syn - (20)

(22)

$$\xrightarrow[\text{MeOH}]{\text{AgNO}_3} \atop 0°C$$

anti-(20)

(21)

b; X = H
c; X = OMe
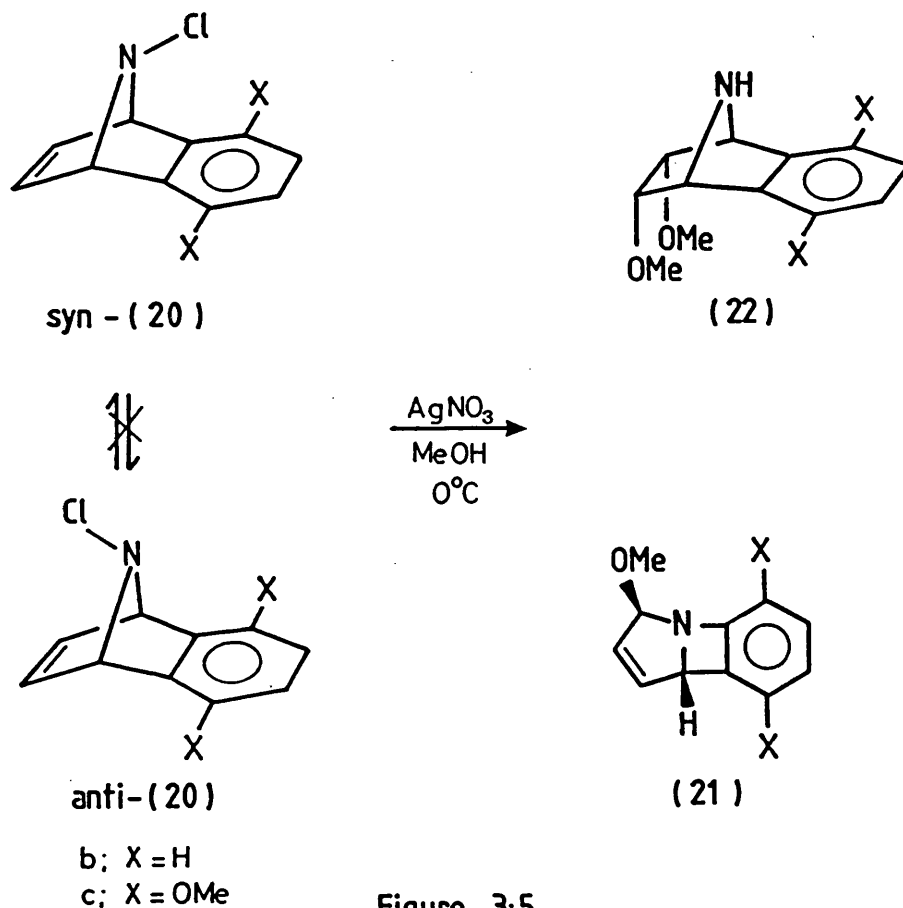
Figure 3·5

The corresponding N-chloroamines with methyl groups at the bridgehead positions (58b,c) were treated under similar reaction conditions, (figure 3.6). Participation of the π-electrons of the etheno-bridge yielded the amines (59b,c). However, in each case a 4-methylquinoline system (60b,c) was unexpectedly produced and in good yield.
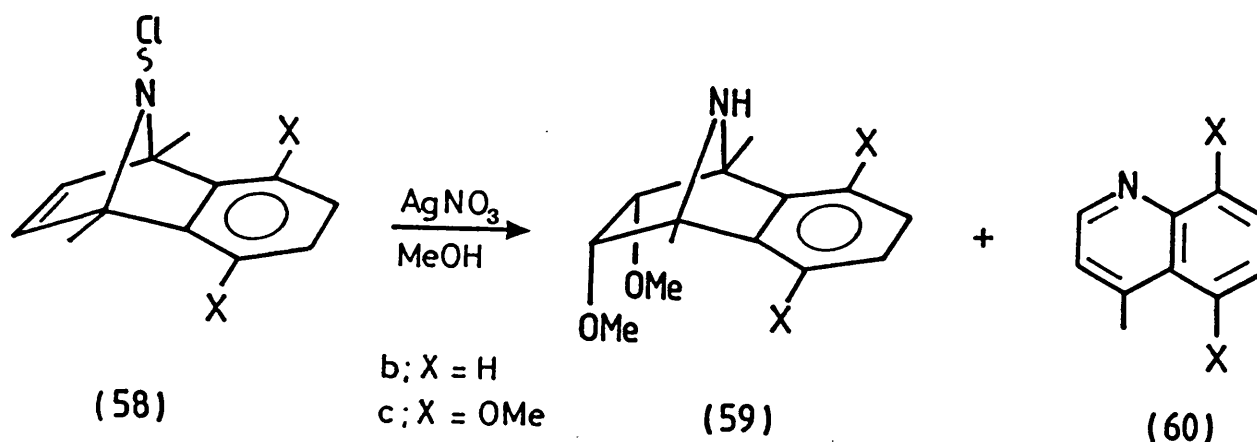
Figure 3·6

These unusual rearrangements resulting in the formation of 4-methylquinolines were thought worthy of further investigation. Study of the solvolytic behaviour of analogous N-chloroamines containing just one methyl group at the bridgehead position may go some way to explaining these extraordinary reactions. Thus, the N-chloro derivatives of amines (61) and (62) were synthesised and their solvolytic behaviour investigated, (figure 3.7).

a; X = Y = F,
b; X = Y = H
c; X = OMe, Y = H

unsaturated ; (61)
saturated ; (62)
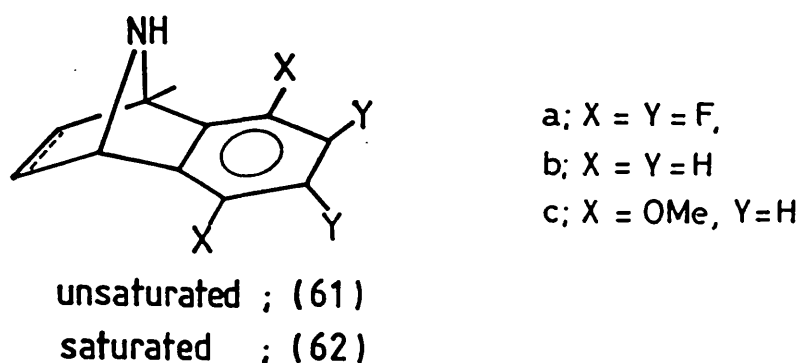
Figure 3·7

These N-chloroamines also allow introduction of the idea of investigating a 'non-symmetrical' system so as to examine the regio-selectivity of their solvolytic behaviour.

3. II. SYNTHESIS AND SPECTROSCOPIC INVESTIGATIONS

Treatment of pyrrole with dimethylformamide and phosphorus oxychloride yielded pyrrole-2-carboxaldehyde (63)[73] which was subsequently reduced with lithium aluminium hydride to give 2-methyl pyrrole (64),[74] (figure 3.8). Reaction of (64) with potassium and trimethylsilyl chloride gave N-trimethylsilyl-2-methyl pyrrole (65). The Diels-Alder cycloadditions of this pyrrole derivative with the

i) POCl₃
   Me₂NCHO
ii) CH₃CO₂Na·3H₂O

LiAlH₄

(63)

(64)

i) K
ii) Me₃SiCl

(62)

(61)

H₂
Pd/C

i)
ii) H₂O

SiMe₃
(65)
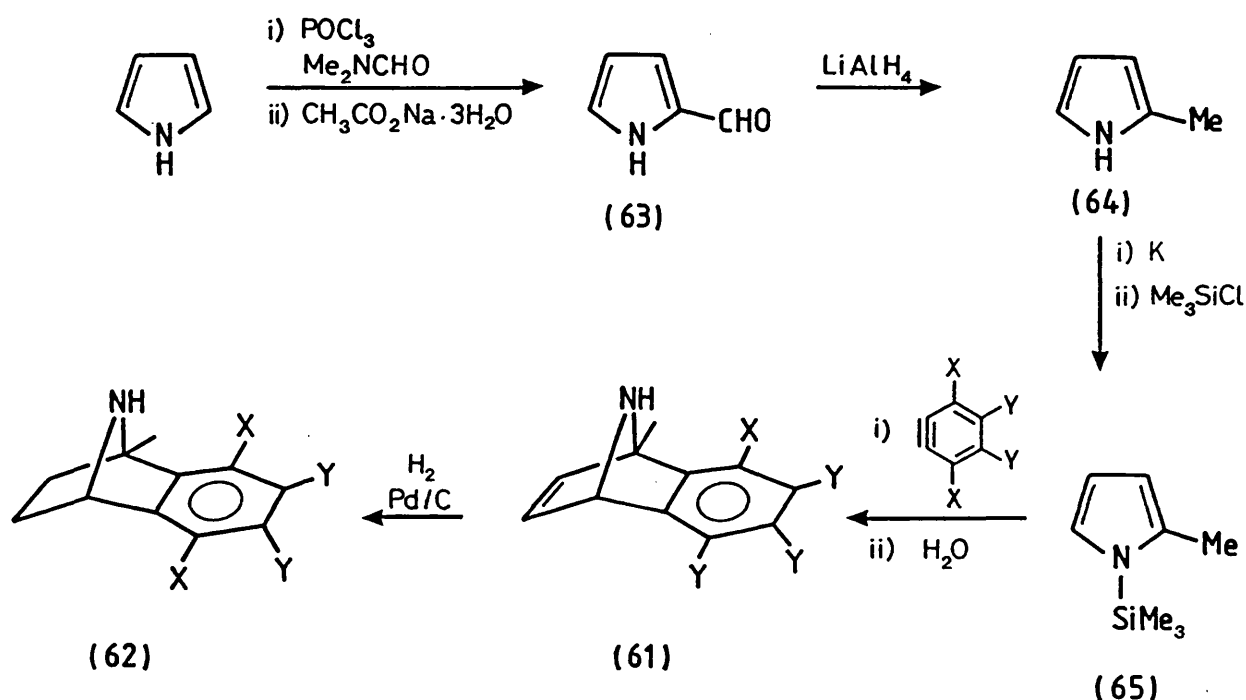
a; X = Y = F
b; X = Y = H
c; X = OMe, Y = H

Figure 3·8

appropriately substituted benzynes (prepared by the action of n-butyllithium on pentafluorobenzene, 2-bromofluorobenzene or 1,4-dimethoxy-2-chlorobenzene respectively) afforded the 1,4-dihydro-1-methyl-1,4-iminonaphthalene system (61) directly; the trimethylsilyl group was removed in the aqueous work-up. These amines were readily converted to their 2,3-dihydro- derivatives (62) by catalytic hydrogenation.

Each of the amines (61a-c) and (62a-c) were dissolved in deuterochloroform at low temperature and chlorinated wth NCS. The ratios recorded at -50°C [at which temperature the product N-chloro-amines (66a-c) and (67a-c) could not interconvert; conditions of kinetic control] were found to be stable to 0°C. When the solutions were warmed to room temperature, inversion became rapid and a thermodynamic equilibrium was established, (figure 3.9).

unsaturated; (61)
saturated; (62)

syn- (66)
syn- (67)

anti - (66)
anti-(67)

Kinetic ratio

a; X=Y=F
b X=Y=H
c X=OMe, Y=H

warm to ambient temperature

Thermodynamic ratio
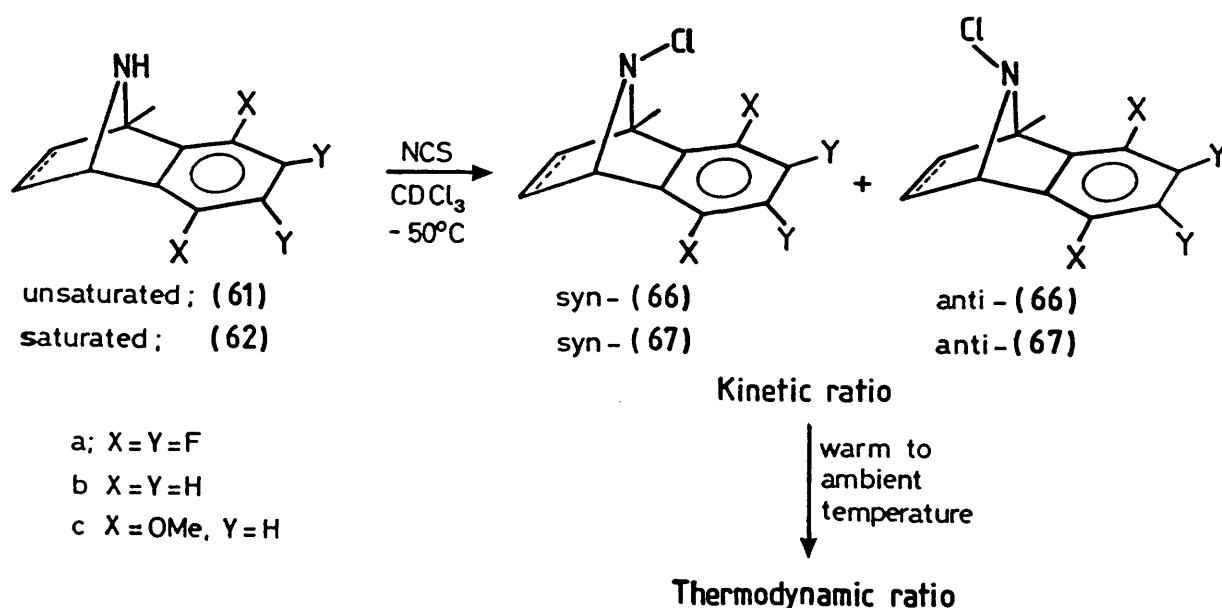
Figure 3·9

The kinetic and thermodynamic invertomer ratios were determined for two reasons. Firstly, as a basis for subsequent heterolytic reactions, and secondly for comparison with ratios from earlier studies.[44,63]

Comparison of these results with those of the corresponding systems with hydrogen atoms (20, 48)[44] or methyl groups (58, 52)[63] at the bridgehead positions shows that these ratios fall within the range of the two, as anticipated, (table 3.1).
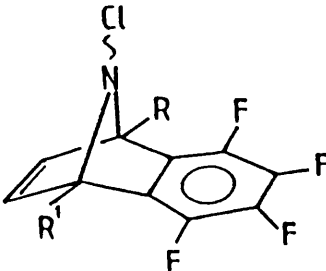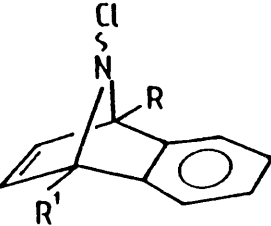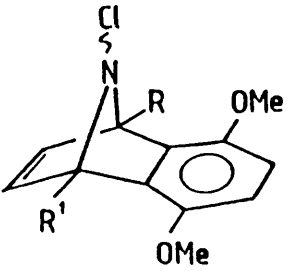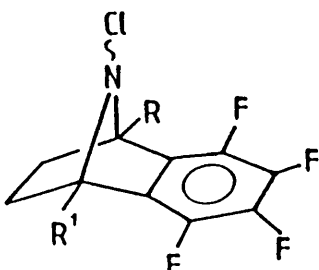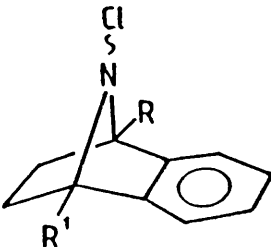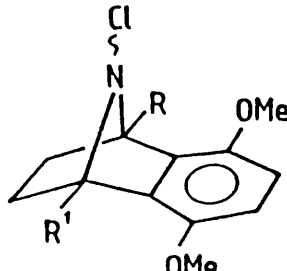
COMPOUND   INVERTOMER RATIOS

			Kinetic syn : anti	Thermodynamic syn : anti
(20a)	R = R^1 = H		68 : 32	84 : 16
(66a)	R = Me, R^1 = H		69 : 31	91 : 9
(20b)	R = R^1 = H		28 : 72	60 : 40
(66b)	R = Me, R^1 = H		31 : 69	65 : 35
(58b)	R = R^1 = Me		33 : 67	72 : 28
(20c)	R = R^1 = H		34 : 66	67 : 33
(66c)	R = Me, R^1 = H		32 : 68	71 : 29
(58c)	R = R^1 = Me		29 : 71	80 : 20
(48a)	R = R^1 = H		20 : 80	80 : 20
(67a)	R = Me, R^1 = H		22 : 78	69 : 31
(48b)	R = R^1 = H		6 : 94	53 : 47
(67b)	R = Me, R^1 = H		5 : 95	53 : 47
(52b)	R = R^1 = Me		5 : 95	52 : 48
(48c)	R = R^1 = H		5 : 95	54 : 46
(67c)	R = Me, R^1 = H		14 : 86	62 : 38
(52c)	R = R^1 = Me		21 : 79	71 : 29

TABLE 3.1

Examination of the trends observed in table 3.1 shows that attack of NCS on the amines with unsubstituted and dimethoxy-substituted aryl rings occurs predominantly from the anti-direction. However, there is an increasing tendency to approach nitrogen from over the benzenoid ring as the substituents in the ring become more electron withdrawing. This can be rationalised by considering the transition state discussed in Chapter 2, i.e. an interaction between the developing negative charge on the trailing imide nitrogen and the aromatic ring.[44] This would be expected to exert a greater stabilising influence as the electron density over the aryl ring is reduced by electron withdrawal by the fluorine substituents, (figure 3.10).
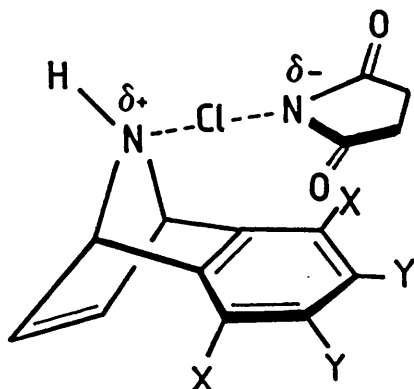
Figure 3·10
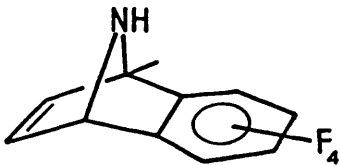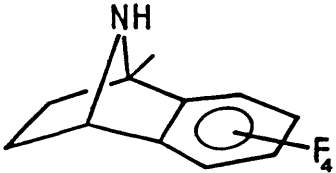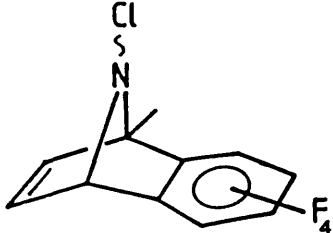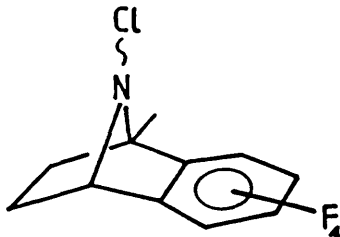
The decreased tendency for anti-attack in the etheno-bridged compounds compared to the ethano-bridged series is unexpected on steric grounds but may be due to a repulsive secondary orbital interaction between the π-bond and the incoming chlorine.[75]

However, it is difficult to understand the relatively subtle effects which result from the replacement of one or two bridgehead protons with a methyl group in these systems.

In each of the unsaturated N-chloroamines (66a-c), the ^{1}H NMR showed that the bridgehead proton exhibited allylic coupling in the syn-invertomer but not in the anti-, suggesting a distortion of the molecule depending on the orientation of the chlorine. Such distortions have been observed in similar systems by X-ray analysis[9] (see Chapter 4) where stabilising interactions between the N-Cl bond and the anti-periplanar C-C bonds were proposed.

Interestingly, the high field ^{1}H NMR spectra of the amines (61a), (62a) and their corresponding N-chloroamines (66a) and (67a) exhibited long range ^{1}H-^{19}F spin-spin coupling. The results are summarised in table 3.2.

Table 3.2. Coupling Constants (Hz)

		J_{Me-F}	J_{H-F}
(61a)		0·9	2·0
(62a)		1·1	2·1
(66a)	syn	0·8	1·8
	anti	1·2	1·7
(67a)	syn	1·3	2·0
	anti	1·3	1·5

The N-chloroamines (66a) and (67a) were found to exhibit different ^{1}H-^{19}F coupling constants depending on the orientation of the chlorine, again suggesting distortion of the molecules.

Such ^{1}H-^{19}F coupling has been observed in 1,4-dihydro-1,4-epoxy-naphthalenes (68) and related systems, (figure 3.11)[76] and was initially assumed to involve a four-bond benzylic coupling between a bridgehead proton and the proximinal fluorine. However, on further consideration, it seemed that the H_aF_a internuclear distance was too great for a 'through-space' contribution to the coupling mechanism, and a more likely H-F coupling mechanism was a five-bond zig-zag coupling between a bridgehead proton and the distal fluorine, e.g. H_bF_a.

(68)

$$J_{H_bF_a} = 1 \cdot 9 Hz$$
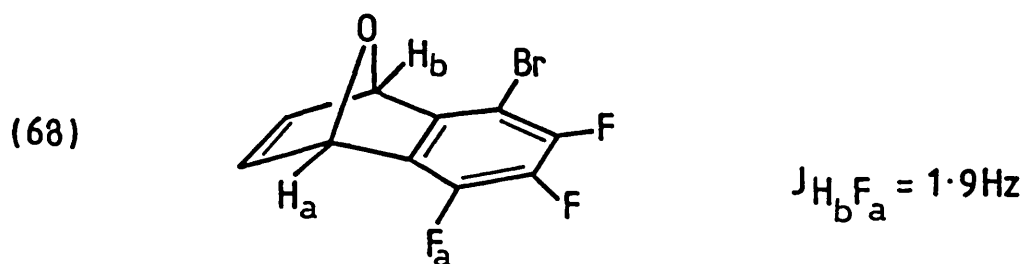
Figure 3·11

3. III. REARRANGEMENT CHEMISTRY OF N-CHLORO-5,6,7,8-TETRAFLUORO-1,4,-DIHYDRO-1-METHYL-1,4-IMINONAPHTHALENE (66a)

Treatment of N-chloroamine (66a) with silver tetrafluoroborate in toluene in the presence of two molar equivalents of methanol at room temperature yielded two products, (69) and (61a), (figure 3.12).

syn - (66a)

anti-(66a)

AgBF$_4$

MeOH(2 mol.equiv.)
Toluene
Room temperature

(69)
52%

(61a)
45%
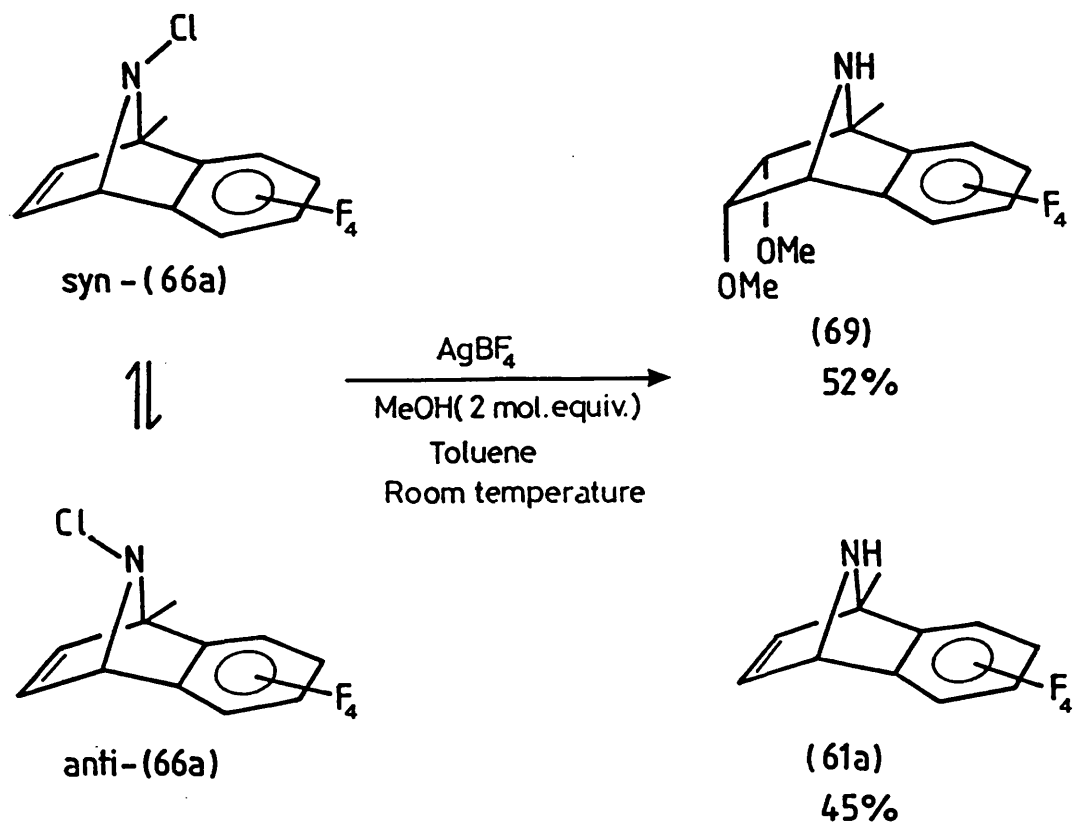
Figure 3·12

The bis—endo—methoxy compound (69) is the expected product from the syn-invertomer via participation of the π-electrons of the etheno-bridge, (figure 3.13).

syn -(66a)

MeÖH   (70)

MeOH

OMe
OMe
(69)

(71)
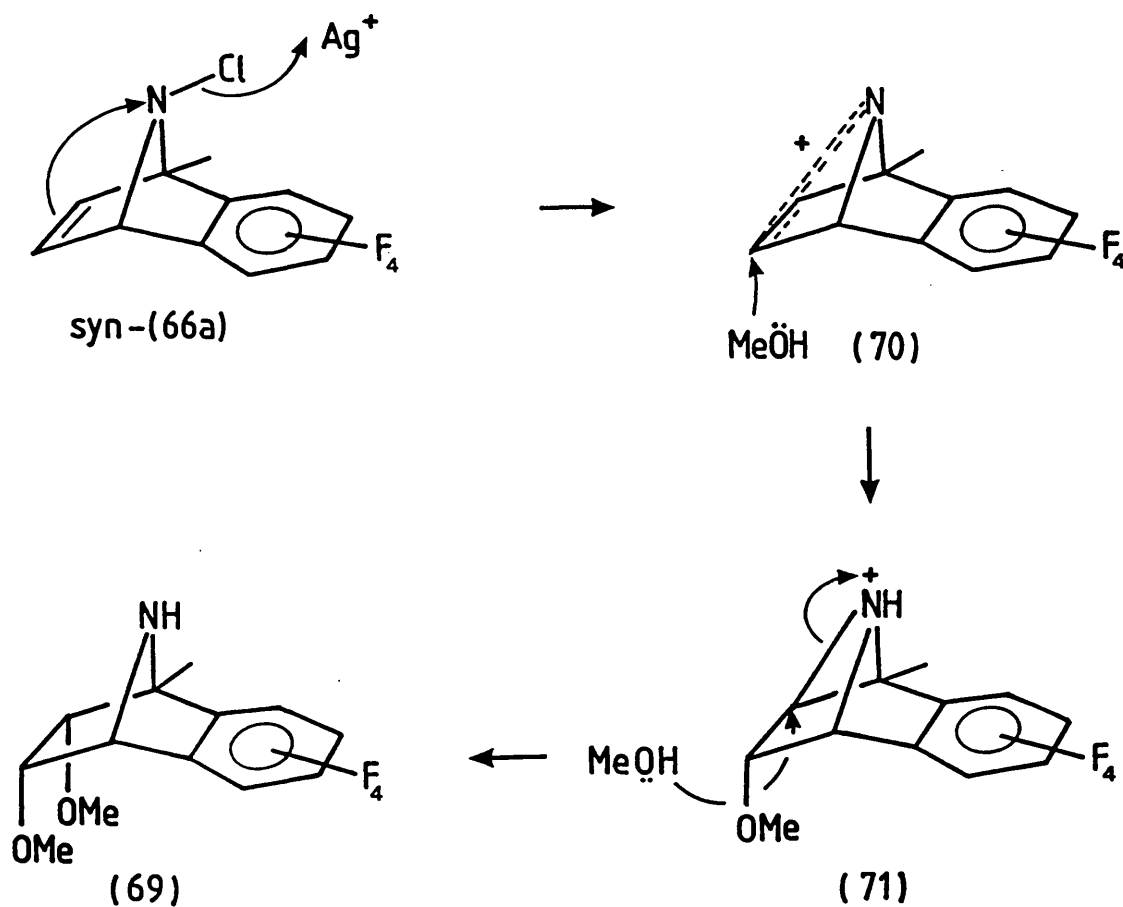
Figure 3·13

The observed endo-stereochemistry of the methoxy groups is mechanistically reasonable if it is assumed that charge delocalisation in the transition state takes place via a non-clasical ion (70). The presence of partial three-centre bonding on the exo-face in the transition state would force the approach of methanol from the endo-face. A strained protonated aziridine (71) is formed and a second molecule of methanol performs a ring-opening step to give the observed bis-endo-methoxy product (69).

No products from aryl participation of a tetrafluorinated benzo-ring have ever been observed due to its low reactivity. Thus, homolysis competes successfully with heterolysis to give the parent amine (69) (see Chapter 2).

3. IV. REARRANGEMENT CHEMISTRY OF N-CHLORO-1,2,3,4-TETRAHYDRO-5,8-DIMETHOXY-1-METHYL-1,4-IMINONAPHTHALENE (67c)

Treatment of the N-chloroamine (67c) under similar conditions used for (66a) gave only the product of homolysis, i.e. the parent secondary amine (62c). However, heterolysis was induced by lowering the temperature of the reaction medium. In fact, chlorination of the amine (62c) and subsequent treatment with silver ion in the presence of methanol was performed below -20^0C, thereby establishing and maintaining the 'kinetic ratio' of invertomers in the reaction medium. After complete reaction of the N-chloroamine (67c) (monitored by t.l.c.), the reaction mixture was reductively worked-up with sodium borohydride in methanol yielding (72) (58%), (73) (13%) and a small amount of the parent secondary amine (62c) (8%), (figure 3.14).

anti-(67c)

86%

(72)

58%

+

i) AgBF₄
   MeOH (1 mol.equiv.)
   Toluene
   -20°C

ii) NaBH₄
    MeOH

(73)

13%

+

syn - (67c)

14%

(62c)

8%
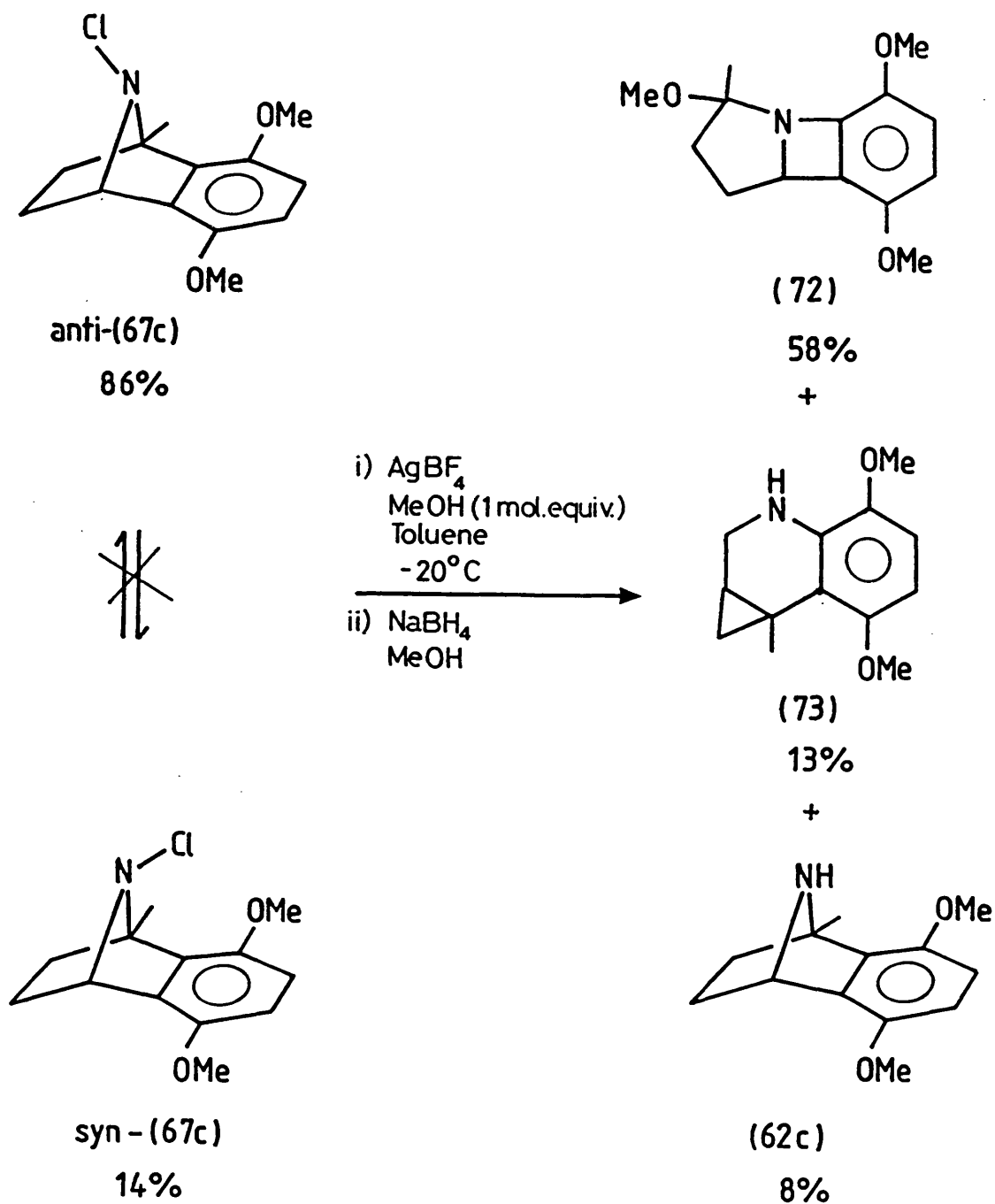
Figure 3·14

The structure of (72) was verified by high field ^{1}H and ^{13}C NMR. The ^{1}H NMR is shown in figure 3.15.
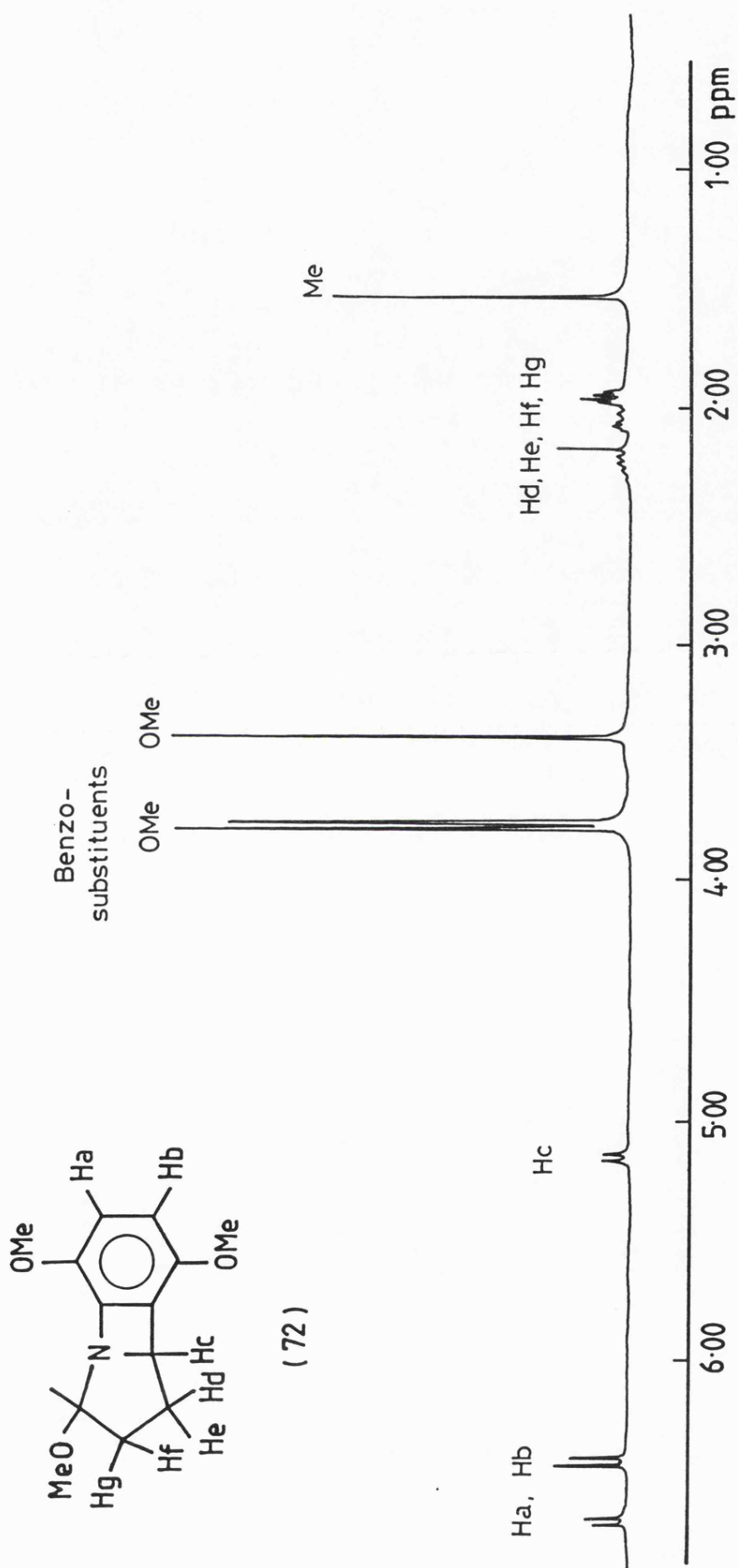
Figure 3·15

The ^{1}H NMR spectrum of (72) consisted of an AB quartet at δ6.43 and 6.67 integrating for two protons which were assigned to the aromatic protons, H_a and H_b. The two singlets at δ3.77 and 3.79 each integrating for three protons were subsequently assigned to the methoxy substituents in the benzo-ring, together with a singlet at δ3.40 which corresponds to the methoxy group in the five-membered ring. The other singlet integrating to three protons was assigned to the methyl group, the multiplet at δ1.96-2.26, which integrates for four protons, corresponding to H_d, H_e, H_f and H_g.
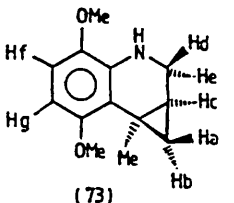
Interestingly, the NMR signal due to H_c appeared as a doublet at 300MHz. Since H_c is adjacent to a methylene group, such multiplicity must arise from the fact that the angle betwen C-H_c and one of its neighbouring protons must be close to 90° (J = 0Hz). This is consistent with the NMR data of compound (50).[42]

Likewise, the structure of (73) was confirmed by ^{1}H NMR and spin decoupling experiments, (figure 3.16). In particular, the upfield signals at δ0.54 and 0.97 were characteristic of a cyclopropyl ring.

The coupling constants are summarised in table 3.3. The structure of (73) was further substantiated by ^{13}C NMR data.

TABLE 3.3

a	b	c	d	e	
0.57	4.2	4.2	–	–	a
	0.94	8.0	–	–	b
		1.23	5.0	7.4	c
			2.85	11.6	d
				3.68	e

Chemical shifts (ppm) along diagonal
Coupling constants (Hz) off diagonal
δ_H (300 MHz, CDCl$_3$)
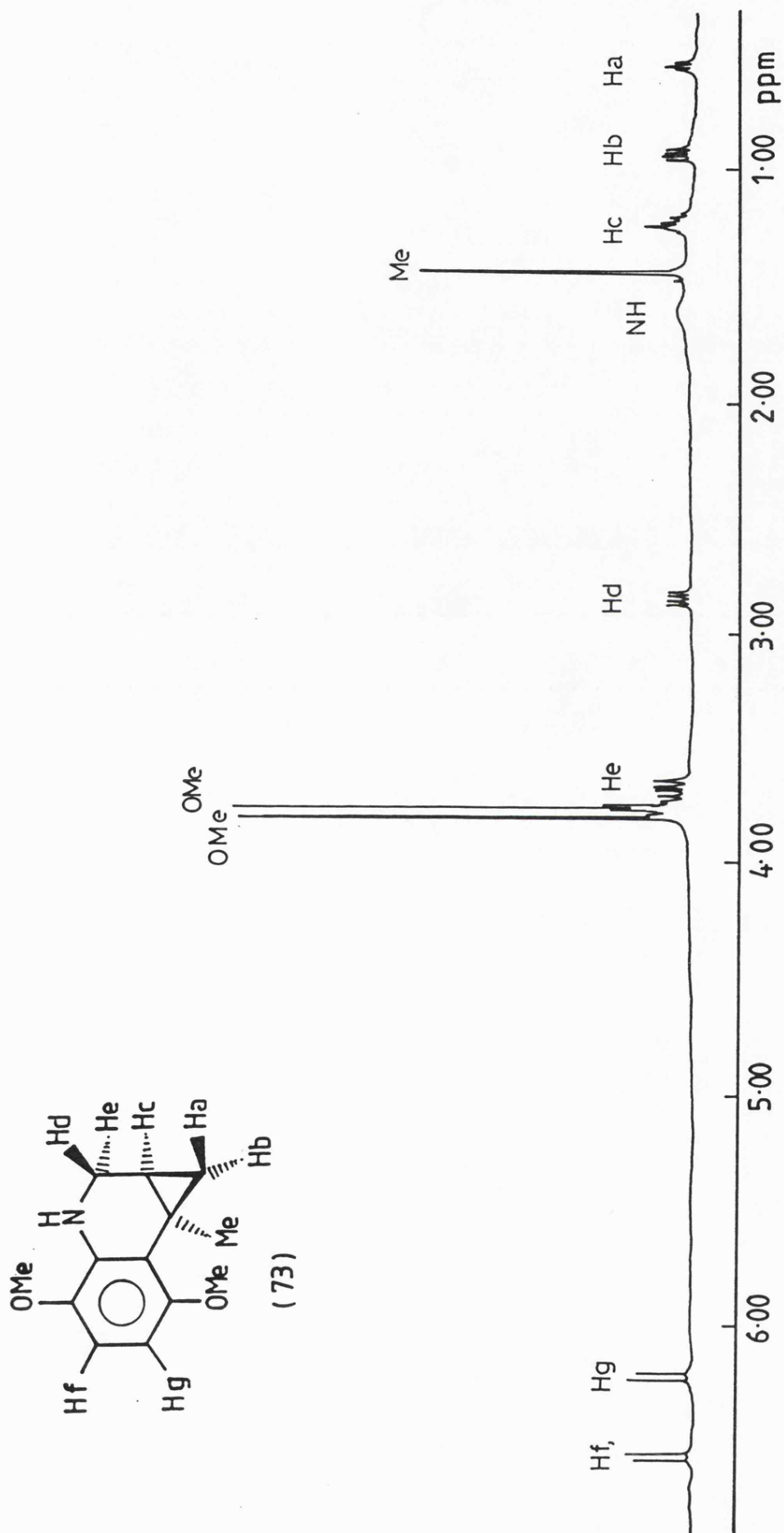
Figure 3·16

The parent amine (62c) is almost certainly being produced <u>via</u> homolysis of the syn-invertomer. However, the rearrangement products (72) and (73) are formed <u>via</u> benzo-participation of the anti-invertomer. It is not possible to determine whether the rearrangement reaction proceeds <u>via</u> a classical or non-classical carbenium ion. Nevertheless, in order to rationalise the above results, the intermediate is more easily represented as the classical ions (74) and (75) (figures 3.17 and 3.18).

Thus, it is suggested that the 6,7-benzo-1-azabicyclo[3.2.0]-heptane derivative (72) was derived from the intermediate (74) <u>via</u> breakage of the C-C bond shown in (76), the tertiary cationic species thus formed (74) demonstrating no tendency to induce ring opening to form a seven-membered ring, (figure 3.17).
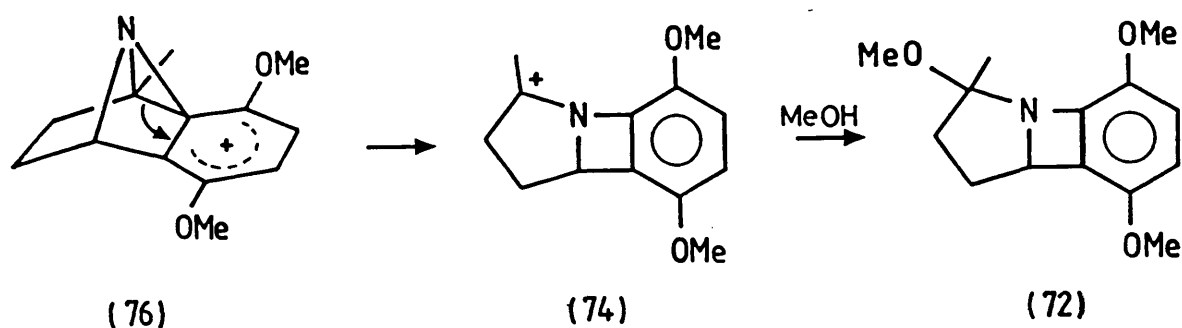
Figure 3·17

Accordingly, the product containing the cyclopropyl ring (73) was derived from the intermediate (75) <u>via</u> breakage of the C-C bond shown in (77). However, this intermediate demonstrates a tendency to ring open to produce a benzazepine-type structure (78) due to the ability of the methyl group to stabilise further the incipient positive charge at the benzylic position. Loss of methanol from (78) leads to

the intermediate (79) which can subsequently undergo a $6\pi \rightarrow 4\pi$ electro-cyclic ring closure, the driving force being the reattainment of aromaticity of the dimethoxy-substituted aryl ring. Reductive work-up of the iminium salt (80) gives the final product (73), (figure 3.18).
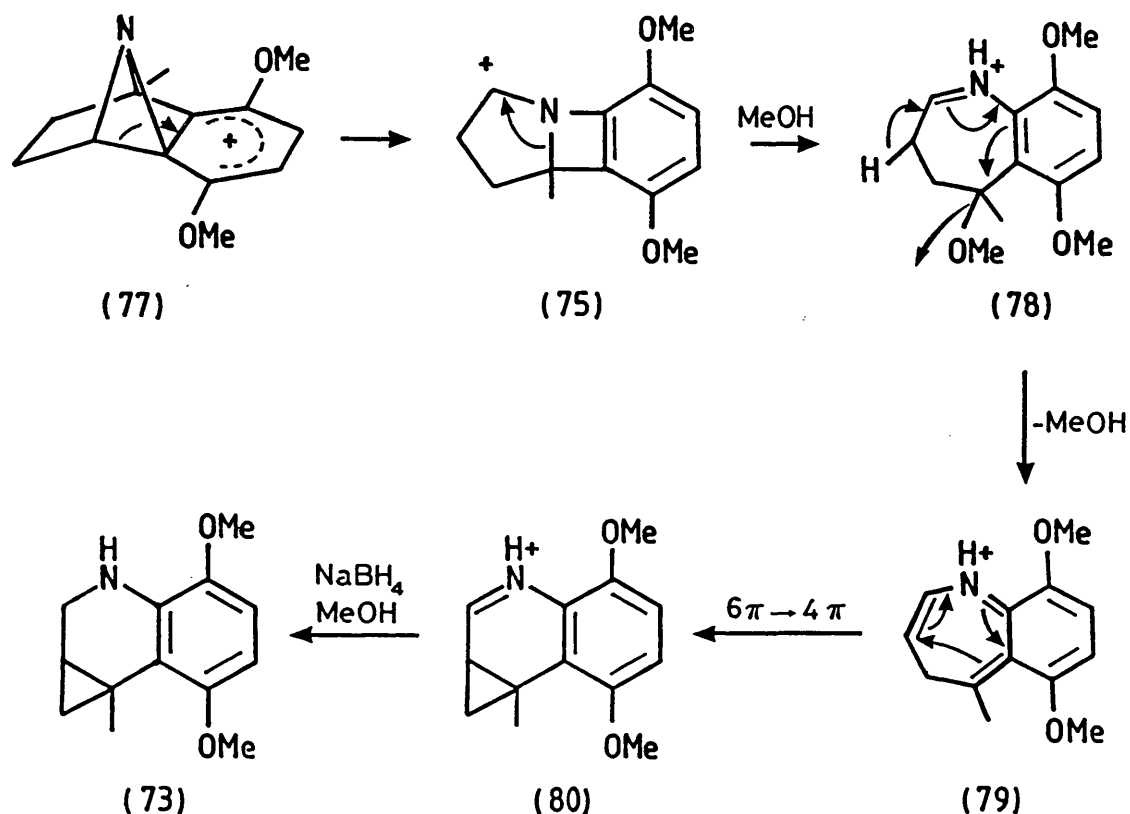
Figure 3·18

The relatively high yield of (72) (58%) indicates a preference for the intermediate (74) rather than (75). This result was anticipated on the grounds that (74) is a more stable tertiary carbenium ion.

Thus, reaction via the intermediate (75) resembles the chemistry of N-chloroamines bearing methyl substituents at the 1,4-positons.[72] In contrast, reaction via the alternative carbenium ion (74) parallels reactions of analogous systems which are unsubstituted at the bridgehead positions.[45]

Hence, this single experiment demonstrates that the bridgehead methyl group exerts modest control over the regiochemistry of the primary rearrangement but controls absolutely the tendency of the bicyclo[3.2.0]heptyl cation (74, 75) to ring open or not in the second stage of the reaction depending on whether the methyl group is now benzylic or α- to the nitrogen.

3. V. REARRANGEMENT CHEMISTRY OF N-CHLORO-1,4-DIHYDRO-1-METHYL-1,4-IMINONAPHTHALENES (66b) and (66c)

Treatment of the N-chloroamine (66b) with silver tetrafluoroborate in toluene in the presence of one molar equivalent of methanol at room temperature failed to encourage heterolysis. The sole product was the parent secondary amine (61b). However, due to the success previously achieved with (67c) as a result of lowering the reaction temperature, the reaction was carried out below -20°C. Chlorination was performed at low temperature so that the 'kinetic ratio' of invertomers was produced and maintained. This maximised the proportion of anti-invertomer which would have become the minor invertomer at room temperature. After work-up and chromatography, the only identifiable product was 4-methylquinoline (60b) in 59% yield, (figure 3.19).

The high yield of 4-methylquinoline (60b) indicates clearly that this compound must be formed via solvolysis of the anti-invertomer (66b) since the reaction was performed under conditions of no inversion.

syn-(66b)
31%

AgBF₄
MeOH (1 mol.equiv.)
────────────────────►
Toluene
-20°C

(60b)
59%

anti-(66b)
69%
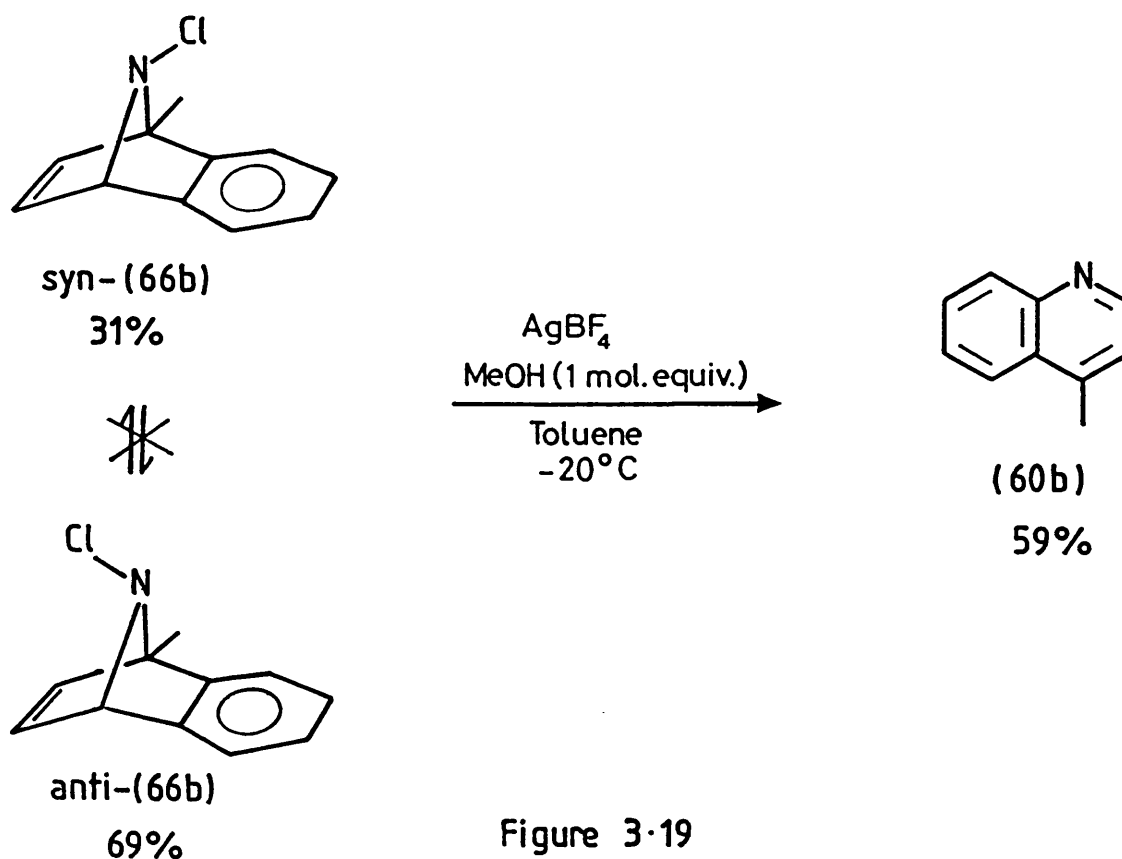
Figure 3·19

Reaction of the N-chloroamine (66c) at room temperature under conditions favouring heterolysis proceeded with the formation of 5,8-dimethoxy-4-methylquinoline (60c) in 30% yield as well as 55% of the parent secondary amine (61c). The high reactivity of the dimethoxy-substituted benzo-ring evidently allowed a certain amount of heterolysis even at room temperature.

Reaction of the 'kinetic ratio' of N-chloroamines (66c) at -20°C under the usual conditions proceeded with the formation of (60c) in an improved yield (42%), (figure 3.20). Small quantities of other products were isolated but could not be identified.

syn-(66c)
32%

anti-(66c)
68%

AgBF$_4$
MeOH(1 mol.equiv.)
Toluene
-20°C

(60c)
42%
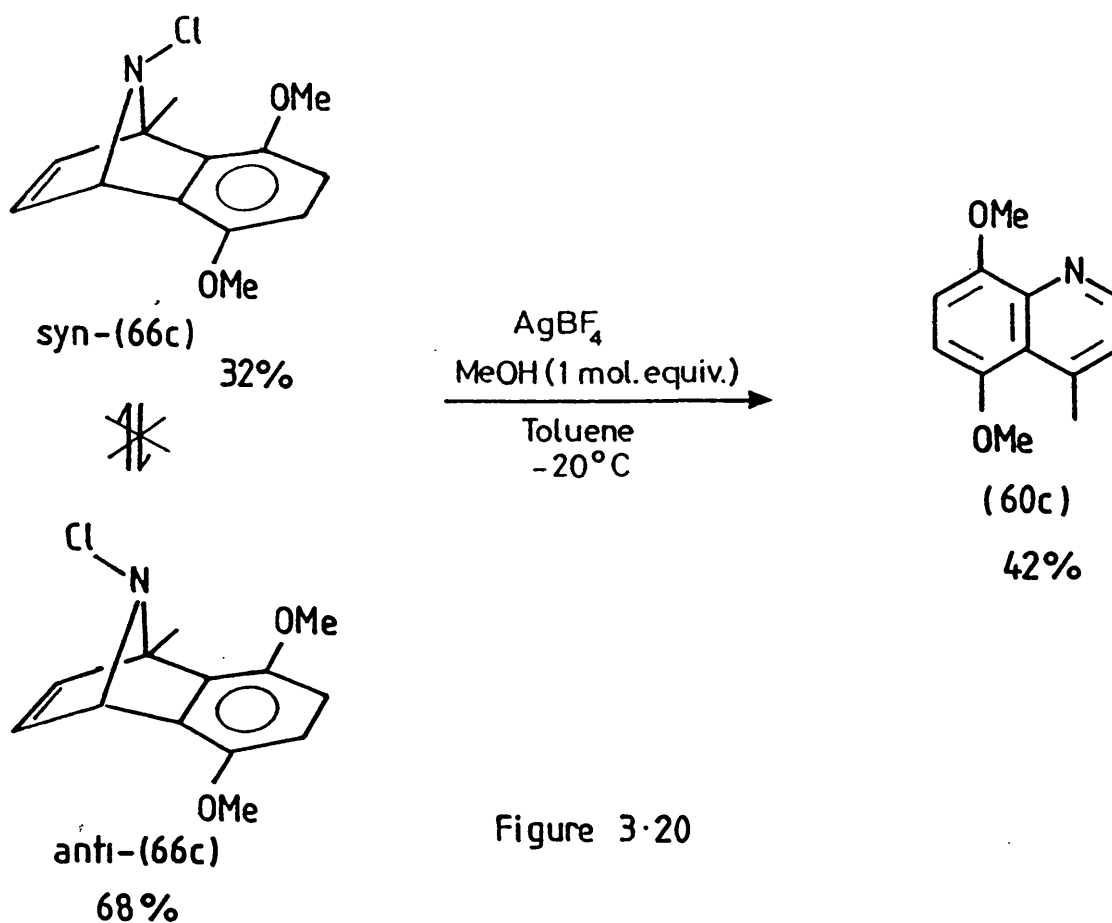
Figure 3·20

As with (60b), the fact that (60c) is produced in 42% yield strengthens the view that the quinoline product is derived from the anti-N-chloroamine.

Heterolysis of the N-chloroamines (58b) and (58c), i.e. the analogous systems containing a methyl group at both of the bridgehead positions proceeded with loss of a two-carbon unit to form the 4-methyl-quinoline derivatives (60b) and (60c). Rearrangement of (66b) and (66c) produced the same products but with loss of only one carbon atom, thus suggesting that the reaction is proceeding with elimination of a bridge-head carbon; in the above examples, the bridgehead carbon without an adjacent methyl group.

The reaction therefore proceeds <u>via</u> aryl participation of the anti-invertomer (66b,c) with the possibility of two intermediates (81) or (82), (figure 3.21). However, as previously discussed, (81) is unlikely to ring open and is thus not considered to be a precursor of the quinoline derivatives (60b,c). The ability of the methyl group to increase the stability of the positive charge at the benzylic position will encourage (82) to ring open to form a benzazatropylium ion (83).

anti-(66)

b: X= H
c: X= OMe

(81)

(82)

(83)
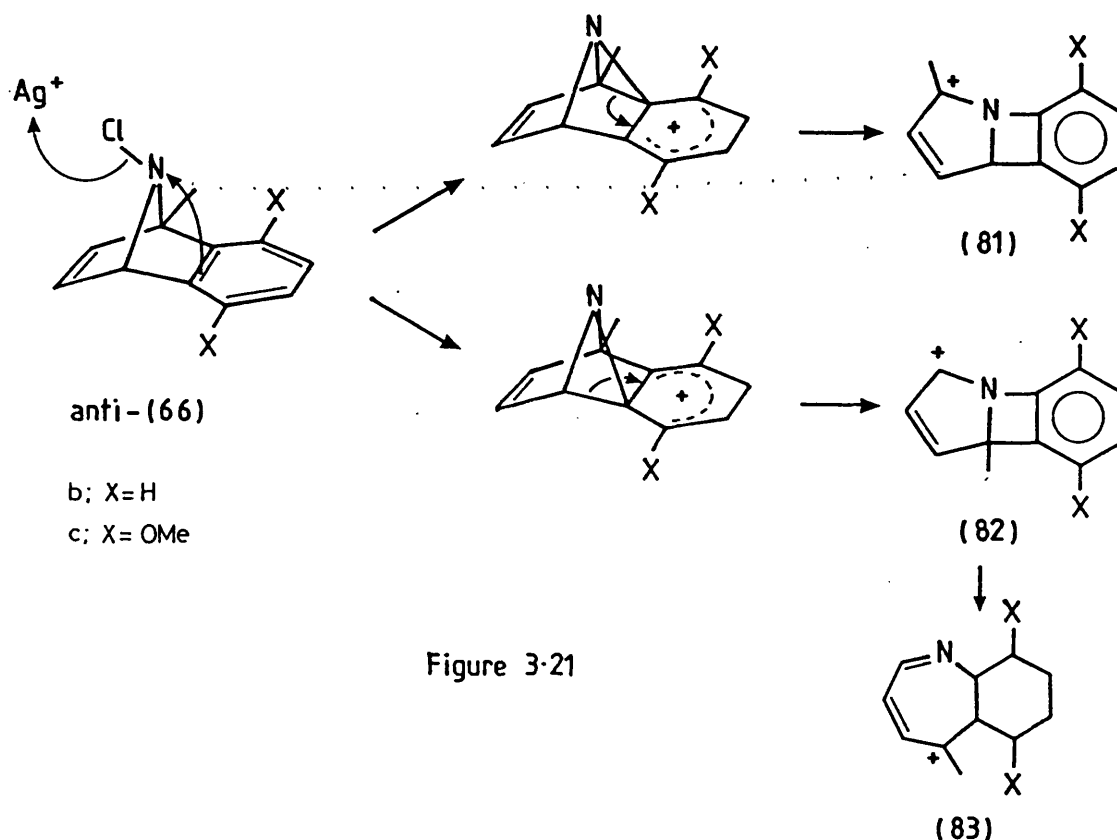
Figure 3·21

Interestingly, this suggests at first sight that the reaction is occurring <u>via</u> the less stable carbenium ion (82) in contrast to the corresponding ethano-bridged systems where the reaction was thought to proceed preferentially <u>via</u> the more stable tertiary carbenium ion (74). However, consideration of molecular models indicates that the bonds that cleave in the reaction (indicated by the dashed lines) overlap to some extent with the p-orbitals of the π-bonds and so perhaps a more complex concerted mechanism may be involved leading directly to (83), (figure 3.22).
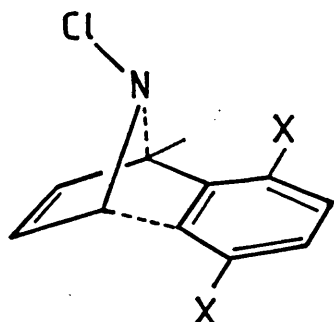
Figure 3·22

The fact that no products were observed from the intermediate (81) is also significant. The modest regioselectivity in the ethano-bridged cases surmises reaction via both pathways. However, since there is only one product, this adds to the pressure for a slightly different mechanism.

The benzazatropylium ion (83) can, in fact, be represented by seven canonical forms, (figure 3.23). The substituent R represents a hydrogen atom or a methyl group in order to extend this proposed mechanism to include the formation of quinoline derivatives from the analogous dimethyl substituted compounds (58b,c).

(83a)   (83b)   (83c)

(83d)   (83e)   (83f)   (83g)
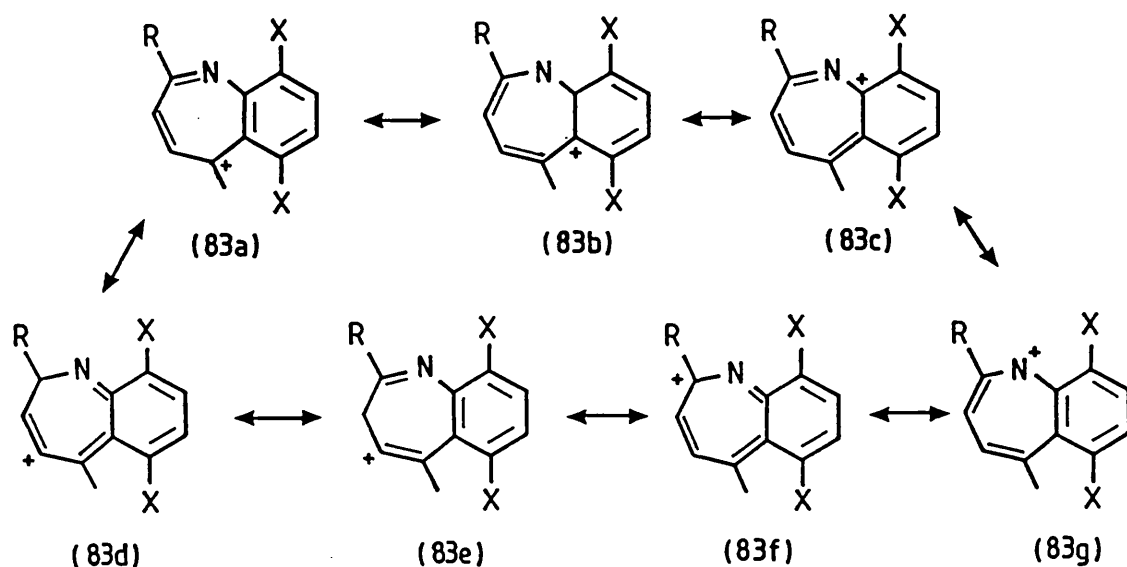
R = H,Me

Figure 3·23

In each case, reaction with methanol leads to a reversible conversion to seven alternative neutral methoxy compounds (84a-g). Formation of a six-membered nitrogen-containing ring can be achieved via a 6π→4π electrocyclic ring closure. However, ring closure of the methoxy compounds (84a,e,g) would result in the undesirable loss of aromatisation of the benzo-ring, and is thus discounted. Similarly, ring closure of (84b,c) would produce unlikely looking structures containing very strained three-membered rings. Examples of both are illustrated in figure 3.24.
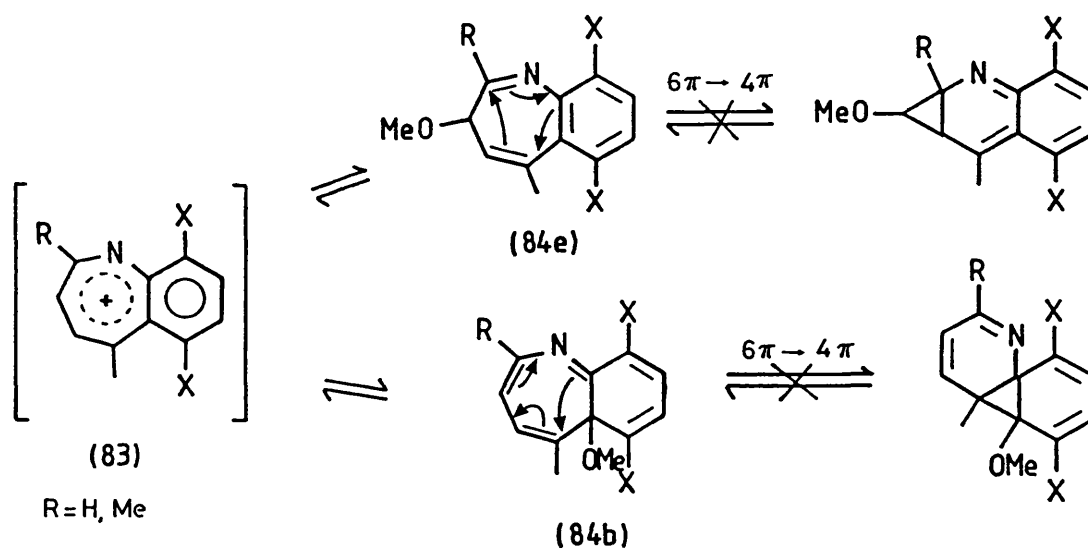
Figure 3·24

Electrocyclic ring closure of the methoxy compounds (84d,f) appear more plausible, the products being (85) and (86). However, the reaction appears to proceed via (86) due to the high stability of the resulting quinoline product (60) (figure 3.25).
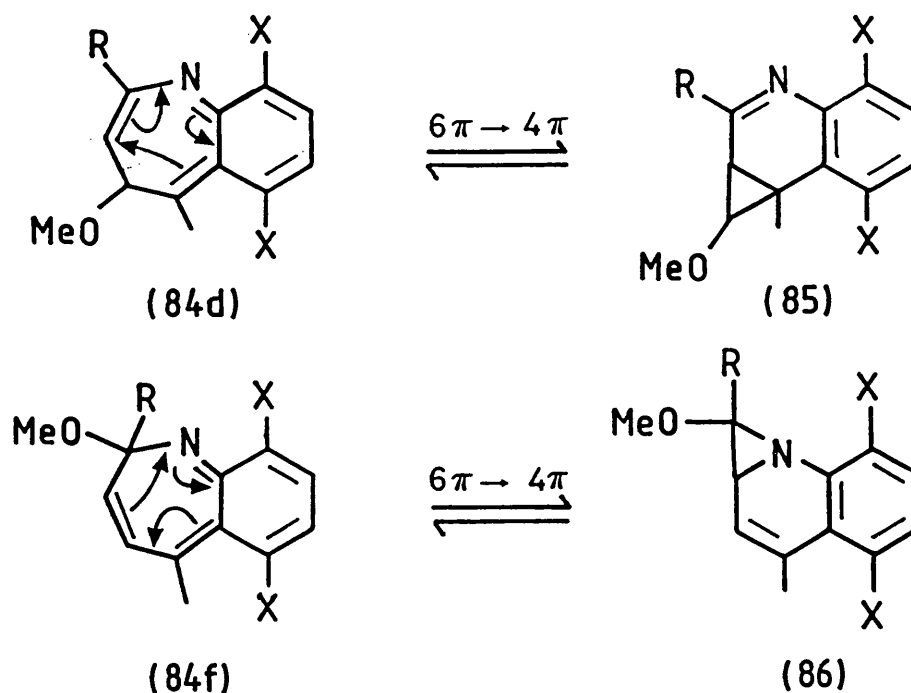
R = H, Me

Figure 3·25

(86) Can break down to form the quinoline structure (60) in three possible ways, (figure 3.26).

Route a involves cleavage of the N-C bond of the three membered ring to form (87). Addition of methanol would produce (88) which could only form the quinoline structure by the unlikely loss of a hydride ion. Cleavage of the C-C bond in route b is equally undesirable due to the formation of an antiaromatic structure (89). Route c provides the only plausible mechanism involving cleavage of the C-C bond shown to form a 1,3-dipole and effective loss of methanol (or ethanol for the dimethyl substituted compound) to form the 4-methylquinoline derivatives (60b,c).

R = H, Me
b : X = H
c : X = OMe
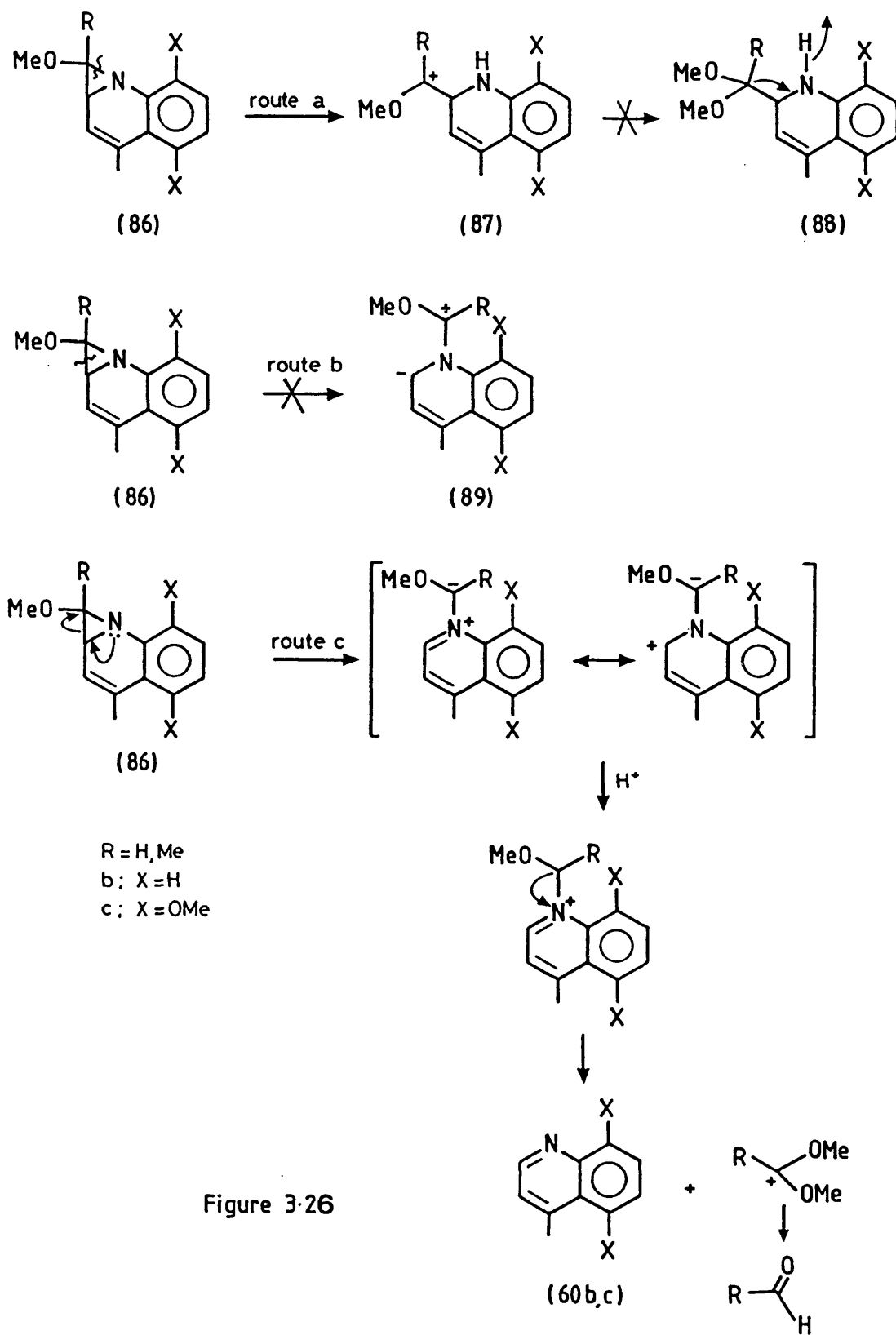
Figure 3·26

Chapter 4

Synthetic Approaches to Nortropane and

Nortrop-6-ene Derivatives

4.I.   INTRODUCTION

In recent years, 7-azabicyclo[2.2.1]heptyl derivatives have been a subject of significant interest particularly since these systems are unique amongst relatively unstrained azacycles in possessing anomalously high nitrogen inversion barriers. The slow inversion at nitrogen in such systems has facilitated the study of invertomer preferences[44] and the stereochemical consequences of reactions at nitrogen.[45] Unusual deshielding of the bridging nitrogen in ^{15}N NMR studies has also been noted (see Appendix 2).[77]

The unusual nature of the bridging nitrogen in the 7-azabicyclo-[2.2.1]heptane system generated interest in homologous systems, particularly 8-azabicyclo[3.2.1]octyl derivatives, (figure 4.1). 8-Azabicyclo[3.2.1]octane is, of course, the skeleton of the tropane alkaloids which are natural products occurring principally in the plant families Solanaceae, Convolvulaceae, Erythroxylaceae, Euphorbiaceae, Proteaceae, and Rhizophoraceae.

X = H: Nortropane

X CH_3: Tropane
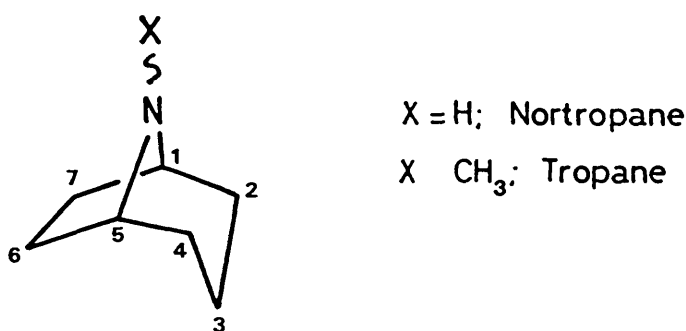
Figure 4·1

The majority of the alkaloids have been known for a long time and very few new alkaloid structures have appeared in the last twenty-five years. Therefore, the main chemical endeavour in this area has been concentrated on synthetic work, stimulated by the interesting pharmacological properties of many of the alkaloids.

Robinson's classical synthesis of one of the simplest alkaloids, tropinone (90), from succinaldehyde, methylamine and acetone dicarboxylic acid[78] is still the industrial basis for its synthesis, the route being simple, direct and efficient, (figure 4.2).
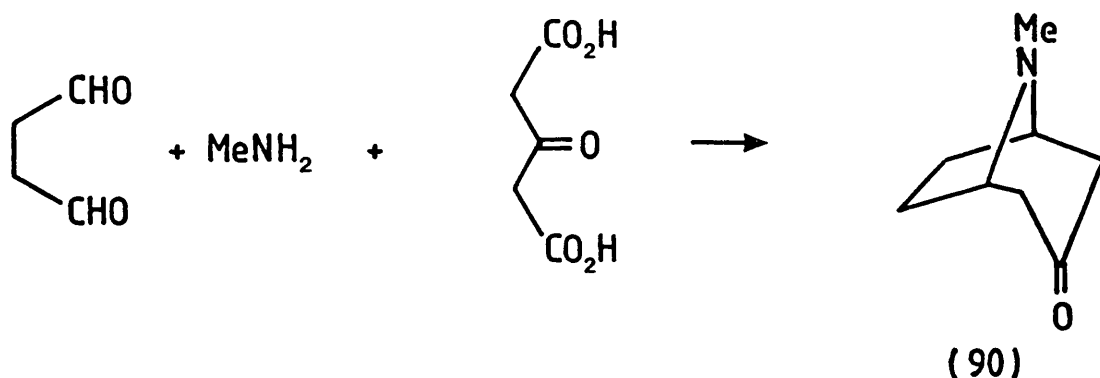
Figure 4·2

An alternative route to tropinone involves the condensation of cyclohepta-2,6-dienone with methanolic methylamine,[79] (figure 4.3).
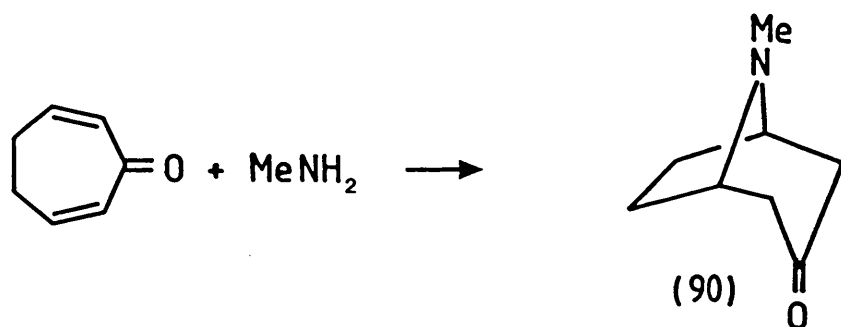
Figure 4·3

Many other synthetic approaches to tropane alkaloids have been investigated. However, most routes reported so far are able to produce derivatives of only certain types in that they usually incorporate a N-methyl substituent, an oxygen function at C(3) and a saturated ethano-bridge.

An important route to trop-6-ene-3-one derivatives, however, has been reported by Hoffmann et al.[80] The reductive halogenation of α,α'-dibromo ketones (91) with sodium iodide in the presence of pyrroles (92) and copper has been found to produce a variety of 6,7-dehydro-tropinones (93), (figure 4.4).

$$\text{(92)} + \text{(91)} \xrightarrow[\text{CH}_3\text{CN}]{\text{NaI, Cu}} \text{(93)}$$
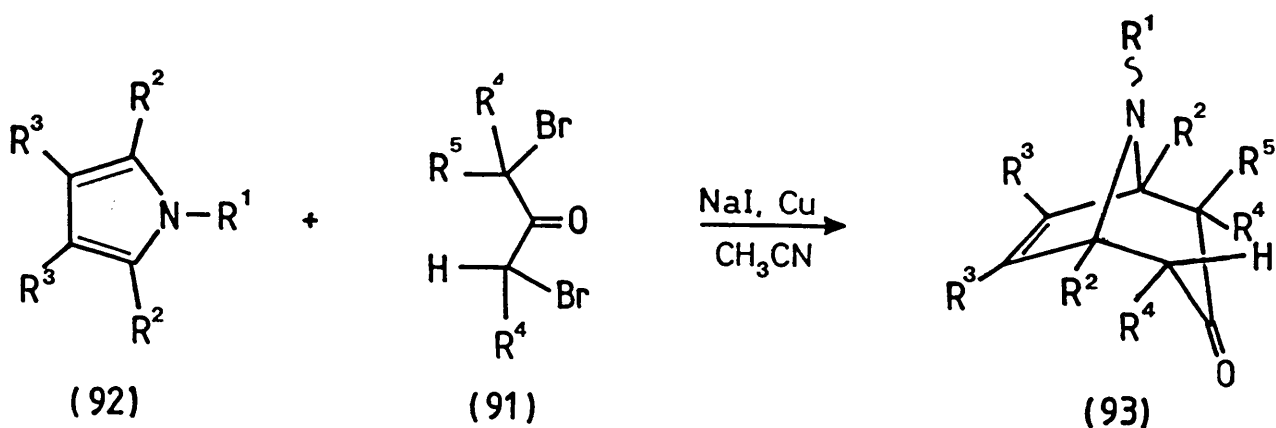
Figure 4·4

Less alkylated derivatives have been synthesised by Noyori et al.[81] using a variation of the above route. The synthesis involves an iron carbonyl-promoted [3+4] cyclocoupling.

Nevertheless, these compounds still contain a N-alkyl substituent and an oxygen function and this disadvantage also limits a new synthetic approach to tropane alkaloids which was noted recently,[82] (figure 4.5).
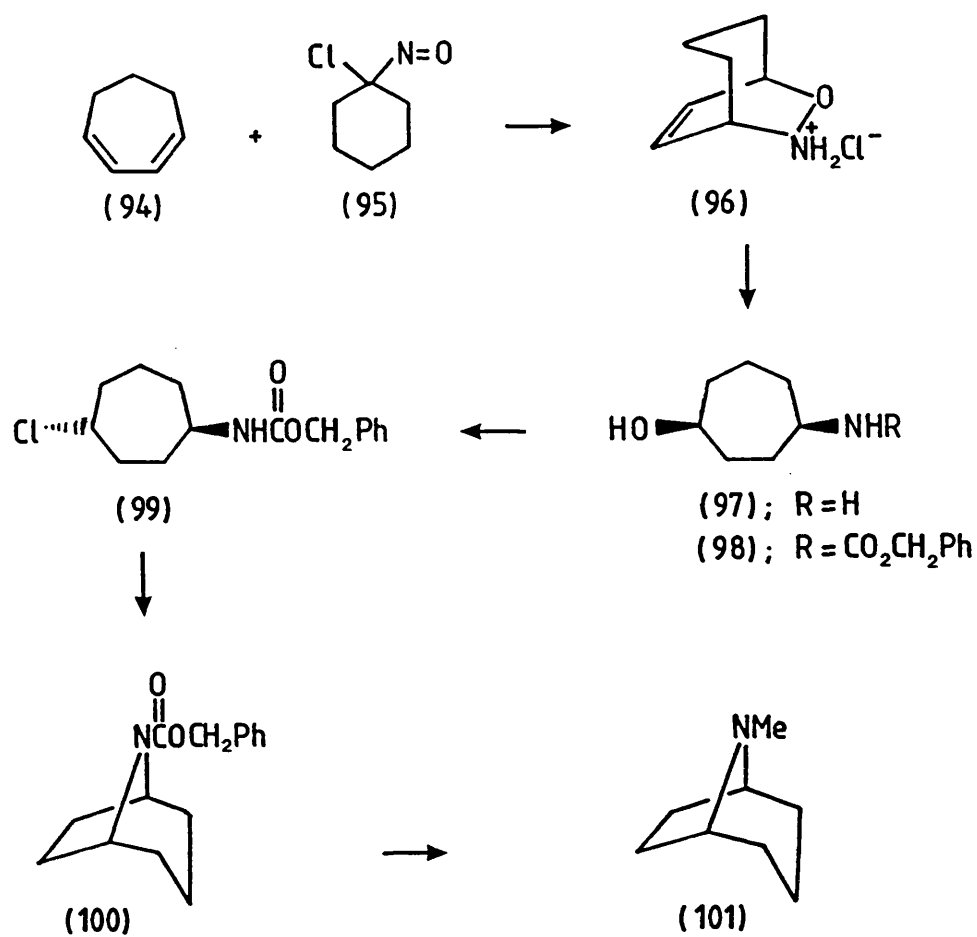
Figure 4·5

This route involves a Diels-Alder reaction of 1,3-cyclohepta-diene (94) and 1-chloro-1-nitrosocyclohexane (95). Reductive treatment involving the N-O fission of (96) to give (97) was followed by amine protection (98). Reaction with thionyl chloride afforded the trans-chloride (99) which was converted to N-carbobenzoxynortropane (100) when subjected to base-induced intramolecular cyclisation. Initial cyclisation attempts however proved unsuccessful, the reaction ultimately only proceeding in the presence of the hazardous cosolvents benzene and hexamethylphosphoric triamide (HMPA). The choice of protecting group on nitrogen was also crucial since hydrolysis of N-benzoyl derivatives of (100) failed. Synthesis of tropane (101) was achieved by lithium aluminium hydride reduction of the benzyl carbamate (100).

Previous experience with the cleavage of N-carbobenzoxy protecting groups (see Chapter 2) renders this method the ideal candidate to develop and to introduce flexibility, thus allowing the preparation of artificial analogues not occurring in plant tissues. Synthetic flexibility is the key to achieving effective drug design because skeletal modification of natural products often increases or improves the specific physiological activities.

Thus, the synthetic approach chosen was an intramolecular cyclisation. This method could also be modified to synthesise other azabicycles. For example, a Diels-Alder reaction involving 1,3-cyclohexadiene might lead to 7-azabicyclo[2.2.1]heptane, and 1,3-cyclooctadiene to 9-azabicyclo[4.2.1]nonane. In addition, this procedure might reasonably be expected to allow the introduction of unsaturation in the two-carbon bridge, (figure 4.6).
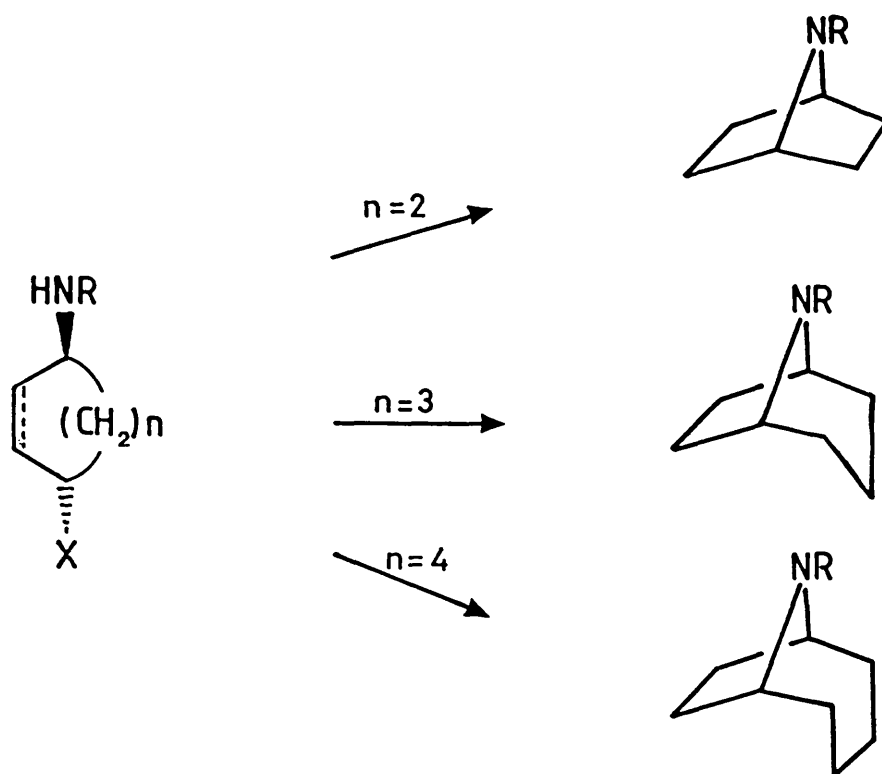
Figure 4·6

Many highly substituted derivatives of 7-azabicyclo[2.2.1]-heptane have been produced by the Diels-Alder reactions of N-alkyl and N-acyl pyrroles with dimethylacetylene dicarboxylate.[83-85] However, one report describes the successful synthesis of the parent saturated amine (102)[86] in an overall yield of 18% from 4-acetamidophenol (103), the crucial step being the cyclisation of the amino mesylate (104), (figure 4.7).

(103) (104) (102)
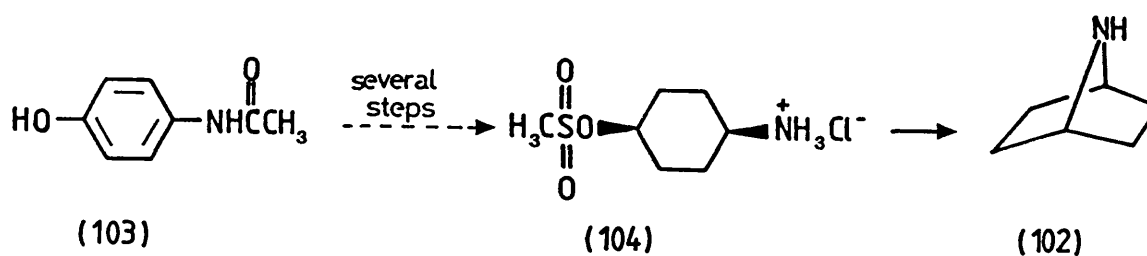
Figure 4·7

The 9-azabicyclo[4.2.1]nonane ring system is of interest due to its occurrence in alkaloids such as anatoxin a (105). The synthesis of this compound has been accomplished using several methods. Gallagher et al.[87] reported the total synthesis of anatoxin a, the key step being the intramolecular alkylation of (106) to give the bicyclic ketosulphone (107), (figure 4.8).

(106) (107) (105)

(±)-anatoxin a
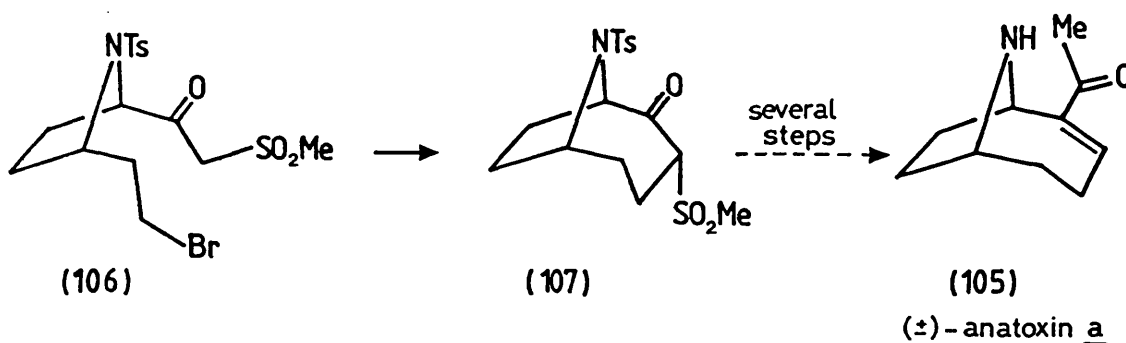
Figure 4·8

Danheiser et al.[88] reported an alternative approach, the key step this time being the transannular cyclisation of (108) to produce the vinyl bromide (109), (figure 4.9).
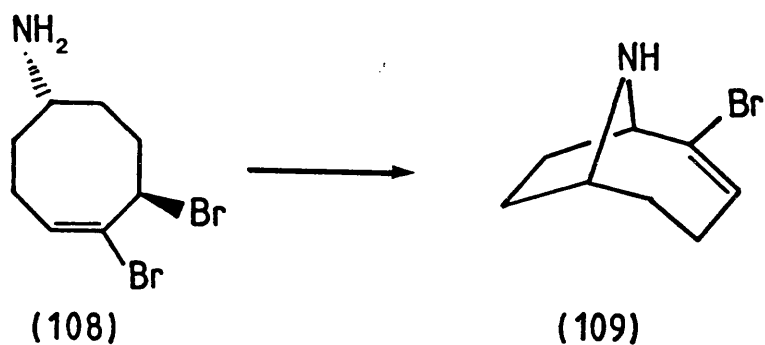
Figure 4·9

Very little work has been reported on the determination of inversion barriers of 8-azabicyclo[3.2.1]octane derivatives. Thus, the nitrogen inversion process of such systems was thought worthy of further study since the question of barriers of the N-chloro compounds has not been clarified totally, especially in the etheno-bridged systems. This would also allow opportunities for study of invertomer preferences and the chemistry of the N-chloro derivatives.

Facial selectivity in such systems is of interest, too. Stereoselectivity in attack at nitrogen would almost certainly be confined to quaternisation since it is likely that most derivatives (even the N-chloro compounds) would invert too rapidly. However, facial selectivity in attack on the π-bond is of real interest as is the part which nitrogen might play both electronically (see Chapter 5) and sterically, i.e. depending on the nitrogen substituent.

Thus, the syntheses of nortropane and its unsaturated analogue, nortrop-6-ene were attempted, together with azabicycles with varying numbers of carbon atoms in the bridging positions. However, this chapter will concentrate primarily on the syntheses of nortropane and nortrop-6-ene.

4.II.   SYNTHESIS AND SPECTROSCOPIC INVESTIGATIONS

Nortropane was prepared from the intermediate azabicycle (100) previously synthesised by Kibayashi et al.,[82] (figure 4.10). The Diels-Alder reaction of 1,3-cycloheptadiene (94) and 1-chloro-1-nitrosocyclo-hexane (95) yielded the cycloadduct (96) as its hydrochloride. The yield was improved from 68%[82] to 83% by extending the reaction time. Catalytic hydrogenation of (96) afforded the amino alcohol (97) (isolated as its hydrochloride salt) almost quantitatively and this was then subjected to selective acetylation with benzyl chloroformate. Treatment of the benzyl carbamate (98) with thionyl chloride in the presence of excess pyridine yielded the trans-chloride (99) (58% yield) which was converted into N-carbobenzoxynortropane (100) in 57% yield when subjected to base-induced intramolecular cyclisation with potassium t-butoxide in a 1:1 HMPA-benzene solution. Cleavage of the protecting group was achieved almost quantitatively when treated with hydrogen bromide in glacial acetic acid to give nortropane (110) which was stored as its hydrochloride salt.

In order to synthesise nortrop-6-ene (111), the hydrogenolytic cleavage of the N-O bond would obviously have to be avoided; thus a modification to this synthetic approach was sought. An alternative dienophile, benzylnitrosoformate (112),[89] was employed which was generated in situ from benzyl N-hydroxycarbamate[90] and tetramethyl-

ammonium metaperiodate.[91]   Reaction of the nitroso compound with
1,3-cycloheptadiene (94) afforded the Diels-Alder adduct (113) in 90%
yield.   However, reductive N-O bond cleavage with 5% sodium amalgam in
ethanol afforded (114) in very poor yield (7%), (figure 4.11).
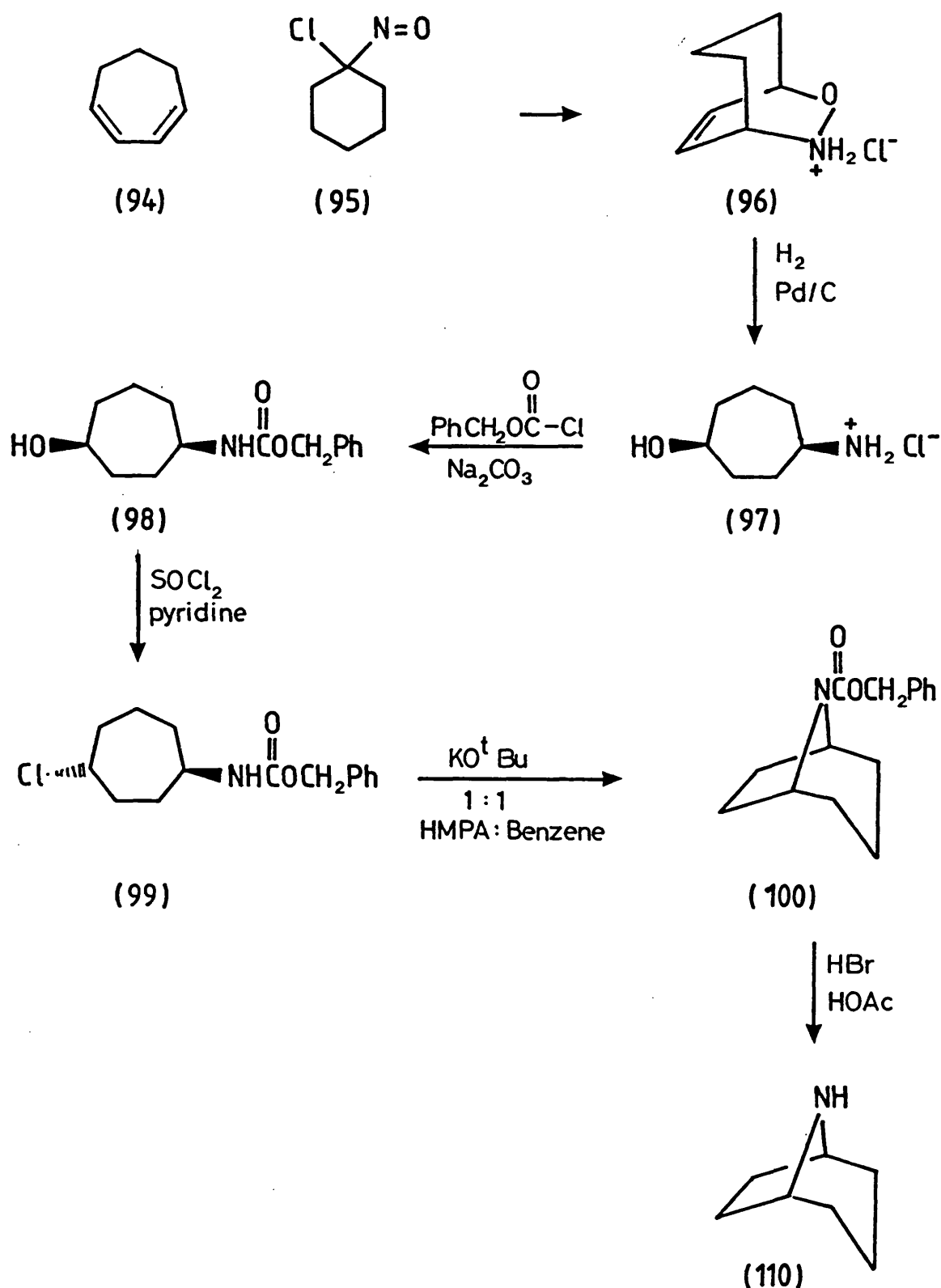
Figure 4·10
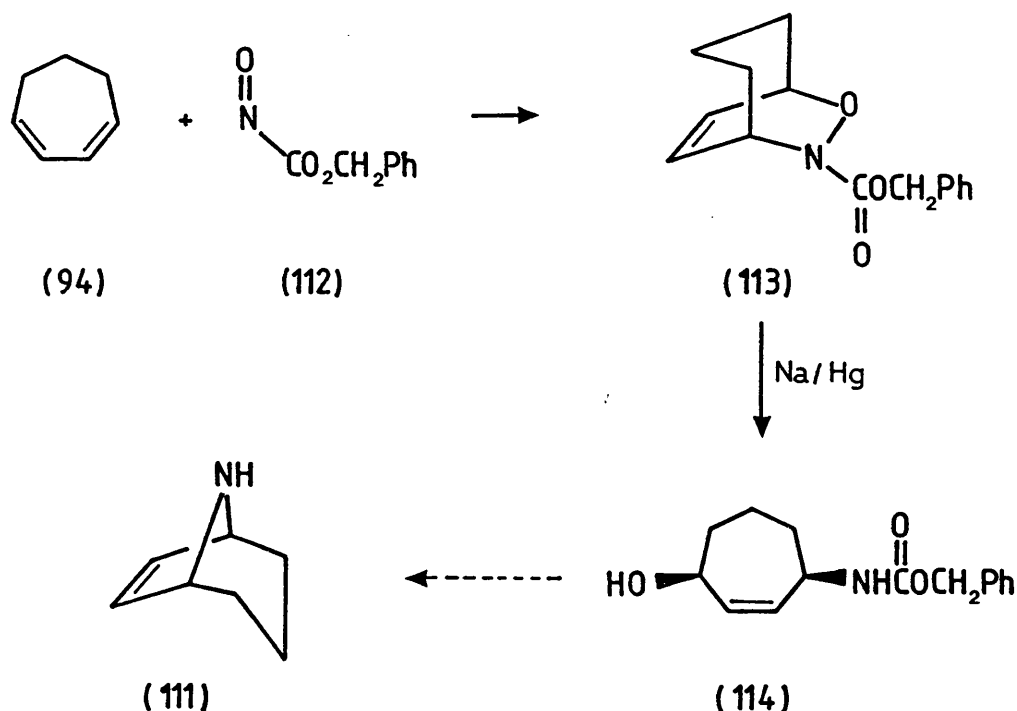
Figure 4·11

Reaction of (113) with zinc in glacial acetic acid[92] also failed to cleave the N–O bond. However, this difficulty was overcome by using a slightly lengthier approach. The carbobenzoxy protecting group was cleaved from the cycloadduct (113) using hydrogen bromide in glacial acetic acid to produce (115) in 72% yield. The N–O bond was subsequently cleaved cleanly and fairly efficiently (64% yield) to give (116) and then the amine protecting group replaced by treatment with sodium hydride and benzyl chloroformate (95% yield). Reaction of (114) with thionyl chloride in the presence of excess pyridine afforded the trans–chloride (118a). However, cyclisation of the chloride (118a) to the trop-6-ene skeleton (119) using a variety of strong bases and differing solvents failed, only starting material being recovered from the reaction mixture. A better leaving group e.g. bromide (118b) might reasonably be expected to facilitate the cyclisation. Nevertheless, after successful synthesis of the trans-bromide (118b), all attempts to induce cyclisation were unproductive, (figure 4.12).
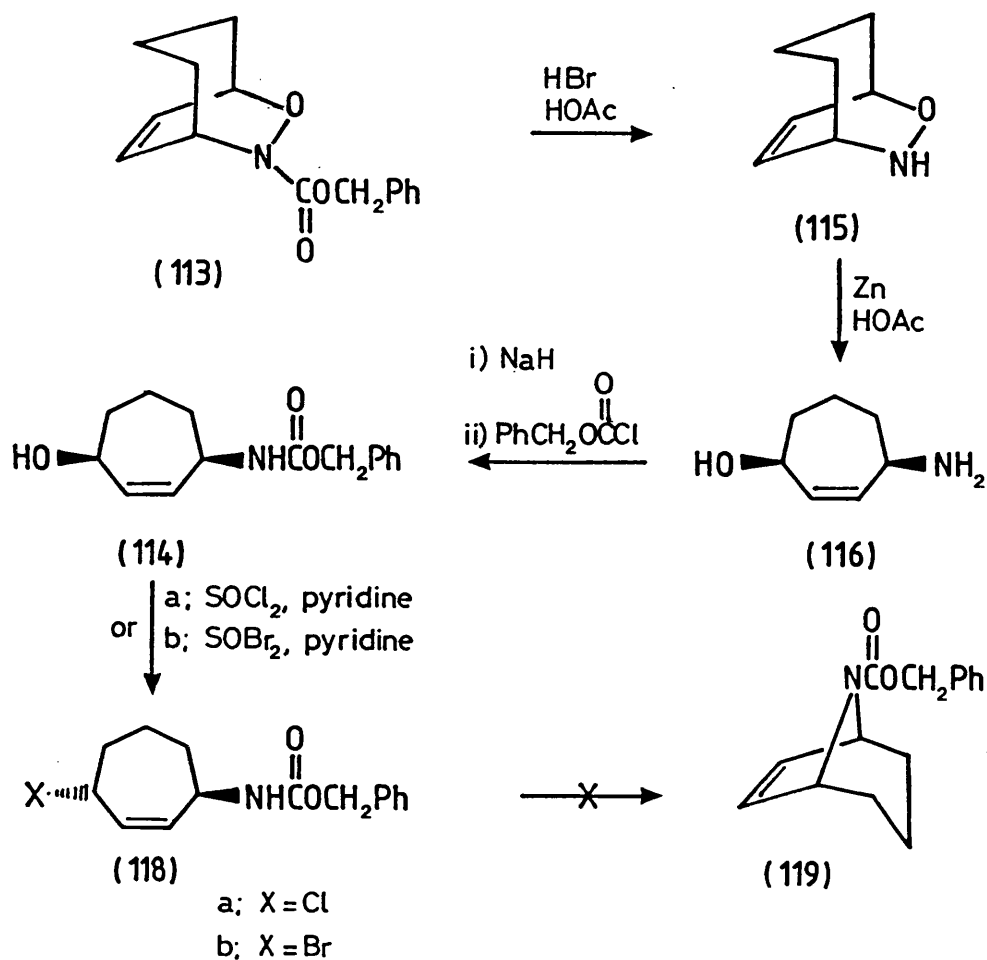
Figure 4·12

Failure of the trans-halides (118a,b) to cyclise necessitated an alternative procedure. Trost et al.[93] has synthesised a number of alkaloids using palladium-catalysed cyclisations. Palladium (0) catalysts react with allylically oxidised compounds (120), (figure 4.13), to yield π-allyl palladium complexes. The catalytic cycle consists of an initial activation stage to form a π-allyl complex (121) which involves coordination of a coordinatively unsaturated palladium (0) species with the alkene on the face opposite that of the leaving group. Loss of the leaving group generates a π-allyl cationic intermediate (122). This is followed by a substitution stage, in which, the nucleophile normally attacks the face of the allyl unit opposite to palladium (123). Thus, palladium (0) initially serves as a nucleophile,

and having done so, becomes a leaving group to give the final product (124).
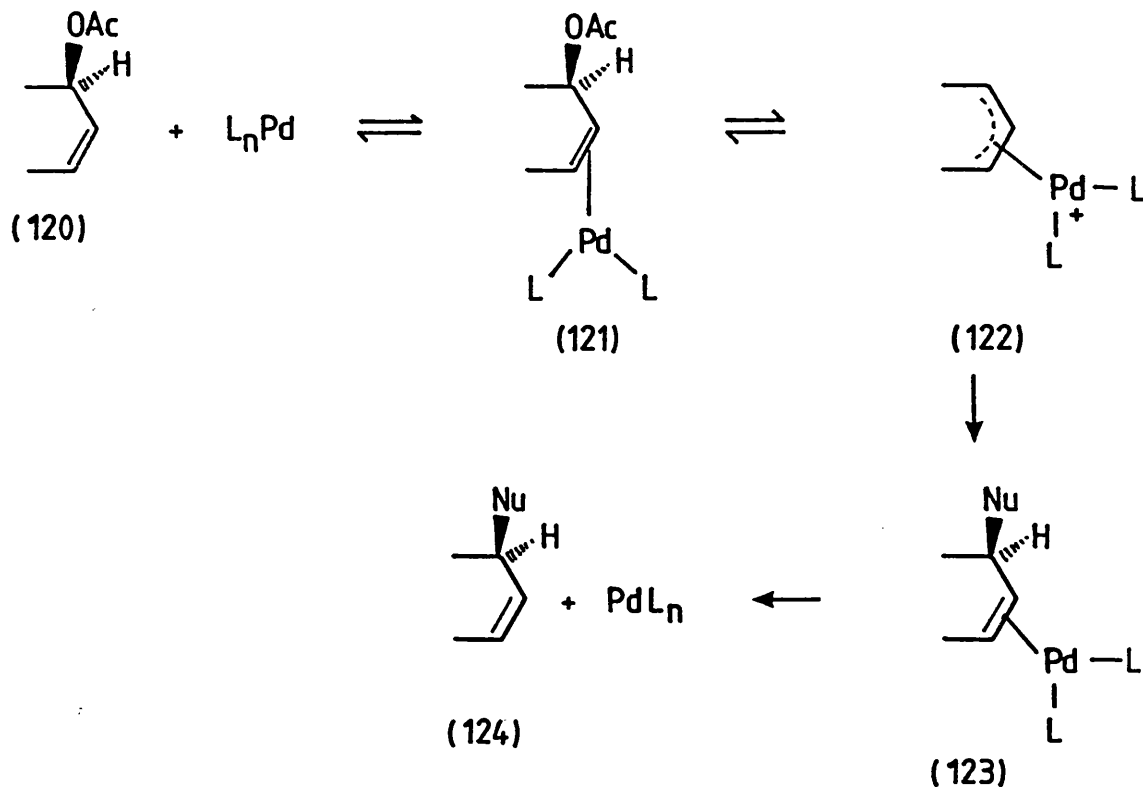
Figure 4·13

Such reactions can be accomplished in an intramolecular sense, i.e. cyclisation. This method has, for example, formed the basis of the synthesis of 6-azabicyclo[3.2.1]oct-3-ene (125).[93] Treatment of the amino acetate (126) with a palladium catalyst in tetrahydrofuran containing triethylamine gave the cyclised amine (125) which is the basic ring skeleton of actinobolamine, (figure 4.14).
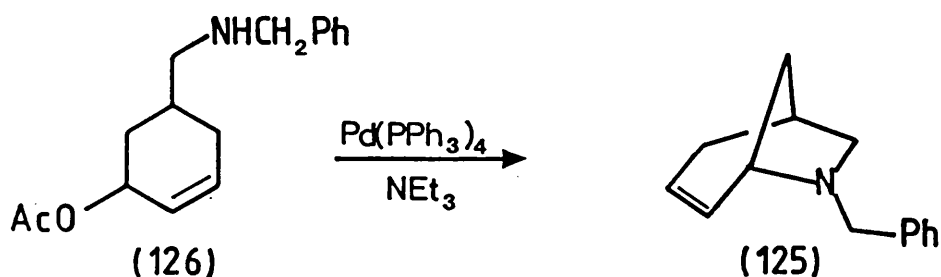
Figure 4·14

This procedure might reasonably be expected to promote the cyclisation of the acetate (127) to yield the tropane skeleton (119), (figure 4.15). Thus, the alcohol (114) was acetylated using acetyl chloride and pyridine. However, treatment of (127) with Pd(PPh₃)₄ in the presence of triethylamine did not give the desired product; the diene (128) was unexpectedly produced.
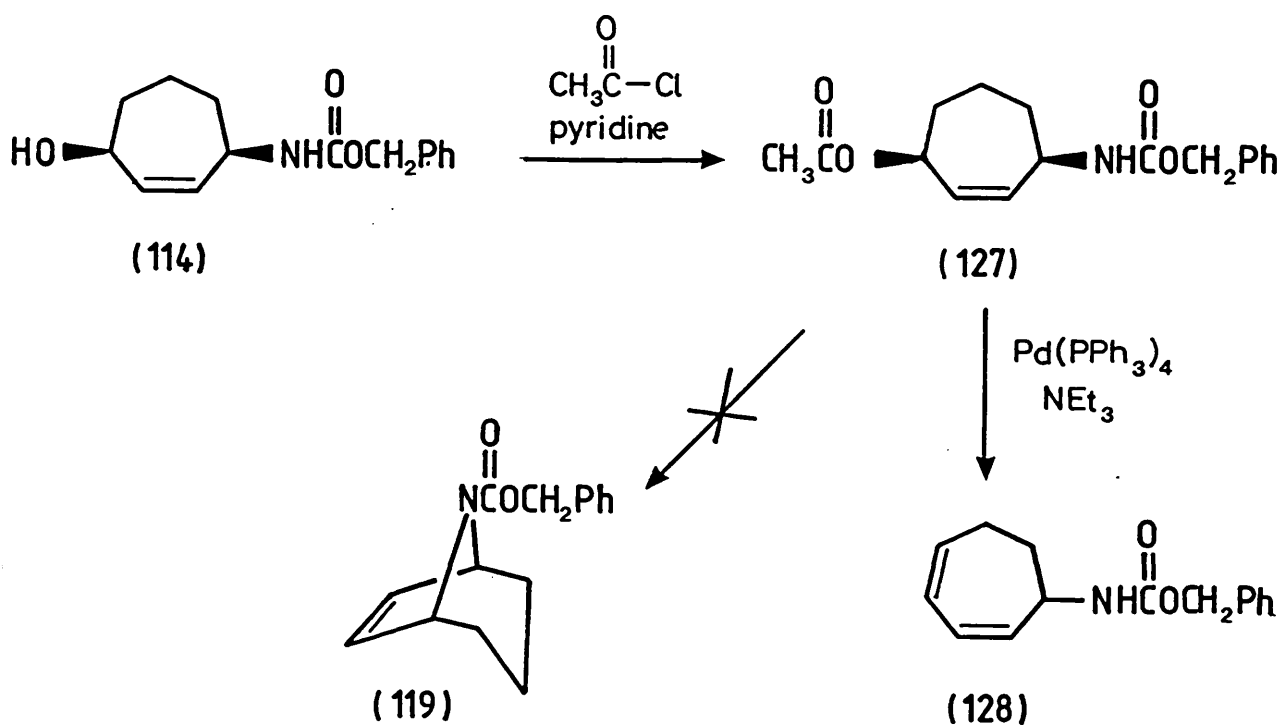
Figure 4·15

Reaction of the acetate (127) under identical conditions but omitting the palladium catalyst yielded only starting material. Thus, the elimination reaction must be palladium-catalysed. This can be explained via the formation of a π-allylic complex (129) by the oxidative addition of the allylic compound (127) to Pd(0). Elimination of acetic acid from the complex liberates the diene (128) and regenerates the zerovalent palladium which recycles, (figure 4.16).

AcO—⟨⟩—NHCOCH₂Ph + Pd°L ⟶

(127)

(129)

↓ NEt₃

AcOH + Pd°L + ⟨⟩—NHCOCH₂Ph ⟵

(128)
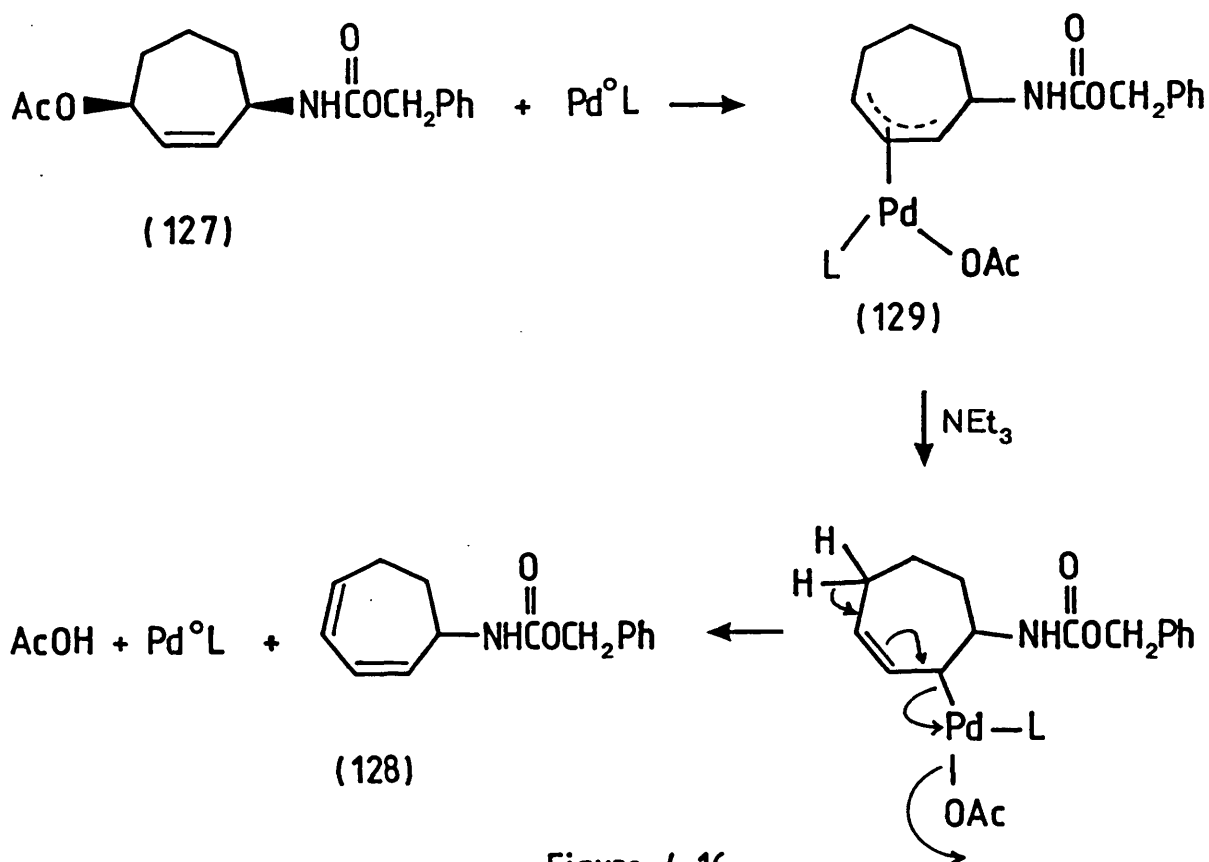
Figure 4·16

This procedure has, in fact, been reported as a preparative method for conjugated diene systems based on the elimination of acetic acid.[94,95]

It appears that elimination is favoured over intramolecular cyclisation and so it was decided to try to make the cyclisation more competitive by increasing the nucleophilicity of the nitrogen. A benzyl protecting group seemed the ideal candidate due to the successful cyclisation of (126) and since the compounds could be easily prepared using a slight modification of the previous synthesis. The range could also be extended to include different sized carbon bridges. The saturated analogues were prepared first in order to determine whether the increased nitrogen nucleophilicity improved the efficiency of the cyclisation.

Thus, the Diels-Alder reactions of the dienes (130a,b,c) with the acyl nitroso compound (131)[82] generated in situ from benzohydroxamic acid and tetramethylammonium metaperiodate yielded the cycloadducts (132a,b,c), (figure 4.17).

(130)   (131)   (132)

a; n = 2   93%
b; n = 3   99%
c; n = 4   92%
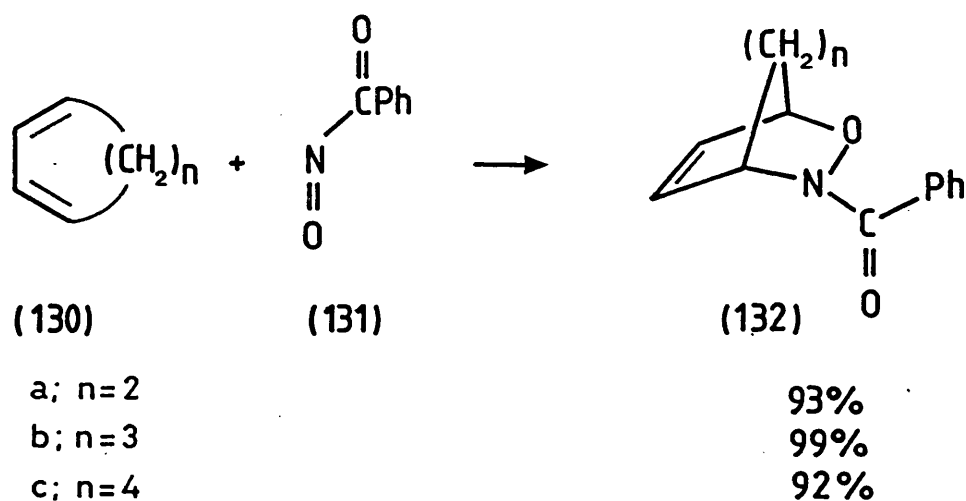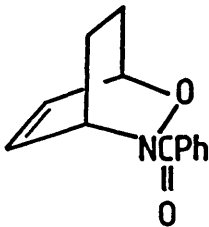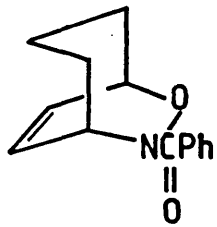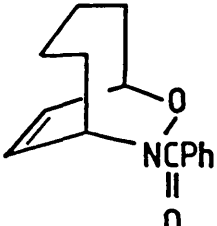
Figure 4·17

Each cycloadduct was found to exist as a pair of rotamers, rotation occurring about the N-CO bond. Low temperature NMR spectroscopy revealed the presence of two separate signals for each proton, thus indicating slow isomerisation. The rotational energy barriers were determined using the technique of variable temperature NMR. The results are summarised in table 4.1.

Determination of the rotational energy barrier of (132c) was not possible due to the presence of two temperature-dependent processes. The other process occurring is presumably inversion of the cyclooctene ring.

Table 4.1. **Rotational Energy Barrier** $\Delta G^{\ddagger}$/kJmol^{-1}

(132a)

O
NCPh
‖
O

57·9

(132b)

O
NCPh
‖
O

55·6

(132c)

O
NCPh
‖
O

Undefinable

Reductive cleavage of the N–O bond of (132a,b,c) was achieved with 5% sodium amalgam. However, significantly improved yields were attained when the cycloadducts were treated with aluminium amalgam in aqueous tetrahydrofuran,[96] (133 a, 97%; b, 92%; c, 71%), (figure 4.18). Hydrogenation over palladium on charcoal to yield the saturated alcohols (134 a, 99%; b, 99%; c, 98%)[82] was followed by treatment with lithium aluminium hydride to afford the corresponding amino alcohols (135 a, 91%; b, 99%; c, 99%) with the required benzyl protecting group.
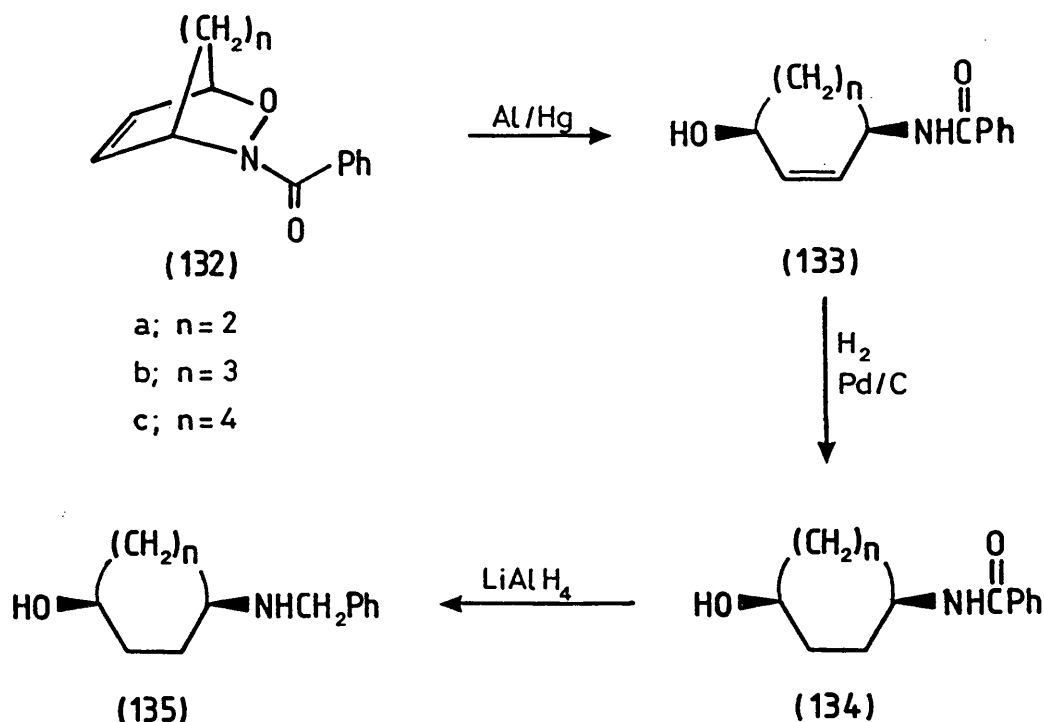
Figure 4·18

Attention was primarily directed at the cyclisation of (135b) in order to form the tropane skeleton. However, treatment with thionyl chloride in the presence of pyridine failed to yield the trans-chloride, producing only unidentifiable products. The only difference between this compound (135b) and the alcohol (98) that had previously been converted into a trans-chloride is the presence of a reactive secondary amine. This must be the underlying cause of the failure of the alcohol to react as required. The obvious way to overcome this situation is to protect the amine. However, consideration of the mechanism of the chlorination reaction rendered conventional amine protection unnecessary.

Thionyl chloride reacts with alcohols to form alkyl chloro-sulphites (136) which undergo SNi reactions. The chlorosulphite is formed with retention of configuration, the R—O bond not being broken during the reaction. The first step involves dissociation into an intimate ion pair. Provided collapse of the ion pair to products occurs

rapidly, then attack by chloride ion is likely to occur on the same side of R^+ from which ^-OSOCl departed i.e. with retention of configuration, (figure 4.19).

$$R-OSOCl \longrightarrow R^+ + {}^-\overset{\overset{\displaystyle O}{\overset{\displaystyle \|}{}}}{O}S-Cl$$

$$(136)$$

$$\downarrow$$

$$RCl \longleftarrow R^+Cl^- + SO_2$$
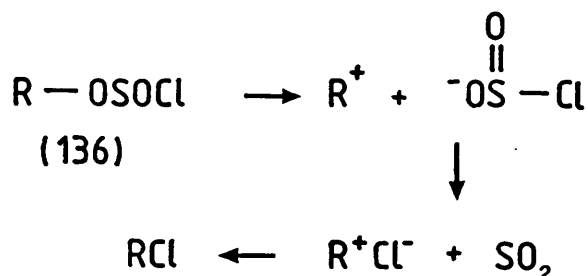
Figure 4·19

However, addition of pyridine to the mixture of alcohol and thionyl chloride results in the formation of alkyl halides with inverted configuration. Inversion results because the hydrogen chloride produced during the formation of the alkyl chlorosulphite is converted by pyridine into $C_5H_5NH^+Cl^-$, and the chloride ion, being an effective nucleophile attacks from the rear in a normal SN2 reaction with inversion of configuration.

The amine in compound (135b) might be able to act in an analogous manner to pyridine, thus protecting the amine in the meantime (137), (figure 4.20). The free chloride ion would be able to attack from the rear, resulting in the required inversion of stereochemistry (138). Subsequent addition of pyridine might be expected to regenerate the free amine to give the required product (139) which should be capable of cyclising to the required N-benzylnortropane (140).
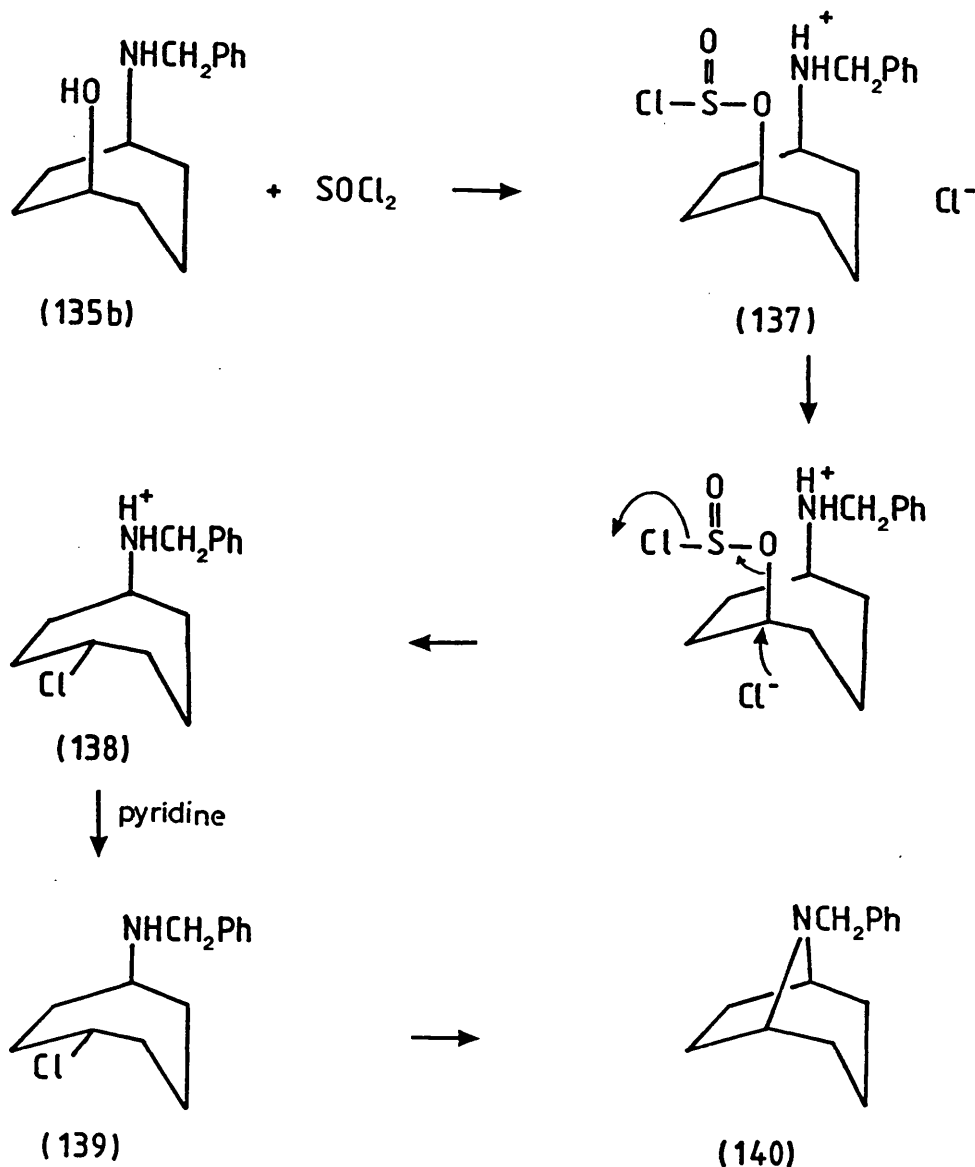
Figure 4·20

Note: The boat conformation of the cycloheptane ring illustrated here is not the most energetically stable conformation.

Indeed, reaction of (135b) with thionyl chloride and subsequent treatment with pyridine gave N-benzylnortropane (140) in unexpectedly high yield (88%), the increased nucleophilicity of the amine apparently being sufficient to induce cyclisation in the reaction medium. The ease of intramolecular cyclisation is reflected in the overall yield of the synthesis to produce the tropane skeleton; 79% compared to Kibayashi's 23%.[82]

N-Benzylnortropane was easily recognisable due to the simplicity of the ^{1}H NMR spectrum reflecting the high symmetry of the system, (figure 4.21).

Low temperature ^{13}C NMR studies indicated the presence of two invertomers. The inversion barrier was determined using the technique of variable temperature NMR and was found to be 36.1kJmol^{-1}. However, it is possible that the process being observed is ring inversion rather than nitrogen inversion, (figure 4.22).

PhCH$_2$

equatorial

⇌

CH$_2$Ph

axial

Nitrogen inversion

PhCH$_2$

chair

⇌

PhCH$_2$

boat

Ring inversion
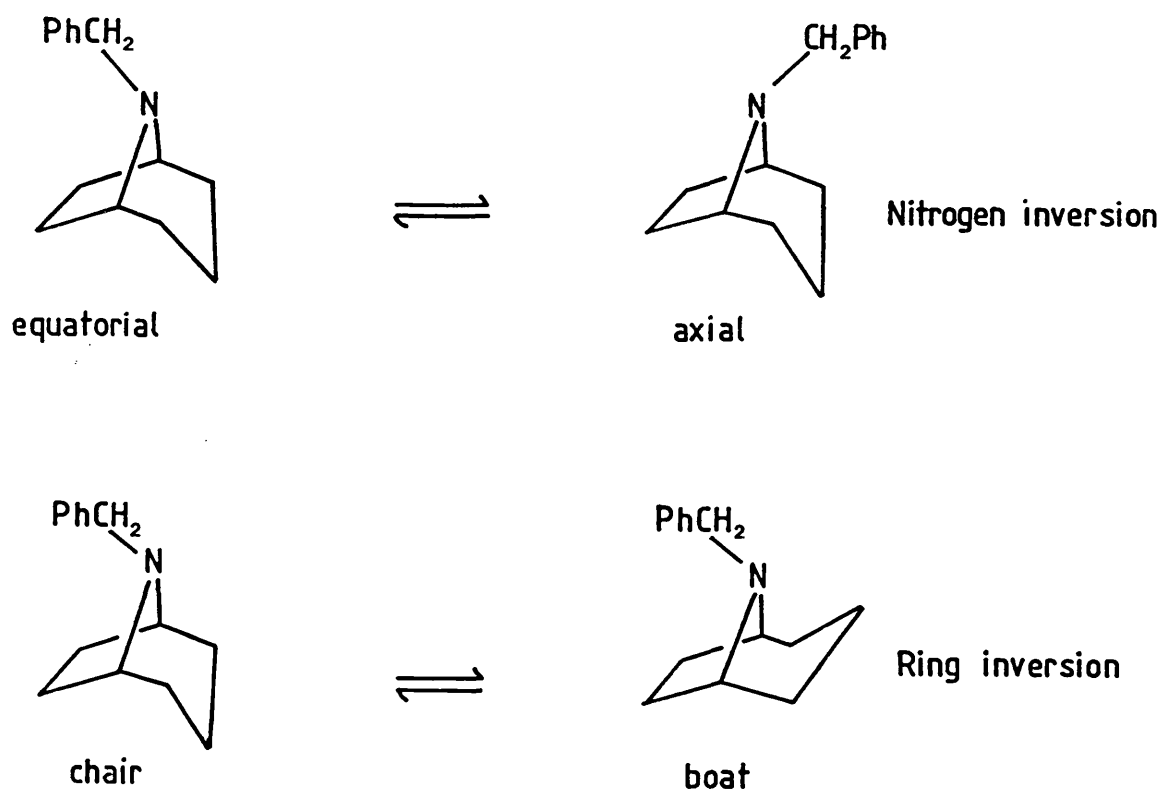
Figure 4·22
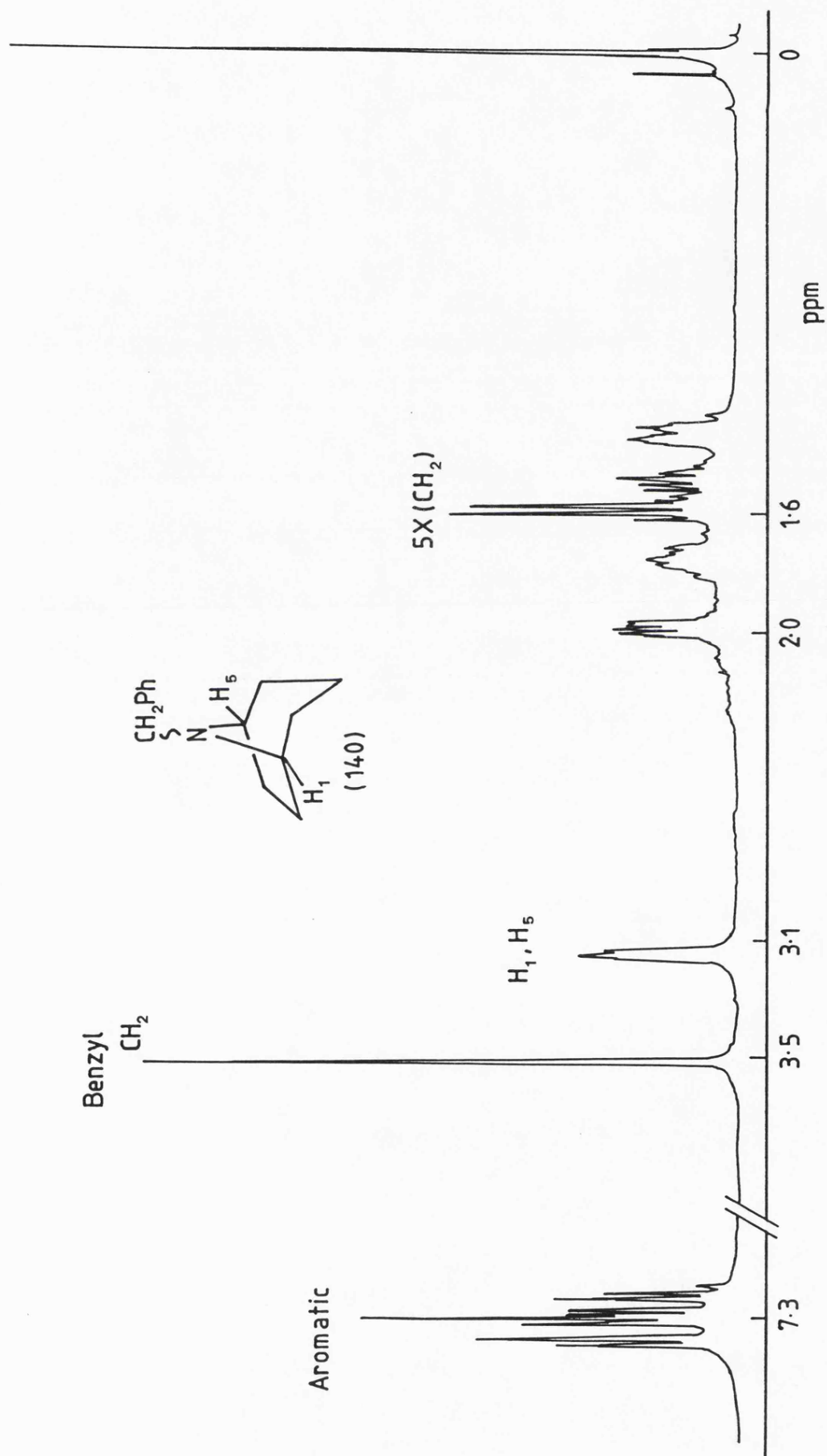
FIGURE 4·21

Stereochemical and conformational aspects of the tropane skeleton have become a subject of great interest in the last twenty years as appropriate spectroscopic methods have developed. Of the two possible conformations of the tropane skeleton i.e. the chair and the boat form, the more stable chair form is almost exclusively found in the ground state. However, evidence for the transitory existence of the boat form is found in the reactions of the isomeric 3-chlorotropanes with nucleophiles.[97,98] Infra-red spectral studies of pseudotropine (141),[99] (figure 4.23) suggested that the boat form also occurred in the ground state but this was disproved by a more recent infra-red study[100] which showed the absence of intramolecular hydrogen bonding, and hence no evidence for its existence in the boat form. Support for this latter conclusion has come from X-ray crystallographic and NMR studies.[101] The only exception to the ground state chair conformation in the simple tropane series is the compound (142), (figure 4.23), where abnormal ultra-violet and infra-red spectra suggested the existence of the boat form and a nitrogen-carbonyl interaction. This conformation serves to decrease steric strain between the 3α-phenyl group and the ethane bridge.[102]

(141)   (142)
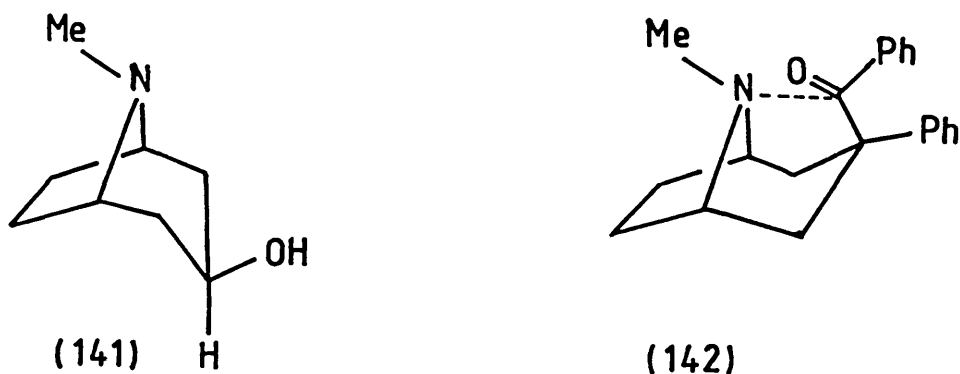
Figure 4·23

This evidence implies that ring inversion of N-benzylnortropane (140) is unlikely to explain the NMR results, leaving nitrogen inversion as a more plausible reason for the variable temperature effect. Dipole moment studies of tropanes with 3β substituents known to have the piperidine chair conformation, show the N-methyl group to be parallel with the equatorial 3β substituent.[103] Participation of nitrogen in nucleophilic reactions at C(3)[97,98] also gives support to a preferential equatorial orientation of the N-alkyl group in the tropanes. Evidence for nitrogen inversion has, in fact, been noted in the study of low temperature ^{13}C NMR spectra of a few tropane derivatives.[104]

After the successful synthesis of N-benzylnortropane, similar cyclisation conditions were employed in an attempt to synthesise the corresponding 7-azabicyclo[2.2.1]heptane (143) and 9-azabicyclo[4.2.1]-nonane derivatives (144), (figure 4.24), but to no avail.

(143)

(135)

a; n = 2
c; n = 4

(144)
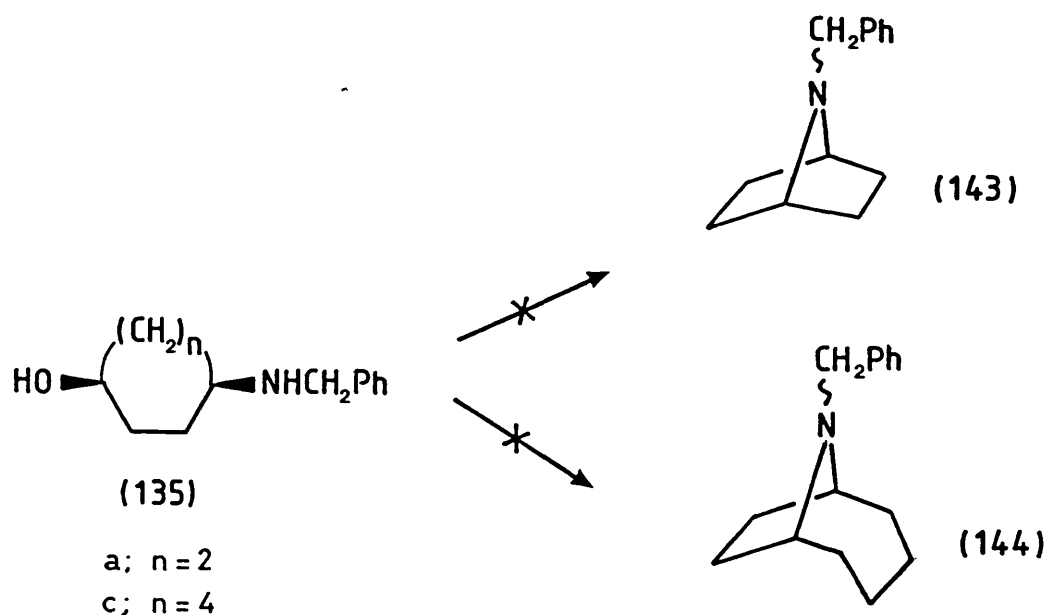
Figure 4·24

Interestingly, reaction of (135a) with thionyl chloride afforded the chlorosulphite derivative (145) which proved to be unexpectedly stable, prolonged heating being required to convert it to the corresponding trans-chloride (146) (figure 4.25). However, (146) failed to cyclise, the reaction resulting in re-isolation of the starting material.
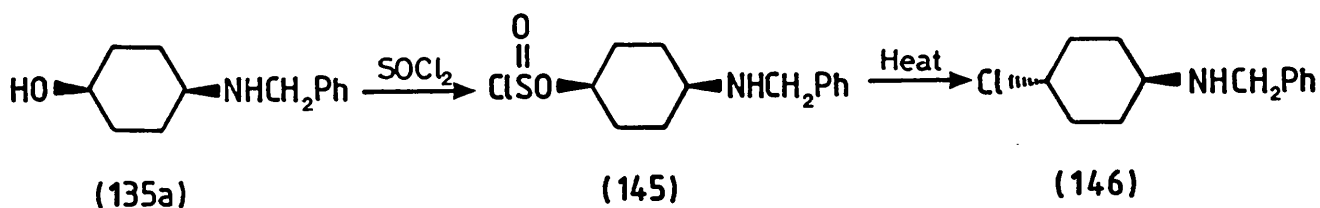
Figure 4·25

Previous reported intramolecular cyclisations to produce the bicyclic amines (102)[86] and (109)[88] have benefited from better leaving groups, i.e. mesylate and bromide respectively. However, reaction of (135a,c) with thionyl bromide under similar conditions also failed to initiate cyclisation.

Treatment of (140) under catalytic hydrogenation conditions succeeded in removing the benzyl protecting group to afford nortropane (110) in an overall yield of 75% which was stored as the hydrochloride salt, (figure 4.26).

Nortropane
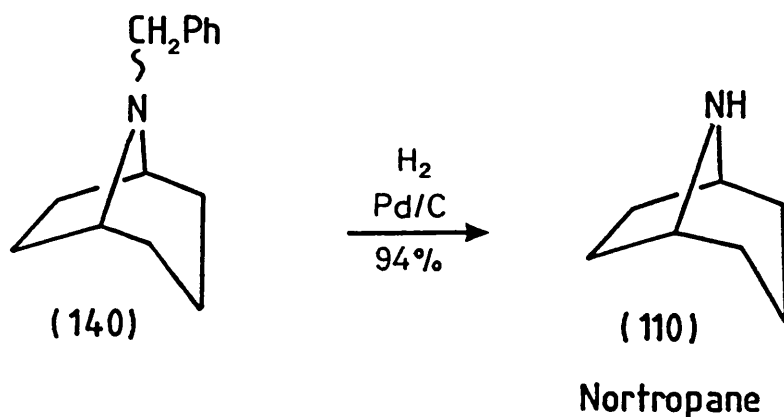
Figure 4·26

Treatment of nortropane hydrochloride (147) with sodium hypochlorite in water yielded N-chlorotropane (148), (figure 4.27).

(147)   equatorial - (148)   axial - (148)
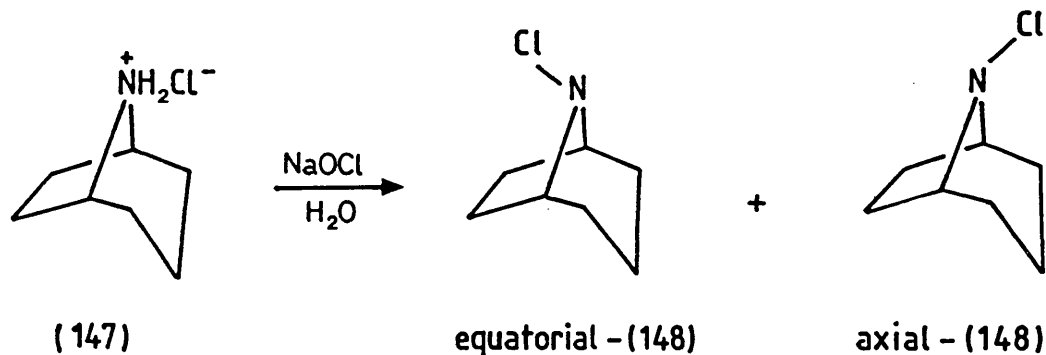
Figure 4·27

Low temperature ^{13}C NMR spectroscopy indicated the presence of two invertomers in the ratio 95:5, the major invertomer being assigned as having the more stable equatorial orientation.[104] The unexpected observation of the axial-conformer may be due to a stabilising interaction between the N-Cl and the C(1)-C(7) and C(5)-C(6) bonds. Such interactions have been observed in N-chloro-derivatives of 1,2,3,4-tetrahydro-1,4-iminonaphthalenes (48c) and (52c),[9] (figure 4.28). Single invertomers of these derivatives have been isolated as crystalline, configurationally stable compounds at ambient temperature.

syn - (48c), R = H
syn - (52c), R = Me

anti - (48c), R = H
anti - (52c), R = Me
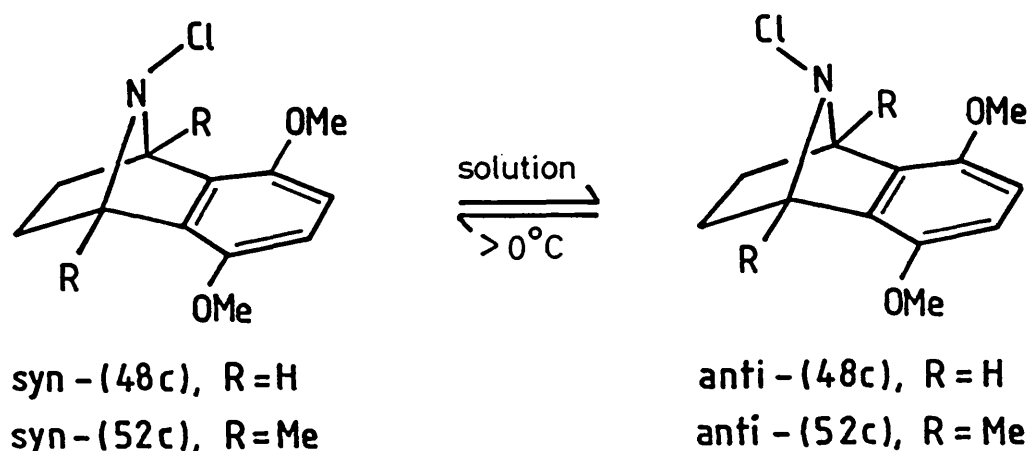
Figure 4·28

X-ray crystal structures have established that the N–Cl bond in syn- (52c) is almost antiperiplanar to the plane contained by C(1) C(2) C(3) C(4), the torsional angle being 173.2°. The corresponding relationship for anti- (48c) is even closer to antiperiplanarity, the torsional angle being 176.9°, (figure 4.29).

anti-(48c)

syn - (52c)
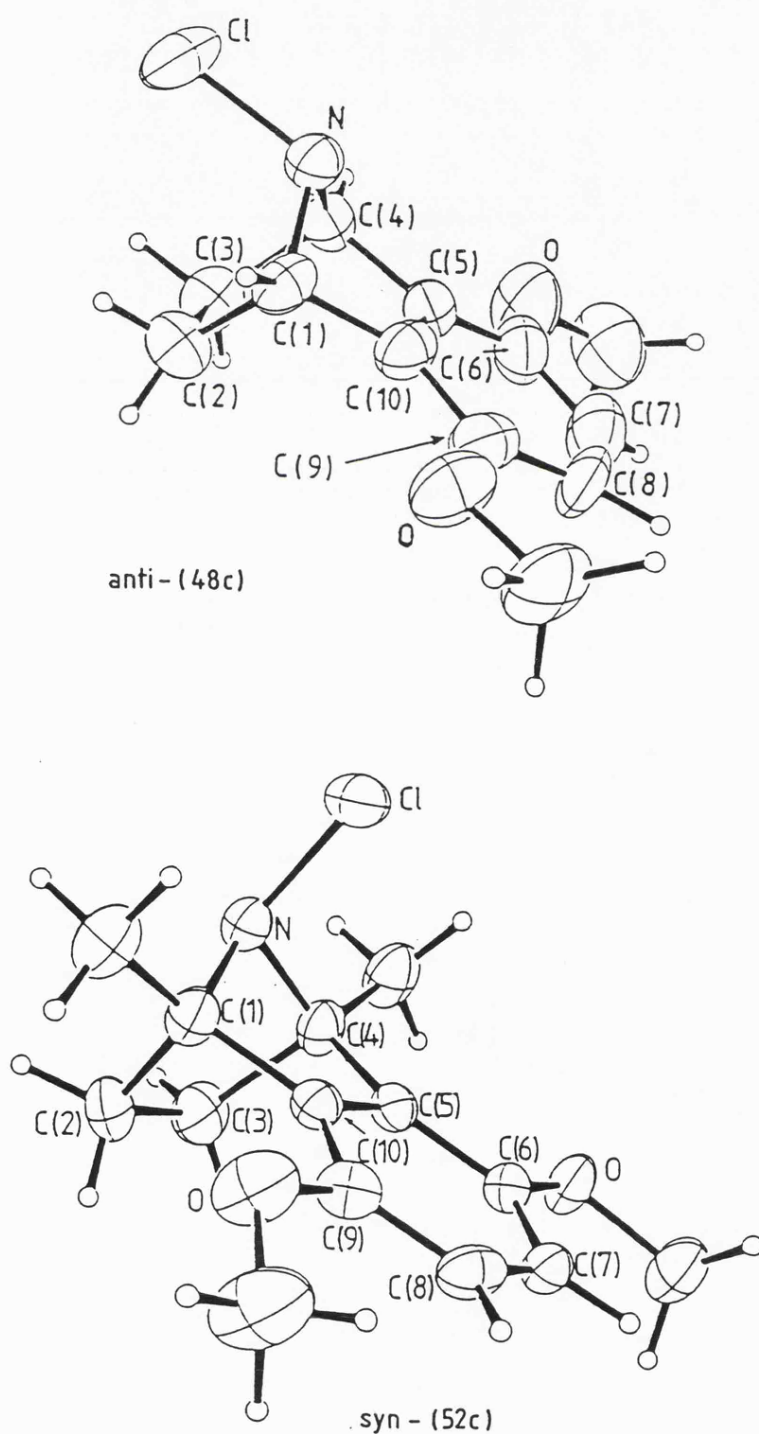
Figure 4.29

These surprising observations may point to a stabilising interaction between the N-Cl bond and the antiperiplanar C-C bonds which are sufficient to distort the molecule substantially. Similar interactions may therefore exist between the N-Cl bond and the C-C bonds of the two-carbon bridge of the axial conformer (148).

The nitrogen inversion barrier of the N-chloroamine (148) was determined using variable temperature NMR spectroscopy; the result was 70kJmol^{-1}.

The silver ion-induced rearrangement of N-chlorotropane (148) has already been investigated by Schell et al.[62] Treatment of (148) with methanolic silver nitrate and then sodium borohydride afforded a 35% yield of pyrrolizidine (149) and a 45% yield of nortropane (110), (figure 4.30).
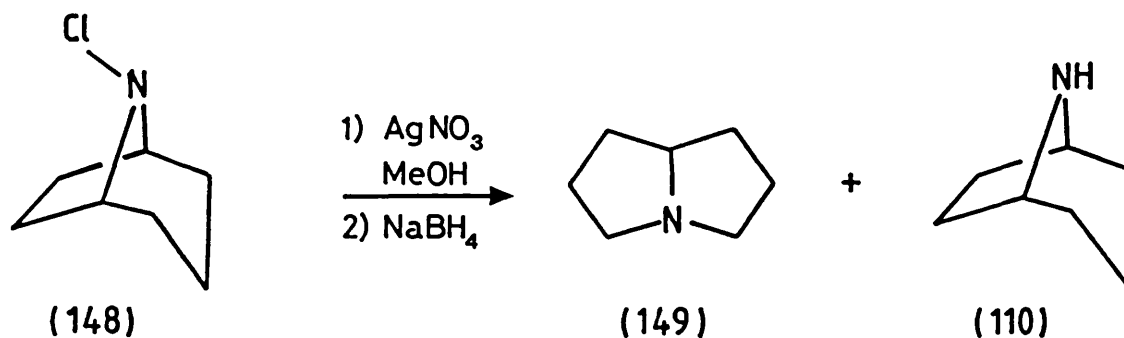
Figure 4·30

The synthesis of nortrop-6-ene (111) was attempted using an analogous method to that devised for nortropane (110) but simply omitting the hydrogenolysis step. This method was also applied to the six-membered analogue in an attempt to synthesise 7-azabicyclo[2.2.1]-heptene.

The unsaturated amido alcohols (133a,b) were treated with lithium aluminium hydride to yield the corresponding amino alcohols (150 a, 92%; b, 97%), (figure 4.31). These compounds appeared to be ideal candidates for palladium catalysed cyclisations, but this necessarily required acetylation at oxygen. However, treatment of (150a,b) with acetic anhydride was found to lead to preferential acetylation at nitrogen. Success of the reaction was found to be dependent on complete protonation of the amine. Thus, the reaction was carried out in the presence of 1.1 equivalents of tetrafluoroboric acid, followed by careful work-up to avoid O to N acetyl migration.[93] Nevertheless, reaction of the acetates (151a,b) with Pd(PPh3)4 in the presence of triethylamine failed to induce cyclisation.
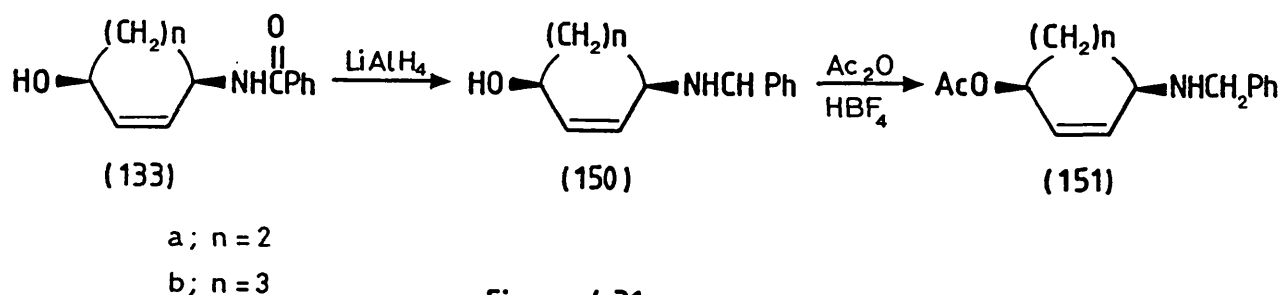
Figure 4·31

Treatment of (150a,b) using the previously devised cyclisation conditions, i.e. reaction with thionyl chloride at room temperature and subsequent treatment with pyridine, failed to give the desired bicyclic amines. The reaction yielded several products which were neither separated nor identified since the ^{1}H NMR spectra of the crude products did not indicate the presence of nortrop-6-ene and the six-membered analogue which would have been easily identifiable due to the symmetry of the systems.

One reason for the failure of these reactions might be the presence of the highly reactive allylic system and so milder cyclisation conditions were sought. (150b) was treated with thionyl chloride at a lower temperature (0°C) and subsequently exposed to the mild heterogeneous base, potassium carbonate, but this was also unsuccessful. However, it is well known that certain heterogeneous reactions benefit considerably when conducted in the presence of ultrasound. Thus, after reaction with thionyl chloride at 0°C, the reaction mixture was sonicated in the presence of potassium carbonate. The reaction afforded the desired N-benzylnortrop-6-ene (152) in 45% yield accompanied by 20% of the aziridine (153) which arose from 1,2-cyclisation, (figure 4.32).
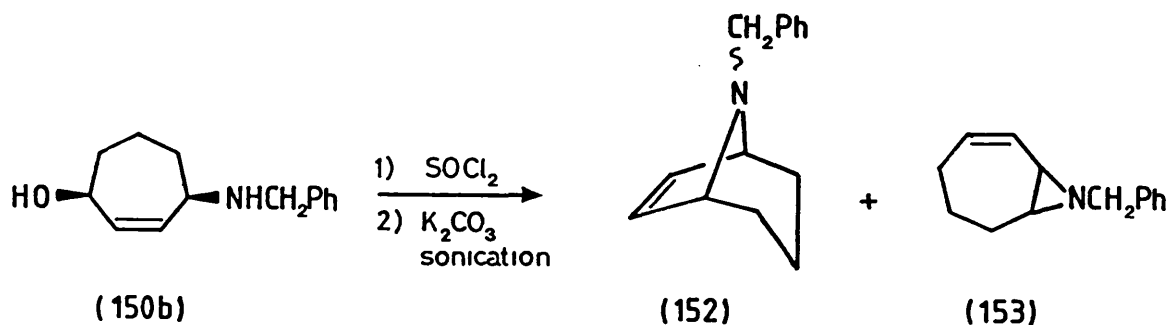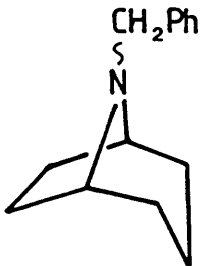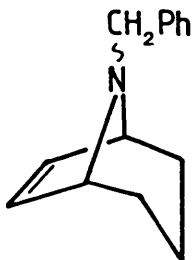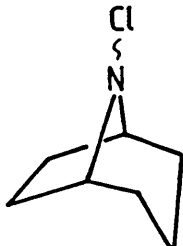
Figure 4·32

The experiment was repeated in the presence of excess lithium chloride in the hope that the provision of more chloride ion nucleophile would encourage a clean bimolecular displacement of the intermediate chlorosulphite. This was successful to a certain extent, particularly when the heterogeneous mixture was exposed to ultrasound; under these conditions, the reaction yielded 65% N-benzylnortrop-6-ene (152) and 10% aziridine (153). Thus, the overall yield to synthesise the trop-6-ene skeleton was 57%.

Low temperature ^{13}C NMR spectroscopy indicated that N-benzyl-nortrop-6-ene (152) existed as two invertomers in the ratio 96:4, the major invertomer having an equatorial benzyl group. The inversion barrier was also determined, the result being 39.0kJmol^{-1}.

Previous studies of the nitrogen inversion barriers in tropane derivatives have been reported by Schneider et al.[104] using the technique of low temperature ^{13}C NMR spectroscopy. This technique was also employed in the determination of the inversion barriers of (140), (152) and (148) (as mentioned earlier). These values illustrate the influence of steric and electronic effects on the magnitude of the inversion barrier, (table 4.2).

Table 4.2

		Inversion Barrier $\Delta G^{\ddagger}/\text{kJ mol}^{-1}$
(140)	CH$_2$Ph	36·05
(152)	CH$_2$Ph	39·0
(148)	Cl	70·0

Replacement of the ethano-bridge in (140) by a shorter etheno-bridge as in (152) resulted in an increase of the inversion barrier by approximately $3kJmol^{-1}$. This may be explained by the increased molecular rigidity imparted by the bridging carbon atoms which consequently raises the angle strain at nitrogen. However, the most remarkable effect was observed when the benzyl group was replaced by an electronegative chlorine atom; the nitrogen inversion barrier increased by almost $34kJmol^{-1}$. This was probably due to a combination of hetero-atom and electron repulsion effects (as explained in Chapter 1). Unfortunately, these inversion barriers were too low to allow the stereochemical consequences of reactions at nitrogen to be investigated.

Removal of the benzyl protecting group from N-benzylnortrop-6-ene (152) proved to be extremely difficult. The previously employed method of hydrogenation of (140) to produce nortropane (110) could obviously not be used here due to the presence of the double bond. Treatment of (152) with various alkali metals in liquid ammonia all failed to cleave the benzyl protecting group, each reaction resulting in the re-isolation of starting material. Reactions with several chloroformates[105,106] to form the corresponding carbamates which could then be cleaved via hydrolysis also proved unsuccessful. Again, only starting material was isolated from the reaction mixtures.

Bäckvall et al. recently reported the application of intra-molecular cyclisation of (154) to produce the tropan-3-ol derivative (155),[107] (figure 4.33).

(154)   (155)
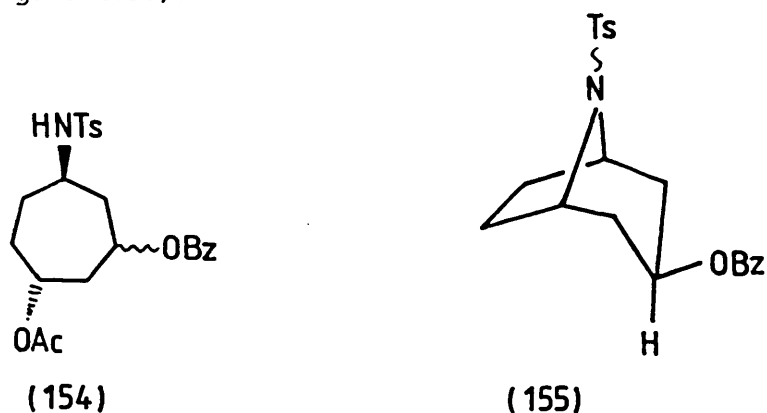
Figure 4·33

This report also described a preparation of a tosyl protected derivative of nortropane. The overall yield of N-tosyl-nortropane was 33% from 1,3-cycloheptadiene; the necessary final detosylation was not reported but would be expected to occur in ca. 80% yield. However, the route to nortropane described in this chapter is believed to be the most practical route to date. It uses simple procedures and common reagents, the synthesis yielding nortropane (110) proceeding in an overall yield of 75% from 1,3-cycloheptadiene.

Bäckvall also reported an unsuccessful attempt to prepare the nortrop-6-ene skeleton.[107] Thus despite being unable to remove the benzyl protecting group from N-benzylnortrop-6-ene (152), the synthesis described in this chapter is the first synthesis of a simple derivative of the parent nortrop-6-ene skeleton which has been achieved in significant yield (57%). This procedure therefore demonstrates the viability of the intramolecular displacement approach given an appropriately nucleophilic nitrogen.

Chapter 5

Reactions of Chlorosulphonyl Isocyanate with

Cyclic Trienes

5. I. INTRODUCTION

Intramolecular π-participation in the silver-ion assisted heterolysis of N-Cl bonds has seen little study. Results from the few reactions that have been accomplished indicate that suitably orientated π-electrons can control the displacement of a nucleofuge from nitrogen. For example, treatment of the N-chloroamine (5) with $AgClO_4$ in methanol gave (16) as the sole product in 94% yield,[39] the chloride ion being removed specifically from the minor invertomer (5), (figure 5.1).

(5)   (16)
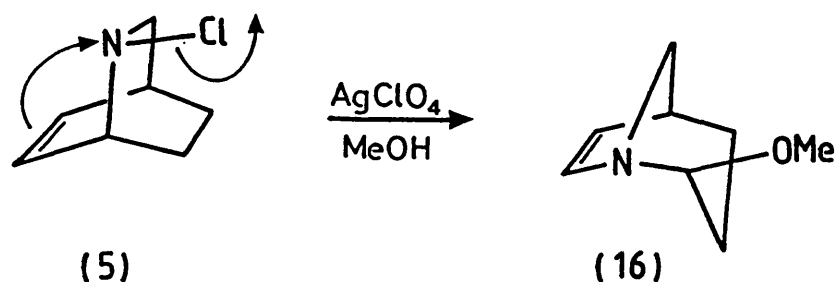
Figure 5·1

Similarly, reaction of (7) with $AgNO_3$ in methanol demonstrated a high degree of π-participation, the reaction occurring via the exo-invertomer to yield (156), (157) and (158), (figure 5.2).

(7)   (156) X=Cl ; 42%   (158) 14%

(157) X = OMe; 1·5%
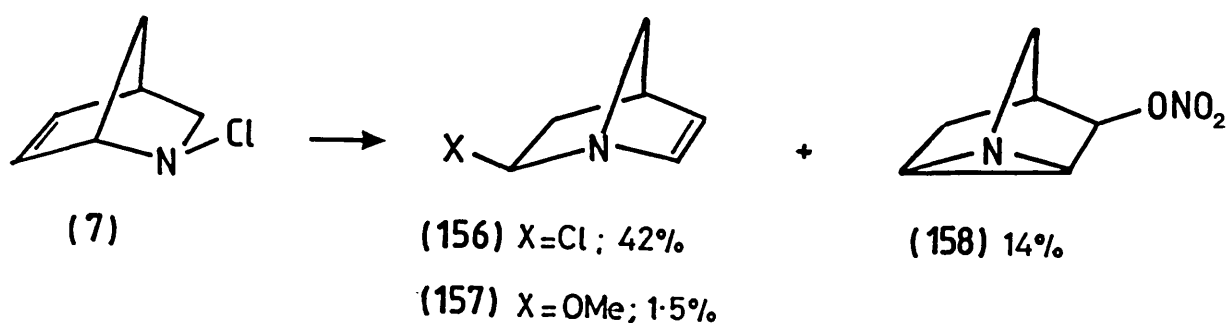
Figure 5·2

Analogous systems containing an alternative leaving group i.e. a tosyloxy group also demonstrate a high degree of π-participation[108, 109,110,111] (see Appendix 1).

Thus, the objective was to extend the range of bicyclic amines

having π-electrons which might participate in such solvolysis reactions

from nitrogen. Such unsaturated systems were of interest for other

reasons also. They would provide an opportunity to probe further the

importance of π-interactions on barriers to inversion at nitrogen and on

invertomer preferences. With appropriate substitution at nitrogen,

there would also be an opportunity to investigate the ability of

nitrogen to influence the facial selectivity shown in reactions at

π-bonds within the same molecule.[112,113] The observation that the

nitrogen atom in N-carboethoxy-1,4-dihydro-1,4-iminonaphthalene can play

a part in directing hydride reduction of the π-bond[114] illustrates the

unexpected and potentially powerful influence of nitrogen in encouraging

unusual, facially selective reactions on π-systems. With this in mind,

the amine (159), (figure 5.3) was chosen for initial study.

(159)
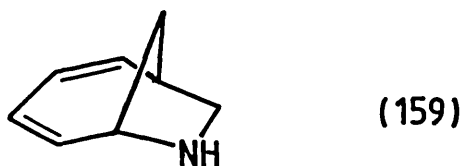
Figure 5·3

The proposed synthesis of such a system involves the cyclo-

addition of chlorosulphonyl isocyanate (CSI) to cycloheptatriene, the

mechanism of which has been a subject of conflicting views.

5.II. SYNTHESIS AND ATTEMPTED REARRANGEMENT OF N-CHLORO-2-AZABICYCLO-[4.2.1]NONANE

Lactam (160) was prepared using the methodology previously

devised by Malpass[115] (figure 5.4). Treatment of cycloheptatriene (161)

with CSI in nitromethane for 3 days at 25°C yielded the N-chloro-

sulphonyl lactam (162) which after hydrolysis with sodium hydroxide in aqueous acetone at pH 7±1 gave pure lactam (160).

(161)   + $O=C=N-SO_2Cl$ $\xrightarrow{\begin{array}{c} CH_3NO_2 \\ \hline 25°C \\ 3\,days \end{array}}$ (162)

NaOH
pH 7±1

(163) $\xleftarrow{\hspace{0.3cm}\times\hspace{0.3cm}}$ (160)
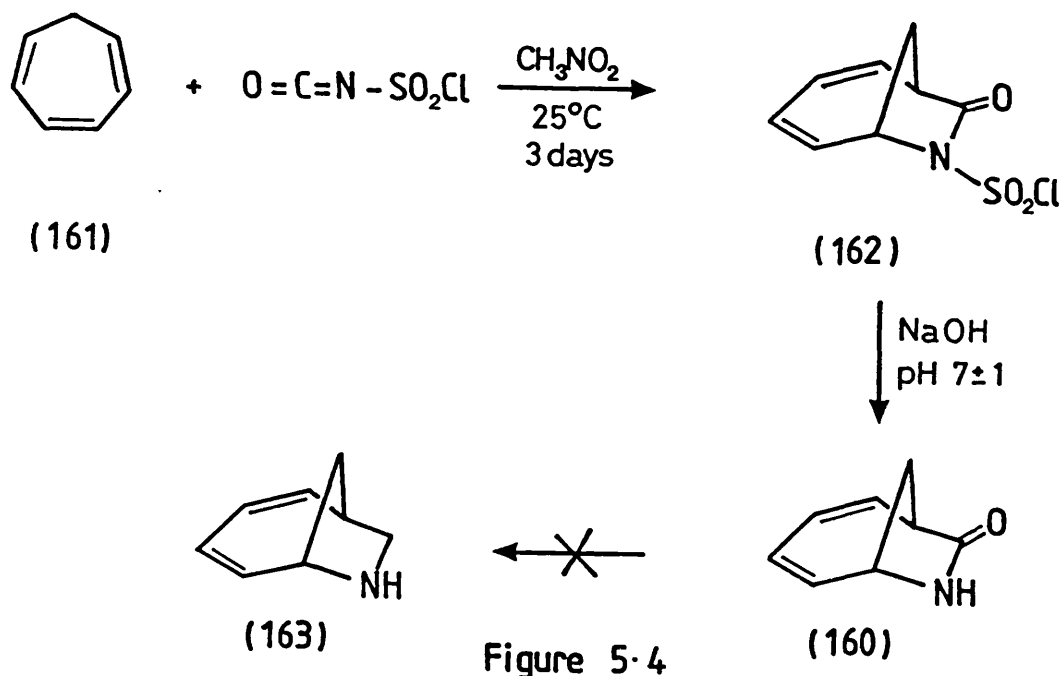
Figure 5·4

The lactam (160) was prepared successfully. However, attempts to reduce it to the desired amine (163) using various hydride reducing agents were unsuccessful. The presence of the nitrogen atom in (160) was possibly influencing the course of the reaction.[112,114] Later studies showed that the analogous saturated system underwent successful lactam reduction to form the corresponding amine, thus implying that the unsaturated lactam (160) was a subject of symbiosis.

These unproductive reactions necessitated re-direction towards an alternative objective. Thus, the unsaturated lactam (160) was hydrogenated over a palladium on charcoal catalyst to yield (164), which was subsequently reduced with lithium aluminium hydride to give the saturated amine (165), (figure 5.5).
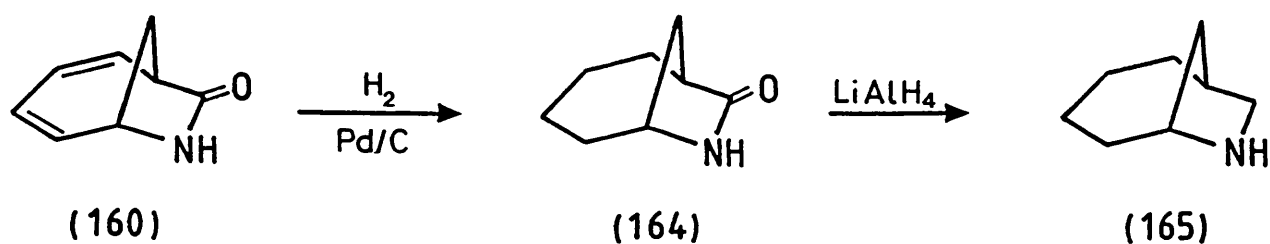
Figure 5·5

Chlorination of (165) gave the corresponding N-chloroamines. The nitrogen inversion barrier was expected to be too low to allow the stereochemical consequences of reaction at nitrogen to be observed. Also, the invertomer ratios were not determined since any heterolysis would presumably proceed via the more reactive exo-invertomer (166). Reaction with silver ion in the presence of methanol might reasonably be expected to induce σ-participation and subsequent incorporation of a methoxy group to give the rearrangement product (167), (figure 5.6).
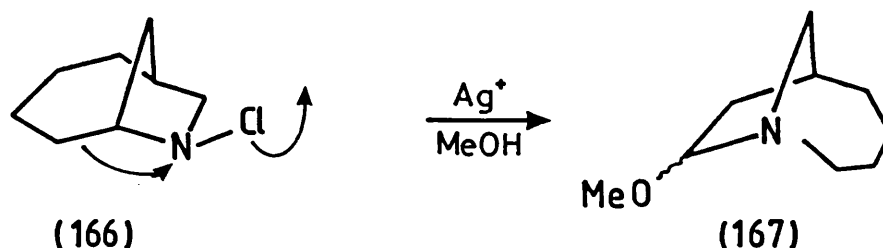
Figure 5·6

However, reaction with a methanolic solution of silver nitrate gave only the dechlorinated product (165), the amine presumably being formed via homolysis (see Chapter 2).

Similar problems were encountered by Schell et al.[62] in an attempt to induce σ-participation in the N-chloroamine (168). However, a method was devised which minimised the production of secondary amines. This involved exposure of the N-chloroamine (168) to silver tetrafluoroborate in an aprotic solvent and isolation of the

precipitated immonium ion (169). The resulting material was subsequently reduced with sodium borohydride to produce δ-coniceine (170) in 92% yield, (figure 5.7).
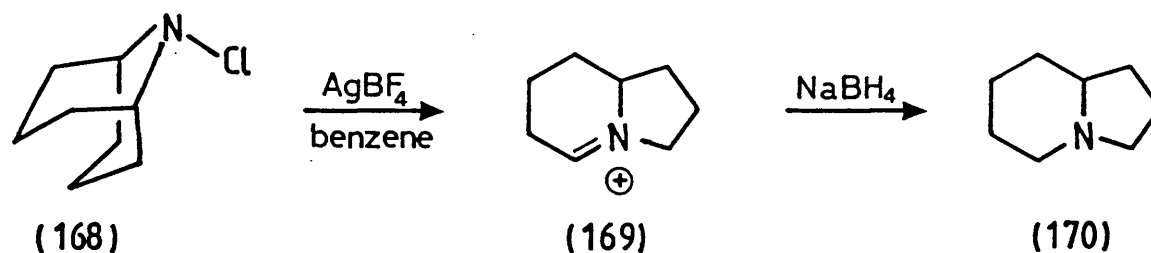
Figure 5·7

Thus, the N-chloroamine (166) was treated with AgBF₄ in toluene. Dry methanol was subsequently added in order to intercept the anticipated immonium ion by attack of a methoxy group to form (167). Nevertheless, the only isolated product was the parent amine (165), thus implying that homolysis of (166) was successfully competing with heterolysis.

5.III. REACTION OF CHLOROSULPHONYL ISOCYANATE WITH CYCLIC TRIENES: A REINVESTIGATION

Although the reaction of CSI and cycloheptatriene has been shown not to be a viable route to bicyclic amines due to difficulties in reduction of the lactam, the mechanism of the reaction itself is worthy of further investigation. The reaction of CSI and triene systems has been a subject of contention.

Malpass[115] investigated the reaction of CSI and cycloheptatriene and proposed a mechanism involving a dipolar addition of the reagents which proceed along a stepwise path culminating in the formation of a N-chlorosulphonyl lactam via 1,6-addition, (figure 5.8).
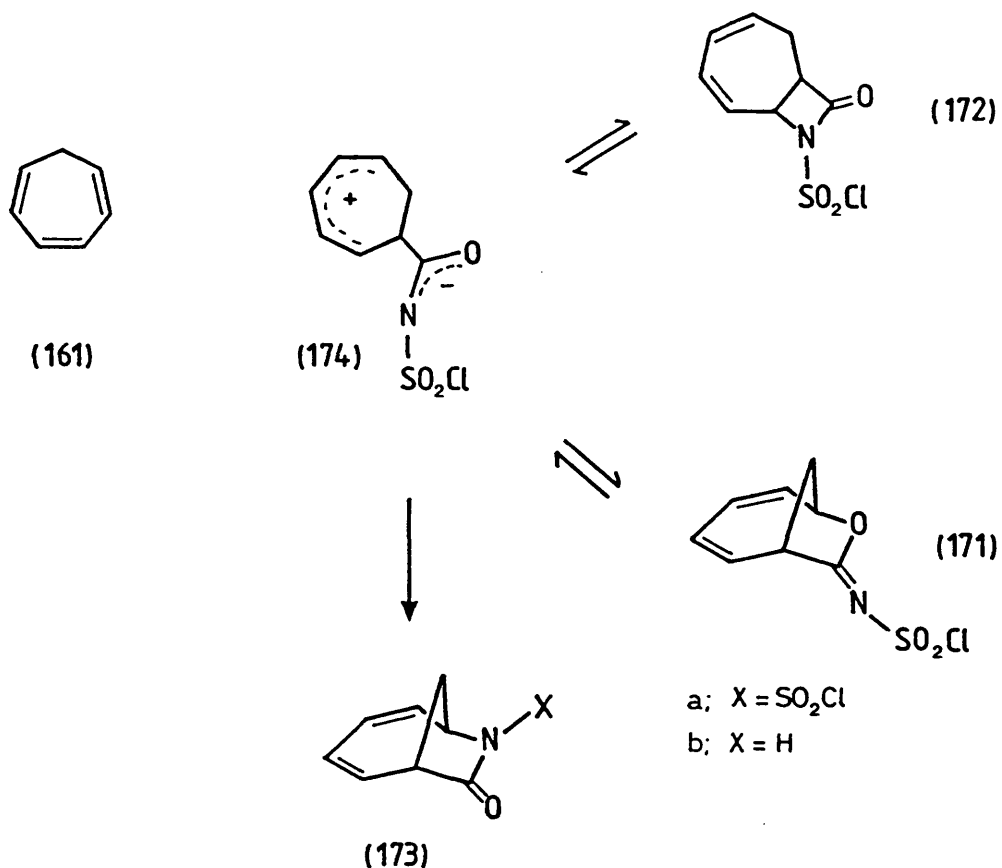
Figure 5·8

By monitoring the reaction by infra-red spectroscopy, it was deduced that reaction of equimolar quantities of cycloheptatriene and CSI in CCl_4 produced the iminolactone (171) over a period of days. During the converion to (171), a small and apparently stationary concentration of N-chlorosulphonyl β-lactam (172) was observed. Subsequently, a new peak at $1772 cm^{-1}$ which was assigned to (173a) grew with time and ultimately became the major product. Reaction in CCl_4 at reflux for 7 days yielded (173a) in approximately 50% yield. However, conversion of (171) into (173a) was achieved most efficiently by the use of a polar solvent. In fact, reaction in nitromethane for 2 days at 25°C yielded (173a) which was uncontaminated with (171). Hydrolysis of (173a) with sodium hydroxide in aqueous acetone at pH 7±1 gave pure (173b) in 50% yield.

Thus, a dipolar addition of CSI was proposed which seems reasonable in view of the considerable stabilisation available to the cationic centre in (174). It was also established that (173a) was the ultimate product of thermodynamic control.

This stepwise conversion should be general. However, it is not recognised by Moriconi.[116,117] Addition of CSI to equimolar amounts of 7-substituted cycloheptatrienes (175) in dichloromethane were reported to yield only the N-chlorosulphonylimino lactones (176) which on alkaline hydrolysis in acetone gave the lactones (177), (figure 5.9).

(175)

a; R = H
b; R = C$_6$H$_5$
c; R = ^{t}Bu

(176)

(177)
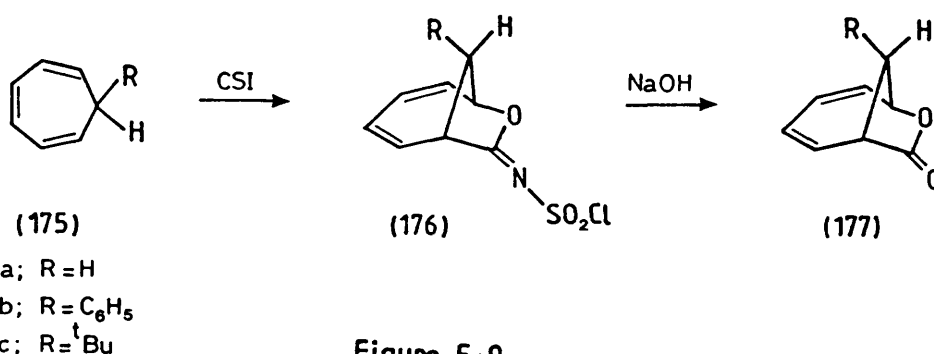
Figure 5·9

Thus, he proposed a mechanism involving an initial near-concerted attack to give β-lactam (178), (figure 5.10). Ring opening of

(175)

(178)

(179)

(176)
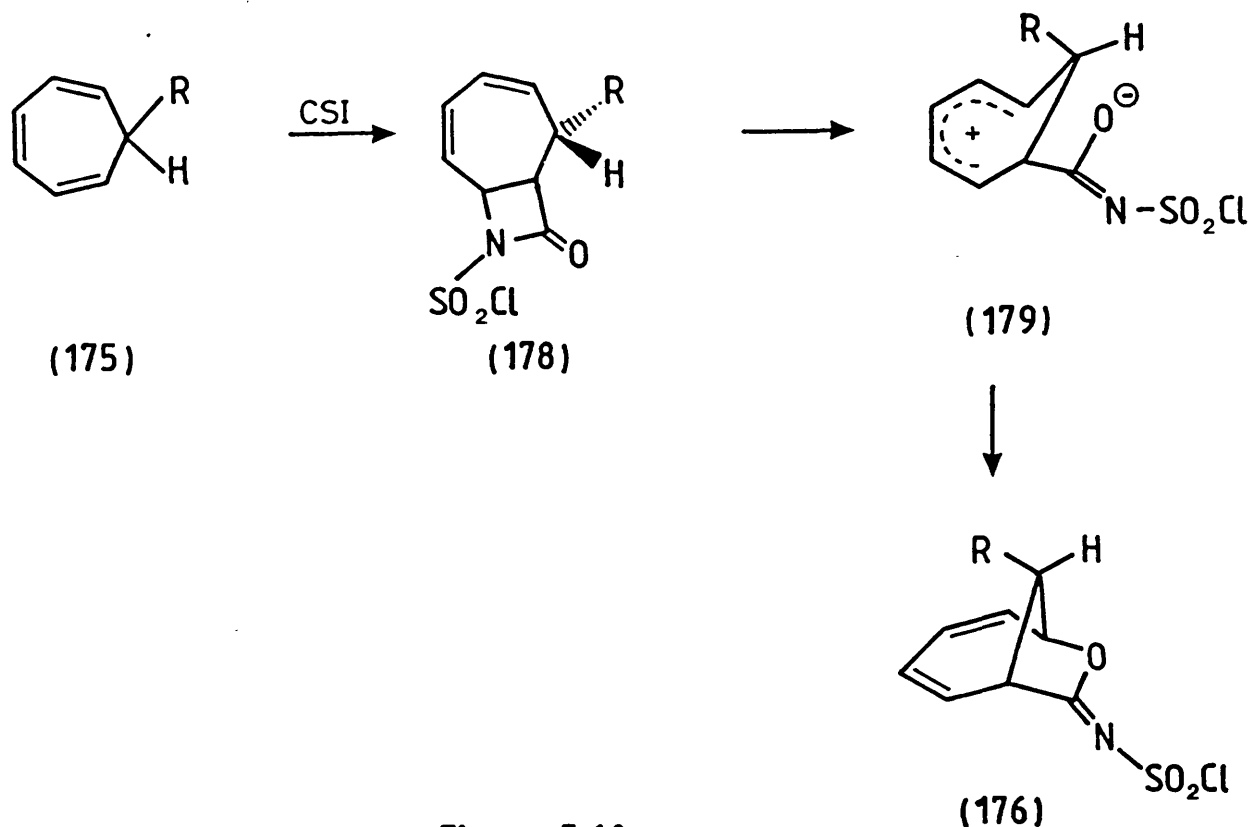
Figure 5·10

the β-lactam produces a pentadienyl cation (179) which upon ring closure at C-6 gives the observed products (176).

However, Moriconi recorded no evidence for β-lactam formation and, more importantly, failed to consider the possibility of completion of the sequence by conversion to a lactam product despite the observation of lactams by others and even in his own work. Thus, Moriconi has denied recognition of the possibility of control over cyclisation pathways which could perhaps result in synthetic applications.[118] These conflicting views therefore initiated further investigation.

5.IV. REACTION OF CHLOROSULPHONYL ISOCYANATE WITH 7-t-BUTYLCYCLO-HEPTATRIENE

When Moriconi reacted 7-t-butylcycloheptatriene with CSI, subsequent alkaline hydrolysis yielded only 20% of the lactone (177c).[117] No other products were observed. Therefore, further study of this reaction was undertaken.

Tropylium fluoroborate (180)[119] was prepared by treatment of cycloheptatriene with phosphorus pentachloride and then fluoroboric acid, (figure 5.11). Reaction of (180) with sodium methoxide in dry methanol yielded 7-methoxycycloheptatriene (181)[120] which was subsequently treated with t-butyl magnesium chloride to give 7-t-butyl-cycloheptatriene (175c).[117]
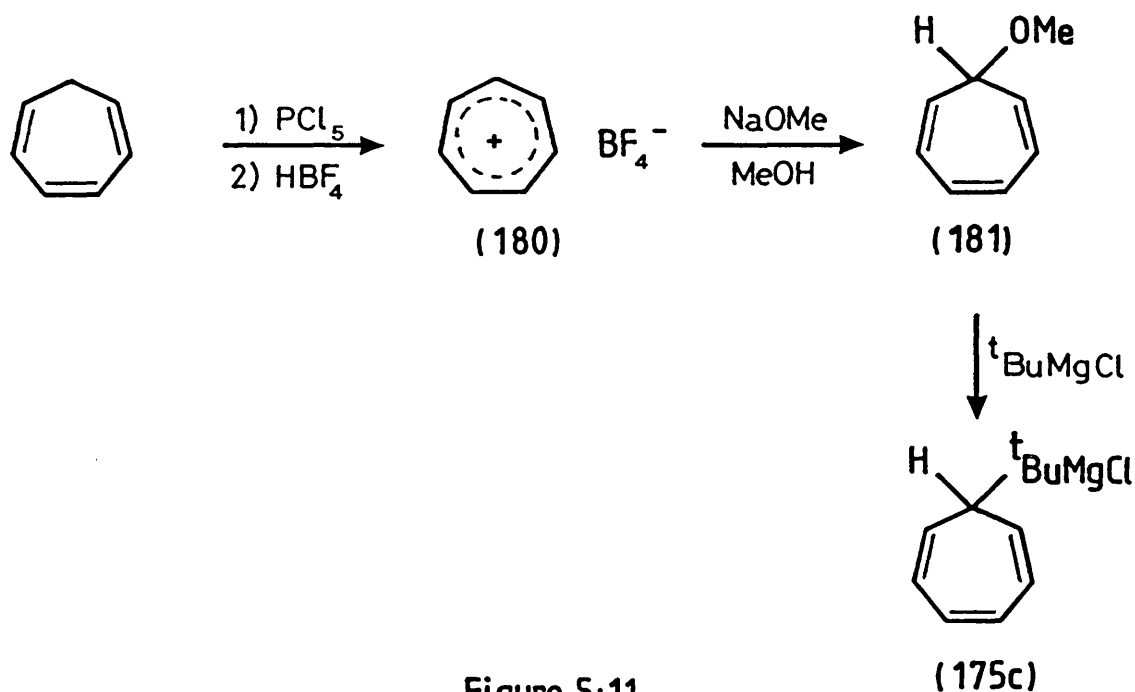
Figure 5·11

Reaction of equimolar quantities of CSI and 7-t-butylcyclo-heptatriene in dichloromethane at 25°C yielded unexpectedly 7-t-butyl-2-N-chlorosulphonyl-carboxamido-1,3,5-cycloheptatriene (182) as the major product, (figure 5.12). Repetition of this reaction in a more polar solvent, nitromethane, again gave (182) as the major product.
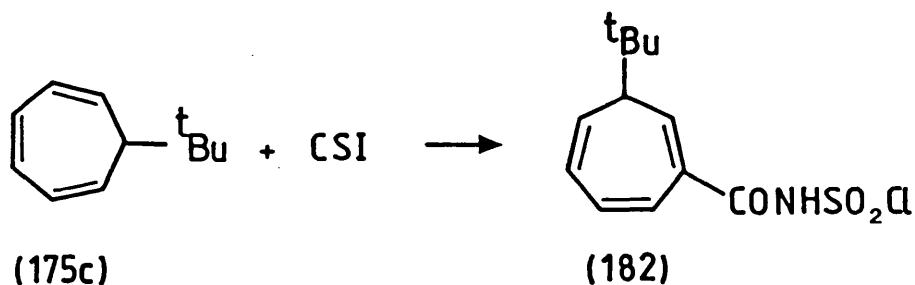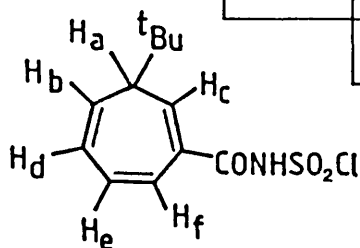
Figure 5·12

The structure of (182) was confirmed by high field ^1H NMR with the aid of selective decoupling experiments (table 5.1).

TABLE 5.1

tBu	a	b	c	d	NH	e	f	
1.07	-	-	-	-	-	-	-	tBu
	1.27	7.0	6.0	1.5	-	-	-	a
		5.42	-	9.0	-	-	-	b
			6.26	-	-	-	-	c
				6.28	-	5.7	-	d
					6.50	-	-	NH
						6.93	11.1	e
							7.07	f

Structure (182): seven-membered ring (cycloheptatriene) with H_a, tBu, H_b, H_c, H_d, $CONHSO_2Cl$, H_e, H_f.

(182)

Chemical shifts (ppm) along diagonal
Coupling constants (Hz) off-diagonal
δ_H (300 MHz, CDCl$_3$)

The infra-red spectrum exhibited two strong bands; at 3420 and 1725cm^{-1} verifying the presence of the N-chlorosulphonylamide group.

Further substantiation of the structure was obtained by reacting (182) with triethylamine to produce the corresponding nitrile (183),[21] (figure 5.13). The structure of the product was confirmed by ^{1}H NMR and infra-red spectroscopy; the characteristically low nitrile absorption at 2200cm^{-1} verifying that the nitrile group was indeed in conjugation with the double bond.

tBu
<structure: cycloheptatriene ring> CONHSO$_2$Cl

+ NEt$_3$ ⟶

tBu
<structure: cycloheptatriene ring> CN

(182)   (183)
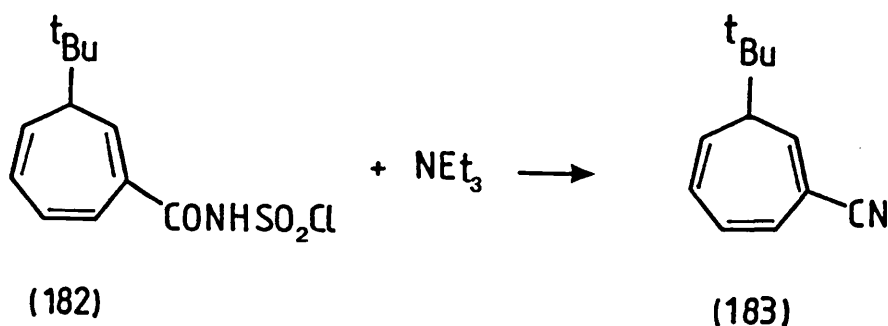
Figure 5·13

The monocyclic structure (182) is presumably a product of proton transfer. However, although proton transfer products have previously been isolated, the position of addition of CSI in this case is unique. In the reaction of 7-methylcycloheptatriene and CSI, Moriconi et al.[117] isolated 7-methyl-1-carboxamido-1,3,5-cycloheptatriene (184) in 6% yield presumably via addition of CSI to the 1-position followed by proton transfer, (figure 5.14).
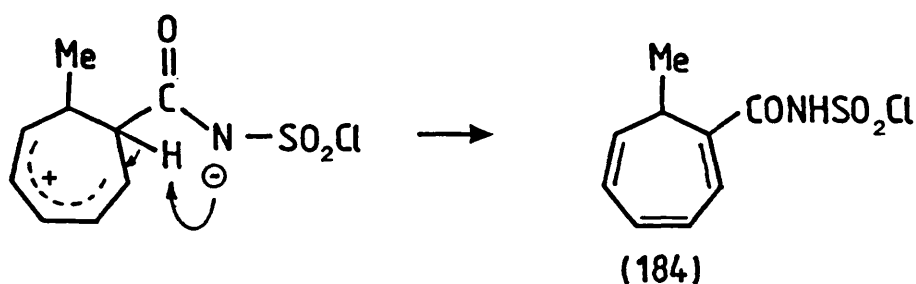
Figure 5·14

However, since the cycloheptatriene skeleton is non-planar, it is perhaps not surprising that addition does not necessarily occur at the 1-position as the double bonds are not in sufficient conjugation to form a stable delocalised cationic species. Attack of CSI at the 1-position may also be sterically hindered, thus favouring addition at an alternative position. An alternative rationalisation may be sought by considering addition of CSI to the norcaradiene form of 7-t-butyl-cycloheptatriene, (figure 5.15). Valence tautomerism is a well-known dynamic process in cycloheptatrienes.[122] Thus, the possibility exists for addition of CSI to the 2-position of the norcaradiene valence isomer, the cationic species so formed (185) exhibiting greater stabilisation due to the planar diene moiety.
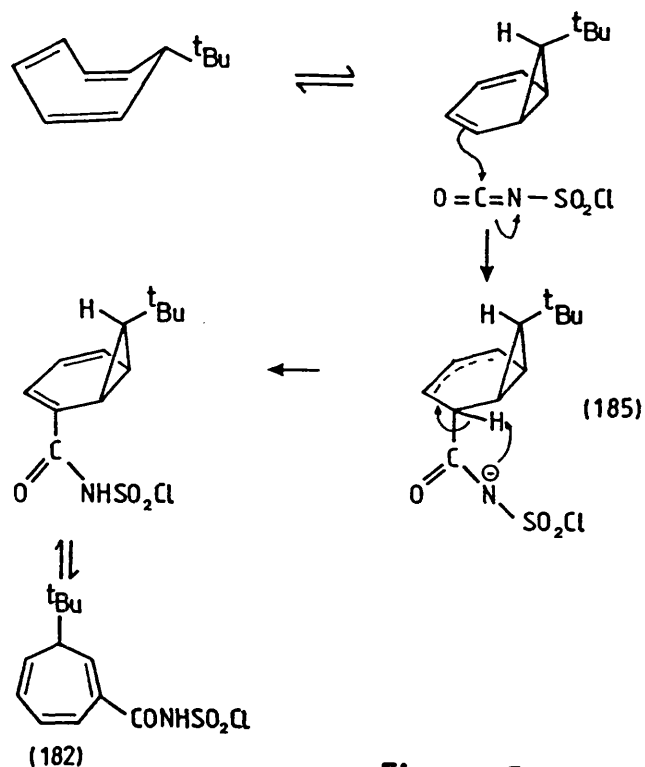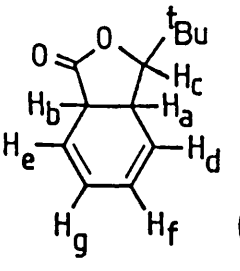
Figure 5·15

Interestingly, after alkaline hydrolysis of the reaction mixture, a further minor product (186) was isolated. The structure of the product was confirmed by high field ^1H NMR and selective spin-decoupling experiments, (table 5.2).

TABLE 5.2

^tBu	Ha	Hb	Hc	Hd	He	Hf	Hg	
1.05	–	–	–	–	–	–	–	^tBu
	3.45	12.0	7.5	4.4	–	1.5	–	Ha
		4.07	–	–	3.9	–	2.2	Hb
			4.13	–	–	–	–	Hc
				5.69	–	9.8	–	Hd
					5.89	0.5	9.8	He
						6.05	5.3	Hf
							6.26	Hg

Chemical shifts (ppm) along diagonal
Coupling constants (Hz) off-diagonal
δ_H (300 MHz, $CDCl_3$)

A possible mechanism may involve addition of CSI to the 1-position of 7-t-butylcycloheptatriene (187) and subsequent carbenium ion rearrangement, such reactions not being without precedent.[123] Thus, breakage of a C-C bond to form the dipolar species (188) and attack of the oxygen anion at the cationic centre results in the formation of the five-membered oxygen-containing ring (189). Subsequent alkaline hydrolysis yields the lactone (186), (figure 5.16).
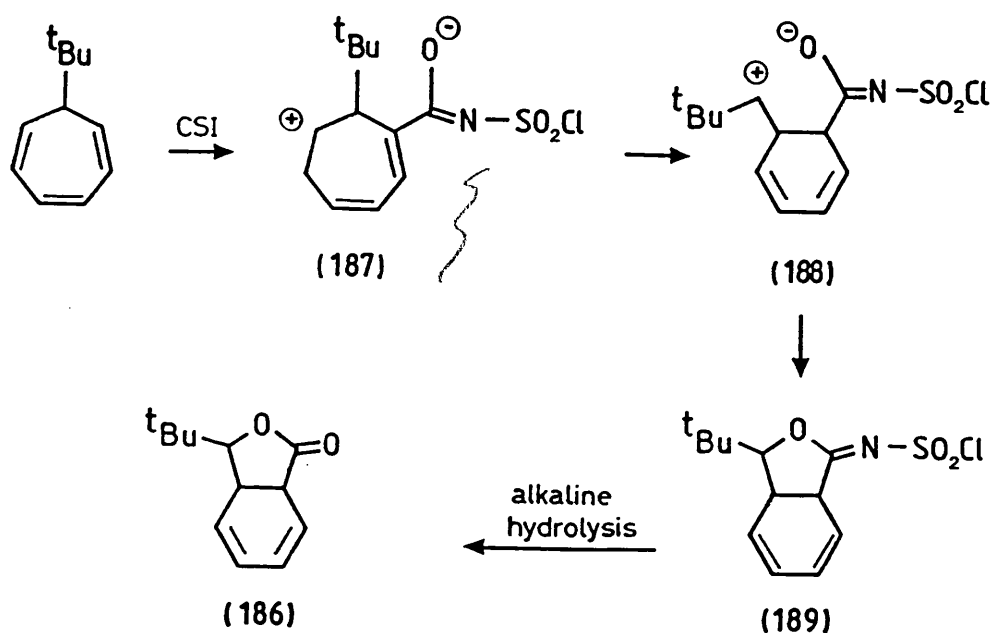
Figure 5·16

An alternative mechanism involving attack of CSI on the norcaradiene form of 7-t-butylcycloheptatriene (190) is superficially attractive but this would involve attack of CSI from the more hindered face of the bicyclo[4.1.0]hepta-2,4-diene system, (figure 5.17).
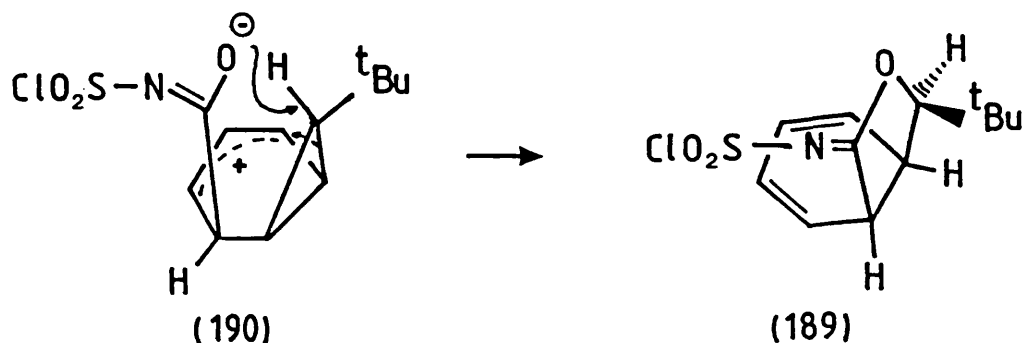
Figure 5·17

Nevertheless, in the reaction between cis-bicyclo[6.1.0]nona-trienes and CSI exo-attack of the electrophile on the folded conformation (191), (figure 5.18), was invoked in order to explain cleavage of the cyclopropyl ring and the ultimate stereochemistry.[124] Preferential exo-attack also occurs in the reaction between CSI and cyclooctatetraene.

(191)
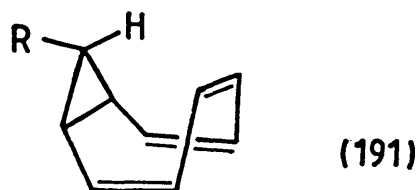
Figure 5·18

On comparison with results obtained by Moriconi,[117] it appears that the reaction of CSI with 7-t-butylcycloheptatriene yields totally different products despite using essentially identical procedures. Thus, it has not been possible to reproduce Moriconi's results. Substantial variations in observed products from similar work in different laboratories are not without precedent. Other workers have pointed to the striking sensitivity of CSI reactions to changing conditions.[125]

Complexities presumably arising because of the bulky t-butyl group would demand considerable work on reproducibility and stereo-chemistry of attack of CSI. Thus, the reaction of CSI and 7-methyl-cycloheptatriene was investigated.

5.V. REACTION OF CHLOROSULPHONYL ISOCYANATE WITH 7-METHYLCYCLO-HEPTATRIENE

Moriconi et al.[117] noted that addition of CSI to an equimolar amount of 7-methylcycloheptatriene (192) in dichloromethane at 25°C proceeded with the formation of the iminolactones (193 a,b). Alkaline hydrolysis of (193 a,b) gave the lactones (194 a,b) in 33% yield as well as a product of proton transfer (195) in 6% yield, (figure 5.19).

(192)

+ CSI ⟶

(193)

a; R¹ = Me, R² = H

b; R¹ = H, R² = Me

alkaline hydrolysis

(194)

+

(195)

a; R¹ = Me, R² = H

b; R¹ = H, R² = Me
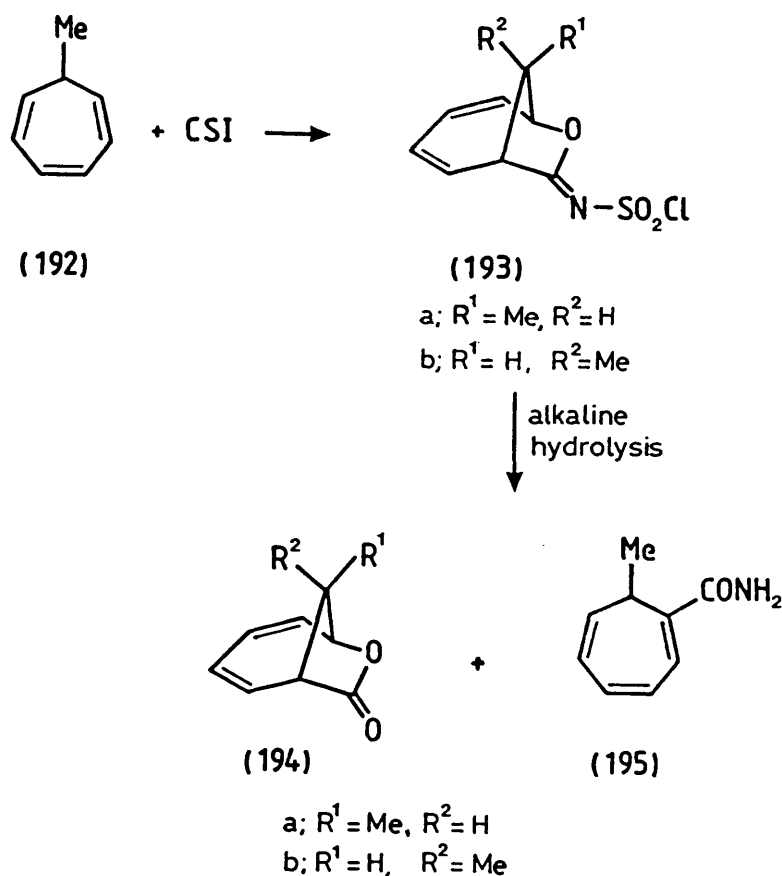
Figure 5·19

This reaction offered the opportunity to consider the question of control over stepwise cyclisation processes without the complicating influences of the large t-butyl group. At the same time, the question of facial selectivity in attack upon the cycloheptatriene system could still be addressed.

In the present work, repetition of the reaction between CSI and 7-methylcycloheptatriene revealed the presence of lactams contrary to Moriconi's belief that only oxygen-cyclised adducts are produced. If the suggestion that CSI undergoes dipolar reactions with cyclohepta-trienes which proceed along a stepwise path culminating in the formation of N-chlorosulphonyl lactams is correct, then it should, in principle, be possible to isolate the imino-lactone and convert it to an N-chloro-sulphonyl lactam by dissolution in a more polar solvent.

Hence, 7-methylcycloheptatriene was synthesised via the reaction of 7-methoxy-1,3,5-cycloheptatriene with the appropriately substituted Grignard reagent. The reaction of equimolar quantities of 7-methyl-cycloheptatriene and CSI in dichloromethane was monitored by infra-red spectroscopy. An infra-red absorption at $1585cm^{-1}$ appeared over a matter of hours indicating the presence of the chlorosulphonylimino-lactones (193 a,b), (figure 5.20). Evaporation of the solvent at
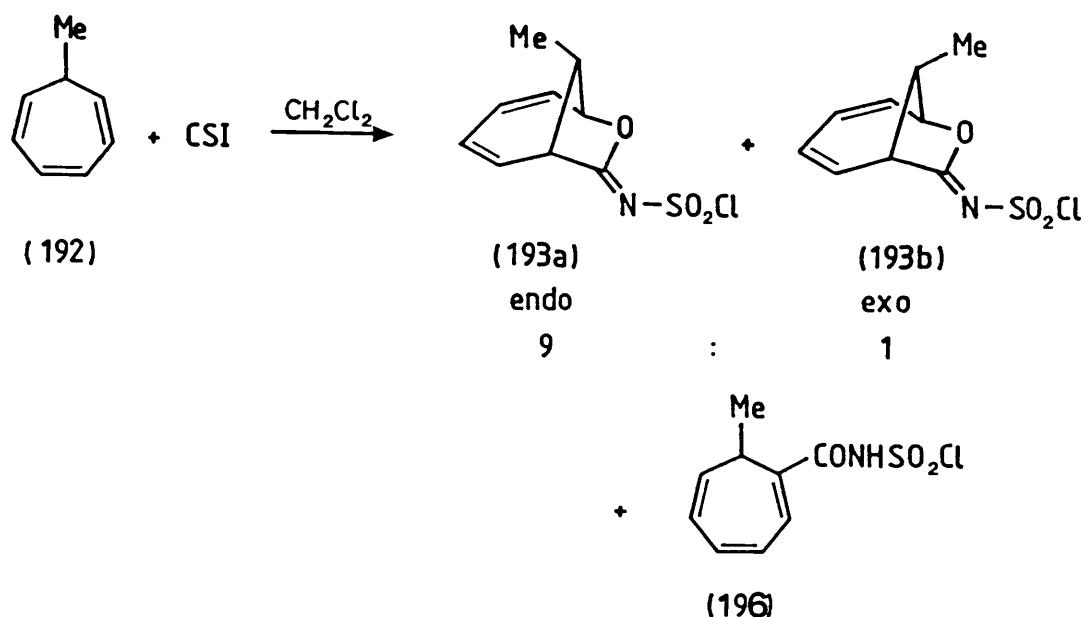
Figure 5·20

reduced pressure afforded the two isomers in 25% yield (which could be successfully converted to the corresponding lactones via alkaline hydrolysis) as well as a hydrogen transfer product (196) in 11% yield. The ^{1}H NMR spectrum of these imino-lactones (table 5.3) exhibited two methyl doublets at δ1.10 and 1.65 in the ratio 9:1 respectively. The doublet at δ1.10 was assigned to the endo-methyl group (193a) since it was situated over the diene system and shielded relative to the exo-methyl group (193b) at δ1.65.

The preference for the endo-orientation of the methyl group in the 7-methylcycloheptatriene adducts was unexpected. 7-Substituted cycloheptatrienes exist as equilibrium mixtures with axial and equatorial substituents[126] and it has been shown that there is a preference for the conformation with the substituent equatorial, the free energy of interconversion being approximately 4kJmol^{-1}. Thus, it appears that the adduct has been derived from the less stable axial conformer, (figure 5.21).

(193)
major
(endo)

(193)
minor
(exo)

(192)
minor
(axial)

(192)
major
(equatorial)
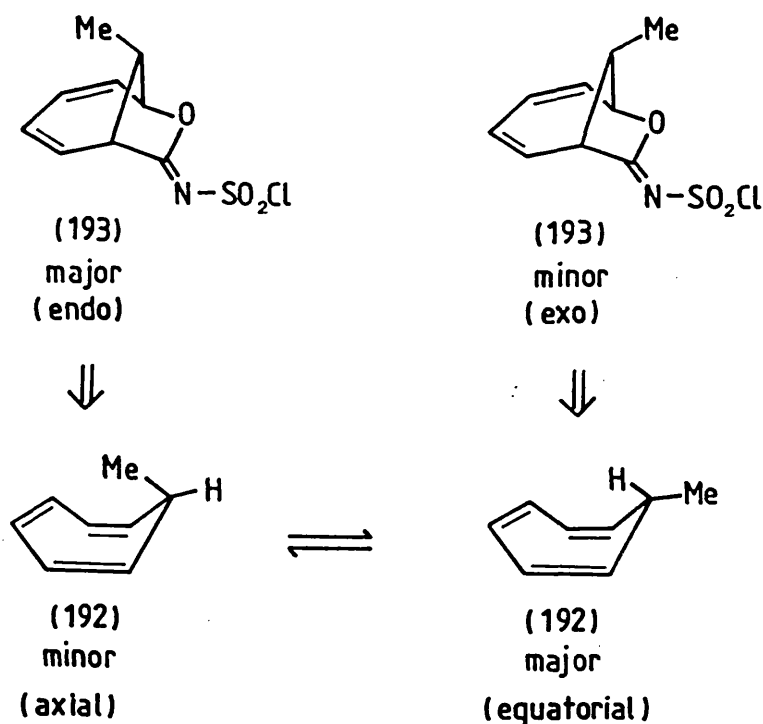
Figure 5·21

However, on further consideration this seems reasonable in view of steric effects. The approach of CSI to the minor conformer is significantly more facile, thus reaction occurs preferentially via the less stable conformer.[127]

The iminolactones (193 a,b) were subsequently dissolved in acetonitrile and the reaction monitored by infra-red spectroscopy. An infra-red absorption at 1760cm^{-1} grew with time and ultimately became the major product. This new peak was assigned to the N-chlorosulphonyl lactams (197 a,b), (figure 5.22), the structures being confirmed by ^{1}H NMR spectroscopy, (table 5.3).

a; R^1=Me, R^2= H
b; R^1=H, R^2= Me
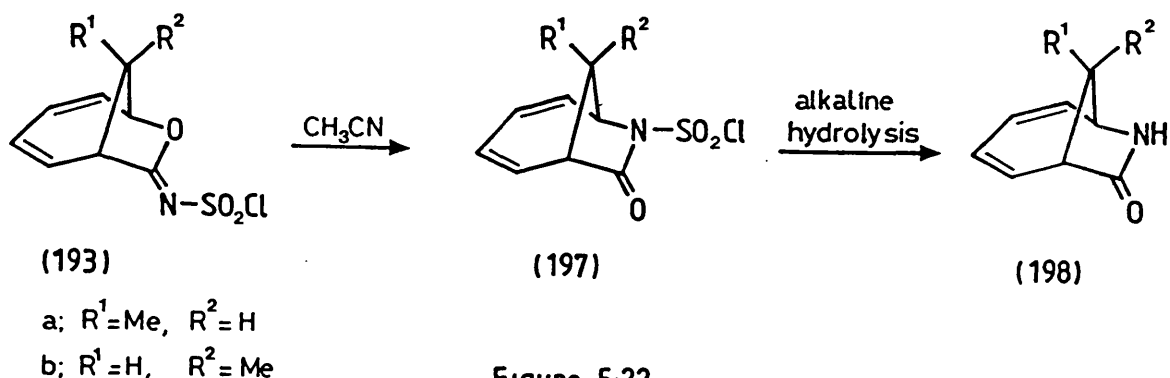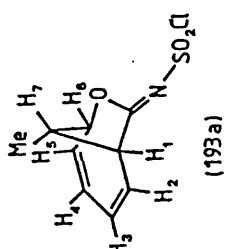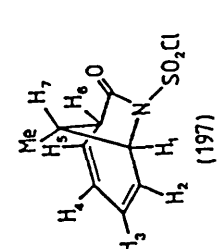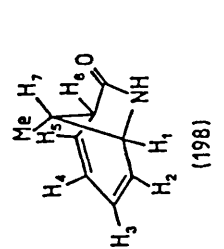
Figure 5·22

The conversion of N-chlorosulphonyliminolactone (193) to N-chlorosulphonyl lactam (197) was virtually quantitative. Alkaline hydrolysis in aqueous acetone at pH 6-7 and subsequent purification by flash chromatography afforded the lactams (198) in the ratio 5:1, the major isomer bearing an endo-methyl group.

NMR data for the major isomers are quoted (table 5.3). The signals due to the endo and exo methyl groups were clearly assignable.

TABLE 5.3

Compound	Chemical shifts (ppm) and multiplicity (Hz)					
	H_1	H_2-H_5	H_6	H_7	endo-Me (major)	exo-Me (minor)
(193a)	3.98 (m)	5.90-6.32 (m)	5.10 (m)	2.94 (sextet, $J=6Hz$)	1.10 (d, $J=6Hz$)	1.65 (d, $J=6Hz$)
(197)	4.70 (dd, $J_{12}=6Hz$, $J_{17}=6Hz$)	5.77-6.43 (m)	3.54 (dd, $J_{65}=9Hz$, $J_{67}=6Hz$)	2.77 (sextet, $J=6Hz$)	0.95 (d, $J=6Hz$)	1.01 (d, $J=6Hz$)
(198)	3.72 (dd, $J_{12}=6Hz$, $J_{17}=6Hz$)	5.82-6.21 (m)	3.24 (dd, $J_{65}=9Hz$, $J_{61}=6Hz$)	2.60 (sextet, $J=6Hz$)	0.83 (d, $J=6Hz$)	1.02 (d, $J=6Hz$)

Thus, Moriconi's proposal that the iminolactone was the thermo-dynamically controlled product of cyclisation is clearly unfounded. Longer reaction times or dissolution of the iminolactone in a more polar solvent results in the formation of a N-chlorosulphonyl lactam, this being the ultimate product of thermodynamic control.

The judicious choice of solvent and reaction time along with careful monitoring has been shown to exert control over the addition of either the C=O or C=N moiety across the termini of the triene unit thereby demonstrating the synthetic utility of the CSI-triene reactions.

Appendix 1

Synthesis and Chemistry of N-Tosyloxy-1,4-

dihydro-1,4-iminonaphthalene

A1.I.   INTRODUCTION

The solvolyses of many bicyclic N-chloroamines using silver salts to try to induce heterolysis of the N-Cl bond have been studied. However, homolytic reactions often interfere and so alternative leaving groups have been sought. A tosyloxy group was considered to be an ideal candidate and has, of course, been widely studied in carbon systems, the compounds undergoing facile ionisation, thereby providing superior solvolysis precursors.

The tosyloxy group has also been used as a leaving group in the rearrangement of 2-azabicycles. Heesing et al.[109] analysed the rearrangement of the 2-azabicyclo[2.2.1]heptane and hept-5-ene systems. Reaction of the hydroxylamine (199) with tosyl chloride proceeded with spontaneous rearrangement of the primarily established N-tosyloxy compound (200) into the 1-azabicyclo[2.2.1]heptane derivative (201), (figure A1.1).
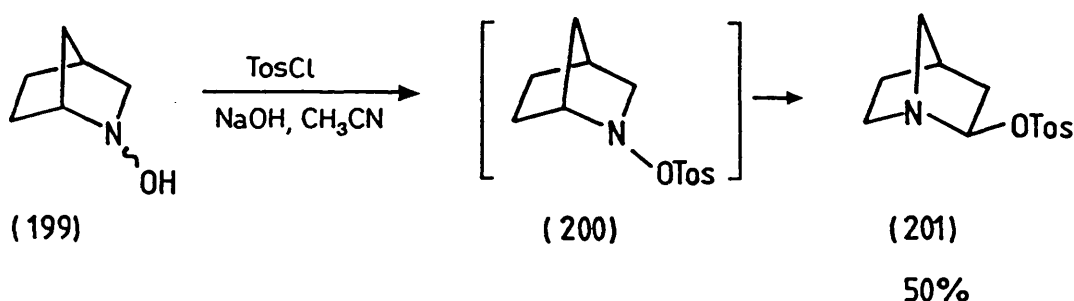
Figure A1·1

When the tosylation of (199) was carried out using methanol as a solvent, the rearrangement product (201) was formed as well as a small quantity of the rearranged compound (202) incorporating a methoxy group, (figure A1.2).
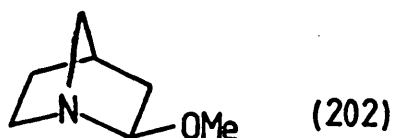
Figure A1·2

Further reports[110] suggested that the tosyloxy group encourages heterolysis, including the results noted by Fleury et al.[111] in which the 2-azabicyclo[2.2.2]octene system (203) underwent rearrangement quantitatively to afford the isomer (204), (figure A1.3).
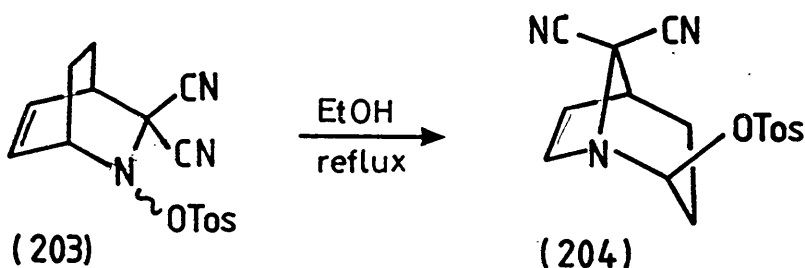
Figure A1·3

Thus, the N-tosyloxy derivative of 1,4-dihydro-1,4-imino-naphthalene (205), (figure A1.4), was synthesised and its solvolytic behaviour investigated with the intention of comparing the products of the reaction with those from the solvolysis of the corresponding N-chloro compound. The mechanistic correlation could be investigated which might, perhaps, confirm ideas on heterolysis and π-participation.

(205)
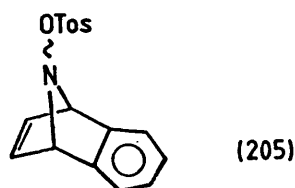
Figure A1·4

A1.II. SYNTHESIS AND REACTIONS OF N-TOSYLOXY-1,4-DIHYDRO-1,4-IMINO NAPHTHALENE (205)

Treatment of amine (9b), (figure A1.5), with benzoyl peroxide in the presence of base afforded the N-benzoyloxy derivative (206) in good yield (86%). Alkaline hydrolysis yielded the N-hydroxylamine (207) which was subsequently converted to the N-tosyloxy derivative (205) when treated with tosyl chloride in the presence of sodium hydroxide powder.
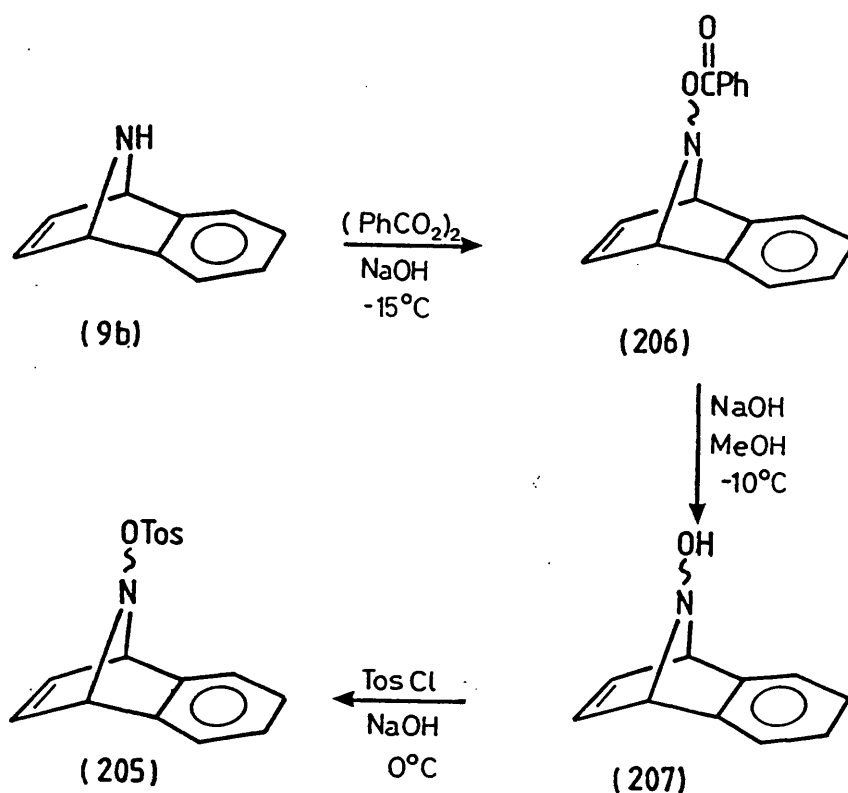
Figure A1·5

However, a methanolic solution of the N-tosyloxy compound (205) failed to rearrange even at reflux. Use of a higher boiling alcohol, t-butanol also failed to induce heterolysis. Thus, dipolar aprotic solvents such as dimethylsulphoxide and dimethylformamide were employed, but again, to no avail.

In order to encourage heterolysis, trifluoroacetic acid was used as solvent due to its high ionising power. However, this simply protonated the amine impelling the molecule to ring-open and aromatise to form the aminonaphthalene system (208), (figure A1.6).
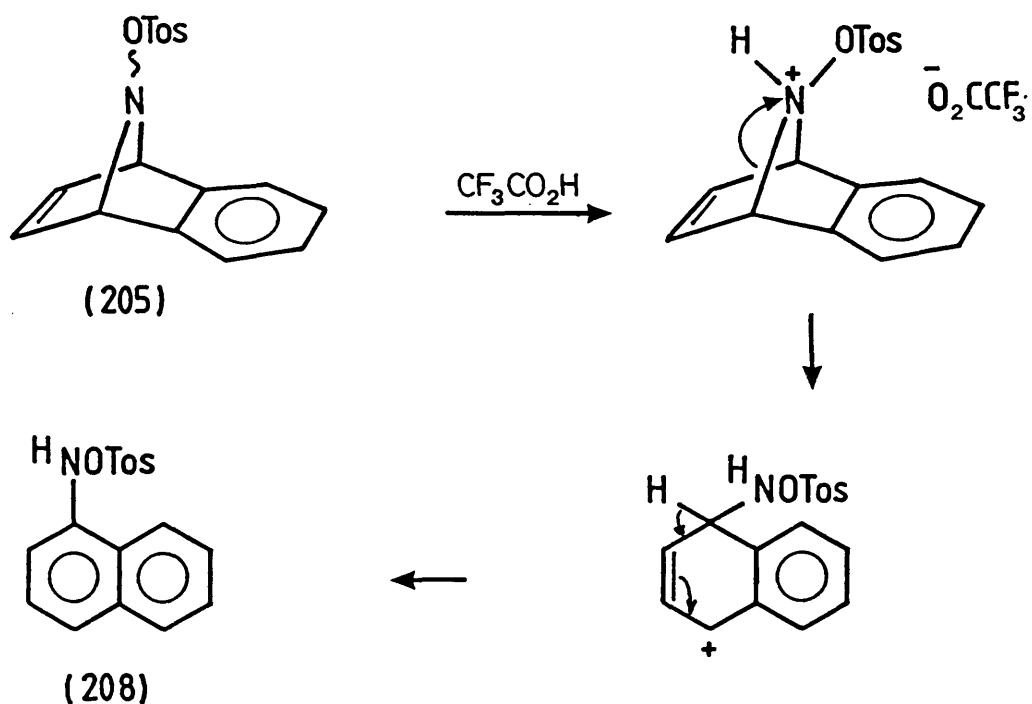
Figure A1·6

Thus, preliminary investigations suggest that the tosyloxy group is not a satisfactory leaving group in the study of the heterolysis of 7-azabicyclo[2.2.1]heptene derivatives.
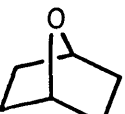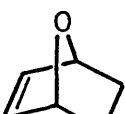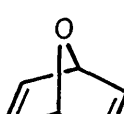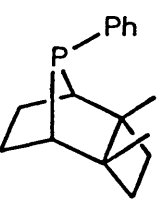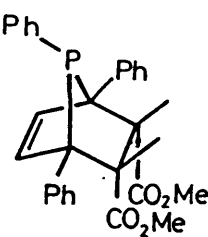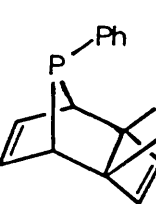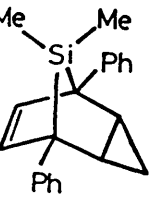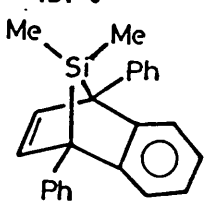
Appendix 2

^{15}N NMR Spectra of Bicyclic Amines

A2.I.   INTRODUCTION

It has been observed that bridging atoms in [2.2.1] bicyclic systems display unusually large deshielding in their NMR spectra, (table A2.1).

Table A2.1.   Chemical Shifts of 7-Position Atom (ppm)

δ_c [128]	38·4	48·5	75·1
δ_o [129]	85·5	110·0	192·5
δ_p [130]	22·0	137·0	147·0
δ_{si} [131]	58·5	76·9	

It seems unlikely that angle strain at the 7-position is the major factor for this deshielding phenomenon as atoms in strained rings are normally highly shielded. Table A2.1 illustrates the dependence of deshielding on the degree of unsaturation of the two-carbon bonds. The greater the unsaturation in the bicyclo[2.2.1]heptyl skeleton, the

larger the downfield shift of the atom in the 7-position. A possible explanation for this effect may involve ground state polarisation arising from $\sigma - \pi$ conjugation.[130b,131] Such conjugative effects would give rise to positive character at the 7-position, thus causing deshielding, (figure A2.1).
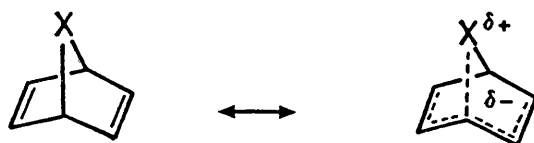
Figure A2·1

The acquisition of ^{15}N NMR spectra from samples containing ^{15}N at natural abundance is not simple[132] due to the low natural abundance (0.36%) and relative sensitivity of the ^{15}N nucleus. Thus, it is necessary to use sensitive high field Fourier Transform NMR spectrometers together with highly concentrated samples. The slow relaxation time of the ^{15}N nucleus necessitates exceptionally long spectral acquisition times. Another drawback is that Nuclear Overhauser Enhancement factors are negative for ^{15}N, so that the signals become more negative with proton decoupling.

Typical chemical shifts (relative to nitromethane) of various amines[133] are quoted in table A2.2.
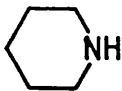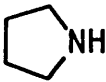
Amine	Chemical Shift (ppm)
RNH_2	- 325 → -380
R_2NH	-300 → -370
R_3N	-325 → -330

-320   -342   -393

Table A2·2

The bridging nitrogen in 7-azabicyclo[2.2.1]heptyl derivatives is unusual, exhibiting anomalously high barriers to inversion and extraordinary solvolytic behaviour. ^{15}N NMR studies[77] revealed that such systems exhibited extraordinary deshielding in the 7-position as with oxygen,[129] phosphorus[130] and silicon.[131] In fact, these amines displayed the lowest field ^{15}N signals yet recorded for secondary and tertiary amines, (table, A2.3).

Table A2.3. ^{15}N Chemical Shifts (ppm relative to CH_3NO_2)[77]

NH

OMe

OMe
- 214·4

NH

OMe

OMe
- 251·7

Cl
$
N

OMe

(52c)

OMe
- 200·1 (syn)
- 218·3 (anti)
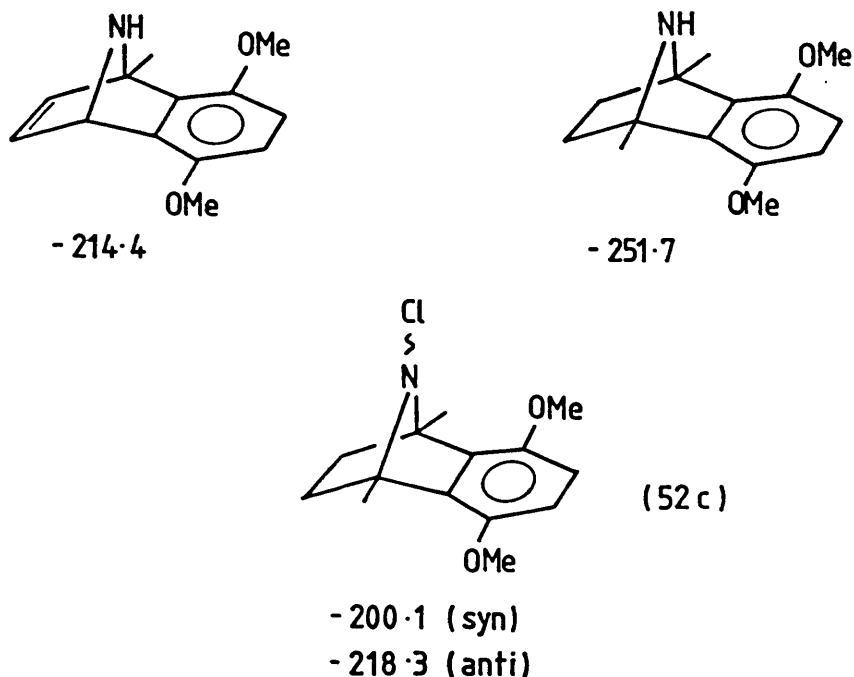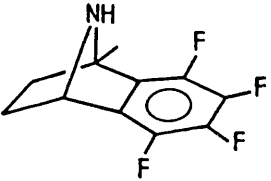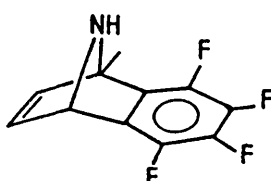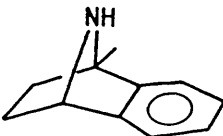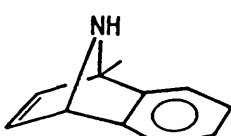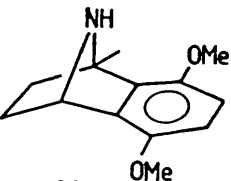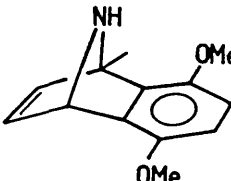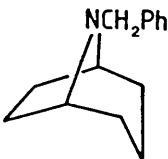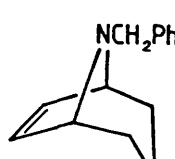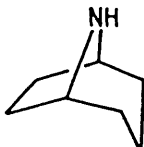
The chloroamine (52c) was of particular interest since it constituted the first example of a system exhibiting separate signals for the two invertomers at a single nitrogen. Previous examples have involved double inversion in bicyclic hydrazines.[134]

A2.II. ^{15}N NMR CHEMICAL SHIFTS OF VARIOUS BICYCLIC AMINES

Table A2.4 presents the ^{15}N NMR spectra accumulated during this study.

Table A2.4. ^{15}N Chemical Shifts (ppm relative to CH_3NO_2)

(62a)

-263.3

(61a)

-226.8

(62b)

-265.8

(61b)

-225.6

(62c)

-265.0

(61c)

-226.2

(140)

-305.8

(152)

-300.4

(110)

-357.5

Amines (140), (152) and (110) all possess average barriers to nitrogen inversion, and interestingly, also have ^{15}N chemical shifts typical of secondary and tertiary amines.

However, all the amines containing a bridging nitrogen at the 7-position in the 7-azabicyclo[2.2.1]heptyl derivatives display low-field ^{15}N NMR signals. The downfield increment of ca. 38 ppm on replacing an ethano-bridge with an etheno-bridge parallels similar trends in carbon,[128] phosphorus[130] and oxygen[129] systems. Relatively little effect is observed on the ^{15}N chemical shift when the substituents on the aryl ring are altered.

The deshielding of nitrogen in the 7-azabicyclo[2.2.1]heptyl derivatives and not in the 8-azabicyclo[3.2.1]octyl derivatives suggests that a correlation exists between the ^{15}N chemical shifts and the inversion barriers at nitrogen.

Chapter 6

Experimental

Instrumentation

^{1}H NMR spectra were recorded on Perkin-Elmer EM 390 and Jeol JNM-PS100 spectrometers. High field ^{1}H NMR (300MHz) and ^{13}C (75MHz) spectra were recorded on a Bruker AM 300 spectrometer while ^{1}H (400MHz) spectra were recorded using facilities provided by the S.E.R.C. at the University of Warwick. Chemical shifts were recorded in ppm (δ) downfield from the internal reference tetramethylsilane (TMS). Signal characteristics are described using the following standard abbreviations:

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

Infra-red spectra were recorded on a Perkin Elmer 298 spectrometer using 0.1mm sodium chloride solution cells or sodium chloride plates. Band positions, given in wavenumbers (cm^{-1}) are described by the standard abbreviations:

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

Routine mass spectra were obtained using a VG Micromass 16B spectrometer. High resolution mass spectra were obtained via S.E.R.C. quota from P.C.M.U. Harwell and University College of Swansea.

Elemental analyses were carried out by C.H.N. Analysis Ltd., Wigston, Leicester and Butterworth Laboratories Ltd., Teddington, Middlesex.

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

Technical

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

Dichloromethane was distilled from calcium hydride.

Petroleum ether was dried over sodium wire and then distilled.

Methanol and ethanol were dried and purified with magnesium and iodine as described by Vogel.[135]

Tetrahydrofuran and toluene were distilled from sodium-benzophenone.

All other solvents and reagents were dried and purified as described by Perrin et al.[136]

Flash chromatography was carried out according to the method of Still et al.[137] using silica gel manufactured by Merck and Co., Kieselgel 60 230-400 mesh.

N-Trimethylsilyl pyrrole (28)[42]

Pyrrole (32.6g, 0.49mol) and hexamethyldisilazane (43.0g, 0.27mol) were heated under reflux with a few crystals of ammonium sulphate for 6h under N$_2$. The reaction mixture was distilled through a 25cm Vigreux column yielding (28) (49.6g, 73%) as a colourless oil: bp 72-76°C (60mm Hg), lit. bp 71-78°C (60mm Hg).

δ_H (90MHz, CDCl$_3$): 0.5 (s, 9H), 6.25 (m, 2H), 6.75 (m, 2H).

5,6,7,8-Tetrafluoro-1,4-dihydro-1,4-iminonaphthalene (9a)[42]

A solution of n-butyllithium (2.5M in hexane, 75ml) was added dropwise over a period of 20min. to a stirred solution of pentafluorobenzene (30.5g, 0.18mol) in dry diethyl ether (400ml) at -78°C under N$_2$. A solution of N-trimethylsilyl pyrrole (28.8g, 0.21mol) in diethyl ether (100ml) was subsequently added over a further 10 min. The reaction mixture was allowed to warm to room temperature overnight with stirring, and then poured into water (300ml). The product was extracted into ether (2 x 200ml) and then the combined organic extracts were washed with cold 2M hydrochloric acid (2 x 200ml). The acidic extracts were combined, cooled and carefully basified with 2M (aq) sodium hydroxide solution. The basic solution was re-extracted with dichloromethane (2 x 200ml) and the organic layers combined before drying over anhydrous magnesium sulphate. The solvent was evaporated at reduced pressure to yield (9a) (16.3g, 42%) as a pale yellow oil.

δ_H (90MHz, CDCl$_3$): 2.53 (br s, exch, 1H), 5.37 (m, 2H), 7.07 (m, 2H).

N-Carbomethoxy-5,6,7,8-tetrafluoro-1,4-dihydro-1,4-iminonaphthalene (29a)

A solution of (9a) (6.88g, 32.0mmol) in dry tetrahydrofuran (50ml) was added dropwise to a suspension of sodium hydride (80% dispersion, 0.97g) in tetrahydrofuran (10ml) under N_2. After stirring for 2h, the solution was cooled to $0^{\circ}C$ and methyl chloroformate (3.60g, 38.0mmol) was added dropwise. The reaction mixture was stirred at $0^{\circ}C$ for 10 min. and for a further 1.5h at room temperature. Water (100ml) was added cautiously and the product extracted into dichloromethane (3 x 50ml). The combined organic extracts were dried over anhydrous magnesium sulphate and the solvent evaporated at reduced pressure to afford (29a) (7.91g, 90%) as a yellow oil.

δ_H (90MHz, $CDCl_3$): 3.53 (s, 3H), 5.75 (m, 2H), 6.88 (m, 2H).

ν_{max} (CH_2Cl_2): 3050w, 2960w, 2860w, 1760s, 1500s, 1440m, 1335s, 1290m, 1245m, 2120w, 1200w, 1130m, 1090m, 1080m, 1055m, 1010w, 990w, 970m, 965m, 960m, 940m, 800m, 790m cm^{-1}.

m/e (%): M^+ 273 (100), 248 (16), 247 (52), 215 (26), 214 (48), 189 (29), 188 (72).

N-Carbomethoxy-5,6,7,8-tetrafluoro-1,2,3,4-tetrahydro-2-hydroxy-1,4-iminonaphthalene (30a)

A solution of borane (1M in tetrahydrofuran, 18ml) was added dropwise to a solution of (29a) (4.91g, 18.0mmol) in dry tetrahydrofuran (40ml) at $0^{\circ}C$ under N_2. After stirring for 10 min. at $0^{\circ}C$, the reaction mixture was allowed to warm to room temperature, stirred for a further 1.5h, and then quenched with water (50ml). 2M (aq) sodium hydroxide solution (10ml) was added, followed by the dropwise addition of hydrogen peroxide (6% w/v, 9.6ml). The product was subsequently

extracted into dichloromethane (3 x 50ml) and dried over anhydrous magnesium sulphate. The solvent was evaporated at reduced pressure to afford (30a) (4.99g, 95%) as a yellow oil.

δ_H (90MHz, CDCl$_3$): 1.83-1.87 (m, 2H), 2.15 (br s, exch, 1H), 3.60 (s, 3H), 4.00 (m, 1H), 5.25 (d, J = 4.5Hz, 1H), 5.40 (s, 1H).

v_{max} (CH$_2$Cl$_2$): 3680w, 3600w, 3500w, 3495w, 3300w, 3025w, 2955w, 2875w, 1740s, 1500s, 1490s, 1440s, 1385m, 1360m, 1350m, 1310m, 1300m, 1245m, 1210m, 1190w, 1170w cm^{-1}.

m/e (%): 248 (9), 247 (100), 203 (48), 202 (19), 186 (6), 188 (15), 162 (7).

observed m/e (M$^+$ - H$_2$C=CHOH) 247.0251

calculated for C$_{10}$H$_5$NO$_2$F$_4$ 247.0251.

N-Carbomethoxy-5,6,7,8-tetrafluoro-1,2,3,4-tetrahydro-2-keto-1,4-iminonaphthalene (31a)

A solution of trifluoroacetic anhydride (5.0ml, 36.0mmol) in dry dichloromethane (10ml) was added to dry dimethylsulphoxide (3.4ml, 47.0mmol) diluted with dichloromethane (20ml) over 0.5h at -78°C. After stirring for 10 min. below -60°C, a solution of (30a) (3.47g, 11.9mmol) in dichloromethane (20ml) was added over 15 min. Stirring was continued for an additional 5 min. below -60°C, and then the solution was allowed to warm to room temperature. Triethylamine (9ml) was subsequently added, the reaction mixture washed with water (40ml) and the product extracted into dichloromethane (3 x 50ml). After drying over anhydrous magnesium sulphate, the solvent was evaporated at reduced pressure. The residue was purified by flash chromatography (50:50, diethyl ether:petroleum ether [40-60°C]) to yield (31a) (2.06g, 60%) as colourless crystals: mp 144-145°C.

δ_H (90MHz, CDCl$_3$): 1.98 (d, J = 16.5Hz, 1H), 2.60 (dd, J = 16.5Hz, J = 4.5Hz, 1H), 3.27 (s, 3H), 5.25 (s, 1H), 5.68 (d, J = 4.5Hz, 1H).

δ_C (75MHz, CDCl$_3$): 38.6 (t), 53.6 (q), 55.5 (d), 65.9 (d), 155.3 (s), 199.6 (s).

ν_{max} (CH$_2$Cl$_2$): 3060w, 1780s, 1730s, 1510s, 1490s, 1440m, 1350m, 1310m, 1275w, 1250m, 1210w, 1140m, 1115w, 1060m, 1005w, 970w, 900w cm^{-1}.

m/e (%): M$^+$ 289 (5), 260 (17), 248 (13), 247 (100), 230 (5), 216 (22), 203 (38), 202 (41), 188 (21), 175 (12), 162 (11), 161 (11).

Found: C, 49.98; H, 2.50; N, 4.80%. C$_{12}$H$_7$NO$_3$F$_4$

requires: C, 49.84; H, 2.44; N, 4.84%.

5,6,7,8-Tetrafluoro-1,2,3,4-tetrahydro-2-keto-1,4-iminonaphthalene (32a)

Trimethylsilyl iodide (0.48ml, 3.4mmol) was added dropwise to a solution of (31a) (0.33g, 1.1mmol) in chloroform (1.5ml). The reaction mixture was heated under reflux for 4h, and then dry methanol (0.18ml, 4.4mmol) was added. After stirring for 10 min. at room temperature, the volatile components were removed at reduced pressure. The reaction mixture was subsequently dissolved in methanol (2ml), sodium methoxide (0.03g, 0.6mmol) was added, and the mixture stirred for 10 min. The volatile components were again evaporated at reduced pressure and then water (10ml) and 2M (aq) sodium hydroxide solution (0.5ml) were added. The product was extracted into dichloromethane (3 x 10ml) and the combined organic extracts were dried over anhydrous magnesium sulphate. The solvent was evaporated at reduced pressure to yield (32a) (0.08g, 30%) as a colourless oil.

δ_H (90MHz, CDCl$_3$): 1.93 (d, J = 16.5Hz, 1H), 2.53 (dd, J = 16.5Hz, J = 4.5Hz, 1H), 3.03 (br s, exch, 1H), 4.70 (d, J = 4.5Hz, 1H), 5.13 (s, 1H).

ν_{max} (CH$_2$Cl$_2$): 3300w, 3020w, 1770s, 1500s, 1485s, 1405w, 1380w, 1355w, 1290m, 1250m, 1135m, 1120m, 1105w, 1060s, 1030w, 1005w, 990m, 930m, 920m, 900m, 840m, 810w cm^{-1}.

$^m/_e$ (%): M$^+$ 231 (5), 230 (8), 204 (11), 203 (35), 202 (100), 201 (11), 190 (53), 189 (98), 188 (11), 175 (19), 162 (38), 161 (11), 143 (13).

N-Chloro-5,6,7,8-tetrafluoro-1,2,3,4-tetrahydro-2-keto-1,4-imino-naphthalene (33a)

A solution of (32a) (0.09g, 0.26mmol) in dry dichloromethane (1ml) was treated with NCS (0.047g, 0.35mmol) under N$_2$. After stirring for 30 min. at room temperature, the solvent was removed at reduced pressure. The residue was triturated with trichlorofluoromethane, and filtered to remove the succinimide and excess NCS. The solvent was evaporated by passing a gentle stream of N$_2$ over it to yield (33a) (0.18g, 95%) as a pale yellow oil.

δ_H (300MHz, CDCl$_3$): syn- (33a), 2.27 (d, J = 16.5Hz, 1H), 2.80 (dd, J = 16.5Hz, J = 4.5Hz, 1H), 4.88 (s, 1H), 5.22 (d, J = 4.5Hz, 1H).

anti- (33a), 2.16 (d, J = 16.5Hz, 1H), 3.10 (dd, J = 16.5Hz, J = 4.5Hz, 1H), 4.69 (s, 1H), 5.17 (d, J = 4.5Hz, 1H).

δ_C (75MHz, CDCl$_3$): syn- (33a), 38.6 (t), 71.6 (d), 77.0 (d), 196.8 (s).

anti- (33a), 32.7 (t), 67.2 (d), 74.9 (d), 204.8 (s).

$^m/_e$ (%): M$^+$ 267, 265 (4, 12), 248 (13), 247 (29), 231 (29), 230 (62), 189 (19), 188 (100).

1-Trimethylsilyl-2,5-dimethyl pyrrole (36)[63]

A stirred solution of 2,5-dimethyl pyrrole (37.6g, 0.4mol) in dry diethyl ether (130ml) and dry benzene (55ml) was treated with small lumps of potassium (14.1g, 0.36mmol) under N_2. The reaction mixture was stirred for 1.5h at room temperature and then heated under reflux for a further 3h. After cooling the potassio-pyrrole slurry to $0^{\circ}C$, tri-methylsilyl chloride (46ml, 0.36mol) was added dropwise. The reaction mixture was stirred overnight at room temperature and then filtered. The solvents were evaporated at reduced pressure, and the product distilled to yield (36) (41.0g, 61%) as a colourless oil: bp 90–93$^{\circ}C$ (15mm Hg), lit. bp 95–97$^{\circ}C$ (15mm Hg).

δ_H (90MHz, $CDCl_3$): 0.50 (s, 9H), 2.27 (s, 2H), 5.83 (s, 2H).

1,4-Dihydro-5,8-dimethoxy-1,4-dimethyl-1,4-iminonaphthalene (37c)[63]

(37c) was prepared using a similar method as that used to prepare (9a). 1,4-Dimethoxybenzyne [generated *in situ* from 1,4-dimethoxy-2-chlorobenzene (20.2g, 0.12mol) and n-butyllithium (2.5M in hexane, 48ml)] reacted with (36) (19.6g, 0.12mol) to afford (37c) (7.9g, 28%) as colourless crystals: mp 115–116$^{\circ}C$, lit. mp 112–117$^{\circ}C$.

δ_H (90MHz, $CDCl_3$): 1.87 (s, 6H), 2.73 (br s, exch, 1H), 3.67 (s, 6H), 6.43 (s, 2H), 6.70 (s, 2H).

N-Carbomethoxy-1,4-dihydro-5,8-dimethoxy-1,4-dimethyl-1,4-imino-naphthalene (38c)

(38c) was prepared using a similar method to that used to prepare (29a). (37c) (2.31g, 10.0mmol) reacted with sodium hydride (80% dispersion, 0.31g) and methyl chloroformate (1.13g, 11.9mmol) to afford (38c) (2.30g, 80%) as a yellow oil.

δ_H (90MHz, CDCl$_3$): 2.14 (s, 6H), 3.50 (s, 3H), 3.67 (s, 6H), 6.47 (s, 2H), 6.60 (s, 2H).

ν_{max} (CH$_2$Cl$_2$): 3240w, 3105s, 2855s, 1720s, 1495m, 1415m, 1395m, 1358m, 1245w, 1170m, 1135w, 1085m, 1005m, 865m cm^{-1}.

$^m/_e$ (%): M$^+$ 289 (52), 274 (26), 263 (41), 258 (37), 234 (46), 229 (38), 230 (67), 205 (61), 204 (100).

N-Carbomethoxy-1,2,3,4-tetrahydro-2-hydroxy-5,8-dimethoxy-1,4-dimethyl-1,4-iminonaphthalene (39c)

(39c) was prepared using a similar method to that used to prepare (30a). (38c) (4.40g, 15.2mmol) reacted with borane (1M in tetrahydrofuran, 15.2ml), 2M (aq) sodium hydroxide solution (8ml) and hydrogen peroxide (6% w/v, 8ml) to yield (39c) (4.58g, 98%) as a colourless oil.

δ_H (90MHz, CDCl$_3$): 1.85-1.92 (m, 2H), 1.98 (s, 3H), 2.00 (s, 3H), 2.14 (s, 3H), 2.41 (br s, exch, 1H), 3.60 (s, 3H), 3.69 (s, 3H), 3.87 (m, 1H), 6.60 (s, 2H).

ν_{max} (CH$_2$Cl$_2$): 3670w, 3600w, 3050w, 2990w, 2940w, 1710s, 1600w, 1385w, 1340m, 1320m, 1280m, 1245s, 1225w, 1180m, 1140w, 1100w, 1050m, 990w, 900w, 800w cm^{-1}.

$^m/_e$ (%): M$^+$ 307 (26), 292 (14), 276 (29), 263 (92), 252 (33), 247 (24), 248 (72), 205 (59), 204 (100).

N-Carbomethoxy-1,2,3,4-tetrahydro-2-keto-5,8-dimethoxy-1,4-dimethyl-1,4-iminonaphthalene (40c)

Chromium trioxide (8.97g, 89.7mmol) was added to a solution of pyridine (14.5ml, 178.8mmol) in dry dichloromethane (225ml) and stirred at room temperature for 30 min. A solution of the alcohol (39c) (4.58g,

14.9mmol) in dichloromethane (20ml) was added in one portion. After stirring for 1h, the solution was filtered through a column of silica, and eluted several times with diethyl ether. The solvent was evaporated at reduced pressure, and then the residue was purified by flash chromatography (50:50, diethyl ether:petroleum ether [40-60°C]) to yield (40c) (2.62g, 58%) as a colourless oil.

δ_H (90MHz, CDCl$_3$): 1.97 (s, 3H), 2.07 (d, J = 16.5Hz, 1H), 2.13 (s, 3H), 2.40 (d, J = 16.5Hz, 1H), 3.52 (s, 3H), 3.63 (s, 3H), 3.67 (s, 3H), 6.60 (s, 2H).

ν_{max} (CH$_2$Cl$_2$): 3050w, 2995w, 2980w, 1760s, 1710s, 1600w, 1500s, 1460m, 1440m, 1385w, 1335m, 1320m, 1280m, 1240s, 1220m, 1200m, 1180m, 1140m, 1110m, 1050m, 990w, 950w, 900w cm^{-1}.

$^m/_e$ (%): M$^+$ 305 (42), 290 (15), 274 (32), 263 (84), 250 (29), 249 (24), 249 (69), 205 (52), 204 (100).

1,4-Dihydro-1,4-dimethyl-1,4-iminonaphthalene (37b)[63]

(37b) was prepared using a similar method as that used to prepare (9a). Benzyne [generated in situ from 2-bromofluorobenzene (15.0g, 86mmol) and n-butyllithium (2.5M in hexane, 34.5ml)] reacted with (36) (15.2g, 79mmol) to afford (37b) (8.14g, 55%) as a pale yellow oil.

δ_H (90MHz, CDCl$_3$): 1.70 (s, 6H), 2.87 (br s, exch, 1H), 6.60 (s, 2H), 6.93 (m, 4H).

N-Carbomethoxy-1,4-dihydroxy-1,4-dimethyl-1,4-iminonaphthalene (38b)

(38b) was prepared using a similar method as that used to prepare (29a). (37b) (7.89g, 46.0mmol) reacted with sodium hydride (80% dispersion, 1.40g) and methyl chloroformate (5.22g, 55.0mmol) to afford (38b) (9.39g, 89%) as a yellow oil.

δ_H (90MHz, CDCl$_3$): 2.07 (s, 6H), 3.50 (s, 3H), 6.60 (s, 2H), 6.98 (m, 4H).

ν_{max} (CH$_2$Cl$_2$): 3040w, 2985w, 2940w, 1710s, 1500m, 1450s, 1385m, 1340w, 1290m, 1275w, 1220w, 1140w, 1125w, 1095w, 1060m, 995w, 950w, 910w cm^{-1}.

$^m/_e$ (%): M$^+$ 229 (31), 214 (28), 204 (41), 203 (82), 200 (29), 170 (46), 145 (61), 144 (100).

N-Carbomethoxy-1,2,3,4-tetrahydro-2-hydroxy-1,4-dimethyl-1,4-imino-naphthalene (39b)

(39b) was prepared using a similar method as that used to prepare (30a). (38b) (3.91g, 17.1mmol) reacted with borane (1M in tetrahydrofuran, 17.1ml), 2M (aq) sodium hydroxide solution (10ml), and hydrogen peroxide (6% w/v, 9ml) to yield a yellow oil. Purification by flash chromatography (20:80, diethyl ether:petroleum ether [40-60°C]) yielded (42) (0.53g, 20%) as a colourless oil.

δ_H (300MHz, CDCl$_3$): 2.62 (s, 6H), 7.5-8.0 (m, 6H).

ν_{max} (CH$_2$Cl$_2$): 3065w, 3020m, 2958s, 2920s, 2860s, 1600m, 1510w, 1480m, 1445s, 1365m, 1255m, 1230m, 1070m, 1060m, 1045m, 1020m, 940m cm^{-1}.

$^m/_e$ (%): M$^+$ 156 (100), 154 (6), 153 (10), 142 (17), 141 (96), 128 (54), 127 (13), 105 (20).

Further elution of the column yielded (39b) (2.95g, 71%) as a pale yellow oil.

δ_H (90MHz, CDCl$_3$): 1.65-1.75 (m, 2H), 1.85 (s, 3H), 1.90 (s, 3H), 2.70 (br s, exch, 1H), 3.55 (s, 3H), 3.95 (m, 1H), 7.00-7.23 (m, 4H).

ν_{max} (CH$_2$Cl$_2$): 3660w, 3610w, 2985w, 1710s, 1440s, 1380m, 1340w, 1290m, 1260m, 1220w, 1190m, 1140m, 1120m, 1090w, 1060m, 1015w, 980w, 960w, 910w cm^{-1}.

$^m/_e$ (%): M$^+$ 243 (31), 232 (12), 218 (22), 204 (43), 203 (82), 188 (51), 145 (61), 144 (100).

N-Carbomethoxy-1,2,3,4-tetrahydro-2-keto-1,4-dimethyl-1,4-imino-naphthalene (40b)

(40b) was prepared using a similar method as that used to prepare (40c). (39b) (3.78g, 15.3mmol) reacted with chromium trioxide (9.18g, 92mmol) and pyridine (14.8ml, 183mmol) which, after flash chromatography (50:50, diethyl ether:petroleum ether [40-60°C]) afforded (40b) (2.24g, 60%) as a colourless oil.

δ_H (90MHz, CDCl$_3$): 1.93 (s, 3H), 2.00 (d, J = 16.5Hz, 1H), 2.10 (s, 3H), 2.50 (d, J = 16.5Hz, 1H), 3.57 (s, 3H), 7.17 (m, 4H).

ν_{max} (CH$_2$Cl$_2$): 3055w, 2980w, 2955w, 1760s, 1710s, 1500w, 1440s, 1380m, 1345s, 1295m, 1255m, 1195m, 1140m, 1095m, 1080m, 1060m, 985w, 910w cm^{-1}.

m/e (%): M$^+$ 245 (23), 230 (15), 216 (17), 204 (42), 203 (69), 186 (72), 145 (59), 144 (100).

observed m/e 245.1048

calculated for C$_{14}$H$_{15}$NO$_3$ 245.1056.

N-Carbobenzoxy-1,4-dihydro-1,4-iminonaphthalene (45)

A solution of (9b) (1.16g, 8.1mmol) in dry diethyl ether (50ml) was added dropwise to a suspension of sodium hydride (80% dispersion 0.29g) in diethyl ether (10ml) under N$_2$. After stirring for 2h, the solution was cooled to 0°C and benzyl chloroformate (1.2ml, 8.1mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred overnight. Water (20ml) was added cautiously and the product extracted into diethyl ether (3 x 20ml). The combined organic extracts were dried over anhydrous magnesium sulphate and the solvent evaporated at reduced pressure to afford (45) (2.21g, 98%) as a colourless oil.

δ_H (90MHz, CDCl$_3$): 4.93 (s, 2H), 5.47 (d, J = 1.5Hz, 2H), 6.83 (m, 4H), 7.10-7.21 (m, 7H).

ν_{max} (CH$_2$Cl$_2$): 3020m, 1710s, 1500m, 1450m, 1390s, 1330s, 1240s, 1220m, 1190m, 1160w, 1130w, 1090s, 1070s, 1030m, 1010w, 960w, 950w, 910w, 870w, 850m cm^{-1}.

m/e (%): M$^+$ 277 (23), 233 (8), 232 (5), 216 (29), 208 (8), 169 (33), 143 (10), 142 (24), 141 (17), 140 (14), 128 (22), 115 (31), 114 (10), 91 (100).

N-Carbobenzoxy-1,2,3,4-tetrahydro-2-hydroxy-1,4-iminonaphthalene (46)

(46) was prepared using a similar method as that used to prepare (30a). (45) (2.25g, 8.1mmol) reacted with borane (1M in tetrahydrofuran, 8.1ml), 2M (aq) sodium hydroxide solution (5ml) and hydrogen peroxide (6% w/v, 4.3ml) to yield (46) (2.36g, 98%) as a glassy oil.

δ_H (90MHz, CDCl$_3$): 1.77 (m, 2H), 2.77 (br s, exch, 1H), 3.90 (m, 1H), 4.93 (s, 2H), 5.00 (m, 1H), 5.10 (m, 1H), 7.08-7.19 (m, 9H).

ν_{max} (CH$_2$Cl$_2$): 3600w, 3500w, 3350w, 1710s, 1460m, 1395m, 1390m, 1355s, 1330s, 1290s, 1260s, 1215m, 1205m, 1190m, 1165m, 1150m, 1050w, 1010w, 970m, 910w, 860w cm^{-1}.

m/e (%): M$^+$ 295 (21), 252 (18), 251 (37), 161 (21), 160 (57), 117 (12), 116 (100), 115 (8).

N-Carbobenzoxy-1,2,3,4-tetrahydro-2-keto-1,4-iminonaphthalene (47)

(47) was prepared using a similar method as that used to prepare (40c). (46) (2.39g, 8.1mmol) reacted with chromium trioxide (4.86g, 48.6mmol) and pyridine (7.8ml, 97.2mmol) which, after flash chromatography (50:50, diethyl ether:petroleum ether [40-60°C]) afforded (47) (1.56g, 66%) as a colourless oil.

δ_H (90MHz, CDCl$_3$): 1.90 (d, J = 16.5Hz, 1H), 2.50 (dd, J = 16.5Hz, J = 4.5Hz, 1H), 4.95 (s, 3H), 5.40 (d, J = 4.5Hz, 1H), 7.05-7.19 (m, 9H).

δ_C (75MHz, CDCl$_3$): 39.3 (t), 60.9 (d), 67.5 (t), 69.1 (d), 120.7 (d), 123.0 (d), 127.6 (d), 127.7 (d), 128.1 (d), 128.4 (d), 128.5 (d), 135.7 (s), 137.2 (s), 145.8 (s), 155.3 (s), 203.8 (s).

ν_{max} (CH$_2$Cl$_2$): 3020w, 1765s, 1710s, 1495w, 1450w, 1390m, 1340s, 1330m, 1240m, 1195m, 1145m, 1125m, 1110m, 1080m, 1030w, 910w cm^{-1}.

m/e (%): 265 (6), 252 (15), 251 (100), 221 (19), 220 (33), 207 (71), 203 (15), 202 (27), 175 (12), 173 (10), 172 (10), 158 (33), 147 (17), 146 (32).

observed m/e (M$^+$ - H$_2$C=CO) 251.0948

calculated for C$_{16}$H$_{13}$NO$_2$ 251.0949.

1,2,3,4-Tetrahydro-2-keto-1,4-iminonaphthalene (32b)

A solution of hydrogen bromide (45% w/v, 1.5ml) was added dropwise to (47) (0.36g, 1.23mmol) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred overnight. Water (10ml) and dichloromethane (10ml) were added. The aqueous layer was cooled and carefully basified with 2M (aq) sodium hydroxide solution. The product was extracted into dichloromethane (3 x 10ml) and the combined organic layers dried over anhydrous magnesium sulphate. Evaporation of the solvent at reduced pressure afforded (32b) (0.16g, 80%) as a pale yellow oil.

δ_H (90MHz, CDCl$_3$): 1.77 (d, J = 16.5Hz, 1H), 2.33 (dd, J = 16.5Hz, J = 4.5Hz, 1H), 2.90 (br s, exch, 1H), 4.20 (s, 1H), 4.67 (d, J = 4.5Hz, 1H), 7.08-7.14 (m, 4H).

ν_{max} (CH$_2$Cl$_2$): 3020w, 2985w, 1875s, 1495w, 1450w, 1395m, 1345s, 1320w, 1240m, 1190m, 1140m, 1120m, 1110w, 1090m, 1020w, 975w, 910w, 890w.

m/e (%): M$^+$ 159 (25), 144 (12), 118 (27), 117 (100).

N-Chloro-1,2,3,4-tetrahydro-2-keto-1,4-iminonaphthalene (33b)

(33b) was prepared using a similar method as that used to prepare (33a). (32b) (0.045g, 0.28mmol) reacted with NCS (0.050g, 0.37mmol) to yield (33b) (0.052g, 96%) as a yellow oil.

δ_H (300MHz, CDCl$_3$): syn- (33b), 2.07 (d, J = 16.5Hz, 1H), 2.67 (dd, J = 16.5Hz, J = 4.5Hz, 1H), 4.50 (s, 1H), 4.87 (d, J = 4.5Hz, 1H), 7.19-7.27 (m, 4H).

anti- (33b), 2.00 (d, J = 16.5Hz, 1H), 3.97 (dd, J = 16.5Hz, J = 4.5Hz, 1H), 4.37 (s, 1H), 4.87 (d, J = 4.5Hz, 1H), 7.19-7.27 (m, 4H).

δ_C (75MHz, CDCl$_3$): syn- (33b), 39.3 (t), 73.6 (d), 80.6 (d), 122.9 (d), 124.9 (d), 128.2 (d), 128.9 (d), 136.3 (s), 146.2 (s), 181.0 (s).

anti- (33b), 33.7 (t), 70.0 (d), 79.0 (d), 121.1 (d), 122.9 (d), 128.4 (d), 129.3 (d), 134.9 (s), 143.3 (s), 179.9 (s).

$^m/_e$ (%): M$^+$ 195, 193 (5, 15), 159 (22), 158 (100), 144 (13), 118 (27), 117 (82).

1-Trimethylsilyl-2-methyl pyrrole (65)

A stirred solution of 2-methyl pyrrole (64) (10.4g, 0.13mol) in dry diethyl ether (45ml) and dry benzene (20ml) under N$_2$ was treated with small pieces of potassium (5.70g, 0.15mol) over 15 min. The reaction mixture was then stirred for 1h and heated at reflux for a further 5h. The potassio-pyrrole slurry thus formed was cooled to 0°C and trimethylsilyl chloride (20ml, 0.16mol) was added dropwise over 15 min. The reaction mixture was heated at reflux for 10h and then filtered. The solvent was evaporated at reduced pressure and fractional

distillation of the residue afforded (65) (11.41g, 58%) as a colourless oil: bp 58-61°C (30mmHg).

δ_H (90MHz, CDCl$_3$): 0.30 (s, 9H), 2.16 (s, 3H), 5.81 (m, 1H), 5.98 (m, 1H), 6.43 (m, 1H).

5,6,7,8-Tetrafluoro-1,4-dihydro-1-methyl-1,4-iminonaphthalene (61a)

A solution of n-butyllithium (2.2M in hexane, 8.5ml) was added dropwise over a period of 10 min. to a stirred solution of pentafluoro-benzene (3.0g, 17.9mmol) in dry diethyl ether (50ml) at -78°C under N$_2$. A solution of (65) (2.80g, 18.3mmol) in diethyl ether (20ml) was subsequently added over a further 10 min. The reaction mixture was allowed to warm to room temperature overnight, with stirring, and then poured into water (100ml). The product was extracted into diethyl ether (2 x 100ml) and the combined organic extracts were washed with cold 2M hydrochloric acid (2 x 100ml). The acidic extracts were combined, cooled and carefully basified with 2M (aq) sodium hydroxide solution. The basic solution was re-extracted with dichloromethane (3 x 100ml) and the organic layers combined before drying over anhydrous magnesium sulphate. The solvent was evaporated at reduced pressure to yield a dark oil. The residue was purified by flash chromatography (70:30, diethyl ether:petroleum ether [40-60°C]) to yield (61a) (1.34g, 32%) as a pale yellow oil.

δ_H (300MHz, CDCl$_3$): 1.98 (d, J_{Me-F} = 0.9Hz, 3H), 2.92 (br s, exch, 1H), 5.20 (dd, J = 2.4Hz, J_{H-F} = 2.0Hz, 1H), 6.81 (d, J = 5.3Hz, 1H), 7.01 (dd, J = 5.3Hz, J = 2.4Hz, 1H).

δ_C (75MHz, CDCl$_3$): 16.5 (q), 63.3 (d), 74.4 (s), 144.9 (d), 147.5 (d).

ν_{max} (CH$_2$Cl$_2$): 3260w, 3015w, 2975w, 2935w, 1485 br s, 1390m, 1355m, 1290w, 1255m, 1190m, 1120m, 1105s, 1040s, 1030s, 985m, 935m, 910m, 880m, 850s, 830s, 820w cm^{-1}.

m/e (%): M^+ 229 (50), 228 (50), 203 (100), 202 (80), 201 (14), 200 (10), 188 (18), 187 (28), 175 (11), 151 (22).

observed m/e 229.0503

calculated for $C_{11}H_7NF_4$ 229.0501.

1,4-Dihydro-1-methyl-1,4-iminonaphthalene (61b)

(61b) was prepared using a similar method as that used to prepare (61a). Benzyne [generated in situ from 2-bromofluorobenzene (3.95g, 22.6mmol) and n-butyllithium (2.5M in hexane, 9ml)] reacted with 1-trimethylsilyl-2-methyl pyrrole (65) (3.15g, 20.5mmol) to afford (61b) (1.73g, 56%) as a yellow oil.

δ_H (300MHz, CDCl$_3$): 1.76 (s, 3H), 3.02 (br s, exch, 1H), 4.79 (d, J = 3.0Hz, 1H), 6.63 (d, J = 6.0Hz, 1H), 6.80-7.29 (m, 5H).

δ_C (75MHz, CDCl$_3$): 15.2 (q), 65.6 (d), 72.7 (s), 119.0 (d), 120.5 (d), 124.4 (d), 124.6 (d), 145.1 (d), 147.1 (d), 151.6 (s), 152.4 (s).

ν_{max} (CH$_2$Cl$_2$): 3020w, 2960m, 2915w, 2865w, 1600w, 1480w, 1445s, 1380m, 1350s, 1200m, 1150m, 1125w, 1090w, 1055s, 1030m, 1005m, 960m, 930w, 920w, 865s, 845s cm^{-1}.

m/e (%): M^+ 157 (100), 156 (93), 131 (25), 130 (25), 129 (24), 128 (26), 127 (14), 116 (26), 115 (21).

1,4-Dihydro-5,8-dimethoxy-1-methyl-1,4-iminonaphthalene (61c)

(61c) was prepared using a similar method as that used to prepare (61a). 1,4-Dimethoxybenzyne [generated in situ from 1-chloro-2,5-dimethoxybenzene (7.10g, 41.1mmol) and n-butyllithium (1.6M in hexane, 26ml)] reacted with 1-trimethylsilyl-2-methyl pyrrole (65) (5.24g, 34.2mmol) to afford a dark oil. Purification by flash chromatography (99:1, diethyl ether:triethylamine) gave (61c) (4.89g, 66%) as yellow crystals: mp 56-57°C.

δ_H (300MHz, CDCl$_3$): 1.96 (s, 3H), 2.69 (br s, exch, 1H), 3.37 (s, 3H), 3.76 (s, 3H), 5.08 (d, J = 2.4Hz, 1H), 6.49 (s, 2H), 6.80 (d, J = 5.3Hz, 1H), 7.00 (dd, J = 5.3Hz, J = 2.4Hz, 1H).

δ_C (75MHz, CDCl$_3$): 17.5 (q), 55.8 (q), 56.0 (q), 62.9 (d), 75.0 (s), 110.8 (d), 111.2 (d), 140.9 (s), 142.1 (s), 145.1 (d), 147.6 (s), 147.9 (d), 149.1 (s).

ν_{max} (CH$_2$Cl$_2$): 2950w, 2960m, 2915m, 2815m, 1490s, 1465m, 1435m, 1350m, 1240m, 1210m, 1180m, 1145m, 1075s, 1045s, 975w, 940m, 850m, 840m, 790m cm^{-1}.

m/e (%): M$^+$ 217 (100), 203 (15), 202 (87), 201 (15), 188 (12), 187 (61), 186 (14), 174 (11), 159 (15), 130 (14).

observed m/e 217.1092

calculated for C$_{13}$H$_{15}$NO$_2$ 217.1091.

5,6,7,8-Tetrafluoro-1,2,3,4-tetrahydro-1-methyl-1,4-iminonaphthalene (62a)

A solution of (61a) (0.20g, 0.87mmol) in dry methanol (10ml) was hydrogenated at 1 atm in the presence of 5% palladium on charcoal for 5h. The reaction mixture was filtered through celite and the solvent evaporated at reduced pressure to yield (62a) (0.19g, 95%) as a colourless oil.

δ_H (300MHz, CDCl$_3$): 1.28-1.47 (m, 2H), 1.76-1.85 (m, 1H), 1.88 (d, J_{Me-F} = 1.1Hz, 3H), 2.14-2.27 (m, 1H), 2.36 (br s, exch, 1H), 4.78 (dd, J = 4.5Hz, J_{H-F} = 2.1Hz, 1H).

δ_C (75MHz, CDCl$_3$): 18.2 (q), 28.5 (t), 32.7 (t), 58.1 (d), 68.7 (s).

ν_{max} (CH$_2$Cl$_2$): 2950m, 1710w, 1665w, 1490s, 1390m, 1365m, 1215w, 1180w, 1115m, 1065m, 1040m, 990m, 945w, 920w, 885w, 870m, 830m cm^{-1}.

m/e (%): M$^+$ 231 (5), 229 (7), 204 (11), 203 (100), 202 (66), 189 (6), 187 (7), 175 (8).

1,2,3,4-Tetrahydro-1-methyl-1,4-iminonaphthalene (62b)

A solution of (61b) (0.53g, 3.37mmol) in dry methanol (30ml) was hydrogenated at 1 atm in the presence of 5% palladium on charcoal for 2h. The reaction mixture was filtered through celite and the solvent evaporated at reduced pressure to yield (62b) (0.54g, 99%) as a yellow oil.

δ_H (300MHz, CDCl$_3$): 1.14-1.35 (m, 2H), 1.70 (s, 3H), 2.05-2.49 (m, 2H), 3.71 (br s, exch, 1H), 4.42 (d, J = 4.5Hz, 1H), 6.98-7.32 (m, 4H).

δ_C (75MHz, CDCl$_3$): 17.2 (q), 29.0 (t), 32.8 (t), 60.6 (d), 67.1 (s), 117.6 (d), 119.0 (d), 125.7 (d), 125.9 (d), 148.5 (s), 149.8 (s).

ν_{max} (CH$_2$Cl$_2$): 3020w, 2955s, 2875m, 1450s, 1380m, 1350w, 1335w, 1195w, 1170w, 1135w, 1115w, 1065w, 1035w, 1000m, 970w, 945m, 905w, 870m, 855m, 815m cm^{-1}.

m/e (%): M$^+$ 159 (3), 142 (6), 141 (5), 132 (11), 131 (100), 130 (47), 117 (9), 115 (8).

1,2,3,4-Tetrahydro-5,8-dimethoxy-1-methyl-1,4-iminonaphthalene (62c)

A solution of (61c) (0.53g, 2.44mmol) in methanol (20ml) was hydrogenated at 1 atm in the presence of 5% palladium on charcoal for 4h. The reaction mixture was filtered through celite and the solvent evaporated at reduced pressure to yield (62c) (0.53g, 99%) as a pale yellow oil.

δ_H (300MHz, CDCl$_3$): 1.27-1.41 (m, 2H), 1.70-1.78 (m, 1H), 1.85 (s, 3H), 2.13-2.18 (m, 1H), 3.76 (s, 3H), 3.78 (s, 3H), 4.62 (d, J = 4.5Hz, 1H), 6.60 (s, 2H).

δ_C (75MHz, CDCl$_3$): 19.3 (q), 28.8 (t), 33.0 (t), 55.9 (q), 56.0 (q), 57.6 (d), 68.2 (s), 110.1 (d), 110.5 (d), 138.2 (s), 139.2 (s), 146.5 (s), 147.9 (s).

m/e (%): M^+ 219 (6), 192 (12), 191 (100), 187 (13), 177 (12), 176 (94), 161 (17).

N-Chloro-5,6,7,8-tetrafluoro-1,4-dihydro-1-methyl-1,4-iminonaphthalene (66a)

A solution of (61a) (0.21g, 0.92mmol) in dry dichloromethane (5ml) was treated wth NCS (0.15g, 1.12mmol) under N_2. After stirring for 1h at room temperature, the solvent was removed at reduced pressure. The residue was triturated with trichlorfluoromethane and filtered to remove any NCS and succinimide. The solvent was evaporated by passing a gentle stream of N_2 over it to afford (66a) (0.23g, 95%) as a pale yellow oil.

δ_H (300MHz, CDCl$_3$): syn- (66a), 1.90 (d, J_{Me-F} = 0.8Hz, 3H), 5.15 (ddd, J = 3.0Hz, J_{H-F} = 1.8Hz, J = 0.7Hz, 1H), 6.84 (dd, J = 6.0Hz, J = 0.7Hz, 1H), 7.02 (dd, J = 6.0Hz, J = 3.0Hz, 1H).

anti- (66a), 1.96 (d, J_{Me-F} = 1.2Hz, 3H), 5.33 (dd, J = 3.0Hz, J_{H-F} = 1.7Hz, 1H), 6.58 (d, J = 3.0Hz, 1H), 6.90 (dd, J = 6.0Hz, J = 3.0Hz, 1H).

δ_C (75MHz, CDCl$_3$): syn- (66a), 14.4 (q), 73.4 (d), 82.1 (s), 140.9 (d), 144.3 (d).

anti- (66a), 14.1 (q), 73.8 (d), 82.5 (s), 140.1 (d), 142.1 (d).

ν_{max} (CH$_2$Cl$_2$): 2960w, 1755w, 1745m, 1720m, 1495s, 1485s, 1395w, 1380w, 1305w, 1140m, 1115m, 1070w, 1045m, 955m, 930w, 845m cm^{-1}.

m/e (%): M^+ 265, 263 (12, 36), 259 (12), 229 (10), 228 (21), 222 (19), 216 (18), 214 (22), 213 (12), 204 (12), 203 (100), 202 (84), 201 (16), 200 (16), 187 (59).

N-Chloro-1,4-dihydro-1-methyl-1,4-iminonaphthalene (66b)

(66b) was prepared using a similar method to that used to prepare (66a). (61b) (0.25g, 1.59mmol) reacted with NCS (0.25g, 1.87mmol) to afford (66b) (0.29g, 95%) as a yellow oil.

δ_H (300MHz, CDCl$_3$): syn- (66b), 1.76 (s, 3H), 4.87 (dd, J = 3.2Hz, J = 0.7Hz, 1H), 6.73 (dd, J = 6.0Hz, J = 0.7Hz, 1H), 6.97 (dd, J = 6.0Hz, J = 3.2Hz, 1H), 7.02-7.37 (m, 4H).

anti- (66b), 1.82 (s, 3H), 5.08 (d, J = 2.0Hz, 1H), 6.45 (d, J = 5.3Hz, 1H), 6.83-7.37 (m, 5H).

δ_C (75MHz, CDCl$_3$): syn- (66b), 13.0 (q), 75.8 (d), 80.7 (s), 121.9 (d), 123.0 (d), 125.3 (d), 125.5 (d), 144.1 (d), 144.2 (d).

anti- (66b), 13.1 (q), 77.3 (d), 81.9 (s), 119.8 (d), 121.0 (d), 125.8 (d), 125.9 (d), 141.4 (d), 141.8 (d).

$^m/_e$ (%): M$^+$ 193, 191 (5, 15), 152 (16), 150 (44), 142 (21), 141 (19), 131 (14), 130 (13), 115 (42), 103 (20), 101 (31), 99 (100).

N-Chloro-1,4-dihydro-5,8-dimethoxy-1-methyl-1,4-iminonaphthalene (66c)

(66c) was prepared using a similar method as that used to prepare (66a). (61c) (0.30g, 1.38mmol) reacted with NCS (0.22g, 1.65mmol) to afford (66c) (0.33g, 95%) as a pale yellow oil.

δ_H (300MHz, CDCl$_3$): syn- (66c), 1.88 (s, 3H), 3.75 (s, 3H), 3.78 (s, 3H), 5.06 (dd, J = 3.1Hz, J = 0.8Hz, 1H), 6.62 (s, 2H), 6.82 (dd, J = 6.0Hz, J = 0.8Hz, 1H), 6.99 (dd, J = 6.0Hz, J = 3.1Hz, 1H).

anti- (66c), 1.93 (s, 3H), 3.74 (s, 3H), 3.76 (s, 3H), 5.24 (d, J = 2.0Hz, 1H), 6.52 (d, J = 5.3Hz, 1H), 6.58 (s, 2H), 6.84 (dd, J = 5.3Hz, J = 2.0Hz, 1H).

δ_C (75MHz, CDCl$_3$): syn- (66c), 15.5 (q), 55.5 (q), 55.6 (q), 73.2 (d), 82.2 (s), 109.8 (d), 110.2 (d), 133.1 (s), 134.0 (s), 144.3 (s), 146.9 (d), 148.5 (d), 151.7 (s).

anti- (66c), 15.1 (q), 55.6 (q), 55.7 (q), 74.1 (d), 83.1 (s), 110.5 (d), 111.0 (d), 133.4 (s), 136.2 (s), 141.1 (d), 141.3 (s), 142.3 (d), 150.7 (s).

$^m/_e$ (%): M$^+$ 253, 251 (5, 15), 216 (100), 203 (13), 202 (79), 201 (14), 188 (10), 187 (71), 184 (9), 159 (10).

N-Chloro-5,6,7,8-tetrafluoro-1,2,3,4-tetrahydro-1-methyl-1,4-imino-naphthalene (67a)

(67a) was prepared using a similar method as that used to prepare (66a). (62a) (0.15g, 0.65mmol) reacted with NCS (0.10g, 0.75mmol) to afford (67a) (0.16g, 93%) as a pale yellow oil.

δ_H (300MHz, CDCl$_3$) syn- (67a), 1.24-1.56 (m, 2H), 1.82 (d, J_{Me-F} = 1.3Hz, 3H), 1.85-1.96 (m, 1H), 2.13-2.26 (m, 1H), 4.84 (dd, J = 4.6Hz, J_{H-F} = 2.0Hz, 1H).

anti- (67a), 1.41-1.56 (m, 2H), 1.84 (d, J_{Me-F} = 1.3Hz, 3H), 1.85-1.95 (m, 1H), 2.07-2.14 (m, 1H), 4.79 (dd, J = 4.6Hz, J_{H-F} = 1.5Hz, 1H).

δ_C (75MHz, CDCl$_3$): syn- (67a), 16.7 (q), 24.0 (t), 30.2 (t), 70.1 (d), 77.1 (s).

anti- (67a), 15.4 (q), 26.7 (t), 29.4 (t), 67.9 (d), 76.6 (s).

ν_{max} (CH$_2$Cl$_2$): 1720w, 1500s, 1485s, 1395m, 1310w, 1160w, 1120m, 1070w, 1045m, 1025w, 850w, 815w cm^{-1}.

$^m/_e$ (%): M$^+$ 267, 265 (3, 9), 237 (27), 229 (8), 228 (8), 214 (11), 203 (46), 202 (100), 201 (11), 187 (12), 175 (12).

N-Chloro-1,2,3,4-tetrahydro-1-methyl-1,4-iminonaphthalene (67b)

(67b) was prepared using a similar method to that used to prepare (66a). (62b) (0.18g, 1.13mmol) reacted with NCS (0.18g, 1.35mmol) to afford (67b) (0.21g, 96%) as a colourless oil.

δ_H (300MHz, CDCl$_3$): syn- (67b), 1.26-1.56 (m, 2H), 1.74 (s, 3H), 1.92-2.03 (m, 1H), 2.50-2.62 (m, 1H), 4.66 (d, J = 4.4Hz, 1H), 7.12-7.28 (m, 4H).

anti- (67b), 1.30-1.56 (m, 2H), 1.72 (s, 3H), 2.06-2.16 (m, 1H), 2.52-2.62 (m, 1H), 4.60 (d, J = 4.4Hz, 1H), 7.12-7.22 (m, 4H).

δ_C (75MHz, CDCl$_3$): syn- (67b), 15.6 (q), 24.1 (t), 29.3 (t), 72.1 (d), 75.5 (s), 120.2 (d), 121.4 (d), 126.6 (d), 126.7 (d).

anti- (67b), 14.8 (q), 26.8 (t), 28.9 (t), 71.1 (d), 75.4 (s), 118.6 (d), 119.7 (d), 126.9 (d), 127.0 (d).

ν_{max} (CH$_2$Cl$_2$): 2940s, 2875w, 1770m, 1720m, 1465m, 1450m, 1380m, 1340w, 1310w, 1155m, 1120w, 1010w, 830m cm^{-1}.

$^m/_e$ (%): M$^+$ 195, 193 (3, 9), 168 (10), 167 (95), 166 (35), 165 (100), 164 (18), 163 (18), 158 (22), 156 (11), 151 (15), 143 (50).

observed $^m/_e$ (M$^+$ - Cl)   158.0960

calculated for C$_{11}$H$_{12}$N   158.0959.

N-Chloro-1,2,3,4-tetrahydro-5,8-dimethoxy-1-methyl-1,4-iminonaphthalene (67c)

(67c) was prepared using a similar method as that used to prepare (66a). (62c) (0.23g, 1.05mmol) reacted with NCS (0.15g, 1.12mmol) to afford (67c) (0.25g, 94%) as a pale yellow oil.

δ_H (300MHz, CDCl$_3$): syn- (67c), 1.25-1.52 (m, 2H), 1.81 (s, 3H), 2.14 -2.21 (m, 1H), 2.48-2.55 (m, 1H), 3.76 (s, 3H), 3.79 (s, 3H), 4.69 (d, J = 4.4Hz, 1H), 6.66 (s, 2H).

anti- (67c), 1.25-1.52 (m, 2H), 1.80 (s, 3H), 2.01-2.07 (m, 1H), 2.48-2.55 (m, 1H), 3.75 (s, 3H), 3.76 (s, 3H), 4.74 (d, J = 4.5Hz, 1H), 6.71 (s, 2H).

δ_C (75MHz, CDCl$_3$): syn- (67c), 16.4 (q), 26.6 (t), 29.2 (t), 55.5 (q), 55.6 (q), 67.8 (d), 76.5 (s), 109.7 (d), 110.2 (d), 131.0 (s), 131.3 (s), 145.9 (s), 147.2 (s).

anti- (67c), 19.1 (q), 28.1 (t), 32.2 (t), 55.3 (q), 55.4 (q), 68.3 (d), 77.3 (s), 109.3 (d), 109.6 (d), 137.2 (s), 138.0 (s), 147.3 (s), 150.5 (s).

$^m/_e$ (%): M$^+$ 255, 253 (4, 12), 218 (100), 192 (16), 191 (94), 187 (15), 177 (15), 176 (92), 161 (20).

Silver-ion assisted methanolysis of (66a) in toluene

To a stirred mixture of silver tetrafluoroborate (0.27g, 1.37mmol) and dry methanol (22μl, 0.54mmol) in dry toluene (5ml) was added a solution of (66a) (0.12g, 0.46mmol) in toluene (5ml) under N_2. After stirring for 4h at room temperature, brine (10ml) and 2M (aq) sodium hydroxide solution (10ml) were added, and the solution subsequently filtered (to remove the silver salt residues). The product was extracted into dichloromethane (3 x 15ml) and washed with water (20ml). The combined organic extracts were dried over anhydrous magnesium sulphate, and the solvent evaporated at reduced pressure. The residue was purified by flash chromatography (70:30, diethyl ether: petroleum ether [40-60°C]). The first fraction afforded (61a) (0.047g, 45%). Further elution gave (69) (0.070g, 52%) as a colourless oil.

δ_H (300MHz, CDCl$_3$): 1.80 (br s, exch, 1H), 1.84 (d, J_{Me-F} = 0.8Hz, 3H), 3.42 (s, 3H), 3.44 (s, 3H), 3.66 (d, J = 7.5Hz, 1H), 4.16 (dd, J = 7.5Hz, 4.3Hz, 1H), 4.89 (dd, J = 4.3Hz, J_{H-F} = 1.8Hz, 1H).

δ_C (75MHz, CDCl$_3$): 17.3 (q), 58.5 (q), 60.4 (q), 70.6 (d), 77.7 (s), 81.4 (d), 82.9 (d).

ν_{max} (CH$_2$Cl$_2$): 2910m, 2900w, 1495s, 1485s, 1395w, 1375w, 1350w, 1200w, 1145m, 1110s, 1045s, 1040m, 1020w, 980m, 930w, 905m, 855m, 845m cm^{-1}.

$^m/_e$ (%): M$^+$ 291 (8), 217 (12), 204 (12), 203 (100), 202 (34), 187 (11), 175 (28), 160 (14), 155 (11).

| observed $^m/_e$ | (M$^+$ - MeOCH=CHOMe) | 203.0340 |
| calculated for C$_9$H$_5$NF$_4$ | | 203.0338. |

Low temperature preparation and rearrangement of (67c) and subsequent reduction of the rearrangement products

NCS (0.075g, 0.56mmol) was added to a solution of (62c) (0.115g, 0.52mmol) in dry dichloromethane (5ml) at -50°C. After stirring for 1h at -50°C, the solvent was evaporated at reduced pressure without allowing the temperature of the reaction mixture to rise above -20°C. The residue was dissolved in cold toluene (5ml) and filtered at low temperature (to remove NCS and succinimide). The resulting solution of N-chloroamine was subsequently added to a mixture of silver tetrafluoroborate (0.40g, 2.02mmol) and dry methanol (25 μl, 0.62mmol) in dry toluene (5ml) at -50°C and stirred at that temperature for 3h. The sample was then treated with sodium borohydride (0.50g, 13.2mmol) in the presence of dry methanol (1ml) and stirred for a further 30 min. Brine (10ml) and 2M (aq) sodium hydroxide solution (10ml) were added and the solution filtered (to remove the silver salt residues). The products were extracted into dichloromethane (3 x 15ml), washed with water (20ml) and dried over anhydrous magnesium sulphate. The solvent was evaporated at reduced pressure to give a colourless oil which was purified by flash chromatography (60:40, diethyl ether:petroleum ether [40-60°C]). The first fraction afforded (73) (0.015g, 13%) as a colourless oil.

δ_H (300MHz, CDCl$_3$): 0.57 (dd, J = 4.2Hz, J = 4.2Hz, 1H), 0.94 (dd, J = 8.0Hz, J = 4.2Hz, 1H), 1.23 (dddd, J = 8.0Hz, J = 7.4Hz, J = 5.0Hz, J = 4.2Hz, 1H), 1.45 (s, 3H), 1.62 (br s, exch, 1H), 2.85 (dd, J = 11.6Hz, J = 5.0Hz, 1H), 3.68 (dd, J = 11.6Hz, J = 7.4Hz, 1H), 6.21, 6.57 (AB quartet, J = 8.8Hz, 2H).

δ_C (75MHz, CDCl$_3$): 15.2 (t), 20.7 (s), 22.7 (q), 24.5 (d), 44.7 (t), 55.9 (q), 56.1 (q), 99.7 (d), 107.5 (d), 115.5 (s), 134.1 (s), 142.3 (s), 153.2 (s).

ν_{max} (CH$_2$Cl$_2$): 3395w, 2950s, 2920m, 2860m, 1600w, 1495s, 1455m, 1370w, 1320w, 1315w, 1230m, 1170w, 1105m, 1085m, 1065m cm^{-1}.

m/e (%): M$^+$ 219 (100), 218 (39), 206 (7), 205 (37), 204 (88), 203 (9), 191 (10), 190 (28), 189 (24), 188 (30), 174 (34).

observed m/e 219.1253

calculated for C$_{13}$H$_{17}$NO$_2$ 219.1252.

Further elution of the column afforded (72) (0.075g, 58%).

δ_H (300MHz, CDCl$_3$): 1.54 (s, 3H), 1.96–2.26 (m, 4H), 3.40 (s, 3H), 3.77 (s, 3H), 3.79 (s, 3H), 5.16 (d, J = 7.5Hz, 1H), 6.43, 6.67 (AB quartet, J = 10Hz, 2H).

δ_C (75MHz, CDCl$_3$): 19.0 (q), 25.8 (t), 37.3 (t), 48.8 (q), 56.1 (q), 56.7 (q), 74.7 (d), 95.3 (s), 110.0 (d), 113.9 (d), 121.5 (s), 141.4 (s), 142.9 (s), 148.0 (s).

ν_{max} (CH$_2$Cl$_2$): 3000w, 2920m, 2815w, 1585m, 1495s, 1455m, 1430w, 1375w, 1360w, 1310w, 1240w, 1215w, 1200m, 1135w, 1100m, 1070s, 1025m, 950w, 795w cm^{-1}.

m/e (%): M$^+$ 249 (77), 235 (15), 234 (54), 221 (18), 220 (100), 219 (17), 218 (75), 206 (39), 203 (17), 202 (17), 192 (35), 190 (26), 188 (28), 176 (23).

observed m/e 249.1359

calculated for C$_{14}$H$_{19}$NO$_3$ 249.1358.

Further elution of the column with diethyl ether afforded (62c) (0.010g, 8%).

Low temperature preparation and rearrangement of (66b)

NCS (0.14g, 1.05mmol) was added to a solution of (66b) (0.15g, 0.95mmol) in dry dichloromethane (8ml) at -50°C. After stirring for 1h at -50°C, the solvent was evaporated at reduced pressure without allowing the temperature of the reaction mixture to rise above -20°C. The residue was dissolved in cold toluene (5ml) and filtered at low temperature (to remove any NCS and succinimide). The resulting solution of N-chloroamine was subsequently added to silver tetrafluoroborate (0.72g, 3.64mmol), dry methanol (46μl, 1.14mmol) in dry toluene (5ml) at -50°C, and stirred at that temperature for 4h. Brine (10ml) and 2M (aq) sodium hydroxide solution (10ml) were added and the solution filtered (to remove the silver salt residues). The products were extracted with dichloromethane (3 x 15ml), washed with water (20ml) and dried over anhydrous magnesium sulphate. The solvent was evaporated at reduced pressure to give a dark oil. The residue was purified by flash chromatography (40:60, diethyl ether:petroleum ether [40-60°C]) to yield small quantities of several compounds which could not be identified. Further elution afforded 4-methylquinoline (60b) (0.08g, 59%) as a pale yellow oil.

δ_H (300MHz, CDCl$_3$): 2.68 (d, J = 0.9Hz, 3H), 7.20 (dd, J = 4.5Hz, J = 0.9Hz, 1H), 7.54 (ddd, J = 8.6Hz, J = 6.8Hz, J = 1.5Hz, 1H), 7.68 (ddd, J = 8.6Hz, J = 6.8Hz, J = 1.5Hz, 1H), 7.97 (ddd, J = 8.6Hz, J = 1.5Hz, J = 0.4Hz, 1H), 8.09 (ddd, J = 8.6Hz, J = 1.5Hz, J = 0.4Hz, 1H), 8.75 (d, J = 4.5Hz, 1H).

δ_C (75MHz, CDCl$_3$): 18.2 (q), 121.6 (d), 123.6 (d), 126.1 (d), 128.0 (s), 128.8 (d), 129.8 (d), 143.9 (s), 147.8 (s), 149.8 (d).

$^m/_e$ (%): M$^+$ 143 (100), 142 (20), 128 (6), 117 (6), 116 (9), 115 (22).

Silver ion assisted methanolysis of (66c) in toluene

To a stirred mixture of silver tetrafluoroborate (0.70g, 3.54mmol) and dry methanol (58µl, 1.43mmol) in dry toluene (10ml) was added a solution of (66c) (0.30g, 1.19mmol) in toluene (15ml) under N_2. After stirring for 4h at room temperature, brine (10ml) and 2M (aq) sodium hydroxide solution (10ml) were added and the solution subsequently filtered (to remove the silver salt residues). The product was extracted into dichloromethane (3 x 15ml) and washed with water (20ml). The combined organic extracts were dried over anhydrous magnesium sulphate, and the solvent evaporated at reduced pressure. The residue was purified by flash chromatography (diethyl ether). The first fraction afforded (60c) (0.072g, 30%) as colourless needles: mp 92-94°C, lit. mp 94-95°C.

δ_H (300MHz, CDCl$_3$): 2.86 (d, J = 0.8Hz, 3H), 3.88 (s, 3H), 4.03 (s, 3H), 6.74, 6.91 (AB quartet, J = 8.6Hz, 2H), 7.14 (dd, J = 4.4Hz, J = 0.8Hz, 1H), 8.71 (d, J = 4.4Hz, 1H).

δ_C (75MHz, CDCl$_3$): 24.4 (q), 55.7 (q), 56.1 (q), 104.8 (d), 106.7 (d), 121.9 (s), 123.9 (d), 141.6 (s), 145.6 (s), 149.0 (d), 149.9 (s), 151.2 (s).

ν_{max} (CH$_2$Cl$_2$): 3030w, 3000w, 2955m, 2915m, 2900w, 2815m, 1610s, 1595s, 1565w, 1515m, 1460s, 1435m, 1395s, 1370w, 1340m, 1235s, 1175m, 1150s, 1120s, 1070s, 1045s, 965w cm^{-1}.

m/e (%): M$^+$ 203 (44), 202 (19), 189 (17), 188 (100), 187 (10), 174 (14), 160 (14), 159 (14), 130 (12).

Further elution of the column yielded (61c) (0.14g, 55%).

Low temperature preparation and rearrangement of (66c)

NCS (0.14g, 1.05mmol) was added to a solution of (61c) (0.21g, 0.97mmol) in dry dichloromethane (10ml) at -50°C. After stirring for 1h at -50°C, the solvent was evaporated at reduced pressure without allowing the temperature of the reaction mixture to rise above -20°C. The residue was dissolved in cold toluene (5ml) and filtered at low temperature (to remove any NCS and succinimide). The resulting solution of N-chloroamine was subsequently added to a mixture of silver tetrafluoroborate (0.77g, 3.90mmol) and dry methanol (47μl, 1.16mmol) in dry toluene (5ml) at -50°C and stirred at that temperature for 3h. Brine (10ml) and 2M (aq) sodium hydroxide solution (10ml) were added and the solution filtered (to remove the silver salt residues). The products were extracted with dichloromethane (3 x 15ml), washed with water (10ml) and dried over anhydrous magnesium sulphate. The solvent was evaporated at reduced pressure to give a dark oil. Purification by flash chromatography (diethyl ether) yielded small quantities of several compounds which were unidentifiable. Further elution afforded (60c) (0.082g, 42%).

8-Oxa-9-azabicyclo[3.2.2]non-6-ene (96)[82]

1-Chloro-1-nitrosocyclohexane (3.33g, 22.6mmol) was dissolved in a mixture of carbon tetrachloride (10ml) and ethanol (7ml). After cooling to -20°C, 1,3-cycloheptadiene (2.0g, 21.2mmol) was added dropwise with stirring, and then the resulting solution allowed to stand for 5 days at -10°C. The separated crystals were collected by filtration and washed with diethyl ether until the blue colour of the nitroso compound disappeared. The product was recrystallised from ethanol-ether to yield (96) (2.86g, 83%) as colourless needles: mp 178-180°C, lit. mp 179-181°C.

δ_H (300MHz, CD$_3$OD): 1.37-2.19 (series of m, 6H), 4.55 (br t, J = 6.5Hz, 1H), 4.97 (br t, J = 6.5Hz, 1H), 6.43 (ddd, J = 9.5Hz, J = 6.5Hz, J = 1.0Hz, 1H), 6.60 (ddd, J = 9.5Hz, J = 6.5Hz, J = 1.5Hz, 1H).

δ_C (75MHz, CD$_3$OD): 18.8 (t), 31.7 (t), 55.8 (d), 79.1 (d), 125.9 (d), 132.1 (d).

m/e (%): M$^+$ - HCl 125 (29), 108 (21), 97 (10), 96 (30), 94 (33), 93 (36), 92 (10), 91 (27), 81 (14), 80 (24), 79 (100).

cis-4-Aminocycloheptanol hydrochloride (97)[82]

A solution of (96) (1.98g, 12.3mmol) in methanol (100ml) was hydrogenated at 1 atm in the presence of 5% palladium on charcoal. After 10h, the catalyst was filtered off and the solvent was evaporated at reduced pressure to yield the hydrochloride salt of (97) (1.93g, 96%) as colourless crystals: mp 170-171°C, lit. mp 171-173°C.

δ_H (90MHz, CD$_3$OD): 1.25-2.15 (series of m, 10H), 3.91 (m, 1H), 4.82 (br s, 1H).

δ_C (75MHz, CD$_3$OD): 20.6 (t), 27.3 (t), 32.8 (t), 34.5 (t), 37.6 (t), 53.4 (d), 71.0 (d).

m/e (%): M$^+$ - HCl 129 (7), 112 (8), 86 (10), 83 (13), 82 (19), 72 (10), 70 (12), 57 (87), 56 (100).

cis-4-([Benzyloxycarbonyl]amino)cycloheptanol (98)[82]

A solution of (97) hydrochloride (1.89g, 11.4mmol) in water (25ml) was suspended in chloroform (35ml), cooled to 0°C and then sodium carbonate (2.34g, 22.1mmol) was added in one portion. After stirring for 30 min. at 0°C, a solution of benzyl chloroformate (1.8ml, 12.5mmol) in chloroform (35ml) was added dropwise to the suspension with vigorous stirring over 30 min. The resulting mixture was allowed to warm to room

temperature and stirred for a further 2h. After separation of the organic layer, the aqueous layer was re-extracted with chloroform (3 x 40ml). The combined organic layers were successively washed with water (50ml) and 2M hydrochloric acid (50ml), dried over anhydrous magnesium sulphate and the solvent evaporated at reduced pressure. The residue was purified by flash chromatography (ether) to yield (98) (2.44g, 81%) as colourless needles: mp 72-74°C, lit. mp 72-74°C.

δ_H (90MHz, CDCl$_3$): 1.27-1.95 (series of m, 10H), 2.10 (br s, exch, 1H), 3.69 (br s, 1H), 3.91 (br s, 1H), 4.96 (br s, 1H), 5.09 (s, 2H), 7.35 (s, 5H).

ν_{max} (CH$_2$Cl$_2$): 3600m, 3520m, 3430m, 3300m, 2930s, 2860m, 1710s, 1500s, 1450m, 1420w, 1370w, 1335w, 1310m, 1220s, 1100s, 1060m, 1025s, 970w cm^{-1}.

m/e (%): M$^+$ 263 (5), 172 (6), 154 (5), 146 (12), 108 (50), 107 (25), 100 (21), 91 (100), 84 (24), 79 (29).

trans-1-([Benzyloxycarbonyl]amino)-4-chloro-cycloheptane (99)[82]

A solution of thionyl chloride (0.75ml, 6.30mmol) in chloroform (10ml) was added dropwise to a solution of (98) (1.0g, 3.80mmol) and pyridine (3ml, 37.4mmol) in chloroform (40ml) at 0°C. After refluxing for 12h, the reaction mixture was poured into ice-water (100ml) and the aqueous layer was extracted with chloroform (3 x 30ml). The combined organic extracts were dried over anhydrous magnesium sulphate and the solvent evaporated at reduced pressure. The residue was purified by flash chromatography (50:50, diethyl ether:petroleum ether [40-60°C]) to yield (99) (0.62g, 58%) as colourless needles: mp 55-56°C, lit. mp 56-57°C.

δ_H (90MHz, CDCl$_3$): 1.27-2.30 (series of m, 10H), 3.75 (br m, 1H), 4.10 (br m, 1H), 4.75 (br s, 1H), 5.05 (s, 2H), 7.30 (s, 5H).

ν_{max} (CH_2Cl_2): 3440m, 3015w, 2940s, 1715s, 1515s, 1500s, 1450m, 1335w, 1310m, 1220s, 1115m, 1070w, 1020m, 910m, 875w cm^{-1}.

m/e (%): M^+ 283 (2), 281 (6), 245 (5), 202 (13), 190 (15), 146 (42), 108 (81), 91 (100), 79 (20).

N-Carbobenzoxynortropane (100)[82]

Potassium t-butoxide (0.26g, 2.32mmol) was added in small portions to a solution of (99) (0.62g, 2.0mmol) in 1:1 benzene-HMPA (15ml) at 0°C. The reaction mixture was allowed to warm to room temperature, stirred for a further 2.5h under N_2 and then poured into ice-water (100ml) containing concentrated hydrochloric acid (2ml). The organic layer was separated and the aqueous layer extracted with benzene (3 x 20ml). The organic extracts were combined, washed with water (50ml), dried over anhydrous magnesium sulphate and the solvent evaporated at reduced pressure. The residue was purified by flash chromatography (40:60, diethyl ether:petroleum ether [40-60°C]) to yield (100) (0.31g, 57%) as a colourless oil.

δ_H (90MHz, $CDCl_3$): 1.30-2.05 (series of m, 10H), 4.21 (br s, 2H), 5.10 (s, 2H), 7.32 (m, 5H).

δ_C (75MHz, $CDCl_3$): 16.7 (t), 27.7 (t), 28.5 (t), 30.8 (t), 31.5 (t), 54.1 (d), 66.5 (t), 127.9 (d), 128.4 (d), 137.4 (s), 153.7 (s).

ν_{max} (CH_2Cl_2): 3015w, 2940s, 2875m, 1690s, 1420s, 1380w, 1350m, 1320m, 1310m, 1260s, 1220m, 1165m, 1100s, 1085m, 1035m, 980w, 950m, 895s cm^{-1}.

m/e (%): M^+ 245 (9), 172 (10), 159 (5), 158 (12), 138 (7), 110 (9), 95 (12), 92 (20), 91 (100).

Nortropane (110)

A solution of hydrogen bromide in glacial acetic acid (45% w/v, 2ml) was added dropwise to (100) (0.31g, 1.26mmol) at 0°C. The reaction mixture was allowed to warm to room temperature, stirred for a further 2h and then poured into ice-water (20ml). The aqueous layer was washed with diethyl ether (20ml), cooled, and carefully basified with 2M (aq) sodium hydroxide solution. The resulting amine was extracted into diethyl ether (2 x 20ml) and acidified by the dropwise addition of concentrated hydrochloric acid. The product was extracted into water (3 x 20ml) and the solvent evaporated at reduced pressure to yield (110) (0.18g, 97%) as the hydrochloride salt.

δ_H (90MHz, $CDCl_3$): 1.38-2.50 (series of m, 10H), 4.01 (br s, 2H), 9.23 (br s, exch, 2H).

N-(Benzyloxycarbonyl)-8-oxa-9-azabicyclo[3.2.2]non-6-ene (113)[82]

To a solution of cycloheptadiene (3.5ml, 32.3mmol) and benzyl-N-hydroxycarbamate (5.79g, 34.6mmol) in dichloromethane (60ml) was added a suspension of tetramethylammonium metaperiodate (9.27g, 35.0mmol) in dichloromethane (20ml) over 30 min. at 0°C. After stirring at room temperature for 1.5h, the reaction mixture was washed with aqueous sodium bisulphite (15%, 3 x 30ml), saturated aqueous sodium hydrogen carbonate (2 x 30ml) and brine (30ml) and dried over anhydrous magnesium sulphate. The solvent was evaporated at reduced pressure and the residue purified by flash chromatography (40:60, diethyl ether:petroleum ether [40-60°C]) to yield (113) (7.54g, 90%) as colourless needles: mp 20-21°C.

δ_H (90MHz, $CDCl_3$): 1.19-1.92 (series of m, 6H), 4.75 (br m, 2H), 5.15 (s, 2H), 6.20 (m, 2H), 7.28 (s, 5H).

ν_{max} (CH_2Cl_2): 3040w, 2940m, 1690s, 1550w, 1500w, 1420s, 1355m, 1260s, 1205m, 1085m, 1030w, 970w, 895m, 760s cm^{-1}.

m/e (%): M^+ 259 (10), 215 (24), 186 (7), 141 (5), 109 (6), 108 (38), 107 (32), 106 (13), 105 (11), 94 (35), 93 (16), 92 (54), 91 (100).

Found: C, 69.70; H, 6.71; N, 5.25%. $C_{15}H_{17}NO_3$

requires: C, 69.48; H, 6.61; N, 5.40%.

cis-4-([Benzyloxycarbonyl]amino)-2-cycloheptenol (114)

Na_2HPO_4 (2.86g, 20.15mmol) was added to a solution of (113) (1.15g, 4.43mmol) in ethanol (40ml). To this suspension was added 5% sodium amalgam (13.2g) in small portions over 30 min. with stirring at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for a further 2h. After filtration, the filtrate was concentrated at reduced pressure. The residue was dissolved in dichloromethane (100ml), washed with water (50ml) and dried over anhydrous magnesium sulphate. The solvent was evaporated at reduced pressure to yield (114) (0.084g, 7%) as a colourless oil.

δ_H (300MHz, $CDCl_3$): 1.40-2.04 (series of m, 6H), 4.26 (br d, J = 10.6Hz, 1H), 4.39 (br d, J = 9.7Hz, 1H), 5.03 (br s, exch, 1H), 5.09 (s, 2H), 5.54 (dddd, J = 12.0Hz, J = 3.9Hz, J = 2.2Hz, J = 0.7Hz, 1H), 5.77 (br dd, J = 12.0Hz, J = 2.8Hz, 1H), 7.20 (s, 5H).

δ_C (75MHz, $CDCl_3$): 24.2 (t), 33.9 (t), 36.0 (t), 51.9 (d), 66.7 (t), 71.4 (d), 128.1 (d), 128.5 (d), 133.0 (d), 133.7 (s), 136.4 (d), 137.4 (d), 169.3 (s).

ν_{max} (CH_2Cl_2): 3600m, 3435m, 3015w, 2930s, 2875w, 1710s, 1510m, 1495s, 1380m, 1305w, 1210m, 1125w, 1085m, 1045m, 1025s, 905w, 810w cm^{-1}.

m/e (%): M^+ 261 (3), 243 (10), 200 (10), 199 (6), 163 (13), 162 (11), 161 (77), 152 (30), 146 (19), 126 (62), 110 (36), 109 (26), 108 (75), 107 (46), 98 (20), 95 (18), 94 (100).

observed m/e 261.1371

calculated for $C_{15}H_{19}NO_3$ 261.1365.

8-Oxa-9-azabicyclo[3.2.2]non-6-ene (115)

A solution of hydrogen bromide in glacial acetic acid (45%, 40ml) was added dropwise to (113) (7.40g, 28.5mmol) at 0°C. The reaction mixture was allowed to warm to room temperature, stirred for a further 2h, and then poured into ice-water (150ml). The aqueous solution was washed with dichloromethane (100ml), cooled, and then carefully basified with 2M (aq) sodium hydroxide solution. The product was extracted into dichloromethane (3 x 150ml) and dried over anhydrous magnesium sulphate. Removal of the solvent at reduced pressure afforded (115) (2.58g, 72%) as a colourless oil.

δ_H (90MHz, $CDCl_3$): 1.10-1.95 (series of m, 6H), 3.62 (m, 1H), 4.54 (m, 1H), 4.65 (br s, exch, 1H), 6.05 (br dd, J = 9.0Hz, J = 6.5H, 1H), 6.43 (br dd, J = 9.0Hz, J = 6.5Hz, 1H).

ν_{max} (CH_2Cl_2): 3055s, 2985m, 2940m, 1500w, 1420m, 1260s, 1155w, 1130w, 1090w, 1065w, 1030w, 995s, 760s cm^{-1}.

m/e (%): M^+ 125 (25), 108 (14), 98 (6), 97 (21), 95 (35), 94 (28), 93 (9), 92 (42), 82 (6), 81 (11), 80 (13), 79 (100).

cis-4-Amino-2-cycloheptenol (116)

To a solution of (115) (3.10g, 24.8mmol) in glacial acetic acid (75ml) was added zinc powder (24.8g, 0.38mol) at 0°C. The reaction mixture was heated at 50-60°C for 4h and then filtered. The residue was

washed with glacial acetic acid (100ml) and the filtrate evaporated at reduced pressure. The residue was cooled, basified with concentrated ammonia solution and the product extracted into dichloromethane (3 x 100ml). The combined organic layers were dried over anhydrous sodium sulphate and the solvent evaporated at reduced pressure to yield (116) (2.02g, 64%) as a colourless oil.

δ_H (90MHz, CDCl$_3$): 1.39-2.20 (series of m, 6H), 2.69 (br s, exch, 3H), 3.45 (m, 1H), 4.20 (m, 2H), 5.42-5.89 (m, 2H).

cis-4-([Benzyloxycarbonyl]amino)-2-cycloheptenol (114)

To a suspension of sodium hydride (80% dispersion, 0.168g) in dry diethyl ether (40ml) was added dropwise a solution of (116) (0.71g, 5.59mmol) in diethyl ether (10ml). After stirring at room temperature for 2h, the reaction mixture was cooled to 0°C, and benzyl chloroformate (0.80ml, 5.60mmol) was added dropwise. The resulting solution was allowed to warm to room temperature, stirred for a further 2h and then poured into water (40ml). After separation of the organic layer, the aqueous layer was extracted with dichloromethane (3 x 20ml) and the combined organic layers dried over anhydrous sodium sulphate. The solvent was evaporated at reduced pressure to yield (114) (1.38g, 95%).

trans-1-([Benzyloxycarbonyl]amino)-4-chloro-2-cycloheptene (118a)

A solution of thionyl chloride (0.27ml, 3.72mmol) in chloroform (5ml) was added dropwise to a solution of (114) (0.30g, 1.15mmol) and pyridine (0.76ml, 9.48mmol) in chloroform (20ml) at 0°C. After stirring for 1h at 0°C, the reaction mixture was poured into ice-water (30ml) and the aqueous layer was extracted with chloroform (2 x 30ml). The combined organic extracts were dried over anhydrous magnesium sulphate.

The solvent was evaporated at reduced pressure to yield (118a) (0.25g, 78%) as a yellow oil.

δ_H (90MHz, CDCl$_3$); 1.46-2.27 (series of m, 6H), 4.31 (m, 1H), 5.02 (br s, exch, 1H), 5.07 (s, 2H), 5.16 (m, 1H), 5.58-5.88 (m, 2H), 7.33 (s, 5H).

δ_C (75MHz, CDCl$_3$); 23.3 (t), 33.5 (t), 33.8 (t), 51.5 (d), 66.6 (t), 72.9 (d), 128.0 (d), 128.4 (d), 132.7 (d), 135.1 (d), 136.3 (s), 137.8 (d), 155.4 (s).

ν_{max} (CH$_2$Cl$_2$): 3415m, 3040w, 2915m, 1715s, 1505s, 1445w, 1320m, 1300w, 1215m, 1100w, 1070w, 1025w, 975w, 945w, 775m, 750m cm^{-1}.

$^m/_e$ (%): M$^+$ 281, 279 (2, 6), 243 (15), 200 (8), 199 (6), 182 (10), 153 (9), 152 (51), 134 (10), 124 (10), 109 (20), 108 (76), 107 (44), 94 (25), 93 (21), 92 (100).

cis-1-([Benzyloxycarbonyl]amino)-4-acetoxy-2-cycloheptene (127)

Acetyl chloride (0.27g, 3.80mmol) was added dropwise to a solution of (114) (0.57g, 2.20mmol) and pyridine (0.60ml, 7.49mmol) in dry dichloromethane (25ml) at 0°C. The reaction mixture was stirred for 2h at 0°C, and then washed with saturated sodium bicarbonate solution (2 x 20ml), copper sulphate solution (2 x 20ml) and water (20ml). The organic extract was dried over anhydrous potassium carbonate and the solvent evaporated at reduced pressure to yield (127) (0.62g, 93%) as a colourless oil.

δ_H (90MHz, CDCl$_3$): 1.39-1.98 (series of m, 6H), 2.01 (s, 3H), 4.25 (m, 1H), 4.90 (br s, exch, 1H), 5.05 (s, 2H), 5.30 (m, 1H), 5.55-5.65 (m, 2H), 7.27 (s, 5H).

ν_{max} (CH$_2$Cl$_2$): 3440m, 3035w, 2940m, 2860w, 1720s, 1500s, 1440m, 1420s, 1370m, 1300m, 1260s, 1230s, 1150w, 1110m, 1065w, 1025m, 985w, 895s, 750s cm^{-1}.

$^m/_e$ (%): M$^+$ 303 (6), 244 (25), 243 (41), 200 (14), 199 (19), 157 (6), 156 (16), 152 (17), 126 (12), 110 (19), 109 (18), 108 (35), 107 (16), 95 (10), 94 (100), 93 (15), 92 (55).

observed $^m/_e$ 303.1465

calculated for $C_{17}H_{21}NO_4$ 303.1470.

1-([Benzyloxycarbonyl]amino)-2,4-cycloheptadiene (128)

To a solution of (127) (0.62g, 2.04mmol) and triethylamine (0.29ml, 2.08mmol) in dry tetrahydrofuran (10ml) was added $Pd_2(dba)_3.CHCl_3$ (0.10g, 0.10mmol) and triphenylphosphine (0.21g, 0.80mmol) under N_2. The reaction mixture was heated at reflux for 14h, filtered through a short column of silica, and then the solvent was evaporated at reduced pressure. The residue was purified by flash chromatography (30:70, diethyl ether:petroleum ether [40-60°C]) to yield (128) (0.31g, 64%) as a pale yellow oil.

δ_H (300MHz, $CDCl_3$): 1.76-2.43 (series of m, 4H), 4.49 (m, 1H), 5.02 (br s, exch, 1H), 5.08 (s, 2H), 5.66-5.96 (m, 4H), 7.31 (s, 5H).

δ_C (75MHz, $CDCl_3$): 26.3 (t), 31.3 (t), 51.6 (d), 66.6 (t), 124.3 (d), 125.8 (d), 127.9 (d), 128.4 (d), 132.6 (d), 135.2 (d), 136.4 (s), 155.2 (s).

ν_{max} (CH_2Cl_2): 3440m, 3035w, 2935w, 1715s, 1500s, 1450w, 1400w, 1340w, 1310m, 1215s, 1130w, 1100w, 1050m, 1025w, 920w cm^{-1}.

$^m/_e$ (%): M$^+$ 243 (8), 182 (12), 152 (75), 135 (8), 134 (15), 120 (13), 109 (9), 108 (69), 107 (44), 106 (18), 93 (6), 92 (19), 91 (100).

observed $^m/_e$ 243.1251

calculated for $C_{15}H_{17}NO_2$ 243.1259.

N-Benzoyl-8-oxa-9-azabicyclo[3.2.2]non-6-ene (132b)[82]

1,3-cycloheptadiene (1.15ml, 10.6mmol) was added to a suspension of tetramethylammonium metaperiodate (3.92g, 14.8mmol) in chloroform (140ml). To ths mixture was added dropwise a solution of benzo-hydroxamic acid (2.07g, 15.1mmol) in dimethylformamide (10ml) and chloroform (30ml) with stirring at room temperature over 20min. After stirring for 3h, the chloroform was distilled at reduced pressure. The residue was dissolved in diethyl ether (200ml) and washed with water (3 x 50ml). The organic layer was separated, dried over anhydrous magnesium sulphate and then the solvent evaporated at reduced pressure to yield (132b), (2.40g, 99%) as colourless crystals: mp 100-101°C, lit. mp 101-102°C.

δ_H (300MHz, CDCl$_3$): Major rotamer, 1.25-1.95 (series of m, 6H), 4.59 (br s, 1H), 5.37 (br s, 1H), 6.15-6.29 (m, 2H), 7.25-7.70 (m, 5H).

Minor rotamer, 1.25-1.95 (series of m, 6H), 4.59 (br s, 1H), 4.94 (br s, 1H), 6.03-6.18 (m, 2H), 7.25-7.70 (m, 5H).

δ_C (75MHz, CDCl$_3$): Major rotamer, 17.6 (t), 27.7 (t), 28.4 (t), 50.2 (d), 75.9 (d), 125.8 (d), 126.8 (d), 127.8 (d), 129.2 (d), 129.5 (d), 133.4 (s), 164.1 (s).

Minor rotamer, 17.1 (t), 28.7 (t), 29.9 (t), 55.0 (d), 75.4 (d), 124.4 (d), 126.5 (d), 127.5 (d), 127.9 (d), 128.1 (d), 133.8 (s), 165.5 (s).

ν_{max} (CH$_2$Cl$_2$): 3050m, 2950s, 2875w, 1640s, 1610s, 1568m, 1495w, 1440s, 1375m, 1308m, 1240m, 1210m, 1170m, 1155m, 1108s, 1022m, 998m, 970m, 950m, 910m, 865w, 828m cm^{-1}.

m/e (%): M$^+$ 229 (6), 138 (3), 122 (5), 106 (9), 105 (100), 103 (3), 77 (33).

N-Benzoyl-7-oxa-8-azabicyclo[2.2.2.]oct-5-ene (132a)

(132a) was prepared using a similar method to that used to prepare (132b). 1,3-cyclohexadiene (3.2ml, 33.6mmol) reacted with the nitroso compound generated from benzohydroxamic acid (6.52g, 47.5mmol) and tetramethylammonium metaperiodate (12.60g, 47.5mmol) to afford (132a) (6.69g, 93%) as a colourless oil.

δ_H (300MHz, CDCl$_3$): Major rotamer, 1.41-1.61 (m, 2H), 2.09-2.38 (m, 2H), 4.66 (m, 1H), 4.98 (br d, J = 6.4Hz, 1H), 6.43 (ddd, J = 6.4Hz, J = 6.4Hz, J = 1.0Hz, 1H), 6.58 (ddd, J = 6.4Hz, J = 6.4Hz, J = 1.0Hz, 1H), 7.32-7.52 (m, 5H).

Minor rotamer, 1.38-1.61 (m, 2H), 2.02-2.38 (m, 2H), 4.75 (m, 1H), 5.44 (br d, J = 6.4Hz, 1H), 6.52 (ddd, J = 6.4Hz, J = 6.4Hz, J = 1.0Hz, 1H), 6.72 (ddd, J = 6.4Hz, J = 6.4Hz, J = 1.0Hz, 1H), 7.32-7.52 (m, 5H).

δ_C (75MHz, CDCl$_3$): Major rotamer, 21.5 (t), 23.0 (t), 51.8 (d), 71.7 (d), 127.4 (d), 128.6 (d), 128.9 (d), 129.8 (d), 131.7 (d), 133.4 (s), 166.7 (s).

Minor rotamer, 20.4 (t), 22.9 (t), 46.3 (d), 71.9 (d), 127.2 (d), 129.6 (d), 130.6 (d), 131.3 (d), 132.6 (d), 133.6 (s), 167.7 (s).

ν_{max} (CH$_2$Cl$_2$): 3040m, 2975w, 2940m, 1630s, 1575m, 1450m, 1400m, 1365m, 1290w, 1235m, 1215w, 1165s, 1115w, 1085w, 1050m, 950m, 925m, 885m, 845w cm^{-1}.

m/e (%): M$^+$ 215 (9), 137 (18), 122 (40), 121 (9), 119 (17), 106 (16), 105 (100), 104 (6), 103 (36).

N-Benzoyl-9-oxa-10-azabicyclo[4.2.2]deca-7-ene (132c)

(132c) was prepared using a similar method to that used to prepare (132b). 1,3-cyclooctadiene (1.02g, 9.43mmol) reacted with the nitroso compound generated from benzohydroxamic acid (1.80g, 13.13mmol) and tetramethylammonium metaperiodate (3.43g, 12.94mmol) to afford (132c) (2.10g, 92%) as a colourless oil.

δ_H (300MHz, CDCl$_3$): Major rotamer, 1.46-2.27 (series of m, 8H), 4.82

(br s, 1H), 5.21 (br s, 1H), 6.23 (m, 2H),

7.34-7.51 (m, 5H).

Minor rotamer, 1.37-2.27 (series of m, 8H), 4.51

(br s, 1H), 5.21 (br s, 1H), 5.90 (m, 1H), 6.06

(m, 1H), 7.34-7.51 (m, 5H).

δ_C (75MHz, CDCl$_3$): Major rotamer, 21.7 (t), 25.5 (t), 30.8 (t), 34.8

(t), 55.4 (d), 78.7 (d), 126.8 (d), 127.9 (d),

128.1 (d), 128.9 (d), 129.8 (d), 133.2 (s), 167.0

(s).

Minor rotamer, 22.5 (t), 24.2 (t), 31.9 (t), 34.1

(t), 51.3 (d), 77.4 (d), 126.0 (d), 127.7 (d),

128.3 (d), 128.5 (d), 130.2 (d), 132.9 (s), 166.1

(s).

ν_{max} (CH$_2$Cl$_2$): 3050w, 2930s, 2860w, 1620s, 1570m, 1450m, 1425m, 1385w, 1320w, 1240s, 1215m, 1180m, 1025m, 1020m, 990w, 930w cm^{-1}.

m/e (%): M$^+$ 243 (82), 226 (5), 225 (5), 138 (7), 122 (25), 107 (14), 106 (100), 103 (13).

cis-4-(Benzoylamino)-2-cycloheptenol (133b)[82]

A solution of (132b) (4.80g, 20.9mmol) in 120ml of aqueous tetrahydrofuran (THF:H$_2$O, 10:1) was cooled to 0°C with stirring under N$_2$. Aluminium amalgam prepared by sequential exposure (10-20 seconds)

of small strips of aluminium foil (4.54g, 0.17mmol) to 1M (aq) potassium
hydroxide solution, distilled water, 0.5% mercuric chloride, distilled
water and tetrahydrofuran, was then added to the solution of Diels-Alder
adduct. Stirring was continued at 0°C for 16h. The reaction mixture
was diluted with tetrahydrofuran (350ml), stirred vigorously for 1.5h,
then filtered through a pad of celite. The filtrate was diluted with
toluene and concentrated at reduced pressure to yield (133b) (4.45g,
92%) as a white crystalline solid: mp 155-158°C, lit. mp 157-159°C.

δ_H (300MHz, $CDCl_3$): 1.43-2.10 (series of m, 6H), 4.38 (br d, J =
10.5Hz, 1H), 4.63 (br d, J = 10.5Hz, 1H), 5.66 (br d, J = 12.0Hz, 1H),
5.79 (br d, J = 12.0Hz, 1H), 7.40-7.55 (m, 3H), 7.75-7.84 (m, 2H).

δ_C (75MHz, $CDCl_3$): 26.7 (t), 35.1 (t), 37.3 (t), 52.7 (d), 72.8 (d),
128.6 (d), 129.7 (d), 132.8 (d), 133.8 (d), 136.0 (s), 139.2 (d), 169.5
(s).

ν_{max} (CH_2Cl_2): 3350w, 3310w, 2955s, 2915s, 2860s, 2520w, 2460m, 2400w,
1620s, 1570m, 1450s, 1435m, 1375m, 1135w, 1080w, 1040m, 990w, 890w,
800w, 720m, 695m cm^{-1}.

m/e (%): M^+ 231 (16), 229 (6), 214 (21), 213 (80), 212 (17), 205 (7),
201 (11), 123 (15), 122 (100), 121 (17).

cis-4-(Benzoylamino)-2-cyclohexenol (133a)

(133a) was prepared using a similar method to that used to
prepare (133b). (132a) (3.92g, 18.2mmol) reacted with aluminium amalgam
(3.80g, 0.14mmol of aluminium foil) to afford (133a) (3.83g, 97%) as a
colourless oil.

δ_H (300MHz, $CDCl_3$): 1.69-1.93 (series of m, 4H), 4.17 (m, 1H), 4.58
(m, 1H), 5.75 (ddd, J = 10.0Hz, J = 3.2Hz, J = 1.0Hz, 1H), 5.94 (ddd, J

= 10.0Hz, J = 3.4Hz, J = 1.8Hz, 1H), 7.33-7.48 (m, 3H), 7.72-7.77 (m, 2H).

δ_C (75MHz, $CDCl_3$): 25.2 (t), 28.8 (t), 45.0 (d), 64.0 (d), 126.9 (d), 128.4 (d), 130.1 (d), 131.4 (d), 132.9 (d), 134.2 (s), 166.9 (s).

ν_{max} (CH_2Cl_2): 3605m, 3440m, 3035w, 2950m, 2860w, 1670s, 1510s, 1485s, 1325m, 1245w, 1150w, 1080w, 1070m, 1050m, 985m, 950w, 835w cm^{-1}.

m/e (%): M^+ 217 (17), 215 (6), 201 (8), 200 (46), 199 (100), 198 (77), 197 (17), 173 (6), 148 (8), 122 (74), 121 (53).

cis-4-(Benzoylamino)-2-cyclooctenol (133c)

(133c) was prepared using a similar method to that used to prepare (133b). (132c) (1.80g, 7.40mmol) reacted with aluminium amalgam (1.54g, 57.1mmol of aluminium foil) to afford a white solid which was recrystallised from toluene to give (133c) (1.29g, 71%) as colourless needles: mp 164-166°C.

δ_H (300MHz, CD_3OD): 1.41-1.99 (series of m, 8H), 4.66 (m, 2H), 5.50 (ddd, J = 10.9Hz, J = 6.9Hz, J = 1.1Hz, 1H), 5.62 (ddd, J = 10.9Hz, J = 8.3Hz, J = 1.5Hz, 1H), 7.40-7.57 (m, 3H), 7.77-7.89 (m, 2H).

δ_C (75MHz, CD_3OD): 24.8 (t), 25.7 (t), 37.5 (t), 39.9 (t), 49.6 (d), 70.4 (d), 128.5 (d), 129.7 (d), 132.8 (d), 133.1 (d), 136.0 (s), 136.3 (d), 169.6 (s).

ν_{max} (CH_2Cl_2): 3600m, 3410m, 3050w, 2915m, 2860w, 1665s, 1580w, 1510s, 1485m, 1365m, 1070w, 1025m, 965w cm^{-1}.

m/e (%): M^+ 245 (4), 243 (4), 228 (17), 227 (61), 226 (11), 225 (6), 198 (17), 140 (6), 130 (34), 124 (75), 123 (14), 122 (84), 121 (37), 107 (11), 106 (100), 104 (98), 103 (18).

Found: C, 73.24; H, 7.73; N, 5.63%. $C_{15}H_{19}NO_2$
requires: C, 73.44; H, 7.81; N, 5.71%.

cis-4-(Benzoylamino)cycloheptanol (134b)[82]

A solution of (133b) (2.25g, 9.73mmol) in methanol (100ml) was hydrogenated at 1 atm in the presence of 5% palladium on charcoal. After 16h, the catalyst was filtered off and the solvent was evaporated at reduced pressure to yield (134b) (2.24g, 99%) as a white crystalline solid; mp 143-145°C, lit. mp 143.5-145°C.

δ_H (300MHz, CD_3OD): 1.30-2.05 (series of m, 10H), 3.88 (br m, 1H), 4.06 (br m, 1H), 7.36-7.53 (m, 3H), 7.76-7.83 (m, 2H).

δ_C (75MHz, CD_3OD): Major rotamer, 21.8 (t), 29.5 (t), 33.8 (t), 36.3 (t), 38.3 (t), 52.2 (d), 72.1 (d), 128.5 (d), 129.6 (d), 132.6 (d), 136.2 (s), 169.3 (s).

Minor rotamer, 22.5 (t), 31.2 (t), 37.1 (t), 41.1 (t), 44.6 (t), 53.7 (d), 72.1 (d), 128.6 (d), 129.7 (d), 132.8 (d), 136.2 (s), 169.3 (s).

ν_{max} (CH_2Cl_2): 3330m, 3240m, 2930s, 2860s, 1630s, 1575m, 1530m, 1490w, 1460m, 1370m, 1325m, 1290w, 1215w, 1120w, 1080w, 1030m, 980w, 805w, 760m, 700m cm^{-1}.

m/e (%): M$^+$ 233 (7), 215 (6), 122 (51), 106 (8), 105 (100), 94 (8).

cis-4-(Benzoylamino)cyclohexanol (134a)

A solution of (133a) (1.34g, 6.17mmol) in methanol (100ml) was hydrogenated at 1 atm in the presence of 5% palladium on charcoal. After 14h, the catalyst was filtered off and the solvent was evaporated at reduced pressure to yield (134a) (1.34g, 99%) as a white solid. An analytical sample was prepared by recrystallisation from toluene to give colourless needles: mp 135-136°C.

δ_H (300MHz, $CDCl_3$): 1.63-1.81 (m, 8H), 2.33 (br s, exch, 1H), 3.94 (m, 1H), 4.03 (m, 1H), 6.31 (br d, J = 7.5Hz, exch, 1H), 7.35-7.51 (m, 3H), 7.70-7.77 (m, 2H).

δ_C (75MHz, CDCl$_3$): Major rotamer, 27.2 (t), 31.3 (t), 47.2 (d), 65.9 (d), 126.8 (d), 128.4 (d), 131.2 (d), 134.8 (s), 166.8 (s).

Minor rotamer, 27.2 (t), 31.3 (t), 47.1 (d), 65.8 (d), 126.7 (d), 128.4 (d), 131.3 (d), 134.9 (s), 166.7 (s).

ν_{max} (CH$_2$Cl$_2$): 3610m, 3440m, 3020w, 2940s, 2960w, 1650s, 1580m, 1515s, 1485m, 1450m, 1415m, 1360w, 1320w, 1130m, 1070m, 1030m, 970s, 910w, 800w cm^{-1}.

m/e (%): M$^+$ 219 (17), 201 (9), 161 (5), 160 (4), 123 (5), 122 (55), 121 (6), 106 (8), 105 (100).

Found: C, 71.21; H, 7.81; N, 6.39%. C$_{13}$H$_{17}$NO$_2$
requires: C, 71.32; H, 7.76; N, 6.33%.

cis-4-(Benzoylamino)cyclooctanol (134c)

A solution of (133c) (0.98g, 3.99mmol) in methanol (50ml) was hydrogenated at 1 atm in the presence of 5% palladium on charcoal. After 15h, the catalyst was filtered off and the solvent was evaporated at reduced pressure to yield (134c) (0.97g, 98%) as a colourless oil.

δ_H (300MHz, CDCl$_3$): 1.50-1.89 (series of m, 12H), 2.14 (br s, exch, 1H), 3.88 (m, 1H), 4.11 (m, 1H), 6.30 (br d, J = 7.7Hz, exch, 1H), 7.36-7.51 (m, 3H), 7.71-7.83 (m, 2H).

δ_C (75MHz, CDCl$_3$): 21.9 (t), 23.5 (t), 27.8 (t), 30.8 (t), 31.3 (t), 33.1 (t), 49.9 (d), 71.0 (d), 126.8 (d), 128.4 (d), 131.2 (d), 134.9 (s), 166.4 (s).

ν_{max} (CH$_2$Cl$_2$): 3600m, 3460m, 3020w, 2935s, 2860m, 1655s, 1580w, 1515s, 1485m, 1445w, 1365m, 1315w, 1270w, 1140w, 1075m, 1030m, 975w, 910m, 800w cm^{-1}.

m/e (%): M^+ 247 (4), 230 (5), 229 (29), 205 (12), 201 (10), 175 (5), 174 (5), 161 (8), 160 (7), 147 (11), 122 (88), 121 (100), 108 (37), 106 (41), 103 (22).

cis-4-(Benzylamino)cycloheptanol (135b)

A solution of (134b) (0.85g, 3.64mmol) in dry diethyl ether (30ml) was added dropwise to a stirred slurry of lithium aluminium hydride (0.60g, 15.8mmol) in diethyl ether (70ml). After refluxing for 10h, decomposition of excess hydride was effected by addition of water. The inorganic solids were removed by filtration, and the organic layer dried over anhydrous magnesium sulphate. The solvent was evaporated at reduced pressure to yield (135b) (0.79g, 99%) as colourless needles: mp 43-45°C.

δ_H (300MHz, CDCl$_3$): 1.30-2.01 (series of m, 10H), 2.69 (br s, exch, 1H), 2.98 (m, 1H), 3.69, 3.78 (AB quartet, J = 12.8Hz, 2H), 4.00 (m, 1H), 7.21-7.41 (m, 5H).

δ_C (75MHz, CDCl$_3$): 18.2 (t), 28.7 (t), 32.6 (t), 34.3 (t), 35.5 (t), 51.5 (t), 55.1 (d), 69.1 (d), 127.0 (d), 128.0 (d), 128.4 (d), 139.6 (s).

ν_{max} (CH$_2$Cl$_2$): 3610w, 3180br m, 3030m, 2960s, 2930s, 1500m, 1440w, 1215w, 1080m, 1065m, 1030m, 945m, 860w cm^{-1}.

m/e (%): M^+ 219 (8), 217 (8), 176 (5), 160 (6), 147 (8), 146 (61), 133 (8), 132 (10), 128 (7), 120 (8), 106 (15), 104 (5), 92 (10), 91 (100).

cis-4-(Benzylamino)cyclohexanol (135a)

(135a) was prepared using a similar method to that used to prepare (135b). (134a) (1.20g, 5.47mmol) reacted with lithium aluminium hydride (0.90g, 23.7mmol) to afford (135a) (1.02g, 91%) as a colourless oil.

δ_H (300MHz, CDCl$_3$): 1.50-1.78 (series of m, 8H), 2.14 (br s, exch, 2H), 2.59 (m, 1H), 3.78 (s, 2H), 3.85 (m, 1H), 7.21-7.33 (m, 5H).

δ_C (75MHz, CDCl$_3$): 27.5 (t), 31.0 (t), 50.9 (t), 53.9 (d), 67.0 (d), 126.8 (d), 128.0 (d), 128.3 (d), 140.5 (s).

ν_{max} (CH$_2$Cl$_2$): 3605m, 3410w, 3015w, 2930s, 2855m, 1450m, 1370w, 1230w, 1120m, 1070m, 1060m, 1040m, 965s, 910s, 855w cm^{-1}.

m/e (%): M$^+$ 205 (17), 187 (6), 147 (3), 146 (100), 133 (14), 132 (12), 131 (5), 130 (5), 120 (7), 119 (6).

cis-4-(Benzylamino)cyclooctanol (135c)

(135c) was prepared using a similar method to that used to prepare (135b). (134c) (0.85g, 3.44mmol) reacted with lithium aluminium hydride (0.50g, 13.2mmol) to afford (135c) (0.80g, 99%) as a colourless oil.

δ_H (300MHz, CDCl$_3$): 1.36-1.84 (series of m, 10H), 2.20 (br s, exch, 2H), 2.68 (m, 1H), 3.76 (s, 2H), 3.82 (m, 1H), 7.22-7.36 (m, 5H).

δ_C (75MHz, CDCl$_3$): 22.3 (t), 24.1 (t), 28.2 (t), 31.0 (t), 31.4 (t), 33.9 (t), 51.4 (t), 56.9 (d), 71.5 (d), 126.8 (d), 128.0 (d), 128.4 (d), 140.6 (s).

ν_{max} (CH$_2$Cl$_2$): 3600m, 3015w, 2920s, 2860m, 1470m, 1450m, 1365w, 1200w, 1100m, 1075w, 1055w, 1030m, 1005w, 975w, 825w cm^{-1}.

m/e (%): M$^+$ 233 (20), 176 (11), 147 (21), 146 (100), 142 (11), 134 (11), 133 (96), 132 (33), 120 (21), 107 (14), 106 (36), 104 (11).

N-Benzylnortropane (140)

To a solution of (135b) (1.25g, 5.70mmol) in chloroform (20ml) was added dropwise a solution of thionyl chloride (0.45ml, 6.20mmol) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for a further 24h. After cooling to 0°C, pyridine (2ml) was

added dropwise and the solution stirred for 1h. The reaction mixture was subsequently poured into 2M (aq) sodium hydroxide solution, and the aqueous layer extracted with dichloromethane (2 x 30ml). The combined organic layers were dried over anhydrous sodium sulphate and the solvent evaporated at reduced pressure. The residue was purified by flash chromatography (90:9:1, petroleum ether [40-60°C]:diethyl ether:triethylamine) to afford (140) (1.01g, 88%) as a colourless oil.

δ_H (300MHz, CDCl$_3$): 1.28-2.03 (series of m, 10H), 3.15 (br t, J = 3.2Hz, 2H), 3.52 (s, 2H), 7.19-7.40 (m, 5H).

δ_C (75MHz, CDCl$_3$): equatorial- (140), 16.0 (t), 25.1 (t), 31.8 (t), 57.0 (t), 58.9 (d), 126.2 (d), 127.7 (d), 128.5 (d), 138.5 (s).

axial- (140), 21.7 (t), 27.8 (t), 34.0 (t), 49.5 (t), 54.5 (d), 127.2 (d), 127.8 (d), 128.1 (d), 137.9 (s).

observed $^m/_e$ 201.1511

calculated for C$_{14}$H$_{19}$N   201.1517.

Nortropane (110)

A solution of (140) (0.27g, 1.34mmol) in dry methanol (20ml) was hydrogenated at 1 atm in the presence of 5% palladium on charcoal. After 4h, the catalyst was filtered off and the solvent was evaporated at reduced pressure to yield (110) (0.14g, 94%) as a colourless oil.

δ_H (90MHz, CDCl$_3$): 1.12-1.91 (series of m, 10H), 3.02 (br s, exch, 1H), 3.29 (br s, 2H).

δ_C (75MHz, CDCl$_3$): 17.1 (t), 29.0 (t), 32.8 (t), 54.6 (d).

N-Chloronortropane (148)

A solution of (147) (0.10g, 0.68mmol) in water (10ml) was treated with sodium hypochlorite (5% chlorine content, 15ml) and stirred at room temperature for 1h. The product was extracted into trichlorofluoromethane (3 x 10ml) and the combined organic layers dried over anhydrous magnesium sulphate. The solvent was evaporated by passing a gentle stream of N_2 over it to yield (148) (0.099g, 100%) as a colourless oil.

δ_H (300MHz, $CDCl_3$): equatorial- (148), 0.95-1.15 (m, 4H), 1.31-1.39 (m, 2H), 1.63-1.77 (m, 2H), 2.13-2.33 (m, 2H), 3.47 (m, 2H).

axial- (148), 0.83-1.15 (m, 4H), 1.24-1.39 (m, 2H), 1.63-1.77 (m, 2H), 2.13-2.25 (m, 2H), 3.24 (m, 2H).

δ_C (75MHz, $CDCl_3$): equatorial- (148), 14.9 (t), 26.7 (t), 33.8 (t), 70.4 (d).

axial- (148), 15.8 (t), 24.3 (t), 25.3 (t), 61.5 (d).

m/e (%): M^+-Cl 110 (12), 96 (6), 95 (37), 94 (100), 84 (6), 83 (16), 82 (56), 71 (27).

observed m/e (M^+-Cl)   110.0917

calculated for $C_7H_{12}N$ 110.0917.

cis-4-(Benzylamino)-2-cycloheptenol (150b)

(150b) was prepared using a similar method to that used to prepare (135b). (133b) (2.26g, 9.77mmol) reacted with lithium aluminium hydride (1.50g, 39.5mmol) to afford (150b) (2.07g, 97%) as a white crystalline solid. An analytical sample was prepared by

recrystallisation from petroleum ether (80-100°C) to give colourless needles: mp 115-116°C.

δ_H (300MHz, CDCl$_3$): 1.50-1.87 (series of m, 7H), 2.17-2.35 (m, 1H), 3.29 (ddd, J = 6.3Hz, J = 6.3Hz, J = 1.7Hz, 1H), 3.69, 3.79 (AB quartet, J = 12.8Hz, 2H), 4.22 (ddd, J = 6.3Hz, J = 6.3Hz, J = 1.7Hz, 1H), 5.87 (dd, J = 11.4Hz, J = 6.3Hz, 1H), 7.22-7.42 (m, 5H).

δ_C (75MHz, CDCl$_3$): 21.1 (t), 31.8 (t), 34.2 (t), 51.6 (t), 55.1 (d), 68.1 (d), 127.1 (d), 128.2 (d), 128.5 (d), 134.4 (d), 139.0 (d), 139.4 (s).

ν_{max} (CH$_2$Cl$_2$): 3610w, 3200br w, 3025m, 2930s, 2850s, 1500m, 1450w, 1320w, 1210w, 1110m, 1085s, 1055m, 1030m, 995m, 950w, 910w cm^{-1}.

m/e (%): M$^+$ 217 (13), 199 (7), 172 (9), 170 (9), 146 (14), 133 (5), 132 (5), 126 (5), 108 (8), 106 (12), 92 (10), 91 (100).

Found: C, 77.45; H, 8.66; N, 6.44%. C$_{14}$H$_{19}$NO

requires: C, 77.38; H, 8.81; N, 6.45%.

cis-4-(Benzylamino)-2-cyclohexenol (150a)

(150a) was prepared using a similar method to that used to prepare (135b). (133a) (1.67g, 7.69mmol) reacted with lithium aluminium hydride (1.20g, 31.6mmol) to afford (150a) (1.44g, 92%) as a colourless oil.

δ_H (300MHz, CDCl$_3$): 1.62-1.79 (m, 4H), 2.50 (br s, exch, 2H), 3.12 (m, 1H), 3.78, 3.85 (AB quartet, J = 13.0Hz, 2H), 4.08 (m, 1H), 5.78-5.82 (m, 2H), 7.21-7.33 (m, 5H).

δ_C (75MHz, CDCl$_3$): 24.7 (t), 29.0 (t), 51.0 (t), 52.1 (d), 64.3 (d), 126.9 (d), 128.0 (d), 128.3 (d), 130.9 (d), 132.3 (d), 140.0 (s).

ν_{max} (CH$_2$Cl$_2$): 3600m, 3420m, 3015m, 2940s, 2860m, 1500w, 1450s, 1440m, 1395w, 1355w, 1215m, 1150w, 1105m, 1060m, 1035w, 995m, 970m, 945m, 860w cm^{-1}.

m/e (%): M^+ 203 (14), 185 (7), 186 (6), 175 (39), 160 (11), 159 (100), 146 (11), 144 (14), 133 (13), 108 (17), 106 (22).

cis-1-(Benzylamino)-4-acetoxy-2-cycloheptene (151)

A solution of (150b) (0.37g, 1.70mmol) in dichloromethane (8ml) was added to a solution of tetrafluoroboric acid-dimethyl ether complex (0.25g, 1.88mmol) in dichloromethane (2ml) at 0°C. Acetic anhydride (0.20ml, 2.12mmol) was subsequently added at 0°C and the solution allowed to warm to room temperature. The reaction mixture was stirred for a further 7h, and then poured into ice-water (40ml). The solution was cooled, carefully basified to pH 8 with sodium bicarbonate solution and dried over anhydrous potassium carbonate. The solvent was evaporated at reduced pressure to yield (151) (0.41g, 93%) as a pale yellow oil.

δ_H (90MHz, CDCl$_3$): 1.30-1.95 (series of m, 6H), 2.02 (s, 3H), 3.29 (br d, J = 9.0Hz, 1H), 3.72 (s, 2H), 5.31 (br d, J = 9.0Hz, 1H), 5.51-5.75 (m, 2H), 7.21 (s, 5H).

ν_{max} (CH$_2$Cl$_2$): 3440w, 3035w, 2935m, 2850w, 1730s, 1495w, 1450m, 1370m, 1240s, 1100w, 1085w, 1025m, 980w, 810m cm^{-1}.

m/e (%): M^+ 259 (5), 200 (10), 199 (21), 170 (12), 156 (13), 108 (13), 106 (12), 105 (11), 92 (14), 91 (100).

N-Benzylnortrop-6-ene (152)

To a solution of (150b) (1.10g, 5.06mmol) and lithium chloride (1.0g) in chloroform (20ml) was added dropwise a solution of thionyl chloride (0.40ml, 5.51mmol) in chloroform (5ml) at 0°C. The reaction mixture was sonicated for 1.5h. Anhydrous potassium carbonate (3.0g) was subsequently added and the reaction mixutre further sonicated for

24h. Filtration and evaporation of the solvent at reduced pressure yielded a pale yellow oil which was purified by flash chromatography (90:9:1, petroleum ether [40-60°C]:diethyl ether:triethylamine). The first fraction afforded (153) (0.10g, 10%) as a colourless oil.

δ_H (300MHz, CDCl$_3$): 1.50-2.28 (series of m, 8H), 3.36, 3.79 (AB quartet, J = 13.9Hz, 2H), 5.65 (dddd, J = 11.4Hz, J = 6.5Hz, J = 3.5Hz, J = 0.4Hz, 1H), 5.82 (dddd, J = 11.4Hz, J = 6.5Hz, J = 1.3Hz, J = 1.3Hz, 1H), 7.20-7.37 (m, 5H).

δ_C (75MHz, CDCl$_3$): 23.5 (t), 29.8 (t), 31.2 (t), 42.4 (d), 47.6 (d), 65.1 (t), 126.2 (d), 126.7 (d), 127.6 (d), 128.2 (d), 133.4 (d), 139.6 (s).

ν_{max} (CH$_2$Cl$_2$): 3010w, 2960m, 2930s, 2875m, 1495m, 1450m, 1350m, 1125m, 1095s, 1075m, 1040m, 1025s, 800s cm^{-1}.

$^m/_e$ (%): M$^+$ 199 (6), 195 (7), 194 (7), 106 (12), 105 (54), 104 (7), 92 (18), 91 (100), 90 (6).

Further elution afforded (152) (0.66g, 65%) as a colourless oil.

δ_H (300MHz, CDCl$_3$): 1.24-1.76 (series of m, 6H), 3.45 (br s, 2H), 3.49 (s, 2H), 5.91 (s, 2H), 7.18-7.37 (m, 5H).

δ_C (75MHz, CDCl$_3$): equatorial- (152), 16.6 (t), 25.6 (t), 57.8 (t), 65.4 (d), 126.5 (d), 128.0 (d), 128.6 (d), 129.2 (d), 140.3 (s).

axial- (152), 15.4 (t), 25.9 (t), 59.0 (t), 66.2 (d), 126.9 (d), 127.2 (d), 130.4 (d), 130.8 (d), 140.1 (s).

ν_{max} (CH$_2$Cl$_2$): 3020w, 2940s, 1495m, 1450m, 1365m, 1330m, 1095m, 1075w, 1055s, 1030m, 995w, 915w, 845m cm^{-1}.

$^m/_e$ (%): M$^+$ 199 (32), 171 (11), 170 (53), 156 (6), 108 (5), 104 (4), 92 (8), 91 (100), 89 (7).

observed m/e 199.1353

calculated for $C_{14}H_{17}N$ 199.1361.

7-Azabicyclo[4.2.1]nona-2,4-dien-8-one (160)[115]

Chlorosulphonyl isocyanate (3.3ml, 37mmol) was added dropwise to a solution of cycloheptatriene (3.50g, 37mmol) in dry nitromethane (75ml) at 0°C. The reaction mixture was stirred for 3 days at 25°C under N_2. Evaporation of the solvent at reduced pressure afforded a crude product of N-chlorosulphonyl-7-azabicyclo[4.2.1]nona-2,4-dien-8-one (162). A solution of the crude N-chlorosulphonyl lactam (162) in acetone (20ml) and 2M (aq) sodium hydroxide solution were added simultaneously, drop by drop, to a stirred 1:1 mixture of acetone and water (90ml) saturated with sodium chloride. The rates of addition were controlled so as to maintain the reaction mixture at pH 6-7. Water (300ml) was added, and the product extracted into dichloromethane (4 x 50ml). The combined organic extracts were dried over anhydrous magnesium sulphate, and the solvent was evaporated at reduced pressure to yield a yellow solid. The product was triturated with cold diethyl ether in order to remove any cycloheptatriene to give (160) (1.71g, 33%) as yellow needles: mp 106-108°C, lit. mp 107-108.5°C.

δ_H (90MHz, $CDCl_3$): 1.70 (d, J = 13.5Hz, 1H), 2.43 (ddd, J = 13.5Hz, J = 8.0Hz, J = 8.0Hz, 1H), 3.27 (dd, J = 8.0Hz, J = 8.0Hz, 1H), 3.90 (dd, J = 8.0Hz, J = 8.0Hz, 1H), 6.00 (m, 4H), 6.90 (br s, exch, 1H).

ν_{max} (CH_2Cl_2): 3420m, 3015m, 2980m, 2975m, 1690s, 1450w, 1400w, 1355w, 1320w, 1280w, 1230m, 1170m, 1135m, 1110m, 1055m, 1025m, 995m, 990w, 880w, 860w cm^{-1}.

m/e (%): M^+ 135 (33), 92 (100), 91 (18).

3-Keto-2-azabicyclo[4.2.1]nonane (164)

A solution of (160) (0.75g, 5.55mmol) in dry tetrahydrofuran (70ml) was hydrogenated at 1 atm in the presence of 5% palladium on charcoal for 12h. The reaction mixture was filtered through celite and the solvent evaporated at reduced pressure to yield (164) (0.74g, 96%) as a yellow oil.

δ_H (90MHz, CDCl$_3$): 1.49-1.95 (m, 8H), 2.38 (m, 2H), 3.70 (m, 2H), 6.77 (br s, exch, 1H).

ν_{max} (CH$_2$Cl$_2$): 3430m, 3050m, 2940s, 2870m, 1690s, 1475m, 1450m, 1415m, 1305m, 1250m, 1185m, 1155m, 1110w, 1065m, 1035w, 1015w, 960w, 910m, 870w cm^{-1}.

m/e (%): M$^+$ 139 (50), 137 (7), 97 (8), 96 (47), 83 (100), 82 (13), 69 (10).

2-Azabicyclo[4.2.1]nonane (165)

A solution of (164) (0.69g, 4.90mmol) in dry diethyl ether (60ml) was added dropwise to a stirred slurry of lithium aluminium hydride (0.41g, 10.7mmol) in diethyl ether (20ml). After refluxing for 4h, decomposition of excess hydride was effected by addition of water. The ethereal solution was washed with 2M hydrochloric acid (3 x 20ml) and the combined extracts dried over anhydrous magnesium sulphate. The solvent was evaporated by passing a gentle stream of N$_2$ over it to yield (165) (0.25g, 41%) as a colourless oil.

δ_H (300MHz, CDCl$_3$): 1.40-1.60 (m, 8H), 1.65 (d, J = 12.3Hz, 1H), 1.83 (ddd, J = 12.3Hz, J = 7.5Hz, J = 7.5Hz, 1H), 1.95 (br s, exch, 1H), 2.40 (m, 1H), 2.73 (d, J = 10.5Hz, 1H), 3.15 (dd, J = 10.5Hz, J = 7.5Hz, 1H), 3.58 (d, J = 7.5Hz, 1H).

m/e (%): M$^+$ 125 (23), 96 (100), 95 (17), 83 (8), 82 (5).

7-t-Butyl-2-N-chlorosulphonyl-carboxamido-1,3,5-cycloheptatriene (182)

t-Butylcycloheptatriene (175c) (0.141g, 0.95mmol) in dry dichloromethane (3ml) was added dropwise to a solution of CSI (83μl, 0.94mmol) in dichloromethane (1ml) at 0°C. The reaction mixture was stirred for 3 days at room temperature and then the solvent evaporated at reduced pressue to yield a dark oil. Purification by flash chromatography (50:50, diethyl ether:petroleum ether [40-60°C]) yielded (182) (0.152g, 55%) as a yellow oil.

δ_H (300MHz, $CDCl_3$): 1.07 (s, 9H), 1.27 (ddd, J = 6.0Hz, J = 6.0Hz, J = 1.5Hz, 1H), 5.42 (dd, J = 9.0Hz, J = 7.0Hz, 1H), 6.26 (d, J = 6.0Hz, 1H), 6.28 (ddd, J = 9.0Hz, J = 5.7Hz, J = 1.5Hz, 1H), 6.50 (br s, exch, 1H), 6.93 (dd, J = 11.1Hz, J = 5.7Hz, 1H), 7.07 (d, J = 11.1Hz, 1H).

ν_{max} (CH_2Cl_2): 3420s, 3320s, 2975s, 1725s, 1600m, 1540w, 1440s, 1410s, 1375s, 1205s, 1180s, 1120w, 1040m, 1010m, 990w, 945w, 900s, 840w cm^{-1}.

$^m/_e$ (%): M^+ 293, 291 (3, 9), 176 (100), 175 (26), 145 (4), 143 (12), 142 (18), 91 (27).

7-t-Butyl-2-cyano-1,3,5-cycloheptatriene (183)

Triethylamine (0.11ml, 0.79mmol) was added dropwise to a solution of (182) (0.21g, 0.70mmol) in dry dichloromethane (2ml). After 1h, the solvent was evaporated at reduced pressure and the residue dissolved in diethyl ether. The resulting solution was passed down a short column of silica in order to remove any triethylamine hydrochloride. The solvent was evaporated at reduced pressure to yield (183) (0.09g, 73%) as a yellow oil.

δ_H (300MHz, $CDCl_3$): 1.03 (s, 9H), 1.28 (ddd, J = 6.0Hz, J = 6.0Hz, J = 1.5Hz, 1H), 5.37 (dd, J = 9.0Hz, J = 7.0Hz, 1H), 6.02 (d, J = 6.0Hz, 1H), 6.29 (ddd, J = 9.0Hz, J = 5.7Hz, J = 1.5Hz, 1H), 6.70 (d, J = 11.1Hz, 1H), 6.85 (dd, J = 11.1Hz, J = 5.7Hz, 1H).

ν_{max} (CH$_2$Cl$_2$): 3030m, 2980s, 2880m, 2220m, 1600s, 1475m, 1375s, 1220m, 1205m, 1185s, 1150m, 1060w, 1030w, 990w, 960w, 940w, 930w, 870m, 820m, 800m cm^{-1}.

$^m/_e$ (%): M$^+$ 174 (18), 148 (22), 147 (8), 91 (100), 90 (21).

9-Methyl-8-chlorosulphonylimino-7-oxabicyclo[4.2.1]nona-2,4-diene (193)

7-Methylcycloheptatriene (192) (0.62g, 5.87mmol) in dry dichloromethane (9ml) was added dropwise to CSI (0.51ml, 5.78mmol) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred overnight. The solvent was evaporated at reduced pressure to yield (193) (0.36g, 25%) as a red oil.

δ_H (300MHz, CDCl$_3$): 1.10 (d, J = 6.0Hz, 3H), 2.94 (sextet, J = 6.0Hz, 1H), 3.98 (m, 1H), 5.10 (m, 1H), 5.90–6.32 (m, 4H).

ν_{max} (CH$_2$Cl$_2$): 3040w, 2985w, 1580s, 1435m, 1375s, 1200m, 1180s, 1155m, 1135m, 1095m, 995w, 965w, 910m, 890m, 855m, 825w cm^{-1}.

$^m/_e$ (%): M$^+$ 251, 249 (3, 9), 106 (32), 105 (16), 91 (100), 90 (5).

9-Methyl-N-chlorosulphonyl-7-azabicyclo[4.2.1]nona-2,4-dien-8-one (197)

A solution of (193) (0.305g, 1.22mmol) in dry acetonitrile (10ml) was heated for 12h at 50°C. The solvent was evaporated at reduced pressue to yield (197) (0.288g, 94%).

δ_H (300MHz, CDCl$_3$): 0.95 (d, J = 6.0Hz, 3H), 2.77 (sextet, J = 6.0Hz, 1H), 3.54 (dd, J = 8.7Hz, J = 6.0Hz, 1H), 4.70 (dd, J = 6.0Hz, J = 6.0Hz, 1H), 5.77–6.43 (m, 4H).

ν_{max} (CH$_2$Cl$_2$): 2960w, 1755s, 1600m, 1590w, 1435m, 1405s, 1365m, 1190s, 1180s, 1165m, 1095m, 1050w, 1015w, 965w, 885m, 865m cm^{-1}.

$^m/_e$ (%): M$^+$ 251, 249 (4, 12), 106 (38), 105 (11), 91 (100), 90 (6).

9-Methyl-7-azabicyclo[4.2.1]nona-2,4-dien-8-one (198)

A solution of (197) (0.18g, 0.72mmol) in dry acetone (3ml) and 2M (aq) sodium hydroxide solution was added simultaneously drop by drop to a stirred 1:1 solution of acetone and water (14ml) saturated with sodium chloride. The rates of addition were controlled so as to maintain the reaction mixture at pH 6-7. The solution was poured into water (20ml) and the product extracted into dichloromethane (5 x 10ml). The combined organic layers were dried over anhydrous magnesium sulphate and then the solvent was evaporated at reduced pressure. The required lactam was isolated by flash chromatography (10:90, methanol:diethyl ether). (198) was obtained as a pale yellow oil (0.097g, 90%).

δ_H (300MHz, CDCl$_3$): 0.83 (d, J = 6.0Hz, 3H), 2.60 (sextet, J = 6.0Hz, 1H), 3.24 (dd, J = 8.7Hz, J = 6.0Hz, 1H), 3.72 (dd, J = 6.0Hz, J = 6.0Hz, 1H), 5.82-6.21 (m, 4H).

ν_{max} (CH$_2$Cl$_2$): 3415m, 3190m, 3025m, 2960m, 1690s, 1380m, 1355m, 1235w, 1220w, 1140w, 1120m, 1085m, 1035m, 880w cm^{-1}.

m/e (%): M$^+$ 149 (10), 106 (50), 105 (12), 92 (9), 91 (100).

observed m/e 149.0831

calculated for C$_9$H$_{11}$NO   149.0832.

N-Benzoyloxy-1,4-dihydro-1,4-iminonaphthalene (206)

A solution of (9b) (0.43g, 3.0mmol) in dry dichloromethane (5ml) was added to a solution of benzoyl peroxide (0.49g, 2.0mmol) in dichloromethane (10ml) over 15 min. at -15°C. After stirring for 30 min., sodium hydroxide (0.29g, 7.30mmol) was added and the reaction mixture stirred for an additional 2h at -10°C. The solution was poured into ice-water and the product extracted into dichloromethane (3 x 20ml). The organic phase was dried over anhydrous magnesium

sulphate and the solvent evaporated at reduced pressure to yield (206) as a yellow oil (0.678g, 86%).

δ_H (90MHz, CDCl$_3$): 5.08 (s, 2H), 6.66–8.01 (series of m, 11H).

ν_{max} (CH$_2$Cl$_2$): 3040m, 2950w, 1730s, 1640m, 1600m, 1580m, 1450m, 1435m, 1390w, 1350m, 1315s, 1270s, 1190m, 1175s, 1100s, 1090s, 1070s, 1025s, 860m, 840s, 820m cm^{-1}.

N-Hydroxy-1,4-dihydro-1,4-iminonaphthalene (207)

A solution of methanolic sodium hydroxide (20%, 0.31ml) was added to a solution of (206) (0.398g, 1.52mmol) in methanol (2ml) at 0°C. The reaction mixture was allowed to warm to 10°C and stirred for an additional 1h. Water (20ml) was added and the product extracted into dichloromethane (4 x 10ml). The combined organic layers were dried over magnesium sulphate and the solvent evaporated at reduced pressure. The crude product was purified by flash chromatography (methanol) to yield (207) (0.050g, 21%) as a red oil.

δ_H (90MHz, CDCl$_3$): 2.93 (br, s, exch, 1H), 4.86 (m, 2H), 6.83–6.87 (m, 4H), 7.13 (m, 2H).

ν_{max} (CH$_2$Cl$_2$): 3660w, 3600–3100 (br m), 3070m, 3040m, 1450m, 1350s, 1275m, 1255m, 1205m, 1195m, 1160w, 1130m, 1090s, 1010m, 910m, 865s cm^{-1}.

m/e (%): M$^+$ 159 (2), 144 (10), 143 (100), 142 (6), 128 (11), 118 (5), 117 (67), 116 (94), 115 (79), 114 (9), 90 (12), 89 (13).

N-Tosyloxy-1,4-dihydro-1,4-iminonaphthalene (205)

To a solution of (207) (0.045g, 0.28mmol) in dry diethyl ether (6ml) was added a solution of tosyl chloride (0.063g, 0.33mmol) in diethyl ether (3ml), followed by sodium hydroxide powder (0.171g, 4.28mmol). The reaction mixture was stirred for 14h at 0°C and then

ice-water (10ml) added. The product was extracted into dichloromethane (4 x 10ml) and the combined organic layers dried over anhydrous magnesium sulphate. The solvent was evaporated at reduced pressure and the residue triturated with cold diethyl ether in order to remove the excess tosyl chloride. (205) was obtained as a white crystalline solid (0.086g, 98%): mp 142-143°C.

δ_H (90MHz, CDCl$_3$): 2.30 (s, 3H), 5.40 (m, 2H), 6.73 (m, 2H), 7.00 (s, 4H), 7.02, 7.40 (AA'BB' system, J = 8.3Hz, 4H).

N-Tosyloxy-1-aminonaphthalene (208)

Dry methanol (14μl, 0.3mmol) was added to a solution of (205) (0.022g, 0.07mmol) in trifluoroacetic acid (0.5ml). After stirring for 1h at room temperature, 2M (aq) sodium hydroxide solution was added until the solution became alkaline. The product was extracted into dichloromethane (3 x 5ml) and the combined organic layers dried over anhydrous magnesium sulphate. The solvent was evaporated at reduced pressure to yield a yellow oil. The crude product was purified by flash chromatography (ether) to yield (208) (0.020g, 91%) as a white crystalline solid: mp 144-145°C.

δ_H (300MHz, CDCl$_3$): 2.34 (s, 3H), 6.98 (br s, exch, 1H), 7.15, 7.64 (AA'BB' system, J = 8.3Hz, 4H), 7.40 (m, 4H), 7.70 (m, 1H), 7.83-7.87 (m, 2H).

ν_{max} (CH$_2$Cl$_2$): 3350w, 3040w, 2960m, 2930m, 1510w, 1450m, 1400m, 1310m, 1190m, 1170s, 1095s, 1050m, 1020m, 915m, 900m, 815m cm^{-1}.

$^m/_e$ (%): 297 (14), 260 (4), 259 (24), 258 (4), 241 (16), 149 (12), 147 (31), 142 (10), 129 (100), 112 (52).

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ABSTRACT

Syntheses and Reactions of Azabicycles by A. Bathgate

Several novel nitrogen containing bicyclic systems have been synthesised and their chemistry investigated.

The kinetic and thermodynamic invertomer ratios of N-chloro-1,2,3,4-tetrahydro-2-keto-1,4-iminonaphthalene derivatives were determined. The results suggested that a repulsive interaction existed between the positive end of the carbonyl dipole and the incoming electrophilic chlorine. Despite reaction under favourable solvolytic conditions, it appeared that homolysis of the N-chloroamines was favoured over heterolysis.

Under conditions of negligible inversion, N-chloro-1,4-dihydro-1-methyl-1,4-iminonaphthalenes underwent heterolytic rearrangement to form 4-methylquinolines. From these experiments it was deduced that the quinoline products must be derived from the anti-N-chloroamines with loss of a bridgehead carbon atom. A mechanism for the formation of these products was proposed.

Nortropane was synthesised in high overall yield and the first synthesis of a simple derivative of nortrop-6-ene which has been achieved in significant yield was also accomplished. The procedure demonstrated the viability of an intramolecular cyclisation approach given an appropriately nucleophilic nitrogen.

Investigation of the reactions of chlorosulphonyl isocyanate with 7-substituted cycloheptatrienes provided evidence that choice of solvent and reaction time along with careful monitoring exerts control over the addition of either the C=O or C=N moiety across the termini of the triene unit.

Additional Experimental

Attempted silver-ion assisted rearrangement of N-chloro-5,6,7,8-tetrafluoro-1,2,3,4-tetrahydro-2-keto-1,4-iminonaphthalene (33a)

Silver nitrate (0.28g, 1.65mmol) was added to a solution of N-chloroamine (33a) (0.18g, 0.68mmol) in dry methanol (2ml). The reaction mixture was stirred for 6h at room temperature under N_2 and then the methanol was evaporated at reduced pressure. To the residue was added brine (5ml), 2M (aq) sodium hydroxide solution (5ml) and dichloromethane (10ml). After filtration (to remove the silver salt residues), the product was extracted into dichloromethane (3 x 10ml) and subsequently washed with water (10ml). The combined organic extracts were dried over anhydrous magnesium sulphate and the solvent evaporated at reduced pressure to afford the amine (32a) (0.14g, 89%).

Attempted silver-ion assisted rearrangement of N-chloro-1,2,3,4-tetrahydro-2-keto-1,4-iminonaphthalene (33b)

In all of the following experiments, work-up involved evaporation of the solvent at reduced pressure. To the residue was added brine, 2M (aq) sodium hydroxide solution and dichloromethane. After filtration (to remove the silver salt residues), the product was extracted into dichloromethane and subsequently washed with water. The combined organic extracts were dried over anhydrous magnesium sulphate and the solvent evaporated at reduced pressure. In each case, the secondary amine (32b) produced in the reaction was isolated by flash chromatography (50:50, diethyl ether:petroleum ether [40-60°C]). No other products were isolated.

i)   Silver nitrate (45mg, 0.26mmol) was added to a solution of N-chloroamine (33b) (38mg, 0.20mmol) in dry methanol (2ml) and stirred for 4h at room temperature under N_2.   Work-up afforded amine (32b) (28mg, 88%).

ii)   Silver nitrate (526mg, 3.10mmol) was added to a solution of N-chloroamine (33b) (99mg, 0.51mmol) in dry methanol (2ml) and stirred for 3h under N_2. Work-up afforded amine (32b) (76mg, 94%).

iii)   A solution of N-chloroamine (33b) (60mg, 0.31mmol) in toluene (3ml) was added to a stirred mixture of silver tetrafluoroborate (110mg, 0.57mmol) and dry methanol (14μl, 0.35mmol) in dry toluene (3ml) and stirred for 3h at room temperature under N_2.   Work-up afforded amine (32b) (45mg, 91%).

iv)   A solution of N-chloroamine (33b) (54mg, 0.28mmol) in dry toluene (1ml) was added to a suspension of silver tetrafluoroborate (280mg, 1.44mmol) in dry toluene (2ml) and stirred for 3h at room temperature under N_2.   Dry methanol (40μl, 0.99mmol) was subsequently added and the reaction mixture stirred for a further 1h.   Work-up afforded amine (32b) (38mg, 85%).

v)   A solution of N-chloroamine (33b) (40mg, 0.21mmol) in dry toluene (1ml) was added to a suspension of silver tetrafluoroborate (196mg, 1.01mmol) in toluene (1ml). After stirring for 10 min. at room temperature under N_2, sodium methoxide (31mg, 0.57mmol) was added and the reaction mixture stirred for a further 2.5h. Work-up afforded amine (32b) (27mg, 81%).

Low temperature preparation and rearrangement of N-chloro-1,2,3,4-tetrahydro-1,4-iminonaphthalene (48b)

NCS (0.276g, 2.07mmol) was added to a solution of 1,2,3,4-tetrahydro-1,4-iminonaphthalene (0.250g, 1.72mmol) in dry dichloromethane (10ml) at -50°C under N_2. After stirring for 2.5h, the solvent was evaporated at reduced pressure without allowing the temperature of the reaction mixture to rise above -20°C. The residue was dissolved in cold toluene (10ml) and filtered at low temperature (to remove NCS and succinimide). The resulting solution of N-chloroamine (48b) was subsequently added to a mixture of silver tetrafluoroborate (0.40g, 2.06mmol) in dry methanol (70μl, 1.73mmol) in dry toluene (10ml) at -50°C. The reaction mixture was allowed to warm to -20°C and stirred at that temperature for 4h. After evaporation of the solvent at reduced pressure, brine (20ml) and 2M (aq) sodium hydroxide solution (20ml) were added, and the mixture subsequently filtered (to remove the silver salt residues). The product was extracted into dichloromethane (3 x 25ml) and washed with water (20ml). The combined organic extracts were dried over anhydrous magnesium sulphate and the solvent evaporated at reduced pressure. The residue was purified by flash chromatography (30:70, diethyl ether:petroleum ether [40-60°C]) to afford a pale yellow oil which was identified as the rearrangement product (50) (0.242g, 81%) by comparison of its ^{1}H NMR spectrum with an authentic sample.[42]

trans-1-([Benzyloxycarbonyl]amino)-4-bromo-2-cycloheptene (118b)

A solution of thionyl bromide (88μl, 1.14mmol) in chloroform (1ml) was added dropwise to a solution of (114) (100mg, 0.38mmol) and pyridine (0.25ml, 3.12mmol) in chloroform (10ml) at 0°C. After stirring for 1h at 0°C, the reaction mixture was poured into ice-water (20ml) and

the aqueous layer extracted with chloroform (2 x 20ml). The combined organic extracts were dried over anhydrous magnesium sulphate and the solvent evaporated at reduced pressure to yield a pale yellow residue which was purified by chromatography (50:50, diethyl ether:petroleum ether [40-60°C]). The first fraction afforded (118b) (37mg, 30%) as a pale yellow oil.

δ_H (90MHz, CDCl$_3$): 1.40-2.02 (series of m, 6H), 4.28 (m, 1H), 4.50 (m, 1H), 4.80 (br s, exch, 1H), 4.92 (s, 2H), 5.52-5.78 (m, 2H), 7.29 (s, 5H).

ν_{max} (CH$_2$Cl$_2$): 3410m, 3020w, 2910m, 1710s, 1510s, 1445w, 1440w, 1335m, 1305w, 1220m, 1105w, 1075w, 975w, 750m, 735m cm^{-1}.

m/e (%): M$^+$ 325, 323 (2, 2) 243 (20), 200 (6), 199 (5), 153 (11), 152 (62), 93 (25), 92 (100).

Further elution of the column yielded recovered starting material (114) (21mg, 21%).

Reaction of cis-4-(benzylamino)cyclohexanol (135a) with thionyl chloride

To a solution of (135a) (70mg, 0.34mmol) in chloroform (2ml) was added dropwise a solution of thionyl chloride (27μl, 0.37mmol) in chloroform (1ml). After 10min. t.l.c. indicated loss of starting material. An aliquot was removed from the reaction mixture and added to a solution of 2M (aq) sodium hydroxide. However, the product decomposed to give a black intractable tar. Therefore, the remainder of the reaction mixture was concentrated and the residue dissolved in deuterochloroform and placed in an NMR tube with approximately one equivalent of pyridine (25μl, 0.31mmol). The ^{1}H NMR and t.l.c. indicated a homogeneous material which was thought to be the chlorosulphite derivative (45).

δ_H (90MHz, CDCl$_3$): 1.52-2.02 (series of m, 8H), 2.10 (br s, exch, 1H), 2.80 (m, 1H), 3.91 (s, 2H), 4.91 (m, 1H), aromatic signals obscured.

Periodic monitoring by ^{1}H NMR indicated a further change in the product which was extremely slow. However, after heating at 50°C overnight, the reaction was complete to give a different compound which again appeared to be homogeneous by ^{1}H NMR and t.l.c., but also decomposed on aqueous work-up. This was assumed to be the chloro-derivative (146).

δ_H (90MHz, CDCl$_3$): 1.50-2.00 (series of m, 8H), 2.09 (br s, exch, 1H), 2.57 (m, 1H), 2.89 (m, 1H), 3.85 (s, 2H), aromatic signals obscured.

After cooling to 0°C, pyridine (0.5ml) was added dropwise and the solution allowed to warm to room temperature over 1h. The reaction mixture was subsequently poured into 2M (aq) sodium hydroxide solution (5ml) and the aqueous layer extracted with dichloromethane (3 x 5ml). The combined organic layers were dried over anhydrous sodium sulphate and the solvent evaporated at reduced pressure. The residue was purified by flash chromatography (70:30, diethyl ether:petroleum ether [40-60°C]) to afford alcohol (135a) (40mg, 57%). Further elution of the column yielded small quantities of several compounds which could not be identified but did not appear to be the required product (143).

Reaction of cis-4-(benzylamino)cyclooctanol (135c) with thionyl chloride

To a solution of (135c) (100mg, 0.43mmol) in chloroform (5ml) was added dropwise a solution of thionyl chloride (34μl, 0.47mmol) in chloroform (2ml) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for a further 24h. After cooling to 0°C, pyridine (1ml) was added dropwise and the solution stirred for 1h. The

reaction mixture was subsequently poured into 2M (aq) sodium hydroxide solution, and the aqueous layer extracted with dichloromethane (2 x 10ml). The combined organic extracts were dried over anhydrous sodium sulphate and the solvent evaporated at reduced pressure. The residue was purified by flash chromatography (70:30, diethyl ether: petroleum ether [40-60°C]) to afford alcohol (135c)(68mg, 68%). Further elution of the column yielded small quantities of several compounds which could not be identified but did not appear to be the required product (144).

Reaction of cis-4-(benzylamino)cyclohexanol (135a) with thionyl bromide

To a solution of (135a) (80mg, 0.39mmol) in chloroform (2ml) was added dropwise a solution of thionyl bromide (33μl, 0.43mmol) in chloroform (1ml) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for a further 24h. After cooling to 0°C, pyridine (0.5ml) was added dropwise and the solution stirred for 1h. The reaction mixture was subsequently poured into 2M (aq) sodium hydroxide solution (10ml) and the aqueous layer extracted with dichloromethane (2 x 15ml). The combined organic layers were dried over anhydrous sodium sulphate and the solvent evaporated at reduced pressure. The residue was purified by flash chromatography (70:30, diethyl ether:petroleum ether [40-60°C]) to afford the alcohol (135a) (59mg, 74%) as the only identifiable product.

Reaction of cis-4-(benzylamino)cyclooctanol (135c) with thionyl bromide

To a solution of (135c) (90mg, 0.39mmol) in chloroform (2ml) was added dropwise a solution of thionyl bromide (33μl, 0.43mmol) in chloroform (1ml) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for a further 24h. After cooling to 0°C, pyridine (0.5ml) was added dropwise and the solution stirred for 1h. The reaction mixture was subsequently poured into 2M (aq) sodium hydroxide solution (10ml) and the aqueous layer extracted with dichloromethane (2 x 15ml). The combined organic layers were dried over anhydrous sodium sulphate and the solvent evaporated at reduced pressure. The residue was purified by flash chromatography (70:30, diethyl ether:petroleum ether [40-60°C]) to afford the alcohol (135c) (49mg, 54%) as the only identifiable product.

Attempted reduction of 7-azabicyclo[4.2.1]nona-2,4-dien-8-one (160)

In all of the following experiments, work-up involved cautious dropwise addition of water and subsequent addition of 2M (aq) sodium hydroxide solution. After extraction of the product into diethyl ether, the combined organic layers were dried over anhydrous magnesium sulphate and the solvent evaporated at reduced pressure.

i)   A solution of lactam (160) (92mg, 0.68mmol) in tetrahydrofuran (10ml) was added to a solution of diisobutylaluminium hydride (1.3ml, 1.0M solution in tetrahydrofuran) in tetrahydrofuran (5ml) and heated at reflux for 5h under N_2. Work-up afforded starting material (160) (81mg, 88%) as the sole product.

ii)   A solution of lactam (160) (147mg, 1.09mmol) in dry tetra-
hydrofuran (10ml) was added to a suspension of lithium aluminium hydride
(48mg, 1.26mmol) in tetrahydrofuran (10ml) and heated at reflux for 4h
under N_2. Work-up afforded starting material (160) (139mg, 95%) as the
sole product.

iii)   A solution of lactam (160) (200mg, 1.48mmol) in toluene (10ml)
was added to a solution of Red-Al (0.9ml, 3.4M solution of sodium bis(2-
methoxyethoxy)aluminium hydride in toluene) in toluene (5ml), and heated
at 60°C for 4h under N_2. Work-up afforded starting material (180mg,
90%) as the sole product.

Reaction of t-butylcycloheptatriene (175c) with chlorosulphonyl iso-cyanate and subsequent alkaline hydrolysis

A solution of t-butylcycloheptatriene (175c) (90mg, 0.61mmol) in
dry dichloromethane (2ml) was added dropwise to a solution of CSI (53μl,
0.61mmol) in dichloromethane (1ml) at 0°C and the reaction mixture
stirred for 3 days at room temperature. The solvent was evaporated at
reduced pressure and the residue re-dissolved in dry acetone (5ml).
This solution and 2M (aq) sodium hydroxide solution were added
simultaneously drop by drop to a stirred 1:1 solution of acetone and
water (5ml) saturated with sodium chloride. The rates of addition were
controlled so as to maintain the reaction mixture at pH 6-7. The
solution was poured into water (10ml) and the product extracted into
dichloromethane (4 x 10ml). The combined organic layers were dried over
anhydrous magnesium sulphate and then the solvent evaporated at reduced
pressure. The residue was purified by flash chromatography (70:30,
diethyl ether: petroleum ether [40-60°C]). Small quantities of several

compounds were isolated but could not be identified. The only identfiable product was (186) (6mg, 5%).

δ_H (300MHz, CDCl$_3$): 1.05 (s, 9H), 3.45 (dddd, J = 12.0Hz, J = 7.5Hz, J = 4.4Hz, J = 1.5Hz, 1H), 4.07 (ddd, J = 12.0Hz, J = 3.9Hz, J = 2.2Hz, 1H), 4.13 (d, J = 7.5Hz, 1H), 5.69 (dd, J = 9.8Hz, J = 4.4Hz, 1H), 5.89 (ddd, J = 9.8Hz, J = 3.9Hz, J = 0.5Hz, 1H), 6.05 (dddd, J = 9.8Hz, J = 5.3Hz, J = 1.5Hz, J = 0.5Hz, 1H), 6.26 (ddd, J = 9.8Hz, J = 5.3Hz, J = 2.2Hz, 1H).

ν_{max} (CH$_2$Cl$_2$): 3040w, 2960m, 2870w, 1755s, 1480m, 1460w, 1355s, 1215m, 1175s, 1135w, 1000w, 930m, 845s, 790m cm^{-1}.

$^m/_e$ (%): M$^+$ 190 (43), 189 (12), 146 (72), 145 (15), 133 (100), 132 (12), 131 (9), 89 (42), 88 (26), 87 (15).

Further Information and Data

Low temperature preparation and rearrangement of (66b) (p.162)

The reaction afforded a product which was identified as 4-methylquinoline (60b) by comparison of its ^{13}C NMR spectrum with an authentic sample (S.R. Johns, R.I. Willing, Aust. J. Chem., 1976, 29, 1617).

Silver-ion assisted methanolysis of (66c) in toluene (p.163)

The reaction afforded a product which was identified as 5,8-dimethoxy-4-methylquinoline (60c) by comparison of its melting point with an authentic sample (C.E. Kaslow, N.B. Sommer, J. Am. Chem. Soc., 1946, 68, 644).

Nortropane (110) (p.183)

The reaction afforded a product which was identified as nortropane (100) by comparison of its ^{13}C NMR spectrum with an authentic sample (E. Wenkert, J.D. Bindra, C. Chang, D.W. Cochran, F.M. Schell, Acc. Chem. Res., 1974, 7, 46).

cis-4-(Benzoylamino)-2-cyclohexenol (133a) (p.177)

| observed m/e | 217.1104 |
| calculated for $C_{13}H_{15}NO_2$ | 217.1103. |

cis-4-(Benzylamino)cycloheptanol (135b) (p.181)

| observed m/e | 219.1625 |
| calculated for $C_{14}H_{21}NO$ | 219.1623. |

<u>cis—4—(Benzylamino)cyclohexanol (135a)</u> (p.181)

observed m/e	205.1471
calculated for $C_{13}H_{19}NO$	205.1467.

<u>cis—4—(Benzylamino)cyclooctanol (135c)</u> (p.182)

observed m/e	233.1777
calculated for $C_{15}H_{23}NO$	233.1780.

<u>cis—4—(Benzylamino)—2—cyclohexenol (150a)</u> (p.185)

observed m/e	203.1313
calculated for $C_{13}H_{17}NO$	203.1310.

Subsequent mass spectral data was obtained from Beecham Pharmaceuticals Research Division, Brockham Park, Betchworth, Surrey.

High resolution mass spectral data (electron ionisation) was obtained using a VG 7070F double focusing mass spectrometer at a resolution of 5000 using perfluorokerosene as reference. Isobutane chemical ionisation spectra were obtained using the VG 7070F mass spectrometer operated at low resolving power (1000).

In cases where molecular ions (M^+) were relatively small when observed by the electron ionisation technique, high resolution mass spectral data was obtained on the principle fragmentation product(s). Molecular masses were verified by chemical ionisation giving values for MH^+.

Elemental analyses were carried out by Butterworth Laboratories Ltd., Teddington, Middlesex.

N-Carbomethoxy-5,6,7,8-tetrafluoro-1,4-dihydro-1,4-iminonaphthalene (29a) (p.138)

E.I.:   observed $^m/_e$ 273.0423

          calculated for $C_{12}H_7NO_2F_4$ 273.0413.

5,6,7,8-Tetrafluoro-1,2,3,4-tetrahydro-2-keto-1,4-iminonaphthalene (32a) (p.140)

C.I.: MH^+ 232.

E.I.:   observed $^m/_e$ (M^+ - CHO)   202.0284

          calculated for $C_9H_4NF_4$ 202.0280.

          observed $^m/_e$ (M^+ - C_2H_2O)   189.0200

          calculated for $C_8H_3NF_4$ 189.0200.

N-Carbobenzoxy-1,4-dihydro-1,4-iminonaphthalene (45) (p.146)

E.I.: observed m/e 277.1109

        calculated for $C_{18}H_{15}NO_2$ 277.1103.

N-Carbobenzoxy-1,2,3,4-tetrahydro-2-hydroxy-1,4-iminonaphthalene (46)
(p.147)

C.I.: MH^+ 296.

E.I.: observed m/e ($M^+ - C_2H_4O$)   251.0940

        calculated for $C_{16}H_{13}NO_2$ 251.0946.

1,2,3,4-Tetrahydro-2-keto-1,4-iminonaphthalene (32b) (p.148)

C.I.: MH^+ 160.

E.I.: observed m/e ($M^+ - CHO$)   130.0666

        calculated for C_9H_8N 130.0657.

        observed m/e ($M^+ - C_2HO$)   118.0656

        calculated for C_8H_8N 118.0657.

1-Trimethylsilyl-2-methyl pyrrole (65) (p.149)

E.I.: observed m/e 153.0967

        calculated for $C_8H_{15}NSi$ 153.0974.

1,4-Dihydro-1-methyl-1,4-iminonaphthalene (61b) (p.151)

E.I.: observed m/e 157.0891

        calculated for $C_{11}H_{11}N$ 157.0891.

5,6,7,8-Tetrafluoro-1,2,3,4-tetrahydro-1-methyl-1,4-iminonaphthalene

(62a) (p.152)

C.I.:   MH$^+$ 232.

E.I.:   observed $^m/_e$ (M$^+$-C$_2$H$_4$)   203.0352

calculated for C$_9$H$_5$NF$_4$ 203.0358.

1,2,3,4-Tetrahydro-1-methyl-1,4-iminonaphthalene (62b) (p.153)

C.I.:   MH$^+$ 160

E.I.:   observed $^m/_e$ (M$^+$-C$_2$H$_4$)   131.0736

calculated for C$_9$H$_9$N   131.0735.

1,2,3,4-Tetrahydro-5,8-dimethoxy-1-methyl-1,4-iminonaphthalene (62c)

(p.153)

E.I.:   observed $^m/_e$ 219.1258

calculated for C$_{13}$H$_{17}$NO$_2$ 219.1259.

N-Benzoyl-7-oxa-8-azabicyclo[2.2.2]oct-5-ene (132a) (p.175)

Found: C, 72.81; H, 6.15; N, 6.56%. C$_{13}$H$_{13}$NO$_2$

requires: C, 72.59; H, 6.09; N, 6.51%.

N-Benzoyl-9-oxa-10-azabicyclo[4.2.2]deca-7-ene (132c) (p.176)

Found: C, 73.85; H, 7.06; N, 5.80%. C$_{15}$H$_{17}$NO$_2$

requires: C,74.05; H, 7.04; N, 5.76%.