SYNTHESIS OF FUSED MEDIUM-RING HETEROCYCLES
BY THE REARRANGEMENT OF
QUATERNARY AMMONIUM DERIVATIVES

by

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Submitted in fulfilment of the requirement for the degree of
DOCTOR OF PHILOSOPHY

UNIVERSITY OF TASMANIA
HOBART
To my parents

and my wife
This thesis contains no material which has been accepted for the award of any other degree or diploma in any University, nor, to the best of my knowledge and belief does it contain any copy or paraphrase of material previously published or written by another person, except where due reference is included in the text.

Signed

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ABSTRACT

The general aim of this study was to develop new modes of access to benz-fused medium-ring heterocycles. The approach adopted was to utilise the rearrangements, with concurrent ring expansion, of heterocyclic quaternary ammonium N-ylides and N-oxides. Of particular interest were new applications of the [2,3] rearrangements of these systems.

Base promoted [2,3] sigmatropic rearrangement of 1-vinyl-2-ethoxycarbonylmethyl-1,2,3,4-tetrahydroisoquinolinium salts at room temperature in acetonitrile afforded functionalised 2,3,4,5-tetrahydro-1H-3-benzazonine derivatives, as mixtures of the olefinic isomers, in high yields. This is the first application of this rearrangement to the synthesis of benz-fused aza-heterocycles. A stereoselective preference for the formation of the E-benzazonines was observed. The E-benzazonines degraded to polar material on p.t.l.c. and acid-catalysed transannular interactions were proposed. The rearrangement reaction at high temperature also provided 1-vinyl-2,3,4,5-tetrahydro-1H-benzazepines, the products of [1,2] Stevens rearrangement. The mechanisms and product distributions of these rearrangements are discussed, with reference to models of the expected concerted transition states.

Application of the [2,3] sigmatropic rearrangement to 1-vinyl-tetrahydroisoquinolinium salts with nitrile or phenacyl ylide stabilising groups provided the appropriate 4-substituted-2,3,4,5-tetrahydro-1H-3-benzazonine derivatives in good yields. Successful [2,3] rearrangement of the phenacyl stabilised ylide was limited to low temperatures, with Stevens rearrangement products being isolated selectively at high temperature. Rearrangement of an unstabilised methylene ylide, generated by fluorodesilylation, gave a 4-unsubstituted 3-benzazonine in low yield. Base-promoted rearrangement of N-methyl-tetrahydroisoquinolinium salts with no ylide stabilising group afforded Hofmann elimination.
products and demonstrated a limitation on the potential synthetic uses of the [2,3] rearrangement.

Rearrangement of vinyl substituted 2-ethoxycarbonylmethyl-tetrahydroisoquinolinium salts gave, in most cases, 6- or 7-substituted-2,3,4,5-tetrahydro-1H-3-benzazonine derivatives via the [2,3] rearrangement. A decrease in the E-stereoselectivity of the rearrangement was observed from C1'-substituted salts and probably reflected changes in the preferred concerted transition state geometry. Limitations to the potential uses of the [2,3] rearrangement were exemplified by the rearrangements of the 2',2'-dimethyl and trans-2'-dimethoxyphenyl salts at room temperature. The former provided a mixture of the [1,2] and [2,3] rearrangement products, indicative of steric interference by the cis-2'-methyl group with the concerted transition state, while the latter gave the Stevens rearrangement product selectively, indicative of promotion of the [1,2] radical pathway by the radical stabilising group at C2'.

Hydrogenation of the E-2,3,4,5-tetrahydro-1H-3-benzazonines gave 2,3,4,5,6,7-hexahydro-derivatives, while the Z-2,3,4,5-tetrahydro-1H-3-benzazonines were unaffected. Hydrogenation of a 6-methyl-2,3,4,5-tetrahydro-1H-3-benzazonine derivative was accompanied by a [1,3] hydrogen shift to an endocyclic olefinic 3-benzazonine. Hydrogenolysis of an N-benzyl-tetrahydro-3-benzazonine could not be obtained preferentially without concurrent hydrogenation. The reaction afforded a secondary amine derivative of the 3-benzazonine system.

The [2,3] rearrangement of a 2-(tetrahydro-2'-furanon-3'-yl)-1-vinyl-tetrahydroisoquinolinium salt afforded the first example of the 2,3,4,5-tetrahydro-1H-3-benzazonine-4-spiro-3'-tetrahydro-2'-furanone ring system in low yield.

An effort to extend the [2,3] rearrangement to the synthesis of unsaturated 3-benzazonines from a 1-ethynyl-tetrahydroisoquinolinium salt gave only the Stevens rearrangement product in poor yield.

Thermolysis of 1-vinylc-tetrahydroisoquinolinium N-oxides unsubstituted at C1' failed to provide [2,3] rearrangement and afforded 1-vinylc-1,3,4,5-tetrahydro-
2,3-benzoxazepines in good yield by the Meisenheimer rearrangement. Neat pyrolysis of the 1-vinyl-benzoxazepines gave an unexpected isomerisation to 1,3,3a,4,9,9a-hexahydroisoxazolo[3,4-b]naphthalene derivatives. This isomerisation may involve the formation and reaction of a nitrone intermediate.

Thermolysis of 1'-substituted-1-vinyllic-tetrahydroisoquinolinium N-oxides gave the first representatives of the 4,3-benzoxazone system in mixtures with the Meisenheimer rearrangement products. The Z-olefinic 1,2,3,5-tetrahydro-4,3-benzoxazones were formed selectively. A stereoselective concerted [2,3] rearrangement of the cis-N-oxides was indicated as thermolysis in refluxing dichloromethane gave the 4,3-benzoxazones with unchanged trans-N-oxides. The structure of a 4,3-benzoxazone was unequivocally established by X-ray structural analysis. The 4,3-benzoxazones were thermally labile and in refluxing xylene gave equilibrium mixtures with, and favouring, the less-strained 1-vinyllic-2,3-benzoxazepines.

Meisenheimer rearrangement of a 5,6-dihydro-4H-s-triazolo[4,3-a]-1,4-benzodiazepine N-oxide afforded a 4,5-dihydro-7H-s-triazolo[4,3-a]-5,1,4-benzoxadiazocine, the first representative of this ring system, with structural similarities to the CNS active agent 'Alprazolam'.

Further extension of the Meisenheimer rearrangement to tricyclic bridgehead N-oxides of the 10b-vinyl-pyrrolo[2,1-a]isoquinoline and 11b-vinylbenzo[a]quinolizine systems gave, in low yield, the first examples of the 3,7-epoxy-3-benzazonine and 2H-3,8-epoxy-3-benzacecine ring systems.

Modification of the Meisenheimer and Stevens rearrangement to give a four atom ring expansion by the inclusion of an α-cyclopropyl substituent was also investigated. Thermolysis of a 1-cyclopropyltetrahydroisoquinoline N-oxide gave the 2,3-benzoxazepine product of the Meisenheimer rearrangement. Thermolysis of a 1-(2'-phenylcyclopropyl)tetrahydroisoquinoline N-oxide derivative gave the Meisenheimer rearrangement product and, in low yield, a 2,3,5,6-tetrahydro-5-phenyl-1H-4,3-benzoxacedine derivative. Formation of the 4,3-benzoxazecine
system, the first example of this ring system, confirmed the plausibility of a modified rearrangement pathway. The 4,3-benzoxazecine structure was confirmed by X-ray crystallography. Base promoted rearrangement of the analogous 1-cyclopropyl or 1-(2'-phenylcyclopropyl)-N-ethoxycarbonylmethyl salts afforded only 3-benzazepine derivatives by the Stevens rearrangement.

*N-Alkylation of a 1-(2'-phenylcyclopropyl)-3,4-dihydroisoquinoline at moderate temperatures with iodomethane gave an unexpected Cloke rearrangement and a new route to the pyrrolo[2,1-\(a\)]isoquinoline system. The structure of the N-methyl-2,3,5,6-tetrahydropyrrolo[2,1-\(a\)]isoquinolinium iodide product was unequivocally established by X-ray structural analysis.

The global minima and low energy conformations of the 2,3,4,5-tetrahydro-\(1H\)-3-benzazonine, 1,2,3,5-tetrahydro-4,3-benzazonine, and 2,3,5,6-tetrahydro-\(1H\)-4,3-benzoxazecine systems were determined with the molecular mechanics-based program PCModel and, where possible, compared with X-ray crystallographic results. The implications of the conformers found for the properties of these compounds are discussed. It is envisaged that these studies may allow the future assessment of the potential of these compounds as CNS active agents.

The present study has provided the synthesis of many novel isoquinoline derivatives necessary for the investigations described above and has established new synthetic routes to five known and six new benz-fused medium ring heterocyclic systems.
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1.1 General Introduction

The past thirty years have seen a tremendous drive towards the synthesis of novel nitrogen-containing heterocycles. This has occurred due to the large demand for synthetic access to natural alkaloids and the recognised commercial potential of many heterocyclic compounds as, typically, agricultural chemicals, dyes, or pharmaceuticals. In particular many nitrogen heterocycles containing aromatic moieties have found application as central nervous system (CNS)-active pharmaceutical agents.

Although benz-fused medium-sized (8- to 11-membered) heterocycles containing nitrogen, or both nitrogen and oxygen, have a high potential for CNS activity, research in this area has been limited and sporadic. The CNS potential of the benz-fused medium-sized nitrogen heterocycles arises from the presence of the aromatic and nitrogen atom moieties. Lloyd and Andrews proposed\(^1\) a primary pharmacophore for activity over all CNS receptor types using these two moieties. In particular, medium-sized rings may be used to provide constrained analogues of known drugs with less side-effects. Nefopam hydrochloride, a 2,5-benzoxazocine (Figure 1.1) is a non-narcotic analgesic with muscle relaxant, anti-cholinergic and anti-histaminic properties\(^2\) which acts as a cyclised, constrained, analogue of the parent antihistamine diphenhydramine.\(^3,4,5\) It is also possible that a medium-sized ring may substitute for a rigid combination of smaller rings. For example, the structure of the dopamine agonist apomorphine (Figure 1.1), known for its emetic effect,\(^6\) suggests that a 6,7- or 7,8-unsaturated 3-benzazecine derivative would have a high potential for CNS activity.

Considerable scope remains for the synthesis of new benz-fused medium-sized nitrogen heterocycles. For example, only 18 of the 100 possible medium-sized
benzoxaza- skeletons are presently known. In addition, alternate methods of access to those already known are required to enable detailed structure-pharmacological property relationship studies incorporating new functionalities.

1.1.1 Project Aims

The aims of this project were to examine a set of ring interconversion reactions involving the rearrangements of N-ylides and N-oxides, and to develop their application to the syntheses of benz-fused medium-sized nitrogen heterocycles. The reactions to be investigated are outlined schematically in Figure 1.2.
1.2 Introduction to [1,2] Rearrangements

The [1,2] rearrangements of N-ylides and N-oxides, termed the Stevens and Meisenheimer rearrangements respectively, have been extensively studied and are the subject of several reviews.\textsuperscript{8,9,10,11} The rearrangement may be viewed formally as a nucleophilic substitution at the migrating carbon with an anionic centre replacing the electron deficient nitrogen. The Meisenheimer rearrangement occurs thermally from an N-oxide. The Stevens rearrangement proceeds via \textit{in situ} generation of an N-ylide, typically in the presence of a base. The [1,2] rearrangement may provide a one atom ring expansion and 1,2-oxaza heterocycles (Figure 1.2).

1.2.1 Mechanism

A radical-pair mechanism is currently accepted for these rearrangements, with homolytic cleavage of the C-N bond prior to radical rearrangement and recombination in a solvent cage (Figure 1.3). The radical-pair mechanism was adopted, rather than a comparable ion-pair mechanism, as chemically induced dynamic nuclear polarization (CIDNP) spectra, indicative of free-radicals, were observed during the rearrangements.\textsuperscript{12} Experiments showing retention of configuration in the migrating group (R\textsuperscript{1}), contrary to orbital symmetry principles, have precluded a concerted mechanism. In practice, electron delocalising migrating groups have provided the highest rearrangement yields. Benzylic and allylic groups are most often used.

\[ \begin{align*}
\text{R}^3_{\text{Y}} \text{N}^+_{\text{R}^2} &\rightarrow \begin{bmatrix}
\text{R}^3_{\text{Y}} \text{N}^+_{\text{R}^2} \\
\text{R}^1 
\end{bmatrix} \rightarrow \begin{bmatrix}
\text{R}^3_{\text{Y}} \text{N}^+_{\text{R}^2} \\
\text{R}^1 
\end{bmatrix} \\
\text{N-ylides, } \text{Y} = \text{CHR}^4
\end{align*} \]

\[ \begin{align*}
\text{R}^3_{\text{Y}} \text{N}^+_{\text{R}^2} &\rightarrow \begin{bmatrix}
\text{R}^3_{\text{Y}} \text{N}^+_{\text{R}^2} \\
\text{R}^1 
\end{bmatrix} \rightarrow \begin{bmatrix}
\text{R}^3_{\text{Y}} \text{N}^+_{\text{R}^2} \\
\text{R}^1 
\end{bmatrix} \\
\text{N-oxides, } \text{Y} = \text{O}
\end{align*} \]
1.2.2 Competing Reactions

The Hofmann and Cope eliminations of quaternary ammonium salts and N-oxides (Figure 1.4) containing a beta-hydrogen atom can interfere with other rearrangements. The Hofmann elimination may compete with N-ylide generation when the prevalent technique of ylide generation by the removal of an alpha-hydrogen with a strong base is used. The elimination may be prevented by selection of the appropriate base and incorporation of an electron-withdrawing group (R\(_4^4\)) to provide an acidic alpha-hydrogen. The Cope elimination requires a five-membered transition state and may not be possible from many rigid systems.

\[
\begin{align*}
\text{Hofmann elimination products} & \quad \text{Cope elimination products} \\
\text{Hofmann elimination products} & \quad \text{Cope elimination products}
\end{align*}
\]

The Sommelet-Hauser rearrangement\(^{13}\) (Figure 1.5) often competes with the Stevens rearrangement of benzylammonium salts and under the appropriate conditions may provide the major product. Non-polar solvents and increased reaction temperatures favour the Stevens rearrangement.\(^9\) The rearrangement provides migration of a group to the ortho position of the benzene ring. The mechanism may involve a concerted [2,3] shift followed by aromatisation.
The Sommelet-Hauser rearrangement has been exploited for the synthesis of medium-sized heterocycles.\textsuperscript{14,15,16} For example, the rearrangement of the 2-aryl heterocycles 1 afforded the benzaza-derivatives 2. Derivatives of the 2,5-benzoxazocine\textsuperscript{17} and 5,2-benzoxazonine\textsuperscript{18} systems were obtained in a similar manner.

1.2.3 Ring Expansion via [1,2] Rearrangements

[1,2] Rearrangements have provided the one atom expansion of simple 4-, 5-, and 6-membered heterocyclic rings. The initial investigations of pyrrolidine and piperidine salts\textsuperscript{9} and N-oxides\textsuperscript{19,20,21} showed that beta-aryl substituents were necessary to prevent the prevalence of eliminations or non-expansive rearrangements, however, beta-unsubstituted azetidinium\textsuperscript{22} salts and unsaturated pyrrolidine derivatives\textsuperscript{23} underwent ring expansion readily. The relief of ring strain promoted the ring expansion in the latter cases. Recently the Meisenheimer rearrangement was used...
to provide access to 1,5,2-dioxazine\(^{24}\) and 1,6,2-dioxazepine\(^{25}\) derivatives from the appropriate 5- and 6-membered cyclic N-oxide precursors.

The Meisenheimer rearrangement has afforded access to a number of benz-fused heterocycles. The 2,3-benzoxaza medium ring heterocycles 4 were obtained in high yields from the 1-phenyl-2-benzaza precursors 3.\(^{26,27}\) Rearrangement without the additional 1-phenyl substituent provided a lower yield and substantial deoxygenation.\(^{28}\) Replacement of the benzene ring of 3 (\(n = 1\)) by [2,3]indolo, [3,2]thieno or [2,3][1]benzothieno moieties\(^{29}\) provided the respective analogues of 4 (\(n = 1\)). The Meisenheimer rearrangement was also extended to the production of the benzodioxaza derivatives\(^{30}\) 5 and benzodiaza derivatives\(^{31,32}\) 6.

The Stevens rearrangement has provided few benz-fused medium-sized aza heterocycles. The N-allyl salts\(^{33}\) 7 rearranged to the 3-benzazonine and 3-benzazecine derivatives 8 in good yield. Otherwise only the metacyclophane\(^{34}\) 9 and the 3-benzazecine\(^{35}\) 10 were reported to be produced by the Stevens rearrangement. These compounds were observed as minor byproducts during investigations of the Sommelet-Hauser rearrangement.
1.3 Introduction to [2,3] Rearrangements

The [2,3] rearrangements of sulfur-ylides have attracted considerable interest and are now an established technique for the formation of C-C bonds\(^{10,36}\). The [2,3] rearrangements of \(N\)-ylides and \(N\)-oxides have attracted less interest, although they are well documented in acyclic cases\(^{10}\). The rearrangement may provide a three atom ring expansion from a precursor with both the vinylic and anionic groups exocyclic to the original ring (Figure 1.2). Two reviews examining the production of medium rings via [2,3] sigmatropic rearrangements are available\(^{10,37}\). The reaction has found particular application to the synthesis of macrocyclic sulfur heterocycles by a series of [2,3] shifts\(^{38,39}\).

1.3.1 Mechanism

A concerted mechanism is currently accepted for the [2,3] rearrangement. The high regio-, diastereo- and enantioselectivities observed in these rearrangements, and the lack of evidence for other mechanisms, led to the proposition of a concerted symmetry-allowed\(^{40}\) transition state (Figure 1.6, shown for \(N\)-ylides). The rearrangement is thermally allowed via suprafacial-suprafacial attack of the ylide on
the allylic group. Six electrons participate from the olefin \( \pi \)-orbital, the carbanion, and the N-C \( \sigma \)-bond of the precursor.

![Diagram](image)

**Figure 1.6**

### 1.3.2 Ring Expansion via [2,3] Sigmatropic Rearrangements

The [2,3] rearrangement of small-ring \( N \)-ylides has allowed access to medium-sized heterocycles. The 2-vinylpyrrolidine\(^{41} \) and piperidine\(^{42} \) salts 11 provided the azocine and azonine products 12 in high yields. Mixtures of the \( E \) and \( Z \) geometric isomers were obtained. The \( E/Z \) ratio was dependent on both the ring size and the stereochemistry of the initial salts. These factors were postulated to alter the preferred transition state geometry and thus the product ratio. Rearrangement of a carbanion generated \( \alpha \) to an amide nitrogen, rather than an \( N \)-ylide, produced ring expansion\(^{43} \) of the highly strained 4-vinyl-2-azetidinone 13 to the seven-membered lactam 14.
The ethynyl group may replace the vinyl group in [2,3] sigmatropic rearrangements. This type of rearrangement afforded ring expansion of the ethynylpiperidine N-ylide derivatives 15 to the unstable allenic azonines\textsuperscript{44} 16 in moderate yields. The allenic products may in some cases undergo rapid isomerisation to stable conjugated dienes prior to isolation. Thus rearrangement of the N-imides analogous to 15 gave conjugated trienes directly.\textsuperscript{44}

\[
\text{Me}^+ \text{CH}_2\text{CO}_2\text{Et} \quad \text{Br}^- \quad \text{DBU} \quad \text{THF} \quad \text{R} = \text{Me, n-Bu, Ph} \n\]

Although the 1-vinylisothiochroman\textsuperscript{45} S-imide 17 and 1-ethynylisothiochroman\textsuperscript{46} S-ylides 19 are known to undergo [2,3] rearrangements to the medium-sized benz-fused derivatives 18 and 20, the similar [2,3] rearrangements of N-ylides to benz-fused nitrogen-containing heterocycles have not been investigated. Much scope remains for investigations in this field.

\[
\text{Me}^+ \text{CH}_2\text{CO}_2\text{Et} \quad \text{R} = \text{Me, n-Bu, Ph} \n\]

Few attempts have been made to develop the ring expansion of allylic N-oxides via [2,3] rearrangement. An examination of the rearrangements of 2-
vinylpiperidine \(N\)-oxides\(^{47,48}\) found that only the 1,2-oxazepine derivatives were formed via the Meisenheimer rearrangement. This behaviour, in contrast to that of 13 (\(n=2\)), suggested the [2,3] shift was less favourable for \(N\)-oxides. Two successful cases were, however, reported from more complex ring systems containing allylic \(N\)-oxides. The catharanthine \(N\)-oxide 21 rearranged quantitatively\(^{49}\) to 22 at 40°C. The azetopyrido[3,4-\(b\)]indole 23, upon treatment with \(meta\)-chloroperoxybenzoic acid (\(m\)-CPBA) at 0°C in dichloromethane, gave\(^{50,51}\) the oxazepine derivative 24 in high yield via the preferential formation and rearrangement of the \(N\)-oxide with the oxygen and vinyl moieties \(cis\) to each other in the azetidine ring.

\[
\text{C}_{21} \quad R = \text{CO}_2\text{Me}, \text{CH}_2\text{O}_2\text{CMe}
\]

\[
\text{C}_{22} \quad \text{Me}
\]

\[
\text{C}_{23} \quad R = \text{H}, \text{Et}
\]

\[
\text{C}_{24} \quad \text{MeO}_2\text{C}
\]

1.4 Introduction to a Cyclopropylcarbinyl Rearrangement

Cyclopropylcarbinyl radicals are known to undergo rapid ring opening to give homoallylic radicals. It was thus proposed that the incorporation of a cyclopropyl group would allow the modification of the Meisenheimer or Stevens rearrangements and a four atom ring expansion (Figure 1.2) via a diradical mechanism (Figure 1.7). A concerted mechanism may also be possible.
A single report\textsuperscript{52} of an acyclic rearrangement of this type was revealed in the literature. The rearrangement conditions were not specified. Thermal treatment of the N-oxide \textsuperscript{25} provided mainly deoxygenation with the hydroxylamine \textsuperscript{26} isolated in low yield. No further investigations of this rearrangement are known. An examination of the Sommelet-Hauser rearrangement\textsuperscript{53} of N-ylides did, however, indicate that the cyclopropyl group could promote the reaction in the same way as an allylic double bond. No products of cyclopropyl ring opening were observed.

A recent report\textsuperscript{54} involved a cyclopropylcarbinyl radical rearrangement and highlighted the potential for the investigation of the rearrangement proposed above. Photolysis of the \(\alpha\)-keto ester \textsuperscript{27} produced the 1,4-diradical which underwent cyclopropylcarbinyl radical rearrangement then radical recombination to give the 7-membered lactone \textsuperscript{28} in 25\% yield.
1.5 Thesis Outline

The results of studies aimed at developing the syntheses of 3-benzazinones and 4,3-benzoxazinones via the [2,3] rearrangements of 1-vinyl isoquinoline-N-ylides and \( N \)-oxides are presented in Chapters 2 and 3 respectively. These investigations form the core of this work.

Further applications of the [1,2] rearrangements in heterocyclic synthesis are examined in Chapter 4. These include the production of an 8-membered ring analogue of the potent benzodiazepine therapeutic Alprazolam\(^{55}\) and epoxy-bridged benzazonine and benzazecine derivatives.

Studies on the development of a four atom ring expansion by the rearrangement of 1-cyclopropylisoquinoline \( N \)-ylides and \( N \)-oxides are presented in Chapter 5.
2.1 Introduction

The absence of reported work on the synthesis of benz-fused N-heterocycles by ring expansion technology utilising the [2,3] sigmatropic rearrangement of allylic N-ylides was noted in Chapter 1. In view of this deficiency it was decided to investigate the rearrangements of 1-vinylic-tetrahydroisoquinoline N-ylides (Figure 2.1). It was anticipated that the results of this study would be applicable to the rearrangements of many benz- or other aromatic- ring-fused aza-heterocycles and the development of a new synthetic technique for the production of aromatic ring-fused medium sized aza heterocycles.

The isoquinoline-based system was investigated due to the synthetic accessibility of the necessary 1-substituted tetrahydroisoquinolines and the potential for the development of a new route to highly functionalised 3-benzazonine derivatives. The present methods available for the synthesis of 3-benzazonines are limited and are summarised in Section 2.2. Functionalised 3-benzazonines are desirable as precursors for the synthesis of other 3-benzazonine derivatives and the full evaluation of the pharmaceutical potential of this heterocyclic system. In addition, it was anticipated that the 1-vinylic isoquinoline system would allow the investigation of the competition between the [2,3] and [1,2] rearrangement pathways. It was reasoned that this competition would provide a sensitive indicator of the reaction variables either beneficial or detrimental to the [2,3] rearrangement and aid in the development of this synthetic approach.

In this study it was proposed to investigate, in particular, the effects of the reaction temperature, olefinic substituents, R^{1,2}, and ylide stabilising groups, R^3, on the course of the N-ylide rearrangements (Figure 2.1). The olefinic and ylide
substituents shown were suggested for study. It was anticipated that this series would be modified according to the synthetic accessibility of the required compounds. The olefinic substituents were selected to allow the investigation of stereoelectronic effects on the [2,3] sigmatropic transition state. The ylide substituents were selected primarily to examine the effect of the electron delocalising, and thus radical stabilising, nature of these groups.

**Figure 2.1**

R₁, R₂ from H, Me, Br, I, CN, CO₂Et or Ph.
R₃ from H, CO₂Et, COPh or CN.
2.2 Review of 3-Benzazonines

Derivatives of the 3-benzazonine ring system were first reported upon the degradation of alkaloids from the seeds of *Erythrina* species. The vast majority of the limited subsequent synthetic reports have used the ring destruction of reduced pyrrolo[2,1-α]isoquinolines to provide access to this system. A variety of techniques were developed that provided the necessary heterolytic cleavage of the benzylic C-N bond. The Emde-type reduction of pyrroloisoquinolinium salts with sodium or lithium and liquid ammonia, as exemplified by the conversion of 29 to 30, provided 3-benzazonines in good yields. The similar treatment of the *N*-oxide 31 with an alcohol as the proton source gave the secondary amine 32.

\[
\begin{align*}
29 & \quad R, R_1 = \text{Me, H} \\
& \quad \text{Ph, H} \\
& \quad \text{Ph, OMe} \\
\end{align*}
\]

\[
\begin{align*}
31 & \quad \text{MeO} \\
\end{align*}
\]

Cleavage of the pyrroloisoquinolines 33 was achieved photolytically with concurrent solvolysis, allowing the synthesis of the 7-methoxy or 7-hydroxy derivatives 34. In a similar technique, cyanogen bromide in the presence of a hydroxylic solvent promoted the ring cleavage and solvolysis of the quaternary salts 35 to the 3-carbonitriles 36 in good yields. These induced-solvolysis methods
were extended to the production of benzoxazinone and benzoxacine derivatives in
good yields (Sections 3.2 and 5.2).

\[ R = H, Me \]

The elimination reactions of pyrroloisoquinolinium salts, such as the Hofmann
elimination\textsuperscript{67}, have provided several examples of unsaturated 3-benzazonines. The
chloroformate ester-induced elimination of the 10b-methyl derivative \textsuperscript{37} gave
selectively the exocyclic olefin \textsuperscript{38}.\textsuperscript{62} Cyanogen bromide-induced elimination of the
10b-phenyl derivative \textsuperscript{39} gave \textsuperscript{40}, the only reported 2,3,4,5-tetrahydro-1H-3-
benzazonine.\textsuperscript{68}
Only three reports have appeared on accessing the 3-benzazonine system by non-ring destruction methods. The N-chloroacetamide 41 cyclised on photolysis in low yield. The scope of this reaction appears limited. Similarly, ring expansion of the secondary amino acid 43 gave the 1,2-dihydro-3-benzazonine 44 in only low yield. The Stevens rearrangement afforded the successful ring expansion of the 2-benzazocines 45 to the 3-benzazonines 46 in good yield.29

\[
\begin{array}{c}
\text{MeO} \quad \text{MeO} \\
\text{(CH}_2)_4 \\
\text{NH} \\
\text{COCH}_2\text{Cl} \quad \text{hv, MeCN} \\
\text{MeO} \quad \text{MeO} \\
41 \quad 42
\end{array}
\]

\[
\begin{array}{c}
\text{NH} \\
\text{COOH} \\
\text{HC}=\text{CCO}_2\text{Me} \\
(\text{CH}_2=\text{O})_n \\
\text{Toluene 100°C} \\
\text{MeCOOH} \\
\text{CO}_2\text{Me} \\
43 \quad 44
\end{array}
\]

\[
\begin{array}{c}
\text{Me} \\
\text{N} \\
\text{R} \\
\text{Br}^- \\
\text{NaNH}_2/\text{NH}_3 (l) \\
\text{R} = \text{CH}=\text{CH}_2 \text{ or } \text{Ph} \\
\text{R}_1 = \text{H} \text{ or } \text{Me} \\
\text{R} \quad \text{Me} \\
\text{R}_1 \\
45 \quad 46
\end{array}
\]

2.3 Rearrangement of 2-Ethoxycarbonylmethyl-1-vinyltetrahydroisoquinoline Derivatives

A preliminary investigation of the rearrangement of simple 1-vinyltetrahydroisoquinolines N-ylides was conducted in the presence of an ester ylide stabilising group. The N-ylides were derived from N-methyl derivatives by
deprotonation with base. The ester ylide stabilising group was adopted as the 'standard' ylide substituent throughout this work due to its synthetic availability, via the N-alkylation of the appropriate amines with ethyl bromoacetate, and the acidity of the methylene protons of the N-ethoxycarbonylmethylene group. The rearrangement was investigated with both N-methyl and N-benzyl derivatives. The latter system was investigated for the purpose of examining the subsequent hydrogenolysis of any N-benzyl-3-benzazonines formed, a reaction which would provide access to 3-benzazonines with the synthetically useful secondary amino group present.

2.3.1 Synthesis of the Precursor Quaternary Salts

The 3,4-dihydroisoquinoline 47 was prepared by a modification of the standard Bischler-Napieralski cyclisation technique\textsuperscript{71} and then converted to the iminium halides 48. Conducting the Grignard reaction of 48a with vinylmagnesium bromide by the conditions published\textsuperscript{72} for the reaction of vinylmagnesium bromide with 6,7-methylenedioxy-3,4-dihydroisoquinolinium iodide, involving refluxing in tetrahydrofuran, gave the 1-vinylisoquinoline 49a in only 38\% yield. A 1:1 mixture of the isomeric 6-hydroxy-7-methoxy- and 7-hydroxy-6-methoxy-2-methyl-1-vinyl-1,2,3,4-tetrahydroisoquinoline compounds was also isolated in 31\% yield. This mixture was identified by spectroscopic means and by conversion to 49a on reaction with diazomethane. Conducting the Grignard reaction at low temperature avoided the O-demethylation. Thus, adding 48 to a solution of four equivalents of the Grignard reagent in tetrahydrofuran at low temperature (≤-50°C) then stirring the mixture for 10-20 hours with warming to room temperature provided, after workup, the 1-vinylisoquinolines 49 as crystalline solids in high yields.

Compounds 49 were fully characterised by elemental analysis and spectroscopic techniques. The presence of the 1-vinyl group was clearly indicated by a base peak at (M-27)\textsuperscript{+} in the mass spectrum and a set of characteristic signals in the \textsuperscript{1}H and \textsuperscript{13}C NMR spectra (Figure 2.2).
Alkylation of 49 with ethyl bromoacetate at room temperature provided, in good yields, the quaternary amine salts 50 as hygroscopic solids. The alkylation of 49a proceeded very rapidly in neat ethyl bromoacetate, while the alkylation of 49b at room temperature required nineteen days for the satisfactory conversion of 49b to 50b. Although this reaction was very slow a clean crystalline product was obtained. The attempted quaternization of 49b at elevated temperatures, or with ethyl iodoacetate in acetonitrile, provided either no reaction or degradation of the amine to highly coloured material.

The quaternary salts 50 were mixtures of the possible trans and cis B-ring diastereomers and were identified primarily by NMR analyses. The $^1$H NMR spectra
of the diastereomeric mixtures were complex and difficult to interpret, however, the 13C NMR spectra afforded rapid confirmation of the proposed structures. Two-dimensional COSY experiments and the examination of materials containing different levels of the trans and cis isomers enabled the assignment of the respective NMR signals for the isomers of 50a (Table 2.1). The proportions of the isomers were determined by comparing the 1H NMR peak areas of the corresponding protons. A considerable preference, approximately 2.3-3:1, was observed for the formation of one isomer at room temperature.

![Diagram of chemical structure](image)

50a: R = Me 70:30 dr  
b: R = Bz 75:25 dr

<table>
<thead>
<tr>
<th>Table 2.1 NMR Shifts of the Trans and Cis Diastereoisomers of 50a</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1H NMR</strong></td>
</tr>
<tr>
<td>H1</td>
</tr>
<tr>
<td>H1'</td>
</tr>
<tr>
<td>H2'</td>
</tr>
<tr>
<td>H2</td>
</tr>
<tr>
<td>NCH2CO</td>
</tr>
<tr>
<td>NCH2CO</td>
</tr>
<tr>
<td>NCH3</td>
</tr>
<tr>
<td>H3</td>
</tr>
<tr>
<td>H8</td>
</tr>
</tbody>
</table>

The quaternization of 1-substituted-1,2,3,4-tetrahydroisoquinolines was reported73,74 to proceed preferentially by attack trans to the 1-substituent. The chemical shifts of the N-methyl groups on the resultant trans 2-alkyl-2-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinolinium salts were upfield of the cis isomers. As the
major isomer of $50a$ exhibited a chemical shift for the $N$-methyl protons upfield of that for the minor isomer (3.55 δ cf. 3.70 δ), the major isomer was assigned the trans configuration. This assignment was supported by experiments which confirmed that the $N$-methyl group in the trans-$N$-oxide $128a$ had a chemical shift upfield of the cis-$N$-oxide. Definitive assignment of the identity of the diastereomers of $50a$ was sought, however, as piperidine derivatives were reported to undergo $N$-alkylation preferentially by axial approach of the alkylating agent, a process which would provide predominantly the cis isomer of $50$ by alkylation of the low energy conformer of $49$ with the vinyl group equatorial. Nuclear Overhauser experiments were conducted on $50a$ but the complexity of the proton spectra prevented the confident assignment of the interactions observed. Similar experiments on the methiodide salt $54a$ failed to determine conclusively the position of the $N$-methyl signals cis and trans to the vinyl group. Compound $54a$ was only slightly soluble in the common deuterated solvents and residual non-deuterated solvent peaks interfered with the $N$-methyl signals.

As the trans and cis $N$-ylides of many heterocyclic systems undergo contrasting sigmatropic rearrangements the separation of the diastereomers of $50a$ was attempted. Recrystallisation of a diastereomeric mixture of $50a$ was examined. It was hoped that the trans isomer would be enriched in the crystalline solid. Recrystallisation of $50a$ (trans/cis=1.70) from ethanol/tetrahydrofuran instead provided a crystalline solid (62%, trans/cis=1.33) and mother liquor (trans/cis=0.67) in which both were depleted in the trans isomer. Recrystallisation of the first crop provided a similar result with the level of the trans isomer reduced in both the crystalline solid (65%, trans/cis=1.12) and mother liquor (trans/cis=0.60). These results were replicated over several experiments and indicated a mechanism for the conversion of trans-$50a$ to cis-$50a$ existed, with the cis isomer favoured as the thermodynamic product. The interconversion of the isomers was rationalised by proposing a reversible $N$-dealkylation promoted by the bromide ion.
The selectivity of the $N$-alkylation of 49a in neat ethyl bromoacetate was examined. The reaction was temperature dependent, but neither diastereomer could be produced selectively. At $-15^\circ C$ and $110^\circ C$ respectively 4:1 and 1:1 mixtures of trans and cis-50a were obtained. It was reasoned that the elevated temperature increased the population of a high energy conformer of 49a, from which the cis isomer was formed by attack with the alkylating agent. The reaction of 49a with ethyl bromoacetate in acetonitrile at room temperature afforded a precipitate which was found to be enriched in trans-50a ($trans/cis=9.0$) to a degree sufficient for the analysis of later rearrangements.

2.3.2 Modelling of the Concerted Transition States

The concerted transition states possible for the $N$-ylides 51 and the analogous $N$-oxides 123 were modelled to predict: (i) whether the cis and trans isomeric salts could both attain a concerted transition state, (ii) the likely stereochemistry of any concerted rearrangement products, and (iii) the effect, if any, of substituents on the allylic group.

Two types of conformers were identified for each diastereomer of 51 by consideration of the normal axial/axial, equatorial/equatorial, and axial/equatorial arrangements of the low-energy distorted chair conformation for the isoquinoline ring. An additional criterion, the rotation of the 1-vinyl group, provided four conformational minima for each diastereomer of 51 (Figure 2.3). Clearly, the axial/axial trans-systems I and II were unsuitable for the formation of a five-centre concerted transition state. The energy and geometry of the remaining conformers III-VIII were modelled using PCModel (Table 2.2), a molecular mechanics based computer modelling system.76 The cis-conformer V, in which the ylide component was axial, possessed both the lowest energy and the lowest minimum distance between the ylide carbanion and C2', making this the most favoured conformation for a concerted rearrangement. The trans-conformer III by comparison attained a less favourable geometry. As III was not significantly different to the structure achievable
in the trans-2-vinylpiperidine-N-ylides, which were reported\textsuperscript{42} to undergo the [2,3] rearrangement, it was proposed that both the cis and trans diastereomers of 51 would undergo the [2,3] sigmatropic rearrangement. It should be noted, however, that the PCMModel studies were for the molecules \textit{in vacuo} and no solvent interactions were modelled.

Table 2.2 Data from PCMModel for the N-Ylide Conformers of 51a

<table>
<thead>
<tr>
<th>Structure</th>
<th>H\textsubscript{f}\textsuperscript{a}</th>
<th>D\textsubscript{X-C2'}\textsuperscript{b}</th>
<th>min.D\textsubscript{X-C2'}\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td>1.36</td>
<td>3.56</td>
<td>2.90</td>
</tr>
<tr>
<td>IV</td>
<td>1.75</td>
<td>3.89</td>
<td>-</td>
</tr>
<tr>
<td>V</td>
<td>0.00</td>
<td>3.98</td>
<td>2.55</td>
</tr>
<tr>
<td>VI</td>
<td>1.06</td>
<td>3.63</td>
<td>2.63</td>
</tr>
<tr>
<td>VII</td>
<td>1.98</td>
<td>3.32</td>
<td>-</td>
</tr>
<tr>
<td>VIII</td>
<td>2.28</td>
<td>3.72</td>
<td>-</td>
</tr>
</tbody>
</table>

\textsuperscript{a} energy above that of V at H\textsubscript{f}=79.58 (kcal)
\textsuperscript{b} distance from C\textsubscript{-} to C\textsubscript{2'} at the energy minimum (Å)
\textsuperscript{c} the minimum distance between C\textsubscript{-} to C\textsubscript{2'} upon rotation of C1-C1' (Å)

The configuration of the developing olefinic bond and stereoselectivity of the [2,3] sigmatropic rearrangement of \(\alpha\)-substituted-allylic-N-ylides was discussed by Marko.\textsuperscript{10} The five-centred transition state was assumed to adopt a conformation similar to the 'folded envelope' conformation of cyclopentane. In this system the \(E\)-isomer will be formed if the \(\alpha\)-substituent is in a psuedo-equatorial position, and the \(Z\)-isomer if the \(\alpha\)-substituent is psuedo-axial (Figure 2.4). Following this technique the conformers III-VIII were assigned as pro-\(E\) or pro-\(Z\) structures (Figure 2.3).

These results clearly indicated that the major products of the \(N\)-alkylation, the \textit{trans}-salts 50, would undergo base promoted concerted rearrangements stereoselectively to the \(E\) double bond derivatives via the conformers III and IV. The stereoselectively of the [2,3] rearrangement of the \textit{trans}-salts, although possibly not the rearrangement type, would be independent of the substituents present on the vinyl
Figure 2.3 Conformational minima for 1-vinylisoquinoline N-ylides 51 (X=CHR) and N-oxides 123 (X=O). The 6,7-methoxy groups are omitted for clarity.

Figure 2.4 Folded cyclopentane geometry of the allylic-N-ylide (Y=NR₂) transition state.
group. The cis-salts of 50 were also expected to undergo preferentially a [2,3] rearrangement to the E-benzazonines, as the lower energy pro-E conformers, particularly V in which the equatorial nature of the vinyl group was maximised, would predominate over the higher energy pro-Z conformers.

After consideration of the conformers V and VII it was proposed that a substituent on the olefinic group at Cl' would reverse the relative energies of these conformers, allowing access to significant amounts of the Z-benzazonine derivatives from the cis-salts. The bulky Cl' substituents in the cis-salts could be accommodated preferentially in the equatorial position provided by conformer VII. This proposal was supported by modelling several Cl'-substituted-N-ylide derivatives in conformations analogous to V and VII (Figure 2.5).

![Figure 2.5 The energy difference between conformer types V and VII with Cl' substituents (R)](image)

2.3.3 Formation and Characterisation of 3-Benzazonine Derivatives

The detection of all possible rearrangement products from this rearrangement, and others examined in this work, was ensured by an initial purification to a 'rearranged fraction', containing the non-polar compounds which eluted rapidly through an alumina column with dichloromethane/20% light petroleum. This fraction was then analysed by t.l.c., NMR and GC-MS techniques. Where mixtures were present the proportions of the compounds were determined from 1H NMR peak areas. Residual polar salts were retained on the column while traces of the precursor bases 49, if present, generally eluted with dichloromethane/5% light petroleum.
Treatment of the 1-vinylisoquinolinium compounds 50 in acetonitrile at room temperature with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), a non-nucleophilic base, gave the [2,3] sigmatropic rearrangement products, the 2,3,4,5-tetrahydro-1H-3-benzazonines 52, in excellent yields (Table 2.3). The rearrangement was assumed to proceed via the allylic-N-ylides 51. The E-benzazonines were obtained almost stereoselectively, as predicted (Section 2.3.2). The N-benzyl derivative E-52b was a colourless oil which required no further purification as the Z-isomer was not detected. In contrast, NMR analysis of the N-methyl benzazonine fraction 52a revealed the presence of a minor amount of the Z-isomer (E/Z ratio = 19). The isomers of 52a were separated to give E-52a as a colourless waxy solid and Z-52a as a colourless oil. The structures were confirmed primarily by spectroscopic means. All data was consistent with the proposed structures.

Over a temperature range between -40°C and 82°C the rearrangement products from 50a were almost unchanged (Table 2.3), with the [2,3] sigmatropic rearrangement occurring preferentially. The results confirmed the anticipated low energy requirement of the [2,3] concerted pathway when compared to the diradical mechanism of the [1,2] rearrangement. At the highest temperature the Stevens rearrangement product, the 1-vinyl-3-benzazepine 53a, was observed in low yield. The stereoselectivity of the [2,3] rearrangement was slightly reduced at high temperature (E/Z = 10.0). At -40°C the reaction was complete in six hours. The rearrangement of 50a to 52a proceeded satisfactorily in tetrahydrofuran, however, the precursor salts were only partially soluble in this solvent. Acetonitrile was used subsequently.

The observed stereoselectivity of the [2,3] rearrangement was rationalised in Section 2.3.2. The yields of 52 apparently confirmed that both the diastereomeric salts of 50 could undergo the concerted rearrangement. However, in one reaction of 50a (trans/cis=3.0) where DBU was the limiting reagent (0.7 equivalents) the alumina
Table 2.3 Rearrangement Conditions and Products from 50

<table>
<thead>
<tr>
<th>Reactant</th>
<th>Reaction Temp (°C)</th>
<th>Total % Yielda</th>
<th>Product Distributionb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50a</td>
<td>-40</td>
<td>86</td>
<td>E-52 95, Z-52 5, 53 -</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>90</td>
<td>E-52 95, Z-52 5, 53 -</td>
</tr>
<tr>
<td></td>
<td>82</td>
<td>70</td>
<td>E-52 87, Z-52 9, 53 4</td>
</tr>
<tr>
<td>50b</td>
<td>25</td>
<td>93</td>
<td>E-52 100, Z-52 - 53 -</td>
</tr>
</tbody>
</table>

a yield to a non-polar rearranged fraction
b from $^1$H NMR integrals

column was stripped with ethanol and the residual salts examined. The cis diastereomer of 50a was recovered exclusively, suggesting either a substantial difference in the reaction rates of the diastereomeric salts or the rapid interconversion of trans-50a to cis-50a by reversible deprotonation at the benzylic Cl position. The interconversion of $\alpha$-vinyl-S-allyl sulfonium salts$^{39,42}$ by DBU is known, while conversion of trans-50a to cis-50a occurred during the recrystallisation of 50a.
(Section 2.3.1). Thus the [2,3] rearrangement could conceivably have occurred solely via cis-50a. Some support for this proposition was provided by the observation that, although a variety of diastereomeric mixtures of 50a (from trans/cis=9.0 to trans/cis=1.0) were rearranged in this work, the product ratio of E to Z-52a was constant. The accuracy of the measurement technique, using $^1$H NMR integrals with low levels of the Z-isomer, however, suggests caution in the interpretation of these results.

The $^1$H NMR (Figures 2.6 and 2.7) and $^{13}$C NMR (Figure 2.8) spectra of E and Z-52a were assigned unambiguously by nuclear Overhauser and two dimensional homo- and heteronuclear decoupling experiments. The magnitude of the H6-H7 coupling constant gave the identification of each isomer. Compound E-52a displayed a doublet for H7 at 6.43 $\delta$, with a coupling constant of 16.1 Hz, while the Z-52a isomer displayed a doublet for H7 at 6.67 $\delta$, with a coupling constant of 10.7 Hz.

The assignment of the isomers was confirmed by a nuclear Overhauser effect (nOe) between H5 and H7 for E-52a, and not Z-52a, and the upfield position of C5 at 32.63 $\delta$, compared to 36.32 $\delta$, in the Z-isomer. The 3-benzazonines displayed characteristic multiplets at 5.8-5.5 $\delta$ and 3.6-3.4 $\delta$, for H6 and H4, and two olefinic $^{13}$CH peaks between 135-130 $\delta$ for C6 and C7.

The mass spectra of 52 displayed a base peak at M-73 as the only prominent ion, apart from the benzyl ion at m/z 91 for 52b. The base peak was consistent with the loss of the ethoxycarbonyl side chain and formation of a cyclic iminium ion.

Substantial difficulties were encountered in this work with the separation and purification of the E and Z 3-benzazonine isomers. Although analytical t.l.c. demonstrated separation of the isomers of 52a the E-benzazonine was degraded by p.t.l.c. or column chromatography on silica, with the formation of polar material. The Z-benzazonine was, however, recovered successfully. Analysis of the $^1$H NMR spectrum of the polar material indicated several quaternary salts were formed by the degradation of E-52. It was proposed that the pyrrolo[2,1-a]isoquinolinium salts 54,
Figure 2.6 $^1$H NMR spectrum and assignments for the E-isomer of 52a in CDCl$_3$
Figure 2.7 $^1$H NMR spectrum and assignments for the Z-isomer of 52a in CDCl$_3$. 
were formed by a transannular reaction of the nitrogen and olefin groups under the acidic conditions. Attempted purification of 52a by p.t.l.c. on alumina, or silica slurried with 0.5M potassium hydroxide, however, also resulted in the degradation of E-52a.

With the failure of the standard chromatographic techniques to provide purified E-52a, several alternative methods of purification were examined. Sublimation under high vacuum at 95°C proved an effective means for providing highly purified 52a,
but the product, a colourless waxy solid (m.p. 90-92°C), remained a mixture of the isomers.

The reverse phase HPLC analysis of 52a on a C18 column with an unbuffered system of acetonitrile/20% H2O provided baseline resolution of the E and Z isomers. The Z-isomer exhibited a more polar nature and eluted prior to the E-isomer. The method was scaled-up to a semi-preparative scale (50-100 mg applications) and successfully provided the pure E and Z isomers of 52a, with an excellent recovery of material. The isolated yields were in agreement with the proportions determined by 1H NMR analysis. Modifications of this preparative HPLC method were invaluable for the isolation of the isomeric, often unstable, unsaturated 3-benzazonines, or other medium-ring heterocycles, produced from the various rearrangements throughout this work.

The present results clearly indicated the rearrangement of 2-ethoxycarbonylmethyl-1-vinylisoquinoline-N-ylides 51 could provide a good route to 2,3,4,5-tetrahydro-1H-3-benzazonine derivatives.

2.3.4 Conformational Modelling of 2,3,4,5-Tetrahydro-1H-3-Benzazonines

The large difference in the stability of the E and Z-isomers of 52a reflected differences in the ring strain incurred by the double bond. The inclusion of a E double bond in a medium-ring heterocycle would be expected to become difficult as the ring size decreases. Derivatives of the eight-membered azacyclooct-4-ene system41 exhibited a similar behaviour to the tetrahydro-3-benzazonines with the E-isomers, but not the Z-isomers, degraded on silica gel. Derivatives of the larger nine-membered E-azacyclonon-4-ene system42 were stable on silica, indicating that, as expected, the fused aromatic ring of E-52a must also contribute to ring-strain. Hand-held models confirmed E-52a would experience substantial ring strain.

The conformations available to the parent E- and Z-2,3,4,5-tetrahydro-1H-3-benzazonines were investigated with PCModel.76 It was envisaged that a knowledge
of these conformers would aid in the rationalisation of the chemical behaviour and the possible CNS activity of derivatives based on these systems. It should be noted that substituents on these parent derivatives, such as the $N$-methyl and 4- groups of 52a, would be expected to affect the relative energies and populations of these conformers. It was assumed, however, that the global minimum would still be based on one of the identified conformers.

Five low energy conformations were identified for each of the $E$- and $Z$-2,3,4,5-tetrahydro-1$H$-3-benzazonines (Tables 2.4 and 2.5). The structures which are not shown in either Figures 2.9, 2.11 or 2.12 are included in Appendix A. The Boltzmann distribution afforded the expected populations of the respective conformers at 293 K. The relative positions of the aromatic and nitrogen moieties were calculated to describe each conformer.

The five conformers identified for the parent $E$-benzazonine were within 3 kcal of the global minimum (Table 2.4). Conformer 1 (Figure 2.9) would be predominant (85%) at room temperature, however, any of the five conformers could contribute significantly to the chemical and potential CNS activity. These conformers generally possessed structures in which the medium ring adopted a non-folded, planar, conformation, as expected for a medium-ring incorporating a trans-double bond. In conformers 1, 3, and 4 the nitrogen atom was only slightly removed (< 0.8 Å) from the plane of the aromatic ring. The $E$-benzazonine system therefore may be useful as an alternative to other ring systems, such as that in the serotonin receptor ligands (+)-lysergic acid diethylamide (LSD) and R-(−)-10-methyl-11-hydroxyaporphine (MHA) (Figure 2.10), which constrain the nitrogen atom near the aromatic ring plane by a composite of small rings. In support of the proposed transannular degradation of $E$-52a to 54 both conformers 1 and 2 possessed structures in which the nitrogen and C7 olefin atoms were in close proximity.

The $^1H$ NMR analysis of the 3,4,5-trisubstituted-3-benzazonine $E$-87b (pg. 63-64) in chloroform suggested that conformer 4 (Figure 2.9) was adopted by the $E$-benzazonine system in this relatively non-polar solvent.
Figure 2.9 Three perspectives of (a) conformer 1 and (b) conformer 4 for the
E-benzazonine system
Table 2.4  Low energy conformations of the E-benzazonine system

<table>
<thead>
<tr>
<th>conformer</th>
<th>E (kcal)</th>
<th>(H_f)</th>
<th>Population(^a)</th>
<th>(N)-elevation(^b)</th>
<th>(N)-Ar planar(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34.02</td>
<td>47.92</td>
<td>85.3%</td>
<td>0.74</td>
<td>4.73</td>
</tr>
<tr>
<td>2</td>
<td>35.48</td>
<td>47.69</td>
<td>7.3%</td>
<td>1.49</td>
<td>4.24</td>
</tr>
<tr>
<td>3</td>
<td>35.90</td>
<td>49.28</td>
<td>3.6%</td>
<td>0.79</td>
<td>5.08</td>
</tr>
<tr>
<td>4</td>
<td>36.22</td>
<td>48.50</td>
<td>2.0%</td>
<td>0.70</td>
<td>4.95</td>
</tr>
<tr>
<td>5</td>
<td>36.31</td>
<td>50.57</td>
<td>1.8%</td>
<td>2.09</td>
<td>3.72</td>
</tr>
</tbody>
</table>

\(^a\) from the Boltzmann distribution at 293 K
\(^b\) distance of \(N\) above the aromatic plane (Å)
\(^c\) distance of \(N\) from the aromatic centre in the aromatic plane (Å)

Figure 2.10 Several CNS active agents with constrained phenylethylamine components

Of the five lowest energy conformers identified for the parent Z-benzazonine system three were within 1 kcal of the global minima (Table 2.5). These conformers (Figures 2.11 and 2.12) may all be significantly populated at room temperature, however, only one conformer of Z-52a was observed on NMR analysis. It was assumed that solvent or substituents effects had produced a preference for one of these conformers. The X-ray crystallographic analysis of the 3,4,6-trisubstituted Z-benzazonine Z-75b (Figure 2.14, pg. 53) confirmed that a structure based on conformer 1 was adopted in the solid state for the Z-benzazonine system.

The low energy conformers identified for the Z-benzazonine system were comparatively folded structures, with the nitrogen atom displaced from the aromatic
plane by 1.7-2.4 Å. The Z-benzazonine system therefore may be useful as an alternative to other ring systems, such as that of morphine\(^6\) (Figure 2.10), which place the nitrogen atom out of the aromatic ring plane.

Table 2.5 Low energy conformations of the Z-benzazonine system

<table>
<thead>
<tr>
<th>conformer</th>
<th>E (kcal)</th>
<th>H(_f)</th>
<th>Population(^a)</th>
<th>N-elevation(^b)</th>
<th>N-Ar planar(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27.35</td>
<td>41.16</td>
<td>61.3%</td>
<td>1.75</td>
<td>4.36</td>
</tr>
<tr>
<td>2</td>
<td>27.95</td>
<td>42.30</td>
<td>22.2%</td>
<td>2.24</td>
<td>3.54</td>
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<tr>
<td>3</td>
<td>28.13</td>
<td>42.56</td>
<td>16.4%</td>
<td>2.41</td>
<td>3.04</td>
</tr>
<tr>
<td>4</td>
<td>31.94</td>
<td>45.40</td>
<td>&lt;0.1%</td>
<td>1.91</td>
<td>4.50</td>
</tr>
<tr>
<td>5</td>
<td>32.34</td>
<td>46.22</td>
<td>&lt;0.1%</td>
<td>2.42</td>
<td>2.58</td>
</tr>
</tbody>
</table>

\(^{a}\) from the Boltzmann distribution at 293 K
\(^{b}\) distance of N above the aromatic plane (Å)
\(^{c}\) distance of N from the aromatic centre in the aromatic plane (Å)

Figure 2.11 Three perspectives of conformer 1 for the Z-benzazonine system
Figure 2.12 Three perspectives of (a) conformer 2 and (b) conformer 3 for the Z-benzazonine system
The isomers of 52a were examined exhaustively by NMR techniques, including two-dimensional nOe analysis (NOESY), in an attempt to determine the conformations adopted by these derivatives in solution. The H1 and H2 protons, however, were not resolved to a degree permitting the confident assignment of transannular nOe effects with the H5, H6 or H7 protons, and the conformers of E and Z 52a were not identified.

2.4 Effect of the Ylide Stabilising Group on the [2,3] Rearrangement

2.4.1 Attempted Generation and Rearrangement of N-Methylene Ylides with Lithium Diisopropylamide

Although electron-withdrawing, potentially ylide-stabilising, groups are typically incorporated to facilitate the formation of N-ylides, strong bases have promoted the formation and rearrangement of the unstabilised methylene N-ylides. The reaction of N-benzyl-N-methyl-2-vinylpiperidinium iodide with lithium diisopropylamide (LDA) afforded the [2,3] and [1,2] rearrangement products via a methylene N-ylide. The analogous reactions of the isoquinolinium salts 55 were investigated in this work.

![Chemical structures](image-url)
The $N$-alkylation of 49 with iodomethane afforded 55a,b. Compound 55a exhibited signals for the two $N$-methyl groups at 3.59 and 3.36 $\delta$ in the $^1$H NMR spectrum. The signals were attributed to the $N$-methyl groups occupying the $cis$ and $trans$ positions with respect to the 1-vinyl substituent. Compound 55b was a 54:46 mixture of the B-ring diastereomers.

Treatment of 55 with LDA at -20°C in tetrahydrofuran afforded the Hofmann elimination products, the ring-opened diolefins 56, in good yield. No [2,3] or [1,2] rearrangement products were detected. The spectroscopic characteristics of the diolefins were consistent with the proposed structures. Two-dimensional NMR correlation experiments confirmed the presence of the separate vinylic and allylic moieties of 56.

2.4.2 Rearrangement of an $N$-Methylene Ylide Generated by a Fluoride-Catalyzed Desilylation

Alternatives to the generation of $N$-ylides by the deprotonation of ammonium salts are known. In particular, the direct generation of $N$-ylides from the reaction of a carbene, typically from a diazonium salt, with an amine lone-pair has attracted widespread use. A method for the specific generation of methylene $N$-ylides by the desilylation of trimethylsilylmethyl ammonium salts with cesium fluoride was developed and applied recently in investigations of the Sommelet-Hauser rearrangement. The application of this method to the synthesis of the 4-unsubstituted 3-benzazonine 61, via the methylene $N$-ylide 60, was investigated.

Preparation of the trimethylsilylmethyl ammonium precursor 59 was attempted via treatment of the $N$-methyl amine 49a with iodomethyltrimethylsilane, but without success. Little reaction was observed. It was concluded that the large steric bulk of the alkylating agent prevented access of the reagent to the lone-pair of the tertiary amine. An alternative approach to 59, via the reaction of trimethylsilylmethyl trifluoromethanesulfonate with the secondary amine 57 and alkylation of the resultant trimethylsilylmethyl amine 58 with iodomethane, was examined.
Compound 57 was obtained in moderate yield by the direct action of vinylmagnesium bromide on the imine 47. Other examples of the direct reaction of alkenylmagnesium halides with Schiff's bases of type C₆H₅CH=NR, rather than their iminium salts, are known but are rare. The reaction was conducted in a diethyl ether/tetrahydrofuran mixture as the basicity of tetrahydrofuran was reported to provide reduced yields in reactions of this type, but 47 was insoluble in diethyl ether alone. Reaction at room temperature over 24 hours gave, surprisingly, a 1.4:1.0 mixture of 57 and the N-methyl compound 49a. Subsequent experiments confirmed the formation of 49a reached significant levels only with reaction times above four hours. A reaction time of 3.5 hours afforded 57 in 33% yield free of 49a and eliminated the need for a lengthy purification of 57.
The reaction of trimethylsilylmethyl trifluoromethanesulfonate with 57 in acetonitrile at room temperature afforded 58 in good yield. $^1$H NMR analysis revealed the NCH$_2$Si protons at 2.39 and 1.78 $\delta$ with geminal coupling (14.7 Hz) while the silylmethyl protons absorbed at 0.07 $\delta$. Quaternization of 58 with iodomethane in acetonitrile at 60°C afforded 59, a crystalline solid, as a 51:49 mixture of the cis and trans B-ring diastereomers.

The reaction of 59 with cesium fluoride was conducted in dimethylformamide at room temperature. The method was adapted from that described by Sato et. al.\textsuperscript{a} A single non-polar product was isolated and identified by spectral analyses as the desired [2,3] rearrangement product, the E-2,3,4,5-tetrahydro-1H-3-benzazonine 61 (30% yield). The 4-unsubstituted 3-benzazonine derivative exhibited a $^{13}$C NMR resonance at 61.08 $\delta$ for C4.

A polar solid was also isolated from the reaction of 59 with cesium fluoride. The compound was identified as the $N,N$-dimethyl salt 55a (59% yield), assumed to be formed by the reaction of moisture with the intermediate $N$-ylide 60. The high yield of 55a was surprising as all efforts were made to exclude moisture from the reaction. Time constraints prevented the repetition of the experiment to obtain an improved yield of 61.

2.4.3 Rearrangements of Nitrile and Benzoyl Stabilised $N$-Ylides

Quaternization of the tertiary amine 49a with iodoacetonitrile or phenacyl bromide in butanone at room temperature afforded the isoquinolinium salts 62a,b possessing the electron-withdrawing nitrile and benzoyl groups. Mixtures of the possible B-ring diastereomers were obtained. The stereoselectivity of the reaction was greater to 62b (78:22 d.r.) than 62a (53:47 d.r.). In each case the major isomer exhibited a more upfield shift of the N-methyl signal in the $^1$H NMR spectrum and was assigned the trans-stereochemistry.

The DBU-promoted rearrangements of 62 were examined at a variety of temperatures in acetonitrile. The results are summarised in Table 2.6.
Table 2.6 Rearrangement Conditions and Products from 62

<table>
<thead>
<tr>
<th>Reactant</th>
<th>Reaction Temp (°C)</th>
<th>Total % Yielda</th>
<th>Product Distributionb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>62a</td>
<td>25</td>
<td>84</td>
<td><strong>E-63</strong>: 78, <strong>Z-63</strong>: 16, <strong>64</strong> major: 6, <strong>64</strong> minor: -</td>
</tr>
<tr>
<td></td>
<td>82</td>
<td>62</td>
<td><strong>E-63</strong>: 80, <strong>Z-63</strong>: 8, <strong>64</strong> major: 12, <strong>64</strong> minor: -</td>
</tr>
<tr>
<td>-30</td>
<td>71</td>
<td>84</td>
<td><strong>E-63</strong>: 94, <strong>Z-63</strong>: 6, <strong>64</strong> major: -2, <strong>64</strong> minor: -</td>
</tr>
<tr>
<td>0</td>
<td>84</td>
<td>91</td>
<td><strong>E-63</strong>: 91, <strong>Z-63</strong>: 7, <strong>64</strong> major: 2, <strong>64</strong> minor: -</td>
</tr>
<tr>
<td>25</td>
<td>66</td>
<td>89</td>
<td><strong>E-63</strong>: 89, <strong>Z-63</strong>: 3, <strong>64</strong> major: 8, <strong>64</strong> minor: -</td>
</tr>
<tr>
<td>65</td>
<td>54</td>
<td>-</td>
<td><strong>E-63</strong>: -78, <strong>Z-63</strong>: 78, <strong>64</strong> major: -22, <strong>64</strong> minor: -</td>
</tr>
</tbody>
</table>

a yield of a non-polar rearranged fraction

b from ¹H NMR integrals

The treatment of 62a with DBU at room temperature provided, in high yield, a rearranged fraction which contained three components observed by ¹H NMR analysis. The major component was isolated by preparative reverse-phase HPLC and identified as the E-benzazonine 63a. Compound E-63a exhibited behaviour similar to E-52a and degraded upon silica gel. The two minor components were not isolated but, by analogy with the rearrangement of 50a, were tentatively attributed to Z-63a and the Stevens rearrangement product 64a. Compound Z-63a exhibited a multiplet at 5.69 δ, consistent with H6 of the proposed structure, while 64a exhibited a ¹H NMR
pattern indicative of the 1-vinyl substituent with H1', H2' and H2' assigned to peaks at 6.08, 5.11, and 4.78 δ respectively. The rearrangement of 62a with DBU in refluxing acetonitrile provided a slight increase in the level of the Stevens rearrangement product 64a, however, E-63a remained the dominant product.

The rearrangements of 62b with DBU in acetonitrile were significantly different to those observed from either 50a or 62a. The rearrangement was greatly effected by the reaction temperature. At room temperature the reaction afforded the E-benzazonine 63b as the major product, while at 65°C the B-ring diastereomers of the 3-benzazepine 64b (3.5:1 d.r.) were obtained. A reaction temperature of -30°C was necessary for the completely selective rearrangement of 62b to the isomers of 63b. The selective formation of 64b from 62b at high temperature suggested this compound was the thermodynamic product, with the less strained 3-benzazepine system favoured over the unsaturated 3-benzazonine system. This was confirmed by the conversion of 63b to 64b as described in Section 2.9.4.

The E and Z isomers of 63b were isolated by preparative reverse-phase HPLC and characterised spectroscopically. The isomers, yellow oils which darkened on storage, exhibited identical mass spectra in which the molecular ion was not observed. A base peak at M⁺-105 was consistent with the loss of the benzoyl fragment from the molecular ion. The E-isomer of 63b exhibited two equally populated conformations in the 1H and 13C NMR spectra at 25°C. The conformers reflected hindered rotation of the C4-CO bond, rather than conformational flexibility of the medium-ring. Hand-held models of the 4-benzoyl-E-benzazonine indicated the bulky conjugated benzoyl group would adopt a position with the H4-C4-C-O dihedral angle at either approximately 180° or between 0-30°. The latter angle would place the benzoyl ring over one face of the heterocycle, at 90° to the molecular plane, and produce the downfield shifts of the heterocyclic protons observed in one conformer. Compound E-63b was degraded on silica p.t.l.c.

The diastereomers of 64b could not be separated, however, NMR and MS analyses of a purified mixture were consistent with the proposed structures and
comparable with the other 3-benzazepines prepared in this work. Typical vinyl signals were observed in the NMR spectra. The major isomer of 64b exhibited H1 and H2 at 4.10 and 4.48 δ in the 1H NMR spectrum, while C1 and C2 appeared at 50.33 and 69.18 δ in the 13C NMR spectrum.

2.4.4 Rearrangement of an N-Butyrolactone Salt

The [2,3] or [1,2] rearrangements of allylic bis(methoxycarbonyl)methyl-N-ylide derivatives are known, however, the rearrangements of few other ylides possessing a tertiary carbanionic centre have been investigated. In this work the commercial availability of α-bromo-γ-butyrolactone, and the possibility of further functional group manipulations, prompted an investigation of the potential for the synthesis of the unusual spirocyclic 3-benzazonine derivative 66 via the [2,3] rearrangement of the butyrolactone salt 65. The rearrangements of N-butyrolactone salts do not appear to have been investigated.

The synthesis of 65 proved difficult. Treatment of 49a with α-bromo-γ-butyrolactone in butanone at 50°C for 40 hours provided a tan powder which displayed only broad resonances in the 1H and 13C NMR spectra, possibly due to a number of diastereomers being present, and could not be identified. Treatment of this material with DBU afforded the precursor 49a and 66, suggesting the original alkylation was incomplete. Alkylation of 49a with α-iodo-γ-butyrolactone afforded,
after column chromatographic purification, a polar fraction attributed to the iodide salt of 65 in low (19%) yield.

Treatment of 65 with DBU gave the lactone derivative 66, the first example of this unusual spiro-annulated medium ring heterocyclic system, in low (29%) yield. The molecular formula of 66 was confirmed by high-resolution mass spectrometry while the NMR spectra were consistent with the proposed structure. The resonances of the C5 and NMe carbons in the $^{13}$C NMR spectrum (Figure 2.13) were shifted respectively 6.1 δ upfield and 5.9 δ downfield compared to those of E-52a (Figure 2.8) by the proximity of the constrained lactone ring. In several attempts to purify 66 by preparative reverse-phase HPLC the compound was not recovered, suggesting the material was degraded by aqueous solvent mixtures.

Figure 2.13 $^{13}$C NMR Assignments for 66

2.4.5 Attempted Formation of a Spiro-ammonium Salt

Numerous cases of the Stevens rearrangement of spiro ammonium salts are reported in the literature. The [2,3] rearrangement of these systems, however, appear to be unknown. It was proposed that the [2,3] rearrangement of the ylide derived from the spiro ammonium salt 68 may provide the unknown 1,4-oxazino-3-benzazonine derivative 69. The preparation of 68 was thus investigated.

2-Chloroethyl bromoacetate was synthesised by the reaction of bromoacetic acid with 2-chloroethanol. The reaction of this ester with 57 gave the proposed precursor amine 67 in moderate yield. It was envisaged that an intramolecular quaternization of 67 to 68 would occur over potassium or sodium iodide, following
halide exchange. The synthesis of 68, however, was not achieved despite investigation of the reaction in acetone, butanone, or acetonitrile, at temperatures between 25°C and the boiling points of these solvents. In each case the majority of 67 was recovered. Any polar material formed contained many components. The failure to achieve the synthesis of 68 prevented the proposed examination of the rearrangements of this spiro ammonium salt.

2.4.6 Discussion of the Effect of the Ylide Stabilising Group

The ylide-stabilising group had little effect on the rearrangement pathway adopted at room temperature, but a substantial effect on the reaction pathway at higher temperatures. The results were consistent with the currently accepted concerted and diradical mechanisms for the [2,3] and [1,2] rearrangements respectively. In all cases the low-energy concerted [2,3] rearrangement occurred preferentially at low temperature. Clearly none of the ylide substituents investigated (hydrogen, ester, nitrile, benzoyl, lactone) lowered the activation energy of the high-energy [1,2] rearrangement sufficiently to allow substantial rearrangement via this pathway at low temperature. At high temperature, however, the selectivity of the rearrangement reflected the radical stabilisation offered by the ylide substituent. Thus the extra radical stabilisation offered by the benzoyl substituent in 62b enabled the selective
[1,2] rearrangement of this derivative. The nitrile and ester substituents did not afford significant [1,2] rearrangement, even at high temperatures, and should be used preferentially in future applications of the [2,3] rearrangement to the synthesis of fused medium-ring aza-heterocycles.

The Hofmann elimination from 55 with LDA reflected the acidic nature of the C4 benzylic proton β to the amino group in this fused aromatic derivative. The results were not surprising given the acidic nature of H4, the strong base used, and the absence of a group promoting the formation of the desired N-ylide. Similar results are likely to be encountered with other aromatic-fused systems, particularly those containing an arylethylamino component. The present results indicated that an ylide-stabilising group was necessary for the successful [2,3] rearrangement of an aromatic-fused system when generating the N-ylide by deprotonation of a precursor salt.

The [2,3] rearrangements of the various ylide-substituted 1-vinylisoquinoline derivatives demonstrated the synthetic potential of this pathway to the 3-benzazonine system. A variety of functionalised 4-substituted 3-benzazonines were prepared which could be useful for the preparation of further derivatives. In addition, the fluoride-catalysed desilylation of 59 demonstrated that, with the exclusion of water, 4-unsubstituted 3-benzazonines could be obtained in high yield. Finally, the rearrangement of the N-butyrolactone salt 65 confirmed the potential for the formation of 4,4-disubstituted 3-benzazonines, including spiro derivatives, in moderate yields.

2.5 Effect of 1'-Substituents on the [2,3] Rearrangement

2.5.1 Synthesis of the 1'-Substituted Precursors

The three 1'-substituted precursor amines 70a-c, possessing respectively the methyl, phenyl, and trimethylsilyl substituents, were prepared by the treatment of 48a with the appropriate Grignard reagent. No negative effect on the Grignard reaction was observed despite the presence of the 1'-substituent in the alkenylmagnesium
bromide reagents. Compounds 70a-c were obtained in excellent yields and were fully characterised by their spectroscopic data and elemental analyses.

Vinylsilane derivatives may be converted to vinylhalide derivatives by iodo- or bromo-desilylation. The reaction proceeds via the formation of an intermediate dihalide then dehydrohalogenation. The reaction of 70c with iodine or bromine in dichloromethane, however, failed to provide the 1'-iodovinyl derivative 70d or the analogous 1'-bromo compound. The alternative synthesis of 70d via the 1-ethynyl amine 71 was then investigated. A recent report described the clean conversion of alkynes to internal alkenyliodides under mild conditions by the addition of hydrogen iodide, generated in situ from a chlorotrimethylsilane/sodium iodide/water system in acetonitrile.

The reaction of 48a with commercial ethynylmagnesium bromide gave 71 in good yield. The compound exhibited characteristic ethynyl NMR resonances for H2' at 2.42 \( \delta \), for C2' at 82.31, and for C1' at 74.57 \( \delta \). A significant byproduct was also isolated from this reaction. The material, a crystalline solid, on \(^1\)H and \(^{13}\)C NMR spectral analysis appeared almost identical to 71 but lacked the terminal ethynyl signals. The detection of an MH\(^+\) ion at 437 by LSIMS-MS was consistent with the bis-acetylene structure 73. The formation of 73 was rationalised by assuming the generation of the ethynyl anion of 71 in the presence of the basic Grignard reagent, then the attack of this anion on 48a.

The treatment of 71 with chlorotrimethylsilane/sodium iodide/water in acetonitrile at room temperature afforded only the hydroiodide salt of 71. Increasing the reaction temperature to 80°C gave, after four hours, the partial conversion of 71 to a mixture of the Markovnikov product 70d and the 1-(cis-2'-iodo)ethenyl product of anti-Markovnikov addition. Surprisingly, only 70d and 71 were detected after eight hours. Column chromatography afforded the isolation of 70d in moderate yield.
Compounds 70a and 70b were N-alkylated by warming the amines with ethyl bromoacetate in butanone. The products 72a,b were mixtures of the expected B-ring diastereomers. In contrast, 70c and 70d failed to react, or gave significant byproducts, on warming with ethyl bromoacetate. The action of ethyl bromoacetate on 70c is discussed in Section 2.8. The N-alkylation of 70c and 70d was achieved by the reaction of the amines with the more reactive triflate alkylation agent, ethoxycarbonylmethyltriflate, under mild conditions. Anion exchange of the crude triflate salts afforded the bromide salts 72c,d. In each case only a single B-ring diastereomer, assumed to have the \textit{trans} configuration, was obtained.

Attempts were made to synthesize the 1-(1'-cyano)vinyl derivative 74a. The necessary Grignard reagent, however, was not formed by the reaction of 2-chloroacrylonitrile with magnesium under a variety of conditions, including the use of magnesium activated by 'dry-stirring' under nitrogen. Similarly, the formation of
the 1-cyclopentenyl derivative 74b failed, as the literature preparation\textsuperscript{91} of cyclopent-1-enyl lithium from lithium and 1-chlorocyclopentene could not be reproduced. The [2,3] rearrangements of acyclic \( \alpha \)-cyclopentenyl\textsuperscript{92} and \( \alpha \)-cyclohexenyl\textsuperscript{92-94} sulfonylides are known. The [2,3] rearrangement of an \( N \)-ylide based on 74b would afford an unusual fused cyclopentyl[5,6]-3-benzazone derivative.

![Diagram](https://example.com/diagram.png)

2.5.2 Rearrangement of the 1'-Substituted \( N \)-Ylides

The DBU-promoted rearrangements of 72 were examined at a variety of temperatures in acetonitrile. The results are summarised in Table 2.7.

The reaction of 72a at both high and low temperatures afforded exclusively the isomers of the 3-benzazone derivative 75a in excellent yield. The 1'-methyl substituent reduced the stereoselectivity of the [2,3] rearrangement to the \( E \)-benzazone isomer and substantial levels of the \( Z \)-benzazone were formed (\( E/Z=1.9 \)).

The reactions of 72b gave primarily the 3-benzazone products 75b, however, some promotion of the Stevens rearrangement by the 1'-phenyl substituent was evident with the formation of significant amounts of 76b, even at low
temperatures. With the 1'-phenyl substituent the stereoselectivity of the [2,3] rearrangement was reversed to afford preferentially the Z-benzazonine isomer \((E/Z=0.7)\).

At high temperature the reaction of 72b afforded a byproduct tentatively identified as 77, which could not be separated from 76b. The identification of 77 was dependant on the NMR spectra and GC-MS analysis of a mixture of these compounds. Compound 77 provided resonances in the NMR spectra consistent with an isolated vinyl group, an isolated olefinic proton, and two isolated \(N\)-methylene groups (singlets at 3.61 and 3.15 \(\delta\) in the \(^1\)H NMR and 58.25 and 55.19 \(\delta\) in the \(^13\)C NMR). The yields suggested the formation of 77 from Z-75b, however, this conversion would appear unlikely mechanistically. The amino ester 77 may arise from the conversion of 72b to a 5-phenyl-3-benzazocinium salt (cf. Section 2.8) at the high temperature, then the Hofmann elimination from this salt.

The rearrangement of the 1'-trimethylsilyl derivative 72c at room temperature afforded selectively the E-benzazonine E-75c in good yield. No other rearrangement products were detected. Repeating the rearrangement at high temperature failed to afford any of the expected products. An unidentified mixture of many components was obtained in low yield.

Treatment of the 1'-iodovinyl derivative 72d with DBU at room temperature provided a complex mixture of polar components. None of the expected [2,3] or [1,2] rearrangement products were formed with only traces of any non-polar material.

Each of the E and Z-isomers of 75a,b were identified unambiguously by their preparative HPLC isolation then nOe difference experiments. Two-dimensional heteronuclear decoupling experiments afforded the positive identification of H7 for the nOe experiments. The NMR spectra for 75b were obtained in deuterated benzene which enabled the discrimination of the various aromatic and olefinic protons present. The Z-isomers gave nuclear Overhauser interactions between the 6-methyl and H7
Table 2.7 Rearrangement Conditions and Products from 72

<table>
<thead>
<tr>
<th>Reactant</th>
<th>Reaction Temp (°C)</th>
<th>Total % Yielda</th>
<th>Product Distributionb (%)</th>
<th>E-75</th>
<th>Z-75</th>
<th>76</th>
<th>Other</th>
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<td></td>
<td>66</td>
<td>34</td>
<td>-</td>
<td>-</td>
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<td></td>
<td>82</td>
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<td></td>
<td>76</td>
<td>24</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>72b</td>
<td>-15</td>
<td>81</td>
<td></td>
<td>38</td>
<td>54</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>81</td>
<td></td>
<td>37</td>
<td>53</td>
<td>8</td>
<td>2 (77)</td>
</tr>
<tr>
<td></td>
<td>82</td>
<td>84</td>
<td></td>
<td>36</td>
<td>35</td>
<td>11</td>
<td>18 (77)</td>
</tr>
<tr>
<td>72c</td>
<td>25</td>
<td>67</td>
<td></td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>82</td>
<td>&lt;10 c</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>72d</td>
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<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>100 (70d)</td>
</tr>
</tbody>
</table>

a yield to a non-polar rearranged fraction
b from ¹H NMR integrals
c unidentifiable mixture
protons for Z-75a, and between the ortho-6-phenyl and H7 protons for Z-75b. No interactions were observed for the E-isomers. The assignments of these isomers were consistent with their stability on silica t.l.c; the E-isomers were not observed if the t.l.c. plate was aged prior to elution. This simple test provided a rapid, although not conclusive, means of discriminating the isomers. It should be noted that the E-isomer of 75b eluted prior to the Z-isomer on HPLC analysis, the opposite order to all other examples in this work.

The isomers of 75b were crystalline solids. Unequivocal evidence for the structure of Z-75b was obtained by X-ray crystallographic analysis\(^9\) (Figure 2.14). Suitable crystals for an X-ray crystal structure of E-75b could not be obtained.

Figure 2.14 X-Ray crystallographic structure of Z-75b
Compound *E-75b* exhibited conformational flexibility upon NMR spectral analysis at room temperature in either deuterated benzene or chloroform. Broad peaks lacking definition were observed. At 75°C in benzene a single set of signals was obtained which afforded confirmation of the proposed structure. At this temperature only the H5 and the ethyl ester protons exhibited poor peak shape. At -50°C in chloroform two sets of signals were observed, confirming the presence of two conformers for this strained system. The relative populations were approximately 1.94:1. The shifts of the N-methyl protons, at 2.36 and 2.69 δ, and the ester methyl protons, at 1.37 and 0.83 δ, were substantially different between the conformers.

The NMR analysis of *E-75c* at -20°C in deuterated toluene afforded two sets of signals indicating that, as for *E-75b*, two conformers existed. The relative populations were 1.56:1. The shifts of the N-methyl protons, at 2.60 and 2.46 δ, and the trimethylsilyl protons, at 0.25 and 0.04 δ, were the major differences between the conformers. The conformers of *75b,c* may reflect transannular interference between the bulky C6 substituents and the C1 or C2 atoms, causing the molecule to favour a more strained conformation of the ring, able to separate these moieties, for a proportion of the time.

The NMR analysis of *E-75c* at 75°C in deuterated tetrachloroethane afforded a single set of signals and confirmation of the proposed structure. Extended analysis times under these conditions, however, resulted in the conversion of *E-75c* to a mixture consistent with two diastereomeric quaternary salts. The reaction had a half-life of 20 minutes, reflecting the strained nature of the 6-trimethylsilyl-*E*-benzazonine. The products, which were not isolated, were tentatively attributed to diastereomers of the pyrrolo[2,1-α]isoquinoline *78*, formed by a transannular reaction in the presence of traces of acid in the chlorinated solvent. Both the ¹H and ¹³C DEPT NMR data appeared consistent with these structures. Similar derivatives were proposed to occur by the degradation of the *E*-benzazonines on silica p.t.l.c. Compound *E-75c* was degraded by silica t.l.c.
2.5.3 Discussion of the Effect of the 1'-Substituent

The results indicated that a 1'-substituent had only a marginal effect on the selectivity of the rearrangement of the 1-vinyl tetrahydroisoquinolines. Each of the methyl, phenyl, and silyl substituents were successfully accommodated in the [2,3] rearrangement to provide the 3-benzazonine products 75a-c in good to excellent yields. The 1'-methyl derivative 72a afforded the highest yield of the 3-benzazonines and the reaction occurred selectively, even at high temperature, suggesting that the 1-alkyl group hindered the [1,2] rearrangement. In contrast, some Stevens rearrangement occurred from the 1'-phenyl derivative 72b at low temperature. As the 1'-phenyl group may not contribute to the promotion of the radical pathway by radical delocalisation it was proposed that the concerted transition state was less favoured in this case, due to steric interference. The failure of the 1'-silyl derivative 72c to afford rearrangement products at high temperature may be attributed to the degradation of the strained E-6-trimethylsilyl-3-benzazonine product, as evidenced by the high temperature NMR experiments on 75c.

The 1'-iodo derivative 72d failed to undergo the desired rearrangements. It was proposed that 72d underwent dehydrohalogenation to a 1-ethynyl derivative which was then degraded by the basic conditions to a variety of products. The promotion of the dehydrohalogenation of alkenyl halides by DBU was previously reported.96

The results for 72a,b demonstrated that the stereoselectivity of the [2,3] rearrangement of the 1-vinyl isoquinoline N-yliides may be controlled by the selection of the 1'-substituent. Whereas the 1'-unsubstituted derivative 50a underwent almost stereoselective rearrangement (E/Z=19) to the 3-benzazonines at room temperature the selectivity was reduced by a 1'-methyl substituent (E/Z=1.9) and reversed by the 1'-phenyl substituent (E/Z=0.7). This behaviour was rationalised and predicted in Section 2.3.2 (pg. 25). An alternative explanation proposing the thermodynamic control of the stereoselectivity was considered, as the bulky 6-substituents would increase the ring strain in the E isomers of 75a, b, but this would
predict a decrease in the $E$-benzazonines at high temperatures. The level of the $E$-benzazonine was increased with the rearrangement of 72a at high temperature (Table 2.7), consistent with an increased population of the high-energy pro-$E$ conformers of 72a at high temperature.

The stereoselective formation of $E$-75c from 72c, in contrast to the behaviour of 72a and 72b, was consistent with the assignment of trans-stereochemistry to the single diastereomer observed for 72c. The results indicated that the Z-isomers of 75a,b were formed predominantly, if not exclusively, from the cis-diastereomers of the precursor salts, in agreement with the conclusions in Section 2.3.2. The results suggest that the stereospecific control of the [2,3] rearrangement could be achieved by the appropriate selection of a 1'-substituent and control of the stereochemistry of the precursor salt.

The results confirmed that the [2,3] rearrangement of 1-vinylic isoquinoline $N$-ylides could provide a good pathway to a variety of 6'-substituted 3-benzazonine derivatives.

2.6 Effect of 2'-Substituents on the [2,3] Rearrangement

2.6.1 Synthesis of the 2'-Substituted Precursors

The reaction of alkenyl Grignard reagents with 48a provided the 2'-(2-methylpropenyl) and 2'-propenyl precursor amines 81a,b. The synthesis of 81a gave the lowest yield (61%) for a reaction of this type; the formation of 2-methylpropenylmagnesium bromide occurred slowly and was clearly hindered by the methyl group $cis$ to the halide. A mixture of the $cis$- and trans-1-propenyl derivatives, 81b1 and 81b2, was obtained from the commercial mixture of 1-bromo-1-propene isomers. The major isomer was assigned the $cis$-geometry on the basis of nuclear Overhauser experiments and $^{13}$C chemical shift data for the terminal methyl group; in the $cis$ derivative the methyl signal was at 13.9 $\delta$, approximately 4.5 $\delta$ upfield of the
same signal in the *trans*-isomer. Efforts to separate the isomers 81b1 and 81b2 by recrystallisation, p.t.l.c., or preparative HPLC were not successful, so the isomeric mixture was used in subsequent reactions.

Synthesis of the 2'-dimethoxyphenyl derivative 81c was achieved by the Bischler-Napieralski cyclisation. This approach allowed the incorporation of the 1-vinyl substituent prior to construction of the isoquinoline ring. The modification of
a published method\textsuperscript{97} afforded the free base \textit{79} which was then converted to the methiodide salt 80. The reduction of 80 with sodium borohydride gave 81c.

The reaction of the amines 81a,b with ethyl bromoacetate at 0-25°C in acetonitrile afforded the quaternary salts 82a,b. Under these conditions 81c was unaffected. The formation of 82c was achieved by the treatment of 81c with ethyl iodoacetate at high temperature in a sealed tube. The quaternary salts 82a-c were mixtures of the B-ring diastereomers.

\[
\begin{array}{c}
\text{81a,b} \xrightarrow{\text{BrCH}_2\text{CO}_2\text{Et}} \text{MeO} \\
\text{50°C} \\
\text{[82a,b]}
\end{array}
\]

The reactions of 81a,b with ethylbromoacetate at 50°C in butanone, or acetone, afforded the ring-opened dienes 83a,b. All spectra were consistent with the proposed structures. Both the geometric isomers of 83b were isolated, with the \textit{cis} isomer formed preferentially (\textit{cis}/\textit{trans}=4.2). The reaction of the 1-propenyl isomers of 81b (\textit{cis}/\textit{trans}=3) confirmed that the elimination occurred only from the amine possessing the \textit{cis} 2'-methyl group, as the \textit{trans}-propenyl salt 82b2 was obtained with 83b. A similar elimination process was observed from a 1-cyclopropyl salt (Section 5.7.1), which gave the isomers of 83b in low yield as byproducts to the Stevens rearrangement at high temperature.

The mechanism for the formation of the dienes is unclear, but was assumed to proceed via the initial formation of 82. The salt 82b1 was converted to the diolefin 83b by refluxing in acetone. The formation of an \textit{N}-ylide from 82 by bromide ion induced deprotonation, then a concerted or diradical \textit{\alpha}-rearrangement may afford 83 (Figure 2.14). However, the intermediacy of the \textit{N}-ylide appears unlikely as the
dienes were not observed from the high temperature rearrangements of 82a,b with DBU. An alternative pathway may involve the tautomer (β) (Figure 2.15).

Figure 2.15 Possible Intermediates in the Formation of the Dienes 83

An alternative route with the potential to provide selectively the trans-1-propenyl isomer 81b2 was investigated. The synthesis98 of the 1-propenyl-dihydroisoquinoline 85 by the Bischler-Napieralski cyclisation of the crotonamide 84a, in benzene with a large excess of phosphorus oxychloride, could not be reproduced despite exhaustive trials. Several additional experiments in toluene or acetonitrile, with either phosphorus oxychloride or phosphorus pentoxide, failed to provide 85. In each case only complex mixtures of many components were obtained.

The synthesis of trans-2'-ethoxycarbonyl- and trans-2'-chloro-1-vinylisoquinoline derivatives was also investigated but without success. The reaction of
homoveratrylamine and fumaric acid monoethyl ester failed to provide the amide 84b, the potential precursor for a 2'-ethoxycarbonyl derivative via the Bischler-Napieralski cyclisation. Similarly, the Grignard reaction of trans-2-chlorovinylmagnesium chloride with 48a failed to give the desired 2'-chloro derivative 86. The incomplete formation of the Grignard reagent or its rapid degradation may have occurred. Some reaction of the magnesium with trans-1,2-dichloroethylene was evident as the magnesium was consumed.

2.6.2 Rearrangement of the 2'-Substituted \( \text{N-Ylides} \)

The DBU-promoted rearrangements of 82 were examined at a variety of temperatures in acetonitrile. The results are detailed in Table 2.8.

At low temperatures the reaction of the 1-(2'-methylpropenyl) salt 82a gave predominantly the 3-benzazonine \( E\)-87a, however, even at -20°C the diastereomers of the 3-benzazepine 88a were also formed. The selectivity was 2.3:1 in favour of the [2,3] rearrangement at -20°C and 1.4:1 at 25°C. The reaction of compound 82a at high temperature gave exclusively the Stevens rearrangement products.

Two different mixtures of the 1-propenyl salts 82b were examined in these rearrangements. The first contained predominantly the diastereomers of the cis-propenyl salt 82b1 (cis:trans propenyl=70:30) and was obtained by the alkylation of 81b at room temperature. The rearrangement of this mixture, at either 0°C or 82°C, afforded a complex mixture of products with diastereomers present for each of the \( E \) and Z 3-benzazonines 87b and the cis-1-propenylbenzazepine 88b1. The additional chiral centre at C5 enabled the formation of the diastereomers of 87b. The \( E \)-benzazonine diastereomers were the major products of the reaction but large amounts of the benzazepines were also formed. The selectivity of the rearrangement was 2.4:1 in favour of the [2,3] rearrangement at 0°C and 1.3:1 at 82°C. Only traces of the \( Z \)-benzazonines were observed.
Table 2.8 Rearrangement Conditions and Products from 82

<table>
<thead>
<tr>
<th>Reactant</th>
<th>Reaction Temp (°C)</th>
<th>Total % Yield</th>
<th>E-87</th>
<th>Z-87</th>
<th>88</th>
<th>Other (%)</th>
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<td>-20</td>
<td>65</td>
<td>70</td>
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<td>84, 16</td>
<td>-</td>
</tr>
<tr>
<td>82b</td>
<td>0</td>
<td>80</td>
<td>42, 23</td>
<td>3, 3</td>
<td>27, 2</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>82</td>
<td>72</td>
<td>39, 14</td>
<td>2, 3</td>
<td>37, 5</td>
<td>-</td>
</tr>
<tr>
<td>82c</td>
<td>-45</td>
<td>72</td>
<td>-</td>
<td>-</td>
<td>83, 17</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>63</td>
<td>-</td>
<td>-</td>
<td>80, 16</td>
<td>4 (90)</td>
</tr>
</tbody>
</table>

a: yield to a non-polar rearranged fraction
b: from 1H NMR integrals
c: from a 73:23 mixture of 82b1 and 82b2
d: from a 10:90 mixture of 82b1 and 82b2

The second mixture of the 1-propenyl salts 82b was obtained fortuitously following the alkylation of 81b at 50°C and the removal of the dienes 83b. The
mixture contained predominantly the diastereomers of the trans-propenyl salt 82b2 (cis:trans propenyl=10:90). The rearrangement of this mixture at low temperature gave a greatly increased preference (15.7:1) for the [2,3] rearrangement and a higher proportion of the Z-benzazonines.

The base-promoted rearrangement of the 1-styrylic derivative 82c afforded the diastereomers of the 3-benzazepine 88c at both 25°C and -45°C, the only selective Stevens rearrangement of a 1-vinylc-isoquinoline derivative observed at room temperature in this work.

The separation of the isomers of 87a and 88a was not achieved, however, they could be detected by the ¹H NMR analysis of a mixture in deuterated benzene. The olefin coupling constant (16.6 Hz) for the single isomer of 87a confirmed the compound possessed the E stereochemistry. Compound 87a was not isolated, however, the skeletal structure was confirmed by the hydrogenation of the reaction mixture of 87a and 88a, then the separation of the hexahydro-3-benzazonine 101c (Section 2.9) from the unchanged 88a.

A combination of alumina column chromatography, to obtain enriched fractions, and preparative HPLC chromatography afforded the isolation of four of the six isomers, at least one from each pair of diastereomers, from the rearrangements of 82b. The major isomer of E-87b, the two Z-87b isomers, and the major isomer of 88b were isolated. All spectral data was consistent with the proposed structures. Each type of isomer provided the doublet methyl signal at a characteristic shift in the ¹H NMR spectrum; for the E-87b diastereomers it was 1.25-1.15 δ, for the Z-87b diastereomers 0.95-0.75 δ, and for the 88b diastereomers 1.65-1.50 δ. The H1'-H2' coupling constant (10.9 Hz) of the major diastereomer of 88b confirmed the compound possessed the cis geometry of the 1-propenyl group.

In Z-87b the magnitude of the H4-H5 coupling constant was substantially different between the diastereomers (11.45 Hz cf. 4.18 Hz). This allowed the assignment of stereochemistry to the compounds. The consideration of the X-ray structure for Z-75b (Figure 2.14, pg. 53) indicated the higher vicinal coupling was
consistent with the trans-B-ring diastereomer of Z-87b, with a dihedral angle between H4 and H5 of approximately 180°, while the smaller coupling was consistent with the cis-B-ring diastereomer. It was proposed that the diastereomers resulted from the inversion of C4 as both exhibited identical vicinal coupling between H6 and H5.

![Proposed Conformation and Stereochemistry of the Major Diastereomer of E-87b](image)

Figure 2.16 Proposed Conformation and Stereochemistry of the Major Diastereomer of E-87b

The major diastereomer of E-87b was recovered intact from p.t.l.c. on alumina while the minor diastereomer was degraded. This suggested that a stable E-benzazonine may be obtained by the inclusion of substituents with the appropriate stereochemistry. The stereochemistry of the major diastereomer of E-87b was investigated by the consideration of $^1$H NMR data. The stereochemistry of the C6 centre was identified by an nOe between H5 and H7, and the coupling constant between H5 and H6 (9.95 Hz). Clearly the C5 to C7 portion of the molecule adopted the geometry shown (Figure 2.16). The H4-H5 vicinal coupling constants for the major (5.76 Hz) and minor (1.28 Hz) diastereomers of E-87b were consistent with the inversion of C4 in conformer 4 (Figure 2.9, pg. 34), previously identified by the molecular modelling of the E-benzazonine system (Section 2.3.4); values of 5.72 Hz
(42°) and 1.01 Hz (72°) were predicted for the cis and trans diastereomers. The results were not consistent with the other low-energy conformers identified for the E-benzazonine system. Values of 11.8-12.2 Hz were predicted for the H4-H5 coupling constant in the trans diastereomers of these conformers. It was concluded that the major diastereomer of E-87b possessed the cis B-ring stereochemistry and that derivatives of the E-benzazonine system adopted structures based on conformer 4 in solution.

The crystalline diastereomers of 88c were isolated by p.t.l.c. on silica with dichloromethane/ethanol. P.t.l.c. with dichloromethane/methanol afforded facile ester exchange to the diastereomers of 89. Compounds 88c and 89 were characterised by spectral and elemental analysis. As some doubt existed over the ability of spectral analyses to differentiate between the isomers of 87c and 88c nuclear Overhauser difference experiments were conducted to provided the confirmation of the molecular geometry. The proton assigned to H1 in 88c (or H5 in 87c) interacted with an aromatic proton on the fused ring, while that assigned to H2' in 88c (or H7' in 87c) interacted with the ortho protons of the phenyl ring. The results (Figure 2.17) were consistent with the benzazepine structure of 88c.

The diastereomers of 88c were identified by nuclear Overhauser difference experiments and the examination of hand-held models; the major isomer was assigned the trans B-ring stereochemistry. Both diastereomers exhibited a strong nOe between
H1 and H2' indicating a dihedral angle of 180° for H1-H1'. The trans diastereomer adopted a conformation with the vinylic group axial in which there was an nOe between H2 and H2', no nOe between H9 and H1', and a moderate H1-H2 coupling constant (5.8 Hz). The cis diastereomer adopted a conformation with the vinylic group equatorial in which there was no nOe between H2 and H2', an nOe between H9 and H1', and a low H1-H2 coupling constant (1 Hz) indicating a dihedral angle of 90°.

A byproduct from the treatment of 82c with DBU at 25°C was isolated in low yield and identified as the 5,6-dihydropyrrolo[2,1-c]isoquinoline 90. The resonances in the $^1$H NMR spectrum for H1 (6.45 δ) and H5 (4.61 δ) were consistent with those observed in similar 2-phenyl- or 3-ethoxycarbonyl-5,6-dihydropyrrolo[2,1-a]isoquinoline derivatives. Additional support for this structure was obtained by nuclear Overhauser experiments which located the lone olefinic proton between, and interacting with, an aromatic proton of the fused ring and the ortho protons of the pendant phenyl ring (Figure 2.17).

The formation of 90 may involve an intermediate iminium salt. The similar formation of an iminium salt by the butyl lithium-induced deprotonation with N-deoxygenation of a tetrahydroisoquinolininium-N-oxide was implicated in the synthesis of an oxazolidine derivative. The deprotonation of the iminium salt would give a dipolar structure which may undergo ring closure and oxidation to 90 (Figure 2.18). The 1,3-dipolar cycloaddition of dipolarophiles with isoquinoline derivatives has often provided access to 5,6-dihydropyrrolo[2,1-a]isoquinoline derivatives, but the intramolecular rearrangement apparently occurring in the formation of 90 does not appear to have been reported previously. This rearrangement could provide a new route to derivatives of the 5,6-dihydropyrrolo[2,1-a]isoquinoline system. The further development of this reaction was deemed outside the scope of this work.
2.6.3 Discussion of the Effect of the 2'-Substituent

As only the cis-1-proplybenzazepine diastereomers were detected from the rearrangement of 82b (cis/trans=3.2) it was assumed that the trans-1-proply salt underwent a selective [2,3] rearrangement. This assumption was consistent with the low levels of the benzazepines formed by the reaction of the predominantly trans-1-proply salt (cis/trans=0.11). The results indicated a relatively non-bulky alkyl substituent could be accommodated at C2' in the trans position without a detrimental effect on the [2,3] rearrangement. The decrease in the E-stereoselectivity (E/Z=2.92) of the [2,3] rearrangement from 82b2 was attributed to the minimisation of 1,3-substituent effects across the pseudo-cyclopentane transition state (refer Figure 2.4, pg. 24).

A substituent at C2' in the cis position clearly decreased the yields of the 3-benzazonines. Thus the preference for the [2,3] rearrangement over the [1,2] rearrangement was reduced to approximately 2:1 for both the cis-1-proply salt 82b1 and the 1-(2'-methylpropenyl) salt 82a at low temperature. This behaviour

---

Figure 2.18 Proposed Mechanism for the Conversion of 82c to 90
was assumed to reflect steric interference of the cis-2'-substituent with the concerted transition state.

Both compounds 82a and 82b1 possessed a cis 2'-methyl group hindering the [2,3] rearrangement and exhibited similar behaviour at room temperature. At high temperature 82a provided the Stevens rearrangement exclusively, while 82b1 afforded a 1.4:1 preference for the Stevens rearrangement. The additional 2'-methyl group in 82a was assumed to promote the [1,2] rearrangement by increasing the stabilisation of the allylic radical through hyperconjugation.

The results for the trans-2'-dimethoxyphenyl salt 82c confirmed that electron delocalising, radical stabilising, groups at C2' promoted the [1,2] rearrangement. Only the Stevens rearrangement products were observed from 82c, reflecting the high electron delocalising nature of the dimethoxyphenyl group. This high electronic activation allowed the [1,2] rearrangement to occur at low temperature (-45°C). The complete lack of any [2,3] rearrangement products from 82c, however, suggested that other factors may have contributed to the deactivation of the concerted rearrangement. Some steric hindrance of the concerted state may occur with the bulky aromatic group while electronic factors could include, for instance, a reduction in the molecular orbital coefficient of the \( \pi^* \) acceptor orbital (LUMO) at C2' due to the extension of the conjugating system. These factors would decrease the efficacy of the orbital overlap necessary for a concerted transition state. In addition, the conjugation of the vinyl and aromatic groups would hinder the migration of the double bond.

The trans stereoselectivity of the Stevens rearrangement of 82c to 88c (trans/cis=4.9) was rationalised by the consideration of the diradical transition states leading to each diastereomer (Figure 2.19); clearly steric interactions would be minimised in the pro-trans state. It was assumed that the trans diastereomers were the major products in the other Stevens rearrangements observed throughout this work.
2.7 Rearrangement of a 1-Ethynlisoquinoline N-ylide Derivative

The rearrangement of α-ethynyl-N-ylides may be viewed as an extension of the behaviour of α-vinyl-N-ylides. The successful [2,3] rearrangements of the α-ethynylpiperidinium salt 15 and 1-ethynlisothiochroman sulfonium salt 19 were noted in Section 1.3.2. The ready availability of the 1-ethynyltetrahydroisoquinoline 71 prompted an investigation of the potential [2,3] rearrangement of an N-ylide based on this derivative.

The reaction of 71 with ethyl bromoacetate gave 91 as a crystalline mixture (trans/cis=3.5) of the B-ring diastereomers. Treatment of the salt mixture suspended in acetonitrile at 0°C with DBU afforded the rapid dissolution of the solid but no significant non-polar rearrangement products. When the reaction was repeated at reflux more non-polar material was obtained. At least five components were present in this fraction. The three major components were isolated by preparative HPLC and characterised by spectroscopic analysis. The two largest components were each isolated in 7% yield and identified as the 3-benzazepine 92 and the isoquinoline derivative 93. Compound 93 may be formed by the deprotonation of 91 at Cl and a subsequent Stevens rearrangement. The third component, isolated in 3% yield, was assigned the isoquinoline structure 94. This compound was an intense yellow colour, consistent with the extensive conjugation. A resonance at 3.11 δ for the N-methyl group in the 1H NMR spectrum supported the enamine structure. The alternative 2,3-
dihydro-3-benzazonine structure 95 was considered less likely on the basis of calculations of the chemical shifts expected\textsuperscript{105} for the olefinic protons. A large downfield shift observed for the central olefinic proton, at 7.97 $\delta$, was reasonably consistent with the predicted value of 7.69 $\delta$ for H2' in 94 with the geometry shown. Chemical shifts of 6.73 or 6.26 $\delta$ were predicted for H6 in 95 with the $E$ or $Z$ C6-C7 geometry. Compound 94 may form by the deprotonation of 91 at Cl then a [1,4] shift of the ethoxycarbonylmethyl group by a diradical or symmetry allowed concerted process. The benzazonine 95 could arise from the [2,3] rearrangement followed by a [1,3] hydrogen shift of the initial strained allenic system.

The low yield of the non-polar material from 91 suggested that deprotonation had occurred to provide the ethynyl anion. It was noted that in the rearrangements of both 15 and 19 2'-substituents were present, which would negate this problem, although a previous report\textsuperscript{106} by the same authors had indicated the successful [2,3]
rearrangement of a simple 2-ethynyltetrahydrothiophene-5-ylide. Several attempts were made to synthesize the 1'-propynyl amine 96 from 71, but without success. The selective generation of the ethynyl anion and subsequent attack with iodomethane was not achieved without concurrent attack at either Cl or the nitrogen lone pair. Thus the reaction of 71 at -78°C in tetrahydrofuran with sodamide then iodomethane afforded only the recovery of a substantial amount of 71 and a crude salt, tentatively assigned as 97 by NMR analysis.

\[
\begin{align*}
71 & \xrightarrow{1. \text{NaNH}_2} 97 \\
 & \xrightarrow{2. \text{MeI}} 96
\end{align*}
\]

The results indicated that the [2,3] rearrangement of 1-ethynyl-tetrahydroisoquinoline-N-ylides would not provide an effective route to 2,3-dihydro-1H-3-benzazonine derivatives.

2.8 Thermal [1,3] Ring Expansion of a 2'-Silyl Substituted Quaternary Salt

Treatment of the 1-(2'-trimethylsilylvinyl) amine 70c in butanone with ethyl bromoacetate at elevated temperatures afforded an isomer of the expected salt 72c in moderate yield. The compound was identified as the 3-benzazocinium salt 98 by spectroscopic and elemental analysis. The olefinic proton, H6, appeared as a singlet at 7.25 δ in the 1H NMR spectrum. The Z-geometry of the olefin bond was
confirmed by an nuclear Overhauser effect between H6 and the trimethylsilyl group. Compound 98 may have formed by a [1,3] C-N bond shift in 72c. The partial conversion of 72c to 98 was achieved by refluxing the former in butanone for several hours.

The formation of 98 was avoided by the N-alkylation of 70c with ethoxycarbonylmethyltriflate at 0°C. The reaction of 70c with ethyl bromoacetate at 25°C gave a mixture (98/72c=1.5) of the isomeric salts.

The [1,3] isomerisation of 1-aryl-1-vinyl-tetrahydroisoquinolines to 3-benzazocine derivatives was reported previously by Bersch et al. The isomerisation was achieved thermally, by heating the free bases neat at temperatures of 170-200°C, or during quaternisation of the amines with iodomethane in refluxing acetone. In the present work no isomerisation of 72c was observed on thermolysis of the compound in a sealed, evacuated tube at 170-200°C. It was also noted that the N-alkylation of 49a to 55a in refluxing acetone with iodomethane proceeded without isomerisation (Section 2.4.1) while 49a was unchanged by thermolysis at 180°C.

The conversion of 70c to 98 represents the first rearrangement of this type without a 1-aryl substituent and with an alkylating agent other than iodomethane. The
further investigation of this rearrangement could lead to the development of an alternative route to functionalised 3-benzazocine derivatives.

2.9 Behaviour of the 2,3,4,5-Tetrahydro-1H-3-Benzazonine Derivatives

2.9.1 Attempted N-Alkylation with Iodomethane

Several attempts were made to synthesize the quaternary salt 99 for X-ray structural analysis and confirmation of the medium ring skeleton. The reaction of 52a with excess iodomethane in refluxing butanone or neat at room temperature, however, afforded the ring opened salt 100. The molecular formula of the cation was confirmed by mass spectrometry (LSIMS). All other spectra were consistent with the proposed structure. The formation of 100 indicated that 99 was formed initially but then underwent nucleophilic attack by the iodide ion at the electron deficient C4 position. Nucleophilic substitution followed by N-alkylation would provide 100 from 99.

When 52a was reacted with 1.2-1.5 equivalents of iodomethane in butanone at 25°C a crystalline solid was isolated in very low yield. The product was identified as 54 and neither 99 or 100 were detected. Compound 54 showed a single N-methyl
resonance at a quaternary position in the $^1$H NMR spectrum with triplets for the H10b and H3 protons at 6.18 $\delta$ and 6.02 $\delta$. The $^{13}$C NMR spectrum showed five methylene carbons, none olefinic, and two downfield CH signals. The formation of 54 could occur with the generation of trace amounts of hydroiodic acid during the reaction (see also Section 2.3.3), as iodomethane freshly distilled from potassium carbonate and dry solvents did not prevent its formation.

The present results indicated that the $N$-alkylation of the 3-benzazonines was hindered and complicated by both the potential transannular degradation of the precursors and nucleophilic attack of the products at C4. It was envisaged that a successful $N$-alkylation might be achieved using an alkylating agent which provided a less nucleophilic anion, but this reaction was not investigated.

2.9.2 Hydrogenation to 2,3,4,5,6,7-Hexahydro-3-Benzazonines

As part of the structural confirmation work and to make further derivatives the hydrogenation of several tetrahydro-3-benzazonine derivatives was investigated. Hydrogenation of the tetrahydro-3-benzazonines (Table 2.9) over palladium on carbon, in ethanol at 1 atmosphere with heating, afforded the hexahydro-3-benzazonines 101a-c by the selective reaction of the $E$-benzazonine isomers. The $Z$-isomers, and any 1-vinylic-3-benzazepine isomers present, were not effected and could be recovered.

Two diastereomers of 101b were isolated. Compounds 101a, the diastereomers of 101b, and 101c were characterised by spectroscopic analysis. One of the diastereomers of 101b exhibited unusual chemical shifts in the $^1$H NMR spectrum with the aromatic H8 proton (5.52 $\delta$) and one methoxy group (3.34 $\delta$) shifted substantially upfield. The results suggested the system adopted a conformation with the pendant phenyl ring positioned over, and shielding, the H8 and methoxy protons. Hand-held models confirmed this conformation was possible for 101b.
Table 2.9 Hydrogenations to hexahydro-3-benzazonines 101

<table>
<thead>
<tr>
<th>Reactant</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E-52a</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>101a</td>
<td>66</td>
</tr>
<tr>
<td>E-75b</td>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>101b</td>
<td>81</td>
</tr>
<tr>
<td>E-87a</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>101c</td>
<td>58</td>
</tr>
</tbody>
</table>

a mixture with the Z isomer which did not react
b mixture with 88a which did not react
c calculated from the unrecovered E-isomer

The relief of ring strain appeared to be the important factor influencing the reactivity of the E-benzazonines compared to the Z-benzazonines in the hydrogenation. This proposition was supported by the hydrogenation of E-75a. This compound gave a mixture of the reduced compound 101d and the two alternative products of a [1,3] hydrogen shift, compounds 102 and 103. Both 102 and 103 exhibited the same stability as the Z-benzazonines once formed and were not hydrogenated. Apparently the removal of the E-olefinic bond from the medium ring afforded a large increase in the stability of the unsaturated derivatives.

The spectroscopic data of 102 and 103 were consistent with the proposed structures. Both exhibited AX patterns in the $^1$H NMR spectra for the geminal protons at H7, with one proton at 4.20-4.15 $\delta$ and the other at 3.3-2.7 $\delta$. The exocyclic 6-methylene group in 102 afforded resonances at 4.99 and 4.79 $\delta$ for the geminal protons and at 112.63 $\delta$ for the olefinic carbon. The related compound 38, with a 7-methylene group, was previously reported.62 Compound 103 was assumed to be the Z-benzazonine but the geometry was not confirmed. Compound 101d was not isolated, but its presence was inferred from the NMR spectra of the mixture. The selective conversion of E-75a to either 101d or 102 was not achieved by lowering
the hydrogenation temperature. At -10°C no reaction occurred. At 25°C the reaction
afforded a mixture (7.7:6.0:1.0) of 101d, 102 and 103. In an additional test the
presence of hydrogen was found to be unnecessary and the selective isomerisation of
E-75a to 102 was achieved in ethanol at reflux over the palladium catalyst.

![Chemical structures](image)

The equipment was not available for the investigation of the hydrogenation of
the Z-benzazonines at elevated temperatures and pressures. The compounds were not
affected by high hydrogen pressures (≤ 4 atm.) at room temperature with a palladium
catalyst. The hydrogenation of these derivatives remains to be investigated with other
catalysts and conditions.

### 2.9.3 Hydrogenation and Hydrogenolysis of an N-Benzyl Derivative

The hydrogenolysis of tertiary amines containing a benzyl group can provide a
useful approach to secondary amines, from which a range of other substituents
may be introduced. Thus the hydrogenolysis of the N-benzy1-3-benzazonine E-52b
was investigated. It was anticipated that the secondary 3-benzazonine 104b would
serve as a useful synthetic intermediate for the future production of a variety of N-
substituted 3-benzazonines.

The reaction of 52b with hydrogen in refluxing ethanol afforded 104b in only
moderate yields. Monitoring the reaction by GC-MS analysis confirmed that the
hydrogenation of 52b to 104a occurred rapidly then was followed by the slow hydrogenolysis of 104a to 104b, reaching 23% after 16 hours. Only traces of the product of the direct hydrogenolysis of 52b, a secondary tetrahydro-3-benzazonine, were detected.

An improved pathway to 104b was developed with the reaction of the hydrochloride salt 105 with hydrogen in methanol. The acidic system catalysed both the hydrogenation and hydrogenolysis reactions and enabled these steps to occur rapidly at low temperatures. At 0°C the hydrogenation was complete within 30 minutes and the hydrogenolysis within 2 hours. The secondary amine was obtained in good yield as a colourless oil which was characterised by spectroscopic analysis.

2.9.4 Thermolysis of Tetrahydro-3-Benzazonine Derivatives

Mass spectral analysis failed to differentiate between the 3-benzazonine and 3-benzazepine isomers, which afforded identical fragmentation patterns. In addition, when analysed by GC-MS the isomers typically afforded identical chromatographs, complete with other minor isomers apparently formed on injection or on-column; the technique was misleading and should not be used for the analysis of these mixtures. It was proposed that the 3-benzazonines were thermally labile and rearranged to the 3-benzazepines on MS analysis. This proposition was tested with the thermolysis of several 4-substituted-3-benzazonines (Table 2.10) in solution.
Table 2.10 Thermolysis of 3-Benzazonines

<table>
<thead>
<tr>
<th>Reactant mixture</th>
<th>R</th>
<th>Solvent</th>
<th>Time (hrs)</th>
<th>Product mixture</th>
<th>Conversion of E-isomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>E-52a:Z-52a:53</td>
<td>CO₂Et</td>
<td>PrCN</td>
<td>11.5</td>
<td>E-52a:Z-52a:53</td>
<td>55%</td>
</tr>
<tr>
<td>87:9:4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E-63a:64a:106</td>
<td>CN</td>
<td>PrCN</td>
<td>18</td>
<td>E-63a:64a:106</td>
<td>41%</td>
</tr>
<tr>
<td>87:13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E-63b</td>
<td>COPh</td>
<td>MeCN</td>
<td>1.25</td>
<td>64b</td>
<td>100%</td>
</tr>
</tbody>
</table>

a ratios from \(^1\)H NMR integrations  
b MeCN and PrCN refluxed at 82°C and 115°C respectively  
c compound 64a was not isolated

The results confirmed the E-benzazonines were thermally labile and rearranged to 3-benzazepine derivatives with prolonged heating. The Z-benzazonine Z-52a, however, was stable at elevated temperatures. The 4-benzoyl derivative 63b rearranged rapidly in refluxing acetonitrile, while the 4-ethoxycarbonyl and 4-cyano derivatives 52a and 63a required extended times in refluxing butyronitrile.

Although the 1-vinyl-3-benzazepine 64a was observed as an intermediate in the pyrolysis of E-63a the 2,3-dihydro-3-benzazepine 106 was obtained as the sole product after 66 hours. Compound 106 exhibited characteristic signals in the \(^1\)H NMR spectrum for the N-methyl enamine function at 2.87 \(\delta\) and 6.31 \(\delta\) and for the propionitrile substituent at 3.79 \(\delta\) and 1.50 \(\delta\). Compound 106 may form by the loss of the cyanide anion and a [1,3] hydrogen shift prior to its reuptake (Figure 2.20).
The isomerisation of the E-3-benzazonines to 3-benzazepines confirmed the latter was the more thermodynamically stable system, or thermodynamic product, and that the interconversion between the two was possible by a [1,3] allylic shift. The observed order of reactivity, greatest with the benzoyl substituent and least with the nitrile, was consistent with the expected promotion of a C4-C5 homolytic cleavage by these substituents, and a radical pathway for this interconversion. The results suggest that the chemical manipulation of the 4-substituents to provide less radical-stabilising functions would afford E-benzazonines of greater stability.

2.9.5 Reduction of an Ester Derivative

The reduction of the ester function of 52a was investigated in a single experiment. The treatment of 52a with lithium aluminium hydride in ether afforded a crude solid which was examined by $^1$H NMR analysis prior to purification. The material displayed conformational flexibility with two sets of broad peaks at 25°C in deuterated chloroform. At 60°C a single set of broad signals was obtained. The signals appeared consistent with the expected alcohol 107, but the poor peak shapes were insufficient for the positive identification of this compound. The purification of this solid by p.t.l.c. on alumina with ethyl acetate/5% hexane surprisingly afforded the pyrrolidine derivatives 108 which were not present prior to the p.t.l.c. treatment. Compound 108b was attributed to the esterification of 108a with ethyl acetate, catalysed by the basic alumina. The formation of 108 can be rationalised by proposing the conversion of 107 to a pyrrolo[2,1-a]isoquinolinium salt which underwent Hofmann elimination under the basic conditions. The results suggested the
reduction of the ester function was achieved, but afforded further evidence for the proposed transannular degradation of the strained $E$-benzononines.

$$\text{MeO}$$
$$\text{MeO}$$
$$\text{N}$$
$$\text{CO}_2\text{Et}$$
$$\text{LiAlH}_4$$
$$\text{MeO}$$
$$\text{MeO}$$
$$\text{N}$$
$$\text{CH}_2\text{OH}$$

2.10 Conclusion

The present results demonstrated that the rearrangement of 1-vinylc-tetrahydroisoquinoline $N$-ylides could afford a good new route to functionalised 2,3,4,5-tetrahydro-$1H$-3-benazonines. The $N$-ylides typically underwent the concerted [2,3] rearrangement preferentially at room temperature, the first application of this type of rearrangement to the synthesis of benz-fused aza-heterocycles, to give mixtures of the $E$ and $Z$-benzonine isomers in high yields.

The [2,3] rearrangement generally afforded the $E$-benzonine isomers almost stereoselectivity. With bulky substituents at the 1'-position, however, the levels of the $Z$-benzonine isomers were increased. The 1'-substituent acted by favouring the appropriate pro-$Z$ concerted transition state geometry in the cis B-ring diastereomer of the precursor salt. The development of a method for the selective synthesis of the cis-salt may enable the stereoselective synthesis of $Z$-benzonine derivatives. The control of the stereoselectivity of the rearrangement would be useful as the $E$ or $Z$ isomers may be expected to afford different types of pharmacological activity. The $E$-
benzazonine derivatives may be active at CNS receptors requiring the nitrogen and aromatic moieties in the same plane, while the Z-benzazonines may be active at receptors in which the nitrogen moiety is removed from the aromatic plane.

The [2,3] rearrangement of the isoquinoline N-ylides tolerated a variety of functional groups on both the ylide and 1'-vinyl positions. The Stevens rearrangement products became significant only when the rearrangements were conducted at high temperatures and were easily avoided. Each of the ester, nitrile, benzoyl and lactone ylide-stabilised derivatives, and the 1'-methyl, 1'-trimethylsilyl, and 1'-phenyl substituted derivatives, afforded the [2,3] rearrangement preferentially. The rearrangement of a methylene N-ylide confirmed that an ylide stabilising group was unnecessary for the selective [2,3] rearrangement. The presence of an ylide-stabilising group was, however, beneficial and afforded higher yields as the N-ylides were easily formed from the precursor salts with a mild base; a strong base promoted the Hofmann elimination of the salts. These results demonstrated that a wide variety of functional groups may be incorporated in the 3-benzazonine system, or others, by this rearrangement methodology.

The presence of 2'-substituents was generally detrimental to the [2,3] rearrangement. A simple methyl group could be accommodated in the trans-2'-position, however, radical stabilising groups in this position promoted the Stevens rearrangement; with the trans-2'-dimethoxyphenyl group the Stevens rearrangement was obtained selectively. A methyl substituent in the cis-2'-position interfered with the formation of the concerted transition state and reduced the selectivity of the rearrangement. These results suggested that only simple alkyl groups, at the trans-position, could be tolerated at C2' for the [2,3] rearrangement. The effects of these groups may, however, be less pronounced for systems without the activation of the Stevens rearrangement afforded by the fused ring of the isoquinoline system.

The E-2,3,4,5-tetrahydro-1H-3-benzazonine derivatives prepared in this work experienced substantial ring-strain and appeared to degrade to pyrrolo[1,2-a]isoquinoline derivatives under a variety of conditions. This degradation may limit
the further chemical manipulation of these derivatives. The hydrogenation of these derivatives could be achieved and these compounds may serve as useful intermediates in the synthesis of stable, substituted 2,3,4,5,6,7-hexahydro-3-benzazonines.
CHAPTER 3
REARRANGEMENTS OF 1-VINYLC
TETRAHYDROISOQUINOLINE N-OXIDES

3.1 Introduction

The absence of literature investigating the synthesis of benz-fused N-heterocycles by the [2,3] sigmatropic rearrangement of allylic N-oxides was noted in Section 1.3.2. It was proposed to investigate the rearrangements of 1-vinylic isoquinoline N-oxides (Figure 3.1) and the synthesis of derivatives of the unknown 4,3-benzoazoxonine system. Derivatives of this type were desired for evaluation of their pharmaceutical properties. It was anticipated this study would afford information relevant to the preparation of other fused oxaza-heterocycles by the same ring-expansion technique.

![Figure 3.1](image_url)
3.2 Review of Benzoxazinones

Of the twenty one possible benzoxazinone skeletons only five, the 1,4-, 2,3-, 2,5-, 2,6-, and 4,1-benzoxazinones, are known (prior to Chem. Abs. 119).

Ring destructive strategies provided access to three of the known skeletons. The 1,4-benzoxazinone 110 was prepared\textsuperscript{109} in low yield by the oxidative removal of the thioether group of 109, attack on the resultant carbocation by water, and rearrangement of the hydroxyamide intermediate. Oxidative cleavage of the pyrano[3,4-\textit{b}]indole 111 with periodate ion gave the 4,1-benzoxazinone\textsuperscript{110} 112 in high yield. The photosolvolysis and cyanogen bromide-induced solvolysis techniques used to produce 3-benzazonines were extended to the production of 2,5-benzoxazinone derivatives in good yields from oxazolo[2,3-\textit{a}]-isoquinolines.\textsuperscript{66,111,112}

\[ \text{MeO} \quad \text{RS} \quad \text{N} \quad \text{O} \quad \text{IO}_4^- \quad \text{i-PrOH/H}_2\text{O} \]
\[ \text{MeO} \quad \text{HO} \quad \text{N} \quad \text{O} \quad \text{OMe} \quad \text{NH} \]
\[ \text{109} \quad \text{R = Me, Et, i-Pr} \quad \text{110} \]

\[ \text{111} \quad \text{H} \quad \text{N} \quad \text{O} \quad \text{NaIO}_4 \quad \text{MeOH/H}_2\text{O} \]
\[ \text{112} \quad \text{H} \quad \text{N} \quad \text{O} \]

The 1,4- and 4,1-benzoxazinone systems were also accessed via ring construction strategies. Condensation of the phenolic propionaldehyde 113 with L-alanine gave the 1,4-benzoxazinone\textsuperscript{113} 114, while an intramolecular Michael
addition in the α,β-unsaturated ester 115 provided the 4,1-benzoxazinone 116 in low yield.

The 2,6-benzoxazinone system was first prepared by a ring construction method involving the dehydration of the amino-alcohol 117 to the 2,6-benzoxazinone 118. Compound 118 was reported to have activity as a diuretic, skeletal muscle relaxant, and CNS stimulant. The 2,6-benzoxazinone 120 was also prepared by a cyanogen bromide-induced four atom ring expansion directly from the isoindole 119.
The synthetic applications of the Meisenheimer rearrangement were extended to the synthesis of the 2,3-benzoxazinones from the 2-benzazocine N-oxides in low yields.

3.3 Rearrangement of Vinyl Unsubstituted and 2'-Substituted N-Oxides

The vinyl unsubstituted and 2'-substituted bases (Table 3.1) were converted to the corresponding N-oxides by m-chloroperbenzoic acid (m-CPBA) in dichloromethane at room temperature. No competing epoxidation of the olefin was observed. Later experiments (see Section 5.3) failed to achieve epoxidation of this system even under forcing conditions. The N-oxides were mixtures of the cis and trans B-ring diastereomers and were used without further purification. The compounds possessed characteristic downfield NMR shifts of the atoms alpha to the electron-deficient quaternary nitrogen, with H1 and Cl at 4.6-5.1 δ and 74.7-84.8 δ respectively. The cis diastereomers were formed preferentially and identified by the more downfield positions of H1 in the 1H NMR.

Thermolysis of the N-oxides in refluxing acetonitrile afforded the 2,3-benzoxazepines in good yield (Table 3.1). No other rearrangement products, such as the [2,3] rearrangement products, were detected by NMR or HPLC analysis of the crude material.
The spectroscopic data of the 2,3-benzoxazepines was consistent with the proposed structures. The compounds exhibited NMR resonances characteristic of this system with H1 at 5.1-5.8 δ and Cl typically at 87.1-87.4 δ. The Cl resonance was shifted upfield to 81.6 δ in the Z-propenyl derivative 124c1.

Further NMR experiments were conducted to confirm the compounds assigned as 124c1 and 124d possessed the benzoxazepine rather than benzoxazonic structures; these isomers could provide similar spectra. An X-H correlation experiment on 124c1 placed the proton vicinal to the methyl group on an olefinic carbon, consistent with the proposed structure. The nOe interactions detected on
analysis of 124d (Figure 3.2) were consistent only with the proposed structure. Compound 125d would not exhibit the required NOE interaction between H5 and H8.

![Figure 3.2 NOE Interactions observed for 124d](image)

Table 3.2 Other Treatments of the N-Oxides 123

<table>
<thead>
<tr>
<th>N-Oxide</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time</th>
<th>Product/s</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>123a</td>
<td>Mesitylene</td>
<td>162</td>
<td>25 min.</td>
<td>124a</td>
<td>15</td>
</tr>
<tr>
<td>&quot;</td>
<td>PrCN</td>
<td>115</td>
<td>30 min.</td>
<td>124a</td>
<td>-</td>
</tr>
<tr>
<td>&quot;</td>
<td>CHCl3</td>
<td>55</td>
<td>7 days</td>
<td>124a</td>
<td>-</td>
</tr>
<tr>
<td>&quot;</td>
<td>DCM</td>
<td>42</td>
<td>6 days</td>
<td>123a:124a (36:64)</td>
<td>-</td>
</tr>
<tr>
<td>&quot;</td>
<td>MeCN</td>
<td>20</td>
<td>3.5 months</td>
<td>123a:124a (21:79)</td>
<td>-</td>
</tr>
<tr>
<td>123c</td>
<td>DCM</td>
<td>42</td>
<td>5 days</td>
<td>124c</td>
<td>54</td>
</tr>
<tr>
<td>&quot;</td>
<td>microwave</td>
<td></td>
<td>5 min.</td>
<td>124c</td>
<td>70</td>
</tr>
<tr>
<td>123d</td>
<td>MeCN</td>
<td>photolysisd</td>
<td>30 min.</td>
<td>complex mixture</td>
<td>-</td>
</tr>
</tbody>
</table>

a from 1H NMR integrals  
b mixtures of the 1-propenyl isomers (Z:E=3:1)  
c microwaved on an alumina support at medium power  
d Hg arc lamp filtered to >225 nm at 5-10°C

A variety of other rearrangement conditions (Table 3.2) were investigated. In higher boiling solvents at reflux the rearrangement occurred rapidly but afforded no new products. Substantial degradation occurred in refluxing mesitylene. At low temperatures in either chloroform, dichloromethane or acetonitrile the Meisenheimer rearrangement occurred slowly. After several months at room temperature in
acetonitrile 79% conversion of 123a to 124a had occurred. No other products were observed. The photolysis of 123d for 30 minutes gave a complex mixture of products, which were not isolated. In a single experiment, the microwave-induced rearrangement of 123c on an alumina support was investigated. Microwave heating on silica or alumina supports\textsuperscript{118-120} has previously altered the course or yields of various thermal reactions. The reaction afforded no change in selectivity but provided the 2,3-benzoxazepine rapidly and in good yield. These conditions may prove useful in future for specific applications of the Meisenheimer rearrangement. The dispersal of the compounds on alumina may minimise intermolecular reactions.

The exclusive [1,2] rearrangement of the 1-vinyl-N-oxides 123a,b, compared to the [2,3] rearrangement of the analogous 1-vinyl-N-ylides 51a,b, was consistent with the behaviour described\textsuperscript{47,48} for the 2-vinylpiperidine derivatives (Section 1.3.2). The results reflected the greater stability of the N-oxides. The molecular orbital energy levels for the N-ylide 51a and N-oxide 123a (Table 3.3) were calculated\textsuperscript{121} with MNDO and confirmed a substantially higher energy difference between the HOMO-LUMO orbitals in the N-oxide, due primarily to the greater stability of the donor HOMO orbital with the anionic charge on the electronegative oxygen atom. The increased energy difference would reduce the efficiency of any orbital overlap and inhibit the formation of a concerted [2,3] transition state from the N-oxides at low temperature.

<table>
<thead>
<tr>
<th></th>
<th>N-ylide 51a</th>
<th>N-oxide 123a</th>
</tr>
</thead>
<tbody>
<tr>
<td>X- (HOMO)</td>
<td>-7.305</td>
<td>-8.889</td>
</tr>
<tr>
<td>π* (LUMO)</td>
<td>0.245</td>
<td>0.625</td>
</tr>
<tr>
<td>ΔE</td>
<td>7.550</td>
<td>9.543</td>
</tr>
</tbody>
</table>

Table 3.3 Calculated Orbital Energies (Hartree) for 51a and 123a
3.4 Pyrolysis of the 1-Vinyl-2,3-Benzoxazepines to Isoxazolo[3,4-b]Naphthalene Derivatives

The 1-vinylbenzoxazepines 124a,b exhibited minor isomeric peaks on GC-MS analysis, which appeared to be artefacts of the thermal analytical technique. It was proposed originally that these isomers were the desired 4,3-benzoxazonines and the pyrolyses of the benzoxazepines were thus investigated.

Pyrolysis of the N-methylbenzoxazepine 124a neat in an evacuated vessel at 180°C afforded no reaction. The compound could be purified by vacuum distillation at this temperature. Pyrolysis at 210°C afforded isomerisation of 124a to a single product in moderate yield. Isomerisation of the N-benzylbenzoxazepine 124b at the lower temperature of 180°C afforded two products (1.89:1.0) in low yield. The major isomerisation products were isolated in each case and identified as the isoxazolo[3,4-b]naphthalene derivatives 126a,b. Only two previous examples of this ring system are known, both with a 4,9-dione structure. The present synthesis provided the first 1,3,3a,4,9,9a-hexahydro derivatives of this rare system. The derivatives were proposed to form via homolysis of the carbon-oxygen bond then [1,5] hydrogen abstraction to afford a nitrone intermediate (Figure 3.3). The intramolecular 1,3-dipolar cycloaddition of the nitrone and olefin functions would afford the isoxazolo[3,4-b]naphthalenes.

![Diagram]

The isoxazolo[3,4-b]naphthalenes were characterised spectroscopically. The analysis of 126b with heteronuclear, short-range homonuclear, and long-range
homonuclear NMR correlation experiments gave a conclusive identification of the
structure and the complete assignment of the NMR spectra (Figure 3.4).

The second pyrolysis product from 124b, a crystalline solid, was identified as
the isoquinoline isomer 127. This compound exhibited chemical shifts in the NMR
spectra at 4.35 δ for H1 and 70.76 δ for Ci, downfield of those for the precursor 49b
and upfield of those for 124b. Compound 127 would arise by the reversion of the
benzoxazepine to the precursor N-oxide, then a Meisenheimer rearrangement with
the migration of the stabilised benzyl radical.
3.5 Rearrangement of 1'-Substituted N-Oxides

3.5.1 Synthesis and Thermolysis

Treatment of the 1'-substituted bases 70 with m-chloroperbenzoic acid at room temperature and workup in the usual manner afforded the N-oxides 128. Substantial (≤ 25%) rearranged material was also isolated from 70a-c (Table 3.4). Subsequent experiments confirmed the rearranged components were the 4,3-benzoazoxazines 129a-c. Only the Z isomers of the benzoazoxazines were observed. The formation of the benzoazoxazines was minimised by cooling the solutions during the workup of the N-oxides, however, the formation of 129b in particular could not be eliminated. The benzoazoxazines were formed by the selective rearrangement of the cis-N-oxides at low temperature; these were present in significant levels only when the solutions were cooled during the workup. The stereoselectivity of the N-oxidation was altered by the bulky 1'-substituents, with the trans diastereomers favoured in their presence and cis diastereomers in their absence.
Table 3.4  Products from Treatment of 70a-d with m-CPBA

<table>
<thead>
<tr>
<th>Input</th>
<th>Workupa</th>
<th>cis:transb</th>
<th>% Yield</th>
<th>N-Oxides 128</th>
<th>Componentsb</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Non-polar Fraction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70a</td>
<td>normal</td>
<td>17:83</td>
<td>29</td>
<td>129a</td>
<td>-</td>
<td>25</td>
</tr>
<tr>
<td>&quot;</td>
<td>cooled</td>
<td>50:50</td>
<td>64</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>70b</td>
<td>normal</td>
<td>0:100</td>
<td>53</td>
<td>129b:130b (44:56)</td>
<td>129b:130b (78:22)</td>
<td>24</td>
</tr>
<tr>
<td>&quot;</td>
<td>cooled</td>
<td>0:100</td>
<td>47</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>70c</td>
<td>cooled</td>
<td>34:66</td>
<td>61</td>
<td>70c:129c (74:26)</td>
<td>-</td>
<td>26</td>
</tr>
<tr>
<td>70d</td>
<td>normal</td>
<td>0:100</td>
<td>82</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

a details given in Section 6.6
b from 1H NMR integrals

Table 3.5  Thermolyses of the N-Oxides 128a-d

<table>
<thead>
<tr>
<th>N-Oxide (cis:trans)a</th>
<th>Conditions</th>
<th>Product Mixturea (%)</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Solventb</td>
<td>Time</td>
<td>128</td>
</tr>
<tr>
<td>128a (50:50)</td>
<td>MeCN</td>
<td>1 h.</td>
<td>-</td>
</tr>
<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>7.5 h.</td>
<td>39</td>
</tr>
<tr>
<td>&quot;</td>
<td>CHCl3</td>
<td>34 h.</td>
<td>53</td>
</tr>
<tr>
<td>&quot;</td>
<td>(0:100)</td>
<td>1 h.</td>
<td>-</td>
</tr>
<tr>
<td>&quot;</td>
<td>DCM</td>
<td>6 days</td>
<td>85</td>
</tr>
<tr>
<td>128b (0:100)</td>
<td>MeCN</td>
<td>1 h.</td>
<td>-</td>
</tr>
<tr>
<td>&quot;</td>
<td>DCM</td>
<td>24 h.</td>
<td>26</td>
</tr>
<tr>
<td>&quot;</td>
<td>DCM*</td>
<td>15 days</td>
<td>88</td>
</tr>
<tr>
<td>128c (34:66)</td>
<td>DCM</td>
<td>36 h.</td>
<td>-</td>
</tr>
<tr>
<td>128d (0:100)</td>
<td>MeCN</td>
<td>1 h.</td>
<td>-</td>
</tr>
<tr>
<td>&quot;</td>
<td>DCM</td>
<td>24 h.</td>
<td>-</td>
</tr>
</tbody>
</table>

a from 1H NMR integrals
b solvents at reflux, except * at 20°C
c the majority was degraded low Rf material

The thermal rearrangements of the isolated N-oxides were examined (Table 3.5). The 1'-methyl, 1'-phenyl and 1'-trimethylsilyl-N-oxides 128a-c afforded mixtures of the Meisenheimer and [2,3] rearrangement products, with a high combined yield based on the unrecovered N-oxides. The 1'-iodoethenyl-N-oxide
128d provided mainly dark degraded material and substantial N-deoxygenation to the precursor amine 70d; the rearrangement products were obtained in low yield.

The course of the rearrangement was dependant on the stereochemistry of the precursor N-oxide and the thermolysis temperature. Rearrangement of the cis N-oxide 128a occurred stereoselectively to give the 4,3-benzoazazonine 129a in refluxing dichloromethane. Under these mild conditions, with moderate reaction times, the trans-N-oxide was unaffected. The benzoazazonine was separated from the unreacted trans-N-oxide and isolated in high yield. The cis-N-oxides 128b and 128c were assumed to undergo a similar stereoselective rearrangement at low temperatures. The formation and low temperature rearrangement of cis-128b during the N-oxidation would account for the observed level of 129b. This assumption could not be confirmed. In refluxing acetonitrile the selectivity of the rearrangement of the cis-N-oxide 128a was decreased (Table 3.6).

**Table 3.6 Selectivity (130/129) of the N-Oxide Rearrangements**

<table>
<thead>
<tr>
<th>N-Oxide</th>
<th>DCM (42°C)</th>
<th>MeCN (82°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cis-128a</td>
<td>0.02</td>
<td>0.22</td>
</tr>
<tr>
<td>trans-128a</td>
<td>2.00</td>
<td>1.94</td>
</tr>
<tr>
<td>trans-128b</td>
<td>4.69</td>
<td>3.35</td>
</tr>
<tr>
<td>trans-128c</td>
<td>1.36a</td>
<td>-</td>
</tr>
<tr>
<td>trans-128d</td>
<td>1.00</td>
<td>2.33</td>
</tr>
</tbody>
</table>

*a calculated assuming selective conversion of cis-128c to 129*

The trans-N-oxides rearranged preferentially to the 2,3-benzoazepines 130a-d at both low and high temperatures. No consistent change in selectivity with temperature was observed. The 1'-substituent on the N-oxides 129a-d had a large effect on the stereoselectivity of the rearrangement (Table 3.6). The phenyl substituent afforded the greatest proportion of the Meisenheimer rearrangement, consistent with its electron delocalising nature, while the trimethylsilyl substituent provided the least. The temperature at which the rearrangement of the trans-N-oxides occurred was also effected by the 1'-substituent and could be placed in the
order phenyl<trimethylsilyl<methyl. The 1'-phenyl and 1'-trimethylsilyl compounds both gave >80% conversion in refluxing dichloromethane after 36 hours, while the 1'-methyl derivative had not rearranged significantly after 6 days. The 1'-phenyl derivative underwent a slow Meisenheimer rearrangement at room temperature.

### 3.5.2 Isolation and Characterisation of the 4,3-Benzoxazonines

Preparative reverse-phase HPLC with acetonitrile/water mixtures enabled the isolation of the 4,3-benzoxazonine derivatives 129b,d and the isomeric benzoxazepines 130b,d from the crude rearrangement mixtures. The benzoxazepines eluted more rapidly and baseline resolution was achieved. In contrast, the isomeric forms of 129a,c and 130a,c were not separated by HPLC analysis. Compound 129a was, however, easily isolated following the selective rearrangement of cis-128a. Compound 129c recrystallised preferentially from a mixture with 130c in methanol. Successive recrystallisations afforded pure material. The benzoxazepine 130c could not be isolated independently.

Compounds 129a,d were respectively colourless and yellow oils, while 129b,c were colourless crystalline solids. Unequivocal evidence for the structure of the 4,3-benzoxazonines was obtained by the X-ray crystallographic analysis of 129b (Figure 3.5).

Variable-temperature experiments were necessary to provide the confirmation of the benzoxazonine structures by NMR analysis. At 25°C in deuterated chloroform the 4,3-benzoxazonines exhibited two broad singlets for the ring protons; at 4.1-4.5 δ for H5 and at 2.8-2.9 δ for H1 with H2 (Figure 3.6). The latter peak typically integrated as only 2-3 protons. The olefinic H7 proton absorbed between 7.44 δ, for 129d, and 6.46 δ for 129a. The measurement of an nOe interaction between H7 and the 6-methyl group of 129a supported the Z-olefin geometry. Improved 1H NMR integrations and 13C NMR spectra (Table 3.7) were obtained at 50°C. At -30°C the broad NMR peaks of 129a resolved to two distinct forms of equal population (Figures 3.6 and 3.7). The two populations were proposed to
reflect the presence of two conformers related by the inversion, or "flipping", of the N3-O4-C5 segment of the structure (see Section 3.7). The displacement of the oxygen atom relative to the N-methyl and 6-methyl groups would explain the large differences in the chemical shifts observed for these groups in the conformers of 129a.

Figure 3.5 The X-Ray crystallographic structure of 129b

Table 3.7 Characteristic $^{13}$C NMR Resonances for the 4,3-Benzoxazinines$^a$

<table>
<thead>
<tr>
<th></th>
<th>129a</th>
<th>129b</th>
<th>129c</th>
<th>134</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>33.24</td>
<td>32.91</td>
<td>33.44</td>
<td>33.15</td>
</tr>
<tr>
<td>NMe</td>
<td>47.41</td>
<td>47.94</td>
<td>47.29</td>
<td>47.35</td>
</tr>
<tr>
<td>C2</td>
<td>62.81</td>
<td>63.00</td>
<td>62.87</td>
<td>62.62</td>
</tr>
<tr>
<td>C5</td>
<td>74.77</td>
<td>74.55</td>
<td>71.42</td>
<td>69.37</td>
</tr>
<tr>
<td>C6</td>
<td>131.10</td>
<td>142.39</td>
<td>145.11</td>
<td>122.71</td>
</tr>
<tr>
<td>C7</td>
<td>127.93</td>
<td>131.32</td>
<td>141.83</td>
<td>144.06</td>
</tr>
<tr>
<td>6-Me</td>
<td>24.36</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6-SiMe$_3$</td>
<td>-</td>
<td>-</td>
<td>-1.17</td>
<td>-</td>
</tr>
</tbody>
</table>

$^a$ ppm at 25°C in CDCl$_3$
Figure 3.6 1H NMR spectra for 129a in CDCl₃ at -30°C and 25°C
Figure 3.7 $^{13}$C NMR spectrum for 129a in CDCl$_3$ at -30°C with two conformers
The mass spectra of the 4,3-benzoxazonines displayed significant ions at M-59 and M-74. These fragments were consistent with the formation of a highly conjugated radical cation (Figure 3.8). The base peak was either at m/z 206 or 204.

![Proposed mass spectral fragmentation of the benzoxazonines](image)

**Figure 3.8** Proposed mass spectral fragmentation of the benzoxazonines

### 3.5.3 Thermal Behaviour of 4,3-Benzoxazonine Derivatives

The isomers 129b and 130b exhibited almost identical mass-spectral fragmentation patterns. This behaviour was rationalised by proposing either an initial cleavage of the O-C bond, in each case to a common delocalised radical cation, or thermal equilibration of the isomers during volatilisation. The thermolyses of the 6-methyl and 6-phenyl benzoxazonines 129a,b were thus investigated.

In refluxing acetonitrile the benzoxazonines 129a,b isomerised slowly by a [1,3] shift to the benzoxazepines 130a,b (Table 3.8). The isomerisation rate was increased in refluxing xylene, affording mixtures of the 9- and 7-membered ring derivatives which were unchanged by longer reaction times. The isomerisation of 130b to an identical mixture of 129b and 130b confirmed an equilibrium was established between the benzoxazonines and benzoxazepines at high temperatures. The equilibrium favoured the benzoxazepines and was consistent with the expected thermodynamic preference for the less strained 7-membered ring. A higher level of
the 6-phenylbenzoxazonine derivative at equilibrium reflected the additional conjugation in this derivative.

![Image of the reaction 129 → 130](Image)

**Table 3.8** Thermal Interconversion of 129 and 130

<table>
<thead>
<tr>
<th>Precursor</th>
<th>Solventa</th>
<th>Time (h.)</th>
<th>Product ratio b 129:130</th>
</tr>
</thead>
<tbody>
<tr>
<td>129a</td>
<td>MeCN</td>
<td>1</td>
<td>93:7</td>
</tr>
<tr>
<td>&quot;</td>
<td>Xylene</td>
<td>&quot;</td>
<td>5:95</td>
</tr>
<tr>
<td>129b</td>
<td>MeCN</td>
<td>1</td>
<td>89:11</td>
</tr>
<tr>
<td>&quot;</td>
<td>Xylene</td>
<td>4</td>
<td>54:46</td>
</tr>
<tr>
<td>&quot;</td>
<td>Xylene</td>
<td>1</td>
<td>24:76</td>
</tr>
<tr>
<td>130b</td>
<td>&quot;</td>
<td>1</td>
<td>22:78</td>
</tr>
</tbody>
</table>

a solvents at reflux; MeCN (82°C), Xylene (137-142°C)
b from 1H NMR integrals.

Literature precedents exist for the thermal [1,3] isomerisation of 2-butenylhydroxylamine derivatives to 2-propenylhydroxylamine derivatives in both acyclic and cyclic systems. A radical pair mechanism was proposed due to the observed extent (20%) of racemisation.

### 3.5.4 Discussion

Modelling studies (Section 2.3.2) predicted that only the cis-N-oxides would undergo a concerted rearrangement to the Z-benzoxazonines. Consequently, the promotion of the concerted rearrangement by the 1'-substituents was linked to the factors able to effect the rearrangement of the cis-N-oxides to the stable Z-4,3-benzoxazonines. The 1'-substituents were proposed to act by lowering the conformational energy of conformer VII below that of conformer V (Figure 2.3, pg. 24). With conformer VII as the global minimum, the activation energy required to achieve the pro-Z concerted state (Figure 3.9) would be lowered, and the [2,3]
rearrangement would be promoted. This behaviour was supported by the observed increase in the proportion of Z-benzazonine isomers formed with the rearrangement of the 1'-substituted salts 72a-c.

![Proposed concerted transition states for 128a-d](image)

Figure 3.9 Proposed concerted transition states for 128a-d

The failure of the 1'-substituted N-oxides to afford any traces of the E-4,3-benzoxazonine isomers, while the Z-benzoxazonines were obtained, clearly indicated that either (i) a concerted pro-E transition state (Figure 3.9) could not be achieved, or (ii) the E-benzoxazonines were not thermodynamically favoured. The latter appeared likely given the strained nature of the similar E-benzazonine derivatives isolated in this work. Considerable ring strain in the E-benzoxazonine system would prevent the rearrangement of the comparatively stable N-oxides at low temperatures and explain the total lack of [2,3] rearrangement from the 1-vinyl and 2'-substituted N-oxides 123a-d, for which the E-benzoxazonine derivatives were the expected major products. It should be noted that in the only previous examples of the [2,3] rearrangement with ring expansion, Z double bond derivatives were formed (Section 1.3.2, pg. 10).

The [1,3] isomerisation of the benzoxazonines afforded the possibility that the benzoxazepines 130a-d (Table 3.5) were formed by a [2,3] rearrangement then [1,3] shift, rather than a direct Meisenheimer rearrangement. The slow rate of the [1,3] shift from 129a,b ruled out this mechanism for these derivatives. It was noted, however, that the isomerisation\textsuperscript{125} of the 2-butenyl-1-phenylhydroxylamine (Figure 3.10) to the more conjugated product occurred under mild conditions. Thus the isolation of the 5-(dimethoxyphenyl)benzoxazonine 125d (pg. 86), and any other 5-arylbenzoxazonines, would be unlikely from the present thermal rearrangements.
Substantial quantities of the Z-benzoxazinones 129a-d were formed on rearrangement of the trans-N-oxides 128a-d (Table 3.6), however, it was predicted (Section 2.3.2) that only a pro-\(E\) concerted state could be formed from the trans-N-oxides. Reexamination of the molecular models suggested that, with the rapid formation of the \(E\)-benzoxazinones blocked, a pro-\(Z\) concerted state might be plausible with the rotation of the olefin group in conformer IV (Figure 2.3, pg. 24) toward the fused ring. The distance between the O- and C2' centres in this geometry, however, would be on the borderline for a successful concerted interaction. An alternative pathway to the Z-benzoxazinones from the trans-N-oxides was proposed by assuming the E-benzoxazinone derivatives formed briefly but reverted, by a radical process, to mixtures of the cis-N-oxides, trans-N-oxides and the 2,3-benzoxazepines. The cis-N-oxide would then undergo a rapid concerted rearrangement to the Z-benzoxazinone. No evidence could be obtained for this proposition.

3.6 Synthesis and Rearrangement of a 1-Aryl N-Oxide

The availability, from another project, of the imine precursor of the 1-fluorophenyl imine salt 131, prompted the investigation of the synthesis and rearrangement of a 1-aryl-1-vinyl-\(N\)-oxide. The reaction of 131 with vinylmagnesium bromide afforded the tetrahydroisoquinoline base 132 in excellent yield despite the steric crowding at the C1 centre.
The $N$-oxidation of 132 with $m$-CPBA in dichloromethane at 20°C afforded substantial rearrangement ($\leq 70\%$) directly without isolation of the $N$-oxide 133. The major component was isolated by p.t.l.c. in moderate yield and identified as the 7-fluorophenyl-4,3-benzoazoxanone 134 by spectroscopic and elemental analysis. The compound, a crystalline solid, behaved similarly to the previously described benzoazoxanones and exhibited two sets of signals on NMR analysis at -30°C. At 25°C in the $^{13}C$ (Table 3.7, pg. 95) and $^1H$ NMR spectra, a single set of well resolved signals was observed with the H5 protons at 4.35 and 3.99 $\delta$, and H6 at 6.52 $\delta$. The Z-stereochemistry of the benzoazoxanone was confirmed by the detection of an nOe between H6 and the ortho-protons of the pendant aryl group.

The facile [2,3] rearrangement of 133 may be due to the relief of steric crowding at the C1 position, together with the increased conjugative stabilisation in 134.
3.7 Molecular Modelling of the Z-1,2,3,5-Tetrahydro-4,3-benzoazoxazine System

In order to obtain a better understanding of the conformational preferences of the 4,3-benzoazoxazine derivatives the parent Z-1,2,3,5-tetrahydro-4,3-benzoazoxazine was investigated with PCModel.\textsuperscript{76} The five lowest energy conformations were identified (Table 3.9). These structures are included in either Figure 3.11 or Appendix A. Several of the conformers (2, 3, and 4) were analogous to those previously identified for the Z-benzazonine system (conformers 2, 5, and 4, Table 2.5, pg. 36). The lower energy conformers adopted a folded structure with the nitrogen atom displaced from the aromatic ring plane by 1.8-2.5 Å.

Conformers 1 and 2 were significantly lower in energy than the others. The Boltzmann distribution predicted a 2:1 mixture at 25°C. These conformers possessed almost the same basic structure, however, in conformer 1 the oxygen occupied an endocyclic position, over the fused aromatic ring, while in conformer 2 the oxygen was exocyclic (Figure 3.11). The presence of these two closely related conformers would explain the observed conformational flexibility of the 4,3-benzoazoxazines during NMR analyses (Section 3.5.2). The two conformers may exchange rapidly with the inversion of the N3-O4-C5 portion of the structure.

<table>
<thead>
<tr>
<th>conformer</th>
<th>E (kcal)</th>
<th>inc H_f</th>
<th>Population\textsuperscript{a}</th>
<th>N-elevation\textsuperscript{b}</th>
<th>N-Ar planar\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23.56</td>
<td>20.34</td>
<td>66.3%</td>
<td>2.28</td>
<td>3.51</td>
</tr>
<tr>
<td>2</td>
<td>23.96</td>
<td>19.65</td>
<td>33.6%</td>
<td>2.45</td>
<td>2.99</td>
</tr>
<tr>
<td>3</td>
<td>30.34</td>
<td>25.77</td>
<td>&lt;0.1%</td>
<td>1.81</td>
<td>4.50</td>
</tr>
<tr>
<td>4</td>
<td>32.19</td>
<td>28.03</td>
<td>&lt;0.1%</td>
<td>2.45</td>
<td>2.59</td>
</tr>
<tr>
<td>5</td>
<td>33.66</td>
<td>30.44</td>
<td>&lt;0.1%</td>
<td>0.82</td>
<td>4.41</td>
</tr>
</tbody>
</table>

\textsuperscript{a} from the Boltzmann distribution at 293 K  
\textsuperscript{b} distance of N above the aromatic plane (Å)  
\textsuperscript{c} distance of N from the aromatic centre in the aromatic plane (Å)
Figure 3.11 Three perspectives of (a) conformer 1 and (b) conformer 2 for the Z-benzoxazonine system
The X-ray crystallographic analysis of the substituted 4,3-benzoxazinone 129b confirmed the modelling predictions and afforded a structure based on conformer 2 of the Z-1,2,3,5-tetrahydro-4,3-benzoxazinone system (Figure 3.5, pg. 95).

3.8 Conclusion

The 1-vinylic-tetrahydroisoquinoline N-oxides generally displayed a lower propensity for the concerted [2,3] rearrangement than the analogous N-ylides examined in Chapter 2. This behaviour reflected the additional stability of the N-oxides and an inability to form the expected E-4,3-benzoxazinone derivatives. Derivatives of the E-4,3-benzoxazinone system are unlikely to be achieved due to the strained nature of the ring and the potential facile homolytic cleavage of the oxygen-carbon bond, enabling isomerisation to the stable 2,3-benoxazepine derivatives.

The successful [2,3] rearrangement of the 1-vinylic-tetrahydroisoquinoline N-oxides required the presence of a 1-aryl or 1'-substituent. The 1'-substituent acted by favouring the appropriate pro-Z concerted transition state geometry in the cis-N-oxides, while the 1-aryl group promoted the formation of a more highly conjugated product. With these substituents, a route was developed which afforded the first examples of the Z-4,3-benzoxazinone system, in moderate yield, via the [2,3] rearrangement. The Z-4,3-benoxazazonines isomerised to equilibrium mixtures favouring the 2,3-benoxazepine isomers at high temperatures, and any future reactions of these compounds should be conducted at low temperatures.

The appropriately substituted cis-N-oxides afforded exclusively the Z-4,3-benoxazazonines at low temperatures (<40°C). In this work, however, the trans-N-oxides were formed preferentially during the N-oxidation. The rearrangements with these diastereomers present afforded, except from a 1-isopropenyl derivative, mixtures of the 2,3-benoxazepines and Z-4,3-benoxazazonines. The development of a method able to afford selectively the cis-N-oxides would enable the present
synthesis to be optimised and afford a high-yielding, convenient route to the Z-4,3-benzoxazinone system.
CHAPTER 4
FURTHER APPLICATIONS OF [1,2] REARRANGEMENTS

4.1 Introduction

4.1.1 General Introduction

The Stevens and Meisenheimer rearrangements have provided the one atom ring expansion of a limited number of heterocyclic systems (Section 1.2.3). Many applications of these rearrangements to the synthesis of medium-sized aza- or oxaza-heterocyclic systems remain to be examined. It was proposed to investigate the rearrangements of the 5,6-dihydro-s-triazolo[4,3-α]-1,4-benzodiazepine derivatives (Figure 4.1) and the tricyclic bridgehead N-ylides and N-oxides (Figure 4.2). The former may afford access to the unknown triazolo[4,3-α]-1,4-benzodiazocine and triazolo[4,3-α]-5,1,4-benzoxadiazocine systems, while the latter would give the novel fused methylene or oxa-bridged medium-sized heterocyclic systems.
4.1.2 Introduction to 5,1,4-Benzoxadiazocines

Many potent CNS active therapeutics have been developed based on the 1,4-benzodiazepine heterocyclic system,\textsuperscript{126-129} including Nitrazepam\textsuperscript{130} 135a and Diazepam\textsuperscript{131} ("Valium") 135b. The addition of a fused triazolo[4,3-\textalpha] ring, as in Alprazolam\textsuperscript{55} 136, provided therapeutics of higher activity. As a class these compounds typically possessed potent anxiolytic, anticonvulsant, muscle-relaxant and sedative activity. Derivatives of the 1,4-benzodiazepine system, or other compounds active at the benzodiazepine receptor, remain the subject of intense investigation\textsuperscript{132} as the multiple clinical actions, habituation, and addiction of many of the known drugs are undesirable.

![Chemical Structures](image)

The ring-expanded analogues of the 1,4-benzodiazepines, the 5,1,4-benzoxadiazocines\textsuperscript{31,32} 139 and the 2,3,7-benzoxadiazonine\textsuperscript{32} 140, were synthesized via the Meisenheimer rearrangement of the N-oxides 137 and 138. These medium-ring heterocyclic derivatives demonstrated CNS activity in preliminary pharmacological tests. Compound 139d exhibited some possible antagonistic activity.
at the 5-HT3 receptor site and may represent a new lead compound of novel structural type for this receptor. Consequently, the proposed synthesis of triazolo[4,3-α]-1,4-benzodiazocine and triazolo[4,3-α]-5,1,4-benzoxadiazocine derivatives (Figure 4.1) was of interest for the further development of this series. It was reasoned that, as in the 1,4-benzodiazepines, the addition of a fused triazolo[4,3-α] ring may provide 5,1,4-benzoxadiazocine derivatives of increased CNS activity.

4.1.3 Introduction to Fused Methylenes or Oxa-bridged Medium-sized Heterocyclic Systems

Bridged fused medium-sized heterocyclic systems have attracted considerable attention, with particular interest in the pharmaceutical applications of derivatives of this class. Some examples include the methylene bridged systems of the analgesic eptazocine, a 1,6-methano-4-benzazonine, and the antitumour alkaloid vinblastine (Figure 4.3), one of the most often used compounds in cancer chemotherapy. Oxa-bridged systems, such as the antitumour antibiotic FR-900482 (Figure 4.3) and its derivatives which possess a 1,5-epoxy-1-benzazocine core, are also of great interest.

It was proposed that the [1,2] rearrangements of the tricyclic bridgehead N-oxides and N-ylides (Figure 4.2) may afford the new oxa- or methylene-bridged
heterocyclic systems of pharmaceutical interest. In addition, the potential [2,3] rearrangements of these derivatives (Figure 4.4), although considered unlikely, were of interest.

![Figure 4.4](image)

Few investigations have been made of the potential for [1,2] rearrangements to provide access to oxa- and methylene-bridged heterocycles. One report of the synthesis of an oxa-bridged heterocycle by the Meisenheimer rearrangement has been published,\textsuperscript{139} in which the tetrahydro-2H-azetopyrido[3,4-b]indole N-oxide 141 rearranged to the 3,6-epoxyhexahydroazocino[5,6-b]indole derivative 142 at room temperature, while the 1-hydroxymethyl N-oxide 141b rearranged to 142b only on heating in tetrahydrofuran to 55°C, and was obtained along with a substantial amount of the Cope elimination product.

![Chemical structures](image)

4.2 Rearrangements of 5,6-Dihydro-s-triazolo[4,3-a]-1,4-Benzodiazepine Derivatives

4.2.1 Synthesis of $N$-Methylidihydroalprazolam

Initially it was thought that $N$-methylidihydroalprazolam 147, required as the precursor for the rearrangement studies, could be made by the $N5$-methylation of
Alprazolam to the iminium salt 143, followed by reduction. The treatment of Alprazolam with iodomethane at 50°C, however, provided a mixture of at least two isomeric methiodide salts (ratio=2.24:1). The major isomer possessed a 1-methyl signal at 3.19 δ, downfield of that for Alprazolam (2.64 δ) and consistent with the 1,2-dimethyl iminium salt 144. The reduction of this crude alkylated material with sodium borohydride afforded the known 140 1,2-dimethyl derivative 145 as the major product. Compound 145 possessed a characteristic doublet in the 1H NMR spectrum for the 1-methyl signal at 1.52 δ, and a quartet for H1 at 4.75 δ. The results were consistent with previous studies which reported the preferential N-alkylation140 or protonation141 of Alprazolam at the triazolo nitrogen atom N2.

The development of an alternative route to N-methyldihydroalprazolam from Alprazolam via dihydroalprazolam 146 was then investigated. It was reasoned that under acidic conditions the protonated 2-, 3- or 5-iminium salts of Alprazolam would exist in equilibrium. The reduction of the non-aromatic 5,6 site may then occur preferentially to give 146. Dihydroalprazolam had been prepared previously,142-145
but only as the direct product of benzazepine ring construction and not from Alprazolam.

\[
\begin{align*}
\text{Me} & \quad \text{N} \\
\text{N} & \quad \text{CI} \\
\text{N} & \quad \text{R} \\
\text{Me} & \quad \text{N-Methyldihydroalprazolam}
\end{align*}
\]

\[
\begin{align*}
\text{Cl} & \quad \text{Ph} \\
146 & \quad \text{Dihydroalprazolam}
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \quad \text{N} \\
\text{N} & \quad \text{R} \\
\text{Cl} & \quad \text{Ph} \\
148a & \quad \text{R} = \text{CH}_2\text{CH}_3 \\
b & \quad \text{R} = (\text{CO})\text{CH}_3
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \quad \text{N} \\
\text{N} & \quad \text{R} \\
\text{Cl} & \quad \text{Ph} \\
147 & \quad \text{N-Methyldihydroalprazolam}
\end{align*}
\]

The treatment of Alprazolam at room temperature with either sodium borohydride in ethanol, sodium cyanoborohydride in methanol/acetic acid, or sodium cyanoborohydride in glacial acetic acid, gave no reaction. The latter system at 50°C afforded three products from which dihydroalprazolam 146, the major component, was isolated in 36% yield. Compound 146 exhibited a $^1$H NMR resonance for H6 at 4.95 $\delta$ as a singlet, consistent with the proposed 4H-5,6-dihydro- structure but not the alternative potential 1H-2,4- or 3H-3a,4-dihydro- isomers. The two minor products, 25% and 11% respectively of the crude product mixture, were tentatively identified as the N-ethyl 148a and N-acetamide 148b compounds by GC-MS analysis. The formation of 148b reflected the condensation of 146 with acetic acid and suggested that the acidification of the mixture with a mineral acid, rather than an organic acid, would provide an increased yield of 146. The subsequent reduction of Alprazolam by sodium cyanoborohydride in methanol acidified with hydrochloric acid afforded 146.
in excellent yield and provided an efficient and mild route from Alprazolam to dihydroalprazolam. The use of sodium cyanoborohydride, a more stable and selective reagent under acidic conditions than sodium borohydride, was critical to the success of this reaction.

The treatment of 146 with formaldehyde and sodium borohydride afforded the expected reductive methylation product, together with several minor byproducts. The purification of 147 by p.t.l.c. on silica failed, however, with the material being degraded to a mixture of four components. The $^1$H NMR spectrum of the mixture indicated the formation of quaternary amine or iminium salts with the signals for the methyl groups between 3.3 and 3.5 $\delta$, downfield of their positions in 146. The impurities in the reductive methylation of 146, and thus the complications inherent in purifying 147, were avoided by conducting the reaction with sodium cyanoborohydride in acidic solution. Under these conditions 147 was formed in almost quantitative yield. No impurities were detected by GC-MS. The NMR (Figure 4.5) and mass spectral data for N-methyldihydroalprazolam were consistent with the proposed structure. The present method appeared to be the first preparation of this potentially CNS active 1,4-benzodiazepine derivative.

Prior to the successful preparation of 147 described above, the one-pot conversion of 136 to 147 was investigated. The reduction with $N$-alkylation of indole, quinoline, and isoquinoline, by a combination of sodium borohydride and the
appropriate carboxylic acid, was described by Gribble et al.\textsuperscript{147,148} The mechanism was proposed\textsuperscript{148} to involve the generation of the free aldehyde from the carboxylic acid, via an acyloxyborohydride species, with the subsequent reductive amination of the saturated amine formed \textit{in situ}. The formation of $N$-ethylhydroalprazolam \textsuperscript{148a} in previous experiments suggested this methodology may be applicable to the direct generation of $N$-methyldihydroalprazolam from Alprazolam.

The treatment of Alprazolam with sodium borohydride and formic acid at $0^\circ$C produced mixtures of 147 and the formamide derivative 149. Compound 149 was identified by MS and NMR spectral analysis. The compound exhibited two conformers in deuterated chloroform at room temperature, reflecting hindered rotation of the amide bond. The ratio of 149 to 147 was dependant on the rate of addition of the formic acid to the reaction mixture. The addition of the acid in one dose produced mainly the amide 149 ($149/147=13.3$), while the slow dropwise addition of the acid produced a significant improvement in the yield of 147 ($149/147=1.0$). The results were consistent with the reaction of 146, generated \textit{in situ}, with either formic acid or formaldehyde. The rate of addition was assumed to control the relative concentrations of these species. A previous study\textsuperscript{146} of this type noted the formation of an amide byproduct and demonstrated this compound was not an intermediate in the one-pot reaction.

\[
\begin{align*}
\text{HCO}_2\text{H} &\quad \text{NaBH}_4 \\
\Rightarrow &\quad [146] \\
\text{Me} &\quad \text{N} \\
\text{N} &\quad \text{N} \\
\text{Cl} &\quad \text{Ph} \\
\text{H} &\quad \text{O} \\
\end{align*}
\]
The further development of the one-pot reaction of 136 to 147 was prevented by time constraints. It appeared likely that the complete optimisation of reaction variables, such as reactant stoichiometry, concentration, and method of addition, would allow the successful one-pot conversion of Alprazolam to N-methyldihydroalprazolam.

4.2.2 Attempted Synthesis of a Quaternary N-Ylide Precursor

In several reactions the selective N-alkylation of 147 to the immediate ylide precursor, the ethoxycarbonylmethyl salt 150, was pursued, but ultimately without success. The treatment of 147 with ethyl bromoacetate in acetone at elevated temperatures failed to provide any alkylation, while the reaction of 147 with ethoxycarbonylmethyltriflate at room temperature afforded a mixture of several salts. Numerous signals were present in the $^1$H NMR spectrum of the material between 2.96 and 2.45 δ, consistent with a downfield shift of the 1-methyl groups' signal by the formation of 2- or 3- iminium salts. These results suggested that, as for Alprazolam, the triazole ring nitrogens of 147 were the preferred nucleophilic sites for N-alkylation.

With the planned synthesis of 150 found to be unsuccessful, the intended synthesis of a triazolo[4,3-α]-1,4-benzodiazocine derivative (Figure 4.1) via the Stevens rearrangement of an N-ylide was abandoned.
4.2.3 Synthesis and Rearrangement of an N-Oxide to a Triazolo[4,3-a]-5,1,4-benzoxadiazocine Derivative

Alprazolam is known\textsuperscript{148} to react selectively with peracids to produce the 5-oxide, in contrast to the reaction of Alprazolam with alkylating agents. The treatment of \ref{147} with m-CPBA, however, gave a mixture of compounds. Analysis of the material by GC-MS indicated the major component possessed a molecular weight of 322 mass units, consistent with the triazolobenzodiazepin-4-one structure \ref{151}. It was proposed that the potential for a highly stabilised radical at C4 allowed hydrogen abstraction and attack by a chlorobenzoate radical, with the formation of a 4-chlorobenzoate derivative. The hydrolysis of this and then oxidation would give \ref{151}. A 3-chlorobenzoate-4,1,5-benzoxadiazocine was isolated after treatment of a 1,3,4,5-tetrahydro-1,4-benzodiazepinone with m-CPBA.\textsuperscript{32} The hydrolysis and tautomerism of 4-acetoxy-4\textit{H}-triazolo[4,3-a]-1,4-benzodiazepine derivatives to 4\textit{H}-triazolobenzodiazepin-4-ones has been reported.\textsuperscript{148}

\[\text{147} \xrightarrow{\text{m-CPBA}} \text{151}\]

\[\text{MMPP} \quad \text{EtOH/H}_2\text{O} \]

\[\text{152} \xrightarrow{\text{MeCN} \quad \Delta} \text{153}\]

The relatively new oxidation agent, magnesium monoperoxyphthalate\textsuperscript{149} (MMPP), demonstrated a clear superiority over m-CPBA for the N-oxidation of \ref{147}. 
This reagent reacted selectively with 147 at room temperature to give a mixture of the \( N \)-oxide 152 and the desired Meisenheimer rearrangement product, the triazolo[4,3-\(a\)]-5,1,4-benzoxadiazocine 153 (152/153=1.9). No other products were observed. The \( N \)-oxide was not isolated but signals at 80.63 \( \delta \) for C6 and 5.61 \( \delta \) for H6 in the \( ^{13} \)C and \( ^{1} \)H NMR spectra were consistent with the expected structure. The compound exhibited broad peaks in the \( ^{1} \)H NMR spectrum and individual signals for the expected cis and trans diastereomers were not observed.

It should be noted that 147 and 153 were not distinguished by t.l.c. with common solvent mixtures on silica. Consequently, monitoring the \( N \)-oxidation of 147 by t.l.c. gave misleading results, as the formation of 153 gave the appearance of incomplete oxidation. A long reaction time was adopted to ensure the removal of 147. In addition, on-column reactions during GC-MS provided a mixture of 147 and 153 from pure 153, preventing analysis by this technique.

The Meisenheimer rearrangement of \( N \)-oxides at room temperature is typically associated with the formation of nine membered, or larger, heterocycles, and was not observed during the \( N \)-oxidation of the 1,4-benzodiazepinones 137. The low temperature rearrangement of 152 reflected the presence of additional ring strain in the triazolo[4,3-\(a\)]-1,4-benzodiazepine ring system when compared to the 1,4-benzodiazepinone system.

Heating the \( N \)-oxidation mixture of 152 and 153 in acetonitrile at reflux promoted the facile Meisenheimer rearrangement of the remaining 152 to 153. The purification of this crude reaction mixture by p.t.l.c. on silica gave the triazolo[4,3-\(a\)]-5,1,4-benzoxadiazocine 153, the first example of this ring system, as a colourless powder in 50% yield from \( N \)-methyldihydroalprazolam.

Compound 153 was characterised principally by \( ^{13} \)C NMR (Figure 4.6), \( ^{1} \)H NMR (Figure 4.7) and MS analysis. The downfield positions of H7 and C7 in the NMR spectra, at 5.98 \( \delta \) and 86.43 \( \delta \) respectively, supported the proposed structure, with the deshielding caused by the adjacent electronegative oxygen exceeding that
present in the N-oxide. The alternative rearrangement of the N-oxide toward C4 was precluded by the comparatively high-field chemical shifts for H4.

Figure 4.6 $^{13}$C NMR assignments for 153

The H4 methylene protons of 153 demonstrated chemical shift nonequivalence and geminal coupling in the $^1$H NMR spectrum. This behaviour is characteristic of the 1,4-benzodiazepine pharmacueticals$^{150}$ and was exhibited by the triazolobenzodiazepine precursors, 146 and 147, and the 5,1,4-benzoxadiazocin-2-ones$^{32}$ $^{139}$. The appearance of the chemical shift nonequivalent protons confirmed that only one conformation of 153 was important at room temperature, with a large energy barrier preventing ring inversion. The shifts of the methylene protons, at 4.43 $\delta$ and 4.22 $\delta$, were assumed to reflect the position of each proton in the shielding region of the anisotropic aromatic ring. In the 1,4-benzodiazepinone therapeutics a much larger shift difference, for example 5.50 $\delta$ and 4.09 $\delta$ for Alprazolam, was observed. The results indicated that 153 did not adopt a folded chair-like conformation in which one proton was significantly nearer the aromatic ring. The upfield position of the 1-methyl signal at 1.79 $\delta$, compared to those for Alprazolam (2.65 $\delta$) and for dihydroalprazolam (2.54 $\delta$), suggested that 153 adopted a conformation with the triazole ring at a greater angle to the aromatic ring, removing the 1-methyl group from the deshielding region in the plane of the aromatic ring.
Figure 4.7 $^1$H NMR spectrum and assignments for 153 in CDCl$_3$
4.3 Rearrangements of Tricyclic Bridgehead N-Ylides and N-Oxides

4.3.1 Synthesis of the Pyrrolo[2,1-a]isoquinoline and Benzo[a]quinolizine Precursors

The vinyl substituted pyrrolo[2,1-a]isoquinoline and benzo[a]quinolizine precursors 158a and 158b, required to test the proposed rearrangements (Figure 4.2, pg. 107), were prepared from the known iminium salts151,152 154 and 156. The Grignard reaction of vinylmagnesium bromide in tetrahydrofuran with 156 did not proceed at room temperature. Refluxing the reaction mixture, however, provided 158b in low yield. In contrast 154 failed to react with vinylmagnesium bromide even in tetrahydrofuran at reflux. The low reactivities of 154 and 156 toward vinylmagnesium bromide reflected the steric crowding around the electrophilic 10b- and 11b-carbon centres of the tricyclic iminium salts. The planar nature of the pyrrole ring in 154 may result in the more efficient shielding of the electrophilic carbon by the α-protons, and thus the lower reactivity of 154. Methylmagnesium iodide reacted with 154 in refluxing diethyl ether.153

The conversion of hindered 1-alkyl-3,4-dihydroisoquinolinium salts to 1-alkyl-1-vinyl-3,4-dihydroisoquinoline derivatives via 1-cyano adducts and their reaction with vinylmagnesium bromide was achieved.105 The application of this technique to the present work allowed the synthesis of the previously unattainable 158a under surprisingly mild conditions. The reaction of the pyrrolo[2,1-a]isoquinoline cyanide adduct 155 with vinylmagnesium bromide gave 158a in good yield at room temperature. The mechanism involved is unclear. The reaction of the benzo[a]quinolizininium cyanide adduct 157 with vinylmagnesium bromide was not attempted, but would be expected to provide an improved yield from 156 to 158b.

The cyanide adducts 155 and 157 were formed by the reaction of the iminium salts with cyanide ion in water/methanol. The benzo[a]quinolizininium salt reacted more readily with this reagent than the pyrrolo[2,1-a]isoquinolininium salt. Thus, elevated
temperatures were required for the conversion of 154 to 155, while 156 gave 157 at room temperature. Both 155, a pale yellow oil, and 157, an off-white solid, developed a red colour on storage and were degraded by heating. The compounds lost HCN on mass spectral analysis and afforded spectra identical with those of the resultant enamines. The molecular ions were not observed. The $^1$H and $^{13}$C NMR spectra of 155 and 157 were consistent with the proposed structures. A quaternary $^{13}$C NMR signal in the 118-127 $\delta$ region confirmed the presence of the cyano group.

The 10b- and 11b-vinyl substituted bases 158a,b were isolated as oils. High resolution MS analyses confirmed the molecular formulae. The loss of the vinyl group provided the base peak (M-27) in the mass spectra of 158a,b. The $^1$H NMR spectra confirmed the presence of the vinylic group, while two-dimensional homonuclear correlation experiments afforded the assignment of the methylene spin
systems. The quaternary carbons alpha to the aromatic, vinyl, and amino moieties in 158a and 158b were shifted downfield to 67.55 and 62.22 δ respectively in the 13C NMR spectra.

Several attempts were made to synthesise the 10b- and 11b-phenyl substituted tricyclic derivatives 159a,b from the iminium salts or cyanide adducts. It was reasoned that the phenyl substituent would provide extra resonance stabilisation of the radical pathway for later N-oxide or N-ylide [1,2] rearrangements. An earlier attempt31 to add a phenyl Grignard reagent to the chloride salt of 154 was unsuccessful. The conversion of 154 to the cyanide adduct 155 failed to promote any reaction with phenylmagnesium bromide and 159a was not obtained. Similarly, the reactions of phenylmagnesium bromide or phenyllithium with 157 failed to produce 159b. Compound 159a is known,61,63 however, time did not permit its synthesis via the published technique involving the formation and reduction of a 10b-phenylpyrrolo[2,1-a]isoquinoline-3-one derivative.

4.3.2 Synthesis and Base-Promoted Behaviour of Quaternary Salts

The tricyclic amines 158a,b were alkylated with ethoxycarbonylmethyl triflate in acetonitrile to provide, after treatment with potassium bromide, the N-ethoxycarbonylmethyl salts 160a,b. Compound 160a was obtained as a single diastereomer which displayed the expected downfield shift of the 10b-carbon signal to 83.88 δ in the 13C NMR spectrum. It is thought likely that 160a was the trans B/C fused diastereomer, as hexahydropyrrolo[2,1-a]isoquinolines typically adopt a low energy trans B/C fused conformation, and the N-alkylation of this conformation would be less sterically hindered than for the cis B/C fused conformers in the presence of the 10b-vinyl group. In contrast, 160b was a mixture (3.3:1) of two conformationally flexible diastereomers. The N-Alkylation to a cis B/C fused diastereomer of 160b may have occurred as the dihedral angle adopted in cis B/C fused 158b, between the nitrogen lone-pair and the vinyl-substituent, would be considerably larger than that in 158a, decreasing the steric hindrance of the reaction.
The base promoted reactions of 160a,b were tested initially at mild temperatures. No reaction occurred upon treatment of 160a,b with DBU in acetonitrile at temperatures below the refluxing point of the solvent. In refluxing acetonitrile minor amounts of non-polar rearrangement products were observed after 10 to 20 hours. Lengthier reaction times failed to increase the level of this material. Similarly, conducting the reactions in refluxing butyronitrile provided no significant increase in the non-polar material and led to darkening of the reaction solution.

The small amount of non-polar material from the reaction of 160a in refluxing acetonitrile was purified by reverse-phase preparative HPLC to give a fraction with approximately 95% purity. The major component was tentatively attributed to the desired 3,7-methano-3-benzazonine 161a and represented at best a 1% yield. The small amount of 161a obtained prevented its unequivocal identification, however, the \(^1\)H NMR and \(^{13}\)C DEPT NMR (Figure 4.8) spectra were consistent with the proposed structure. The presence of a vinyl group and a downfield \(^{13}\)C NMR signal at 64.48 \(\delta\), attributed to the bridging carbon, were indicative of 161a and eliminated the obvious alternative products from either the Hofmann elimination or the [2,3] sigmatropic rearrangement.
The non-polar material from the reaction of 160b in refluxing acetonitrile represented at best a 7% total yield of products. The GC-MS and $^1$H NMR spectral analysis of the material revealed the presence of the precursor 158b (33% of the material), assumed to be present as an impurity in 160b or formed by bromide catalysed N-dealkylation, and three isomers (10%, 36%, and 11% of the material) with the correct molecular weight for 161b and almost identical mass spectra. In view of the low yields no attempts were made to purify the material further.

4.3.3 Synthesis and Thermolyses of the \(N\)-Oxides to Fused Oxa-Bridged Medium-Sized Systems

The oxidation of 158a,b with \textit{m}-CPBA in dichloromethane gave the \(N\)-oxides 162a,b as mixtures of the \textit{cis}- and \textit{trans}-diastereomers which, after isolation, were utilised without further purification. The \(N\)-oxidation was considerably more diastereoselective from 158a than 158b, with a ratio of 13.3:1.0 for the diastereomers of 162a and 5.7:1.0 for the diastereomers of 162b. The $^1$H and $^{13}$C NMR spectra of 162a,b confirmed the proposed structures, with the vinyl group intact and the C10b and C11b signals shifted downfield to 82.24 $\delta$ and 77.69 $\delta$ for the major diastereomers of 162a and 162b respectively.

The \(N\)-oxides 162a,b were unchanged on refluxing in acetonitrile for 48 hours. Refluxing 162a,b in butyronitrile for 1-2 hours, however, gave a small non-polar fraction in each case which was isolated from the largely intact \(N\)-oxide. The reverse phase HPLC purification of these fractions gave the Meisenheimer
rearrangement products, the 3,7-epoxy-3-benzazonine 163a and 2H-3,8-epoxy-3-benzazecine 163b derivatives, in low yields of 5-6%. The formation of these new oxa-bridged systems was confirmed by the downfield positions of the quaternary carbons, C7 at δ 82.87 for 163a and C8 at δ 87.89 for 163b, in the 13C NMR spectra (Figure 4.9). Two dimensional homonuclear and heteronuclear correlation experiments afforded the assignment of the 1H NMR spectra for 163a (Figure 4.10) and 163b (Figure 4.11).

No evidence was obtained for the formation of the other possible Meisenheimer or [2,3] sigmatropic rearrangement products. The precursors 158a,b were, however, detected in the non-polar thermolysis fractions by 1H NMR, at yields about half those of 163a,b. Compounds 158a,b may arise either directly from 163a,b or by the deoxygenation of 162a,b prior to, or after reversal of, the Meisenheimer rearrangement. The stability of 163a was thus tested by refluxing a sample in butyronitrile for 1 hour. After this time traces of 158a were evident in the 1H NMR of the mixture, indicating that the direct deoxygenation and recyclization of the oxa-bridged derivatives could occur, however, the majority of 163a was unchanged. This confirmed the precursors were formed mainly by the deoxygenation of the corresponding N-oxides in the thermolytic reactions. Small amounts of deoxygenation products were previously noted154 to accompany the Meisenheimer
rearrangement, with several mechanisms proposed for the thermal deoxygenation.\textsuperscript{154,155}

A variety of conditions were tested in attempts to improve the yield of 163a, but without success. These included longer reaction times in butyronitrile, thermolysis in DMSO at 130°C, and thermolysis neat in an evacuated tube at 120°C. In each case the deoxygenated precursor 158a became the major product, with no significant increase in the yield of 163a.

The reaction temperature necessary for any significant Meisenheimer rearrangement of the bridgehead N-oxides 162a,b was higher than that required for the rearrangement of the simpler 1-vinylc tetrahydroisoquinoline N-oxide derivatives 123a-d and contrasted greatly with the reported formation\textsuperscript{139} of 142a (pg. 110) from the tetrahydro-2H-azetopyrido[3,4-b]indole N-oxide 141a at room temperature in dichloromethane. Clearly the relief of the azetidine ring strain promotes the low temperature Meisenheimer rearrangement of 141a. The less facile rearrangement of 141b also indicated a role in the activation of the [1,2] rearrangement by the β-ester substituent of 141a.

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Figure 4.9 $^{13}$C NMR spectral assignments for (a) 163a and (b) 163b

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Figure 4.10  $^1$H NMR spectrum and assignments for 163a in CDCl$_3$
Figure 4.11 $^1$H NMR spectrum and assignments for 163b in CDCl$_3$
As the 10b-unsubstituted pyrrolo[2,1-a]isoquinoline N-oxide analogue of 162a did not undergo Meisenheimer rearrangement, the vinylic group of 162a apparently promoted the rearrangement by providing additional stabilisation of the radical intermediate. It was reasoned that a cyano group may also provide radical stabilisation and, as the cyano adduct 157 was accessible in higher yields than 158b, the thermolysis of the 11b-cyanobenz[a]quinolizine N-oxide 164 was investigated. The N-oxidation of 157 with m-CPBA occurred stereospecifically to give one diastereomer of 164, assumed to be the trans B/C fused diastereomer. The thermolysis of 164 in refluxing butyronitrile afforded an ether soluble fraction, in approximately 37% yield, but failed to provide the desired 3,8-epoxy-3-benzazecine derivative. The analysis of this material by GC-MS indicated the presence of two significant components (4.5:1.0), with molecular ions at 246 (N-oxide 164 - O; CN) and 272 (N-oxide 164 - O). Thermolysis of 164 in refluxing dimethylformamide produced a complex mixture with the M⁺ 272 compound the only significant component present. No attempts were made to purify the material further in view of the low yields.

4.4 Conclusion

The applications of the Meisenheimer rearrangement in organic synthesis were extended to the synthesis of the first example of the triazolo[4,3-a]-5,1,4-benzoxadiazocine ring system, compound 153, with the successful [1,2] rearrangement of the triazolo[4,3-a]-1,4-benzodiazepine N-oxide 152. The synthesis
of 153 was achieved in excellent yield overall from the known 1,4-benzodiazepine therapeutic, Alprazolam, via the novel derivative N-methylhydralprazolam 147.

The similar extension of the Stevens rearrangement to the production of a triazolo[4,3-a]-1,4-benzodiazocine derivative was not achieved, as the necessary precursor triazolo[4,3-a]-1,4-benzodiazepine salt 150 could not be obtained. The successful preparation of this, or a similar N-ylide precursor, and the subsequent Stevens rearrangement remains to be investigated.

The first examples of the 3,7-epoxy-3-benzazonine and 2H-3,8-epoxy-3-benzazecine systems, derivatives 163a and 163b, were prepared by the Meisenheimer rearrangements of the tricyclic bridgehead N-oxides 162a,b. The compounds, however, were obtained in low yield and the deoxygenation of the N-oxides was often preferred to the formation of the strained oxa-bridged heterocyclic systems. The results suggested that the Meisenheimer rearrangement may provide only limited access to oxa-bridged, fused aza-heterocycles.

The tricyclic bridgehead quaternary salts 160a,b failed to undergo any significant Stevens rearrangement. The novel 3,7-methano-3-benzazonine derivative 161a was tentatively identified but not fully characterised due to the very low (≤1%) yield. The results indicated that the Stevens rearrangement will not be applicable to the synthesis of methylene-bridged, fused aza-heterocycles.
CHAPTER 5
REARRANGEMENTS OF 1-CYCLOPROPYL-ISOQUINOLINE N-OXIDES AND N-YLIDES

5.1 Introduction

It was proposed that the presence of a cyclopropyl group may modify the Stevens or Meisenheimer rearrangements, allowing a four atom ring expansion (Section 1.4). To evaluate the synthetic potential of this proposition the synthesis and behaviour of 1-cyclopropyl-substituted tetrahydroisoquinoline N-ylide and N-oxide derivatives were examined in this work. The rearrangement had the potential to provide direct access to derivatives of the 3-benzazecine system and the novel 4,3-benzoxazecine system from easily preparable tetrahydroisoquinoline precursors (Figure 5.1). There is a need for new approaches to these fused ten-membered ring systems, either to incorporate new functionality in the known rings or to synthesize new oxaza systems.

![Figure 5.1](image_url)

5.2 Review of Benzoazecines and 3-Benzazecines

Although twenty eight different benzoazecine ring skeletons are possible only the 2,6- and 3,6-benzoazecine systems have been reported (prior to Chem. Abs. 119). Both were prepared by the extension of photosolvolysis and cyanogen bromide-induced solvolysis ring destruction techniques.156,157 Thus the
[1,3]oxazino[2,3-a]isoquinoline and [1,4]oxazino[3,4-a]isoquinoline precursors, 165 and 167, gave the benzoazecines 166 and 168 in moderate yields. A 2,6-benzoazecine derivative was prepared\textsuperscript{97} by the cyanogen bromide-induced four atom ring expansion of an isoquinoline derivative, analogous to the conversion of 119 to 120 (pg. 84).

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {165};
\node (b) at (2,0) {166};
\node (c) at (0,-1) {167};
\node (d) at (2,-1) {168};
\draw[->] (a) -- (b) node[midway,above] {1. hv, MeOH};
\draw[->] (a) -- (b) node[midway,above] {2. basification};
\draw[->] (c) -- (d) node[midway,above] {BrCN, MeOH};
\draw[->] (c) -- (d) node[midway,above] {base};
\end{tikzpicture}
\end{center}

\begin{enumerate}
\item X=0, \ Y=CH\textsubscript{2}
\item X=CH\textsubscript{2}, \ Y=O
\end{enumerate}

A variety of methods are known for the preparation of derivatives of the 3-benzazecine system. The majority involve ring destruction techniques with the same reagents and techniques used for the production of 3-benzazonines\textsuperscript{60,61,64} and 3-benzoazecines,\textsuperscript{156} but from the appropriate benzo[a]quinolizine precursors. Thus Emde reduction of 169 gave the 3-benzazecine 170 in high yield. Compound 170 demonstrated antiinflammatory activity when injected intraperitoneally in the rat.\textsuperscript{158} Elimination accompanied the cyanogen bromide-induced ring opening\textsuperscript{159} of the amino alcohols 171 to afford the 7,8-unsaturated products 172. The stereochemistry about the double bond in 172 was not determined.

A ring construction approach, analogous to the conversion of 41 to 42 (pg. 17), afforded 3-benzazecines in low yield\textsuperscript{69} while the Stevens rearrangement of 2-benzazonines to 3-benzazecines was noted\textsuperscript{33,35} previously (Section 1.2.3).
5.3 Synthesis of 1-Cyclopropyl Rearrangement Precursors

No reports of the preparation of cyclopropylisoquinolines were found in the literature, however, it was envisaged that the cyclopropanation of the 1-vinyltetrahydroisoquinoline \( 49a \) would afford access to the necessary 1-cyclopropylisoquinoline precursors (Figure 5.2). As it was originally proposed that 1-oxiranyl-substituted tetrahydroisoquinoline \( N \)-ylides and \( N \)-oxides may also rearrange to benzoxazecine and benzodioxazecine products the epoxidation of \( 49a \) was also investigated.

**Figure 5.2**
Both allylamine\textsuperscript{160} and 2-methyl-3-amino-propene\textsuperscript{161} were reported to undergo Simmons-Smith cyclopropanation in high yields, however, the reaction of 49a with methylene iodide over a Zn/Cu couple in diethyl ether at reflux provided only an unidentified salt, presumed to be the methiodide salt of 49a. It is possible that the inductive effect of the nitrogen prevented attack of the olefin by the electrophilic carbene. A recent paper\textsuperscript{162} reported the successful cyclopropanation of substituted N-allyl compounds, without competing N-methylation, using diazomethane and bis(benzonitrile)palladium dichloride, but the cyclopropanation of 49a was not investigated further.

The treatment of 49a with three equivalents of \textit{m}-CPBA in a variety of solvents at reflux, including dichloromethane, chloroform, and 1,2-dichloroethane, yielded only the \textit{N}-oxide 123a. The similar treatment of the methiodide and hydrochloride salt of 49a failed to produce any epoxidation; the salts or the free base were recovered after basification. As above, the results indicated that a decrease in the nucleophilicity of the olefin by the inductive effect of the nitrogen had prevented attack by the electrophilic peracid reagent. These problems have been noted previously\textsuperscript{163,164} and epoxidation was achieved by converting the allyl amine derivatives to their trifluoroacetate salts, which were then treated with trifluoroperacetic acid. Chemical restrictions precluded the preparation of trifluoroperacetic acid in the normal manner\textsuperscript{165} in this work. However, several experiments in which the new hydrogen-bonded adduct, urea-hydrogen peroxide\textsuperscript{166} (UHP), was reacted with trifluoroacetic anhydride and the trifluoroacetate salt of 49a were conducted. No epoxidation was observed and the synthesis of 1-oxiranyl-substituted tetrahydroisoquinolines was not pursued further.

The commercial availability of cyclopropanecarboxylic acid, 173a, and \textit{trans}-2-phenyl-1-cyclopropane carboxylic acid, 173b, prompted the investigation of the synthesis of 1-cyclopropyltetrahydroisoquinolines by the Bischler-Napieralski cyclisation\textsuperscript{167} of the cyclopropanecarboxamides 174.
The treatment of homoveratrylamine with 173a,b at elevated temperatures, between 140 and 170°C, gave the cyclopropanecarboxamides 174a,b in good yield. The Bischler-Napieralski cyclisation of 174a,b proceeded smoothly with phosphorus
oxochloride in refluxing acetonitrile to afford the 1-cyclopropyldihydroisoquinolines 175a,b in excellent yields, the first example of the Bischler-Napieralski cyclisation of cyclopropanecarboxamide derivatives. All spectroscopic data was consistent with the proposed structures. The imines were converted to the crystalline iminium salts 176a,b by N-alkylation with iodomethane in acetone and satisfactory elemental analyses were obtained. While the N-alkylation of 175a was conducted in refluxing acetone, the N-alkylation of 175b proceeded to the desired salt only at or below room temperature. At higher temperatures an isomer of 176b was formed. The identification of this isomer is discussed in Section 5.4.

The sodium borohydride reduction of 176a,b in ethanol gave the tetrahydroisoquinoline derivatives 177a,b. Two diastereomers of the t-(2'-phenylcyclopropyl) compound 177b were obtained (SSS/RSS=0.82) with the formation of the chiral centre at C1. The diastereomers of 177b were separated by p.t.l.c. on silica for characterisation purposes and identified by n.O.e. experiments. One diastereomer possessed a 7-methoxy signal considerably upfield of the other (3.57 δ cf. 3.83 δ) consistent with shielding of the methoxy group by an appropriately positioned 2'-phenyl substituent. The examination of hand-held models and computer-aided molecular modelling (PCModel) confirmed the RSS and SSS diastereomers must adopt considerably different conformations to enable shielding of the 7-methoxy protons. In the RSS form H2' would point to the same side of the isoquinoline plane as H1, while in the SSS form H2' and H1 would be on opposite sides of the isoquinoline plane (Figure 5.3). NMR n.O.e. difference experiments confirmed an effect between H2' and H1, and H2' and H8, for the diastereomer with the shielded 7-methoxy signal, allowing this to be assigned the RSS configuration.

The N-oxide rearrangement precursors 178a,b were generated in the usual manner by the reaction of 177a and 177b (SSS/RSS=0.47) with m-CPBA in dichloromethane at room temperature. No rearrangement products were isolated during the workup of the reaction mixture. The N-oxides were obtained as complex
Figure 5.3 The conformers of (a) RSS-177b and (b) SSS-177b able to produce deshielding of the 7-methoxy group, and (c) the $^1$H NMR spectrum of RSS-177b.
mixtures of the possible diastereomers, observable by $^1$H NMR, and were utilised as crude oils.

On consideration of the proposed rearrangements of the quaternary salts 179b, generated from 177b, it was apparent that a diastereomeric mixture of 177b would provide a complex mixture of four diastereomeric benzoxazepines, two diastereomeric E-benzazecines and two diastereomeric Z-benzazecines. To reduce the difficulty of later analyses, particularly the detection of small amounts of benzazecines, a fraction of almost pure SSS 177b (SSS/RSS=19) was obtained by column chromatography on flash silica and this fraction was used in the subsequent $N$-alkylation. Ethyl bromoacetate in refluxing acetone $N$-alkylated 177a,b to give the quaternary salts 179a,b, which were used as crude oils. The salts were mixtures of the B-ring diastereomers.

5.4 A Modified Cloke Rearrangement

The $N$-alkylation of the imine 175b with iodomethane in refluxing acetone produced a precipitate in moderate yield which proved to be an isomer of the expected methiodide salt 176b. Compound 176b was present in the filtrate. The molecular weight of the isomer was confirmed by LSIMS-MS in glycerol, with an ion at m/z 322 for the cationic component. The pyrrolo[2,1-c]isoquinoline enamine structure 180 was proposed after examination of the $^1$H and $^{13}$C NMR spectra and consideration of the likely reaction mechanisms. An alternative 2-phenyl-2,3-unsaturated enamine, however, appeared consistent with the appearance of the single olefinic proton as a singlet, at 7.18 $\delta$. An n.O.e. difference experiment demonstrated an effect between H10 and the olefinic signal and this supported structure 180. Two-dimensional homonuclear and heteronuclear correlation NMR experiments (COSY and X-H correlation) were consistent with this structure and afforded the complete assignment of the NMR signals (Figure 5.4).
Elemental microanalyses on crystals of 180 from either acetonitrile or methanol failed to provide satisfactory results, despite repeated attempts. The unusual enamine structure of 180 was, however, confirmed unambiguously by a single crystal X-ray structure determination. The compound was identified as the diastereomer of 180 with the 3-phenyl and 4-methyl substituents *trans* to each other across the C-ring (Figure 5.5).

Further experiments demonstrated that 180 was formed via the initial conversion of 175b to 176b, then a subsequent cyclopropane ring opening and rearrangement, rather than the alternate sequence. At low temperatures the alkylation of 175b proceeded selectively to 176b. This material, after isolation and removal of
excess iodomethane, was isomerised to 180 in good yield by refluxing in acetone for 24 hours. Attempts to dry 176b at elevated temperatures also produced the partial isomerisation of 176b to 180.

Figure 5.5 X-Ray Crystallographic structure of 180

The formation of 180 is a variation of the Cloke rearrangement\textsuperscript{169} of cyclopropylimines. In this rearrangement the heteroatom may act as either a nucleophile or electrophile to initiate ring opening of the cyclopropane ring and formation of a pyrroline. The promotion of this rearrangement by iodomethane does not appear to have been reported. The Cloke rearrangement normally proceeds from an imine with acid catalysis at elevated temperatures, typically by heating the substrate as a melt, or in xylene, with ammonium chloride above 130°C. The treatment of 175b under these conditions, at temperatures up to 195°C, failed to afford the expected enamine base 181. In each case a complex mixture of products was obtained. The Cloke rearrangement of 1-(1'-methyl)cyclopropylisoquinoline hydrochloride salts was reported\textsuperscript{170} during the course of this work, although neither
the immediate products of the rearrangement, analogous to 181, or the subsequent hexahydropyrrolo[2,1-\(a\)]isoquinoline derivatives were isolated and characterised.

The present results suggest potential for the development of a new route to pyrrolo[2,1-\(a\)-isoquinoline derivatives via the Cloke rearrangement of 1-cyclopropylisoquinolines.

5.5 Rearrangements of the \(N\)-Oxides

5.5.1 Treatment of the 1-Cyclopropyl-\(N\)-oxide

A variety of conditions were tested to investigate the rearrangement of the 1-cyclopropyl \(N\)-oxide 178a, as summarised in Table 5.1.

Surprisingly high temperatures and long reaction times were required to produce the rearrangement of 178a. In acetonitrile at reflux 178a was unaffected. At 130°C in a butyronitrile/xylene mixture some rearrangement was observed, but a temperature of 143°C in a butyronitrile/mesitylene mixture was necessary to afford substantial rearrangement of 178a. Butyronitrile was used to dissolve the polar \(N\)-oxides. It was apparent from these results that the cyclopropyl group was substantially less efficient in promoting the Meisenheimer rearrangement than a vinyl group, reflecting a poor capacity for radical stabilisation.

The crude ether extracts from reactions 2, 3 and 4 (Table 5.1) each contained the same single major component. The p.t.l.c. purification of the product from reaction 4 provided, in good yield, a colourless oil identified as the 1-cyclopropyl-2,3-benzoazepine 182a. All spectra were consistent with the proposed structure. The \(^1\)H and \(^{13}\)C NMR spectra displayed peaks characteristic of the 1-cyclopropyl group (Table 5.3).

Compound 178a was also pyrolysed neat in an evacuated vessel at 215°C to determine whether higher temperatures would promote the formation of the 4,3-benzoazecine 183a. Two components resulted (1.5:1), with the major component being 182a. The NMR spectrum of the mixture indicated the second component was
not 183a. This compound lacked an olefinic peak and possessed the characteristic cyclopropyl signals, and was tentatively assigned as the 1-cyclopropyl-3,2-benzoxazepine formed by the alternate orientation of the Meisenheimer rearrangement towards C3.

![Chemical structure](image)

**178**

\[ \begin{align*}
\text{MeO} & \\
\text{MeO} & \\
\text{Me} & \\
\text{H} & \\
\text{H} & \\
\text{H} & \\
\text{R} & \\
\end{align*} \]

\[ \Delta \]

**182**

\[ \begin{align*}
\text{MeO} & \\
\text{Me} & \\
\text{N} & \\
\text{Me} & \\
\text{O} & \\
\text{H} & \\
\text{H} & \\
\text{R} & \\
\end{align*} \]

**183**

\[ \begin{align*}
\text{MeO} & \\
\text{MeO} & \\
\text{N} & \\
\text{Me} & \\
\text{O} & \\
\text{R} & \\
\end{align*} \]

\( a: R = H \quad b: R = \text{Ph} \)

**Table 5.1** Treatment of the 1-cyclopropyl N-oxide 178a

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Temp.°C</th>
<th>time</th>
<th>Result a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. MeCN</td>
<td>82</td>
<td>3 hr</td>
<td>no reaction</td>
</tr>
<tr>
<td>2. MeCN, sealed tube</td>
<td>111</td>
<td>6 hr</td>
<td>2%</td>
</tr>
<tr>
<td>3. PrCN/Xylene (1:5)</td>
<td>130</td>
<td>5 hr</td>
<td>18%</td>
</tr>
<tr>
<td>4. PrCN/Mesitylene (1:5)</td>
<td>143</td>
<td>12 hr</td>
<td>78% b</td>
</tr>
<tr>
<td>5. neat, evacuated tube</td>
<td>215</td>
<td>15 min.</td>
<td>42%, 2 components</td>
</tr>
<tr>
<td>6. MeCN, hv, duran filter</td>
<td>25</td>
<td>1 hr</td>
<td>no change</td>
</tr>
<tr>
<td>7. MeCN, hv, vycor filter</td>
<td>25</td>
<td>50 min.</td>
<td>15%, 3 components</td>
</tr>
</tbody>
</table>

a yields are for crude ether extracts

b p.t.l.c. gave 182a, 51% yield.

The effect of UV irradiation on 178a in acetonitrile at room temperature was investigated as an alternative to the thermolytic activation of the reaction. Irradiation at wavelengths above 300 nm were ineffective. Irradiation with light filtered to a lower
minimum of 230 nm promoted the formation of tarry material. The diethyl ether extract of this material showed several components by GC-MS and $^1$H NMR, one being 182a. No peaks indicative of 183a were observed. The major component detected by GC-MS had a molecular weight of 231, a loss of 32 mass units from the $N$-oxide. The mass spectrum of this component was identical to that of the imine 175a. The conversion of 178a to 175a may have occurred by rearrangement and homolytic cleavage (Figure 5.6).

![Figure 5.6](image)

### 5.5.2 Thermolysis of the 1-(t-2'-Phenylcyclopropyl)-$N$-oxide to a 4,3-Benzoxazecine Derivative

The thermal rearrangements of 178b ($SSS/RSS=0.47$) were examined under a variety of conditions, as summarised in Table 5.2.

The behaviour of 178b was substantially different to that of 178a. In the presence of the 2'-phenyl substituent the rearrangement was more facile and occurred at lower temperatures. Thus 178b underwent a slow rearrangement in acetonitrile at reflux and a rapid rearrangement in a butyronitrile/mesitylene mixture at 143°C, affording the complete removal of the $N$-oxide after only 1.5 hours. The extra phenyl
group clearly enhanced the radical stabilising nature of the cyclopropyl substituent by additional electron delocalisation, promoting the cleavage of the C1-N bond in 178b.

The $^1$H NMR spectra of the crude rearrangement mixtures from 178b indicated the presence of three components. The ratio of the components was 55:33:12 from the rearrangement in butyronitrile/mesitylene. The proportion of these compounds was, within the accuracy of this technique, unchanged in the two experiments at lower temperatures. The minor component exhibited a complex multiplet at 5.74 ppm consistent with the expected position of the olefinic H7 in the benzoxazecine 183b. Preparative reverse phase HPLC afforded the isolation of each of the three components. The minor component exhibited the least polar nature and eluted with a retention time 35% greater than the nearest component.

Table 5.2 Thermolysis of the 1-(t-2'-Phenylcyclopropyl)-N-oxide 178b

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Temp.°C</th>
<th>time</th>
<th>Result $^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. MeCN</td>
<td>82</td>
<td>60 hr</td>
<td>49%</td>
</tr>
<tr>
<td>2. PrCN</td>
<td>115</td>
<td>2.5 hr</td>
<td>48%</td>
</tr>
<tr>
<td>3. PrCN/Mesitylene (1:5)</td>
<td>143</td>
<td>1.5 hr</td>
<td>84%$^b$</td>
</tr>
</tbody>
</table>

$^a$ yields are for crude ether extracts

$^b$ HPLC gave 182b, 23% (RSS) and 27% (SSS), and 183b, 9% yield.

Table 5.3 Characteristic NMR Signals for the 1-Cyclopropylbenzoxazepines 182

<table>
<thead>
<tr>
<th></th>
<th>182a</th>
<th>182b (RSS)</th>
<th>182b (SSS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$H1$, C1</td>
<td>4.34, 89.93</td>
<td>4.53, 88.78</td>
<td>4.77, 87.00</td>
</tr>
<tr>
<td>$H1'$, C1'</td>
<td>1.23, 15.74</td>
<td>1.55, 22.72</td>
<td>1.57, 21.53</td>
</tr>
<tr>
<td>$H2'$, C2'</td>
<td>0.65$^a$, 4.11$^b$</td>
<td>1.95, 27.94</td>
<td>2.05, 26.99</td>
</tr>
<tr>
<td>$H3'$, C3'</td>
<td>0.52$^a$+0.42$^a$, 3.78$^b$</td>
<td>1.22, 14.69</td>
<td>1.13, 14.07</td>
</tr>
</tbody>
</table>

$^a,b$ assignments are interchangeable
The two major rearrangement products from 178b, isolated in 27% and 23% yields respectively from the HPLC purification, were identified as the diastereomeric 2,3-benzoxazepine derivatives 182b by spectroscopic and elemental analyses. The compounds were crystalline solids and exhibited characteristic cyclopropane, C1, and H1 NMR signals (Table 5.3).

The minor rearrangement product, a crystalline solid, was isolated in 9% yield from the HPLC purification and identified as the desired 4,3-benzoxaceine 183b, the first example of this ten-membered benz-fused oxaza heterocyclic system. The molecular formula of 183b (C21H25NO3) was confirmed by elemental microanalysis. All other spectral data were consistent with the proposed structure. The $^{13}$C (Figure 5.7) and $^1$H (Figure 5.8) NMR spectra confirmed the presence of the olefinic carbon atoms, at 132.25 and 134.45 δ, and the olefinic hydrogen atoms, at 5.74 and 6.65 δ. The magnitude of the H7-H8 coupling constant across the double bond (16 Hz) afforded the identification of the material as the E isomer of 183b.

The E-benzoxaceine 183b was stable on silica and could be isolated from the diastereomers of 182b by p.t.l.c. with dichloromethane/1% methanol. This behaviour, in contrast to that of the E-benzazonine derivatives (e.g. Section 2.3.3), reflected the greater ability of the 10-membered ring to accommodate a trans-double bond without incurring serious ring strain.

The thermal isomerisations of the 2,3-benzoxazepine and 4,3-benzoxazonine derivatives were previously noted (Section 3.5.3) so consequently the thermal behaviour of the 1-cyclopropylbenzoxazepine 182b was briefly examined. It was
Figure 5.8 $^1H$ NMR spectrum and assignments for 183b in CDCl$_3$
thought that at high temperatures some isomerisation of 182b to 183b may occur, although the benzoxazepines were likely to remain the thermodynamically favoured products. The treatment of a diastereomeric mixture of 182b at 210°C in an evacuated sealed tube for 30 minutes, however, produced only slight degradation. No evidence for the presence of 183b, or any other new rearranged isomer, was observed in the ¹H NMR spectrum of the thermolysate.

5.6 Modelling and X-Ray Crystal Structure of a 4,3-Benzoxazecine

The low energy conformations available for the 4,3-benzoxazecine 183b were investigated with PCModel. It was envisaged that the results would aid in any future development of derivatives of the 4,3-benzoxazecine system as CNS active agents. Four low energy conformations within a 5 kcal range were identified for 183b (Table 5.4). The global minimum, conformer 1, was predicted to have a relatively folded structure (Figure 5.9) in which the nitrogen atom was removed from the aromatic plane by 2.35 Å. The Boltzmann distribution predicted that 79% of 183b would adopt this conformation at 25°C. The structures of conformers 2, 3, and 4 are included in Appendix A.

<table>
<thead>
<tr>
<th>conformer</th>
<th>E (kcal)</th>
<th>inc Hf</th>
<th>Populationa</th>
<th>N-elevationb</th>
<th>N-Ar planarc</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47.78</td>
<td>-29.71</td>
<td>79.3%</td>
<td>2.35</td>
<td>3.43</td>
</tr>
<tr>
<td>2</td>
<td>48.84</td>
<td>-29.64</td>
<td>13.2%</td>
<td>1.83</td>
<td>3.92</td>
</tr>
<tr>
<td>3</td>
<td>49.18</td>
<td>-28.25</td>
<td>7.5%</td>
<td>1.54</td>
<td>4.64</td>
</tr>
<tr>
<td>4</td>
<td>52.33</td>
<td>-24.97</td>
<td>&lt;0.1%</td>
<td>1.88</td>
<td>4.28</td>
</tr>
</tbody>
</table>

a from the Boltzmann distribution at 293 K
b distance of N above the aromatic plane (Å)
c distance of N from the aromatic centre in the aromatic plane (Å)
Figure 5.9 Three perspectives of the global minimum predicted for 183b by PCModel

Figure 5.10 X-Ray Crystallographic structure of 183b
The structure of 183b was confirmed unequivocally by a single crystal X-ray structure determination. The unsaturated benzoxazecine formed triclinic crystals with a less-folded conformation (Figure 5.10) than that predicted by PCModel. The X-ray structure corresponded to conformer 3 (Table 5.4) identified by PCModel, with the nitrogen atom only 1.54 Å above the aromatic plane and further from the aromatic centre than in conformer 1.

The discrepancy between the conformation predicted by PCModel and that determined by X-ray techniques may indicate a real difference between the conformers preferred in the solid state, or in solution, and the theoretical vacuum assumed by PCModel. The comparison of several bond lengths predicted by PCModel with those determined by the X-ray analysis (Table 5.5), however, suggested that the parameters used to define the PCModel forcefield were not accurate for the strained medium ring system. These differences may have altered the calculated conformational energies, and thus their order, for the confined medium ring. The results highlighted the limitations of molecular mechanics based modelling programs when applied to strained medium-ring systems and emphasised that care must be taken in interpreting studies of this type. Conformers 1 and 3 of 183b would be predicted to have substantially different CNS activity. Time did not permit further conformational assessments using other modelling programs and the incorporation of solvent (water) molecules.

<table>
<thead>
<tr>
<th>bond</th>
<th>PCModel</th>
<th>X-Ray</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1-C2</td>
<td>1.544</td>
<td>1.519</td>
</tr>
<tr>
<td>N-O</td>
<td>1.483</td>
<td>1.458</td>
</tr>
<tr>
<td>C7=C8</td>
<td>1.342</td>
<td>1.299</td>
</tr>
<tr>
<td>C8a-C12a</td>
<td>1.406</td>
<td>1.390</td>
</tr>
</tbody>
</table>
5.7 Rearrangements of the N-Ylides

5.7.1 Behaviour of the 1-Cyclopropyl Salt

A variety of conditions were examined to determine those necessary to provide the rearrangement of 179a. These are summarised in Table 5.6.

At room temperature in acetonitrile with DBU no rearrangement of 179a occurred. It was necessary to conduct the reaction in refluxing butyronitrile or acetonitrile to obtain substantial rearranged fractions. The results reflected the poor radical stabilisation offered by the cyclopropane group. The $^1$H NMR spectra of the rearranged fractions suggested the major products were the diastereomers of the 3-benzazepine 184a, however, additional olefinic peaks were observed. The fractions were purified by p.t.l.c. on silica with dichloromethane/5% ethanol to give, in each case, four components (Table 5.6).

The two major components isolated by p.t.l.c. were shown by their characteristic NMR spectra to be the products of the Stevens rearrangement, the B-ring diastereomers of the 1-cyclopropyl-3-benzazepine 184a. The two remaining components contained olefinic protons with signals in the $^1$H and $^{13}$C NMR (with DEPT editing) characteristic of a terminal methylene group. Further examination confirmed the compounds were the geometric isomers of the ring opened diene 83b previously isolated in this work (Section 2.6.1). The dienes were formed at approximately the same level relative to the benzazepines in both refluxing acetonitrile and butyronitrile. No trace of the desired 3-benzazecine 185a was detected from these reactions.

A radical pathway involving hydrogen abstraction via the intermediate 186 may account for the formation of the dienes, however, a concerted pathway directly from the $N$-ylide 187 cannot be excluded. The cyclopropane ring is known to participate in place of double bonds in sigmatropic reactions$^{171}$ such as the homodietyl [1,5] hydrogen shift.
Table 5.6 Treatment of the 1-cyclopropyl salt 179a

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Temp. °C</th>
<th>time</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. MeCN, 1.3 equiv. DBU</td>
<td>25</td>
<td>60 hr</td>
<td>no reaction</td>
</tr>
<tr>
<td>2. MeCN, 1.3 equiv. BuLi</td>
<td>40</td>
<td>44 hr</td>
<td>26%</td>
</tr>
<tr>
<td>3. MeCN, 4.6 equiv. DBU</td>
<td>40</td>
<td>48 hr</td>
<td>12%</td>
</tr>
<tr>
<td>4. CHCl₃, 1.3 equiv. DBU</td>
<td>62</td>
<td>67 hr</td>
<td>50%</td>
</tr>
<tr>
<td>5. MeCN, &quot; &quot; &quot;</td>
<td>82</td>
<td>5 hr</td>
<td>48%ᵇ, 4 components</td>
</tr>
<tr>
<td>6. PrCN, &quot; &quot; &quot;</td>
<td>115</td>
<td>8.5 hr</td>
<td>90%ᶜ, 4 components</td>
</tr>
</tbody>
</table>

ᵃ crude fractions obtained by passage through alumina with DCM/10% L.P.
ᵇ p.t.l.c. gave diastereomers of 184a, 32% and 9%, and 83b, 8% and 4%
ᶜ p.t.l.c. gave diastereomers of 184a, 45% and 17%, and 83b, 14% and 5%
As the proposed modified Stevens rearrangement may occur by a concerted mechanism the products obtained from lower temperature reactions (2, 3, and 4 in Table 5.6) were examined. In each case NMR analysis confirmed the benzazepines were the major products with traces of the dienes. No peaks attributable to $185a$ were observed. A large excess of DBU failed to afford the substantial rearrangement of $179a$ at 40°C. It was reasoned that the reversible base may hinder the rate of any rearrangement by allowing the formation of an equilibrium between the ylide and salt forms of $179a$. The reaction rate was increased with the use of the non-reversible base butyl lithium, but no change in the product distribution was observed. The reaction in refluxing chloroform afforded the same products.

5.7.2 Behaviour of the 1-(t-2'-Phenylcyclopropyl) Salt

Compound $179b$ was synthesized for this examination from almost pure $SSS$ $177b$ ($SSS/RSS=19$), thus reducing the number of potential diastereomeric products and minimising the complexity of the expected reaction mixture.

The treatment of $179b$ with DBU in refluxing butyronitrile for 8.5 hours provided, after preliminary purification on an alumina column, a rearranged fraction in 67% yield. The analysis of this material by NMR spectroscopy suggested the B-ring diastereomers of the 1-(t-2'-phenylcyclopropyl)-3-benzazepine $184b$ were present. No peaks were observed in the $^1H$ NMR spectrum between 6.5 and 4.5 $\delta$, precluding the presence of either the desired 3-benzazecine $185b$ or any undesired ring-opened dienes. Preparative HPLC purification afforded a mixture (1.66:1) of the diastereomers of $185b$ in moderate yield. The diastereomers could not be separated and were identified on the basis of the $^1H$ and $^{13}C$ NMR spectra of the mixture. Although three very minor components were isolated by the preparative HPLC analysis each contained substantial impurities and none possessed NMR spectra consistent with the desired 3-benzazecine derivative.
5.8 Discussion

The 1-cyclopropylisoquinoline N-oxides and N-ylides were found to undergo predominantly the normal Meisenheimer and Stevens rearrangements. The cyclopropane substituent provided only weak activation in these rearrangements. Higher temperatures were necessary than for the rearrangements of the 1-vinylisoquinoline analogues. Clearly, however, the cyclopropane ring was able to act in a similar manner to an olefin and partake in a π bonding system, as the addition of a 2′ phenyl substituent significantly increasing the rate of the rearrangement of 178b over 178a, consistent with increased stabilisation of the initial C1-N homolytic cleavage.

The present results supported the formation of the 4,3-benzoxazecine 183b by the proposed radical mechanism (Figure 1.7, pg. 11), with C1-N homolysis followed by ring opening of the substituted cyclopropylcarbinyl radical prior to radical recombination. The 2-phenyl substituent is known to increase the rate constant\(^{172,173}\) for cyclopropylcarbinyl radical ring opening by a factor of approximately \(10^3\), from \(1.2 \times 10^8 \text{ s}^{-1}\) at 37°C for the unsubstituted radical to \(4 \times 10^{11} \text{ s}^{-1}\) at 45°C, and can account for the formation of 183 from 178b and not 178a. At this faster rate significant cyclopropylcarbinyl ring opening apparently occurred before the normal radical recombination of the Meisenheimer rearrangement.

![Figure 5.11 Cyclopropylcarbinyl Radical Geometries.](image)

The observed selectivity of the four atom ring expansion to the \(E\)-4,3-benzoxazecine may be rationalised by considering the non-bonded interactions\(^{174}\) in the \(\alpha\)-substituted cyclopropylcarbinyl radical. The Walsh model\(^{171}\) of cyclopropane
bonding proposed the existence of p orbitals in the plane of the cyclopropane ring able to participate in π bonding. Thus for ring opening the radical would adopt either of the conformers shown in Figure 5.11. Non-bonded interactions will be minimised in the geometry leading to the trans-olefin and the simple α-methylcyclopropylcarbinyl radical produced predominantly the E-olefin (E/Z=1.88) at 37°C. The stereoselective rearrangement of the cyclopropylcarbinyl radicals to E-olefin products may limit the applications of this new ring expansion, as the formation of smaller medium-sized rings with an endocyclic E-olefin will be energetically unfavourable.

The failure of the N-ylide 179b to undergo any four atom ring expansion suggested the Stevens rearrangement occurred with greater rapidity than the Meisenheimer rearrangement, possibly due to the lower stability of the carbon radical and a more concerted-like transition state, possessing less radical nature. The experiments described herein (Chapters 2 and 3) highlighted the greater preference for N-ylides to rearrange via a concerted pathway. The formation of the diene 83b from 179a and not 179b contradicted expectations based on a diradical pathway, for which the phenyl substituent of 179b should promote 2'-hydrogen abstraction. This behaviour may be rationalised by proposing that the less stabilised 1-cyclopropyl 179a adopted a low energy concerted pathway for the formation of the diene, while the greater resonance stabilisation of 1-(2'-phenylcyclopropyl) 179b allowed the diradical Stevens rearrangement to occur at a lower energy than any concerted pathway.

5.9 Conclusion

Although the Meisenheimer and Stevens rearrangements predominated from the reactions of the 1-cyclopropylisoquinoline N-ylides and N-oxides a single example of the proposed four atom ring expansion was observed. Thus it was demonstrated that the proposed reaction was mechanistically feasible and may, with the appropriate modification of the substrate, find synthetic applications in the production of medium
ring heterocycles. The rearrangement provided the first example of the 4,3-benzoxazecine ring system, compound 183b.

The present results suggested two strategies for the future development of the four atom ring expansion and its applications in organic synthesis. Firstly, the further acceleration of the cyclopropylcarbinyl radical ring opening by the appropriate placement of substituents either on the cyclopropane ring, the fused aromatic ring, or at C1, should be examined. A cis-2'-substituent for example may increase the cyclopropylcarbinyl ring opening rate due to the relief of additional steric strain. Secondly, the retardation of the radical attack on the \( \alpha \) carbon by the presence of a bulky \( \alpha \) substituent, or tailoring the ring system to prevent [1,2] radical recombination, could be examined. It should be noted that an \( \alpha \)-phenyl group, effectively present in these 1-cyclopropylisoquinoline rearrangements, reduced the cyclopropylcarbinyl ring opening rate constant.175 Consequently the rearrangements of other non-benz fused ring systems should be investigated.
CHAPTER 6
EXPERIMENTAL

6.1 General Procedures

Microanalyses were carried out by the Central Science Laboratory, University of Tasmania, Hobart.

Melting points were determined on a Yanagimoto Seisakusho micromelting point apparatus, and are uncorrected.

Infra-red spectra were recorded on a Digilab FTS-20E Fourier transform spectrometer.

The ultra-violet spectra were recorded on a Varian DMS 100 UV-Visible spectrophotometer. Analyses were conducted on solutions in acetonitrile.

The $^1$H and $^{13}$C NMR spectra were recorded on a Bruker AM-300 spectrometer at 300 and 75 MHz respectively. The DEPT.AUR microprogram was used routinely to determine the degree of protonation of the carbon resonances. The standard two-dimensional programs, COSY.AUR and XHCORR.AUR, were used when necessary to afford the unambiguous assignment of the resonances. The NOEDIFF.AUR pulse program was used for the measurement of nuclear Overhauser effects by the difference technique. Chemical shifts in ppm ($\delta$) were measured relative to tetramethylsilane. Unless otherwise stated, the NMR spectra were measured in deuterated chloroform. Peaks are reported as singlet (s), broad singlet (bs), doublet (d), triplet (t), quartet (q) or multiplet (m). The $^{13}$C NMR assignments indicated by superscript letters may be interchanged as defined by those letters. Where samples in the $^{13}$C NMR exhibited several conformers, or isomers, the chemical shift for the major form is given first for each signal type; different forms are denoted with superscripts a,b or x,y in the $^1$H NMR spectra.

The mass spectra were recorded on either a VG MM 7070F or a Kratos Concept ISQ mass spectrometer operating at 70 eV. Peak intensities in parentheses
are expressed as a percentage of the base peak. GC-MS analyses were performed on a Hewlett Packard 5790 Mass Selective Detector coupled to an HP 5890 gas chromatograph fitted with a direct capillary interface and an HP-1 capillary column.

Analytical thin layer chromatography (t.l.c.) and preparative thin layer chromatography (p.t.l.c.) were performed on either Merck silica gel 60 F<sub>254</sub> or Camag DSF-5 aluminium oxide. All column chromatography was performed under medium-pressure ("flash chromatography") on either Merck silica gel 60, 230-400 mesh, or on type H aluminium oxide, 100-200 mesh. Preparative HPLC utilised a Dynamax-60A C18 reverse-phase column with a Waters 600 multisolvent delivery system and Waters 486 tunable UV detector. Samples were eluted at 10ml/min and monitored at 254 nm. Mixtures of the chromatography solvents were made up by volume.

Ultraviolet irradiation was conducted at 5-10°C under nitrogen in a water-cooled, immersion-type photochemical reactor (quartz inner vessel) using a Hanovia 450-Watt medium-pressure mercury arc lamp with glass filter sleeves. The solution was stirred magnetically during the irradiation.

Organic solvent extracts were dried with anhydrous sodium sulfate. Where reaction mixture solutions or solvent extracts were concentrated this refers to evaporation under reduced pressure on a rotary evaporator.

Organic solvents and reagents were purified and dried by standard techniques. When anhydrous conditions were necessary the glassware and solvents were dried and the additions or transfers were made via gas-tight syringes or stainless steel tubing, under a positive pressure of nitrogen. Light petroleum refers to a fraction boiling between 60-80°C. Vinylmagnesium bromide was prepared in tetrahydrofuran as described by Normant, with a low temperature condensor (acetone/dry ice) to contain the vinyl bromide. Ethoxycarbonylmethyltriflate was prepared by the method of Vedejs et. al.
Abbreviations for hours (h.), minutes (min.), days (d.), 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU), and meta-chloroperoxybenzoic acid (m-CPBA) are adopted throughout the experimental.

### 6.2 Experimental for Chapter Two

**6.7-Dimethoxy-3,4-dihydroisoquinoline 47**

Homoveratrylamine (32.22 g, 0.178 mol) and formic acid (12.81 g, 0.278 mol) were heated at 170°C under nitrogen for 2 h. The melt was maintained at this temperature for a further 2 h. under a slow stream of nitrogen, to remove the majority of water and excess formic acid, then further dried under oil-pump vacuum at 140°C for 1 h. The melt was allowed to cool below 100°C and dry toluene (375 ml) was added before the melt solidified. The resultant solution was treated with phosphorus oxychloride (98.7 g, 0.644 mol) then refluxed for 2 h. under nitrogen. Upon cooling a dark oil separated. The toluene layer was decanted onto a mixture of ice (50 g) and water (50 ml) while to the residual oil was added ice (150 g). After 45 min. the aqueous solutions were combined and basified by the slow addition of 80% aqueous sodium hydroxide to pH 11, then extracted with chloroform (4 x 150 ml). The organic extracts were concentrated to a volume of approximately 70 ml and extracted with 12% aqueous hydrochloric acid (3 x 45 ml) and water (50 ml). The aqueous extracts were again basified to pH 11, then extracted with chloroform (4 x 75 ml). The organic extracts were dried and then concentrated to give the imine\(^{71} 47\) (25.69 g, 75%) as a yellow oil which was used without further purification. \(^1\)H NMR \(\delta\): 8.23 (s, H1), 6.81 (s, ArH), 6.68 (s, ArH), 3.92 (s, OCH\(_3\)), 3.90 (s, OCH\(_3\)), 3.73 (t, H3), 2.68 (t, H4); MS m/z: 191 (M\(^+\), 100%), 176 (78), 146 (13), 91 (16), 77 (25).

**6.7-Dimethoxy-2-methyl-3,4-dihydroisoquinolinium Iodide 48a**

To 47 (13.05 g, 68.25 mmol) in dry toluene (50 ml) was added iodomethane (31.98 g, 227 mmol). After 30 min. the deposited solid was collected and dried...
briefly under vacuum. Recrystallisation of the solid from ethanol gave the salt\textsuperscript{71} 48a (19.61 g, 86\%) as yellow crystals with m.p. 201-202°C. \textsuperscript{1}H NMR δ: 9.82 (s, H1), 7.62 (s, H8), 6.87 (s, H5), 4.03 (t, H3), 4.01 (s, NCH\textsubscript{3}), 3.93 (s, OCH\textsubscript{3}), 3.94 (s, OCH\textsubscript{3}), 3.32 (t, H4).

2-Benzyl-6,7-dimethoxy-3,4-dihydroisoquinolinium Chloride 48b

To 47 (12.17 g, 63.64 mmol) in dry toluene (50 ml) was added benzyl chloride (25.24 g, 199 mmol). After stirring for 12 h, the deposited solid was collected. The filtrate was warmed at 60°C for 2 h. then concentrated to approximately 20 ml. After cooling a second batch of crystals was collected. The solids were combined and recrystallised from acetonitrile to give the salt 48b (17.93 g, 89\%) as a yellow solid with m.p. 181-183°C. \textsuperscript{1}H NMR δ: 10.84 (s, H1), 7.67 (s, H8), 7.60 (s, 2ArH'), 7.36 (s, 3ArH), 6.86 (s, H5), 5.54 (s, NCH\textsubscript{2}Ar), 3.99 (s, OCH\textsubscript{3}), 3.93 (t, H3), 3.90 (s, OCH\textsubscript{3}), 3.17 (t, H4); \textsuperscript{13}C NMR δ: 166.05 (Cl), 157.85 (C7), 149.07 (C6), 132.24 (C1'A), 132.05 (C8aA), 129.86-129.66 (5C'), 117.65 (C4aA), 116.28 (C5B), 111.10 (C8B), 63.30 (NCH\textsubscript{2}Ar), 56.91 (OCH\textsubscript{3}), 56.83 (OCH\textsubscript{3}), 47.47 (C3), 25.84 (C4).

6,7-Dimethoxy-2-methyl-1-vinyl-1,2,3,4-tetrahydroisoquinoline 49a

(i) Vinylmagnesium bromide in dry tetrahydrofuran (190 ml) under nitrogen was prepared from vinyl bromide (25.8 g, 0.241 mol). The solution was cooled in an acetone/liquid nitrogen slush bath to -78°C, with the deposition of some solid, and then the iminium salt 48a (19.60 g, 58.8 mmol) was added portionwise over 30 min. The mixture was allowed to warm slowly to room temperature with stirring for 12 h, and then ice was added carefully to decompose the excess Grignard reagent. The mixture was then basified by the addition of 40\% aqueous potassium hydroxide and the tetrahydrofuran solution was decanted from the resultant inorganic salts. The tetrahydrofuran solution was treated with diethyl ether (100 ml) and water (50 ml) and the organic layer was collected. The inorganic salts and the aqueous solution
were extracted successively with further portions of diethyl ether (3 x 100 ml). All the organic solutions were then combined and washed with water (2 x 20 ml), then dried and concentrated. Passage of a dichloromethane solution of the crude solid through an alumina plug, then evaporation of the solvent and recrystallisation of the residue from ethanol, gave the \textit{1-vinylisoquinoline} 49a (9.46 g, 69\%) as an off-white solid with m.p. 69-70°C. \textsuperscript{1}H NMR $\delta$: 6.60 (s, ArH), 6.59 (s, ArH), 5.79-5.67 (m, H1'), 5.35 (dd, $J$ 1.5 Hz, 8.8 Hz, H2'), 5.30 (dd, $J$ 1.5 Hz, 17.0 Hz, H2'), 3.83 (s, OCH\textsubscript{3}), 3.80 (s, OCH\textsubscript{3}), 3.66 (d, $J$ 8.8 Hz, H1), 3.06-2.95 (m, 2H), 2.71-2.66 (m, H), 2.56-2.49 (m, H), 2.41 (s, NCH\textsubscript{3}); \textsuperscript{13}C NMR $\delta$: 148.02 (C6\textsubscript{A}), 147.42 (C7\textsubscript{A}), 139.77 (C1'), 127.88 (C4a\textsubscript{B}), 126.51 (C8a\textsubscript{B}), 119.11 (C2'), 111.52 (C5\textsubscript{C}), 111.06 (C8\textsubscript{C}), 69.74 (C1), 56.17 (20CH\textsubscript{3}), 51.57 (C3), 44.17 (NCH\textsubscript{3}), 28.83 (C4); MS m/z: 233 (M\textsuperscript{+}, 29\%); Calcd. for C\textsubscript{14}H\textsubscript{19}NO\textsubscript{2} 233.1415, found 233.140), 232 (19), 207 (40), 206 (100), 190 (43), 103 (16); Anal. Calcd for C\textsubscript{14}H\textsubscript{19}NO\textsubscript{2}: C, 72.07; H, 8.21; N, 6.01\%, found: C, 72.10; H, 8.27; N, 5.95\%.

(ii) Vinylmagnesium bromide in dry tetrahydrofuran (100 ml) under nitrogen was prepared from vinyl bromide (11.8 g, 0.111 mol). To this solution at room temperature was added the iminium salt 48a (9.07 g, 27.2 mmol) portionwise over 30 min. A mild exotherm occurred. The mixture was refluxed for 3 h, then cooled and worked up (as for (i)) to give, on concentration of the dichloromethane solution, a tan solid (5.93 g). A portion of this solid (0.772 g) was purified by p.t.l.c. on silica with dichloromethane/12\% methanol to give 49a (0.313 g) and a mixture (46:54) of the phenolic compounds \textit{6-hydroxy-7-methoxy-2-methyl-1-vinyl-1,2,3,4-tetrahydroisoquinoline} and \textit{7-hydroxy-6-methoxy-2-methyl-1-vinyl-1,2,3,4-tetrahydroisoquinoline} as a yellow oil (0.244 g) from a single band. \textsuperscript{1}H NMR $\delta$: 6.58 (s, ArH), 6.54 (s, ArH), 6.51 (s, ArH), 6.46 (s, ArH), 6.19 (bs, ArOH), 5.82-5.67 (m, 2H), 5.34-5.18 (m, 4H), 3.82 (s, OCH\textsubscript{3}), 3.80 (s, OCH\textsubscript{3}), 3.73-3.57 (m, 2H), 3.08-2.91 (m, 4H), 2.69-2.48 (m, 4H), 2.40 (s, 2NCH\textsubscript{3}); \textsuperscript{13}C NMR $\delta$: 146.52 and 146.00 (C6\textsubscript{A}), 145.24 and 144.54 (C7\textsubscript{A}), 139.79 and 139.41 (C1'), 128.40 and 127.01 (C4a\textsubscript{B}), 126.84 and 125.50 (C8a\textsubscript{B}), 119.34 (C2'), 115.20 and 114.68 (C5\textsubscript{C}), 111.20
and 110.77 (C8), 69.95 and 69.69 (C1), 56.21 (OCH3), 51.66 (C3), 44.26 (NCH3),
28.78 and 28.44 (C4); MS m/z: 219 (M+, 8%), 218 (6), 192 (100), 177 (20), 162 (6).
The treatment of this phenolic mixture in the minimum of dry methanol at 0°C with
excess diazomethane in diethyl ether provided, after stirring at 0°C for 12 h., 49a
(0.205 g, 79%).

2-Benzyl-6,7-dimethoxy-1-vinyl-1,2,3,4-tetrahydroisoquinoline 49b

A solution of vinylmagnesium bromide in dry tetrahydrofuran (195 ml) under
nitrogen was prepared from vinyl bromide (22.7 g, 0.213 mol). The solution was
cooled in an acetone/liquid nitrogen slush bath to -78°C, with the deposition of some
solid, and then the iminium salt 48b (16.98 g, 53.43 mmol) was added portionwise
over 30 min. The mixture was allowed to warm slowly to room temperature with
stirring for 18 h. and then worked up (as for compound 49a) to give the 1-
vinylisoquinoline 49b (15.72 g, 95%) as an off-white solid from ethanol with m.p.
106-107°C. 1H NMR δ: 7.39-7.23 (m, 5ArH), 6.61 (s, ArH), 6.58 (s, ArH), 5.96-
5.84 (m, H1'), 5.34-5.23 (m, H2'), 4.06 (d, J 13.6 Hz, H of CH2Ph), 4.00 (d, J 8.4 Hz,
H1), 3.83 (s, OCH3), 3.80 (s, OCH3), 3.42 (d, J 13.6 Hz, H of CH2Ph), 3.06-2.98 (m,
H), 2.77-2.69 (m, 2H), 2.52-2.44 (m, H); 13C NMR δ: 148.18 (C6A), 147.62 (C7A),
140.72 (C1'), 140.06 (C1''A), 129.42 (C4aB and 2C''), 128.77 (2C''), 127.52 (C8aB),
127.40 (C''), 118.58 (C2'), 111.78 (C5C), 111.72 (C8C), 67.16 (C1), 59.30 (CH2Ph),
56.44 (2OCH3), 46.99 (C3), 29.07 (C4); MS m/z: 309 (M+, 8%), 282 (100), 218 (3),
190 (5), 91 (48), 65 (6); Anal. Calcd for C20H23NO2: C, 77.64; H, 7.49; N, 4.53%,
found: C, 77.64; H, 7.53; N, 4.51%.

2-Ethoxycarbonylmethyl-6,7-dimethoxy-2-methyl-1-vinyl-1,2,3,4-
tetrahydroisoquinolinium Bromide 50a

(i) The N-methyl base 49a (0.392 g, 1.68 mmol) was stirred in ethyl bromoacetate
(2.0 ml, 18 mmol) at 20-25°C for 16 h. The mixture was applied to a short silica
column and the column was eluted with dichloromethane/5% light petroleum, and
then ethanol. Concentration of the ethanolic washings gave a mixture (trans:cis=70:30) of the B-ring diastereomers of the N-methyl-N-ethoxycarbonylmethyl salt 50a (0.481 g, 72%) as an off-white hygroscopic powder.

**trans diastereomer:** $^1$H NMR $\delta$: 6.70 (s, ArH), 6.53 (s, ArH), 6.26-6.24 (m, H2'), 6.05-6.01 (m, H1 and H1'), 5.85-5.81 (m, H2'), 5.11 (d, $J$ 17.4 Hz, H of NCH$_2$CO), 4.69 (d, $J$ 17.3 Hz, H of NCH$_2$CO), 4.49-4.41 (m, H), 4.24 (q, CH$_2$ of Et), 3.97-3.88 (m, H), 3.90 (s, OCH$_3$), 3.87 (s, OCH$_3$), 3.55 (s, NCH$_3$), 3.25-3.06 (m, 2H), 1.28 (t, CH$_3$ of Et); $^{13}$C NMR $\delta$: 165.50 (CO), 150.23 (C6A), 149.37 (C7A), 130.15 (C2'), 129.79 (C1'), 120.98 (C4a and C8a), 111.39 (C5 and C8), 73.50 (C1), 63.35 (CH$_2$ of Et), 58.44 (NCH$_2$CO$_B$), 56.59 (2OCH$_3$), 54.83 (C3$_B$), 47.52 (NCH$_3$), 24.22 (C4), 14.32 (CH$_3$ of Et); IR (thin film from CH$_2$Cl$_2$): 1742, 1520, 1258, 1229, 1117, 924, 731 cm$^{-1}$.

**cis diastereomer:** $^1$H NMR $\delta$: 6.69 (s, ArH), 6.44 (s, ArH), 6.10-6.01 (m, H1'), 5.73-5.64 (m, H1 and H2'), 5.37 (d, $J$ 17.5 Hz, H of NCH$_2$CO), 4.83-4.75 (m, H), 4.39 (d, $J$ 17.1 Hz, H of NCH$_2$CO), 4.26 (q, CH$_2$ of Et), 3.83 (s, OCH$_3$), 3.80 (s, OCH$_3$), 3.76-3.71 (m, H), 3.70 (s, NCH$_3$), 3.29-3.06 (m, 2H), 1.25 (t, CH$_3$ of Et); $^{13}$C NMR $\delta$: 165.33 (CO), 150.24 (C6A), 149.28 (C7A), 131.06 (C1'), 127.48 (C2'), 120.95 (C4a$_B$), 120.67 (C8a$_B$), 111.40 (C5$_C$), 110.97 (C8$_C$), 73.31 (C1), 63.30 (CH$_2$ of Et), 60.76 (NCH$_2$CO$_D$), 56.56 (2OCH$_3$), 55.69 (C3$_D$), 46.41 (NCH$_3$), 23.64 (C4), 14.38 (CH$_3$ of Et); IR (thin film from CH$_2$Cl$_2$): 1744, 1520, 1260, 1230, 1119 cm$^{-1}$.

(ii) Treatment of 49a (0.105 g, 0.450 mmol) as for (i), except with stirring at 110°C for 1 h., gave a 50:50 mixture of the B-ring diastereomers of 50a (0.121 g, 67%).

(iii) Treatment of 49a (0.364 g, 1.56 mmol) as for (i), except with stirring at 0°C for 60 h., gave an 80:20 mixture of the B-ring diastereomers of 50a (0.441 g, 71%).

(iv) Treatment of 49a (0.759 g, 3.25 mmol) as for (i), except with stirring at 37°C for 11 h., gave a 63:37 mixture of the B-ring diastereomers of 50a (0.713 g, 55%).

The recrystallisation of this material from ethanol/tetrahydrofuran gave a 57:43 diastereomeric mixture of 50a (0.442 g) as a solid, while the concentration and analysis of the mother liquor showed a 40:60 diastereomeric mixture of 50a.

Repeating the recrystallisation from the new solid provided a 53:47 diastereomeric
mixture of crystalline 50a (0.288 g), while the concentration and analysis of the mother liquor showed a 38:62 diastereomeric mixture of 50a.

(v) Compound 49a (3.054 g, 13.10 mmol) was stirred in acetonitrile (6 ml) with ethyl bromoacetate (2.8 ml, 25 mmol) at 20-25°C for 20 h. with the precipitation of a solid. The mixture was stored for 24 h. at -5°C and then filtered while cold. The solid was slurried twice with hexane then dried to give a 90:10 diastereomeric mixture of 50a (3.367 g, 64%) as a cream hygroscopic solid. Concentration of the filtrate and trituration of the oily residue with hexane (4 x 20 ml) afforded, after drying, a second batch of 50a (1.397 g, 27%) as a tan hygroscopic powder.

2-Benzyl-2-ethoxycarbonylmethyl-6,7-dimethoxy-1-vinyl-1,2,3,4-tetrahydroisoquinolinium Bromide 50b

(i) Compound 49b (3.010 g, 9.729 mmol) was dissolved in ethyl bromoacetate (13.0 ml, 117 mmol) by warming the mixture briefly at 50°C, then the solution was stored under nitrogen protected from light at 15-25°C for 19 days. The precipitate was collected and washed with several portions of diethyl ether to give, after drying, a mixture (trans:cis=3:1) of the B-ring diastereomers of the N-benzyl-N-ethoxycarbonylmethyl salt 50b (2.718 g, 59%) as an off-white powder. trans diastereomer: \(^1H\) NMR \(\delta\): 6.67 (s, ArH), 6.60 (s, ArH), 1.14 (t, CH\(_3\) of Et); \(^13C\) NMR \(\delta\): 164.84 (CO), 150.09 (C6A), 149.12 (C7A), 133.63 (C2"B), 132.58 (C3"B), 131.78 (C1'), 131.21 (C4"B), 130.16 (C5"B), 129.45 (C6"B), 127.65 (C2'), 121.56 (C4aC), 121.33 (C8aC), 111.49 (C1''), 111.15 (C5 and C8), 74.79 (C1), 66.49 (NCH\(_2\)PhD), 62.59 (CH\(_2\) of EtD), 56.53 (2OCH\(_3\)), 54.51 (NCH\(_2\)CO\(_D\)), 51.40 (C3D), 24.15 (C4), 14.05 (CH\(_3\) of Et). cis diastereomer: \(^1H\) NMR \(\delta\): 6.78 (s, ArH), 6.53 (s, ArH), 1.31 (t, CH\(_3\) of Et); \(^13C\) NMR \(\delta\): 165.18 (CO), 150.21 (C6A), 149.12 (C7A), 133.63 (C2"B), 132.58 (C3"B), 131.40 (C1'), 131.21 (C4"B), 130.16 (C5"B), 129.45 (C6"B), 126.94 (C2'), 121.01 (C8aC), 120.41 (C8aC), 110.76 (C1''), 111.15 (C5 and C8), 73.25 (C1), 63.20 (NCH\(_2\)PhD), 61.56 (CH\(_2\) of EtD), 57.37 (NCH\(_2\)CO\(_D\)), 56.53 (2OCH\(_3\)), 53.66 (C3D), 23.86 (C4), 14.26 (CH\(_3\) of Et).
(ii) The N-benzyl base 49b (0.444 g, 1.44 mmol) was dissolved in ethyl bromoacetate (1.5 ml, 13 mmol) by warming the mixture briefly at 50°C, then the solution was stirred at 25°C for 11 h. No reaction was detected by t.l.c. analysis. The solution was then heated at 60°C for 5 h. A dark colour developed, however, no significant reaction was detected by t.l.c. analysis.

(iii) To 49b (0.427 g, 1.38 mmol) in acetonitrile (4 ml) was added ethyl bromoacetate (1.2 g, 7.1 mmol) and potassium iodide (1.25 g, 7.50 mmol). No reaction was detected after the agitation of this mixture at 25°C for 24 h. The mixture was then heated under nitrogen at 90°C for 3 days. A dark tar formed.

Ethyl 9,10-Dimethoxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazonine-4-carboxylate 52a

(i) To the salt 50a (4.617 g, 11.54 mmol) in dry acetonitrile (125 ml) under nitrogen at 0°C was added DBU (2.14 g, 14.1 mmol) dropwise. After stirring at 0°C for 6 h. the solution was then concentrated and the residue was purified by column chromatography on alumina (100 g) with dichloromethane/20% light petroleum. Concentration of the early fraction (250 ml) gave a mixture (E/Z=19.0) of the 3-benzazonine isomers 52a (3.309 g, 90%) as a colourless, amorphous, waxy solid. A portion (160 mg) of this mixture was purified by preparative reverse phase HPLC with acetonitrile/20% water to give:

(a) after 10.94 min., the Z-benzazonine Z-52a (8 mg) as a colourless oil. ¹H NMR δ: 6.67 (d, J 10.7 Hz, H7), 6.58 (s, ArH), 6.54 (s, ArH), 5.90-5.81 (m, H6), 4.10 (q, CH₂ of Et), 3.87 (s, OCH₃), 3.84 (s, OCH₃), 3.49-3.44 (m, H₄), 3.14-3.07 (m, H₂), 2.90-2.82 (m, H₂), 2.77-2.70 (m, H₁), 2.62-2.56 (m, H₁), 2.58 (s, NCH₃), 2.22-2.12 (m, H₅), 1.23 (t, CH₃ of Et); ¹³C NMR δ: 173.60 (COO), 148.34 (C₉A), 147.53 (C₁₀A), 134.24 (C₁₁aB), 132.42 (C₆C), 131.60 (C₇C), 129.53 (C₇aB), 113.84 (C₈D), 111.89 (C₁₁D), 66.94 (C₄), 60.88 (CH₂ of Et), 56.51 (2OCH₃), 53.07 (C₂), 45.48 (NCH₃), 37.86 (C₁), 32.63 (C₅), 15.00 (CH₃ of Et); MS m/z: 319 (M⁺, 14%; Calcd. for C₁₈H₂₅NO₄ 319.1783, found 319.1778), 246 (100), 215 (2), 203 (3), 189 (6).
(b) after 14.23 min., the \textit{E-benzazonine E-52a} (135 mg) as a colourless waxy solid. 

$^1$H NMR $\delta$: 6.77 (s, H8), 6.62 (s, H11), 6.43 (d, $J$ 16.1 Hz, H7), 5.53-5.42 (m, H6), 4.17-4.04 (m, CH$_2$ of Et), 3.87 (s, OCH$_3$), 3.84 (s, OCH$_3$), 3.54 (dd, $J$ 1.7 Hz, 6.3 Hz, H4), 2.84-2.76 (m, H1 and H5), 2.70 (s, NCH$_3$), 2.73-2.60 (m, H1 and H2), 2.38-2.28 (m, H2 and H5), 1.25 (t, CH$_3$ of Et); $^{13}$C NMR $\delta$: 173.25 (COO), 147.30 (C9A), 147.09 (C10A), 134.69 (C7), 133.87 (C11aB), 132.09 (C7aB), 130.64 (C6), 113.77 (C11), 110.66 (C8), 67.19 (C4), 60.58 (CH$_2$ of Et), 56.40 (2OCH$_3$), 56.00 (C2), 45.24 (NCH$_3$), 38.03 (C1), 36.32 (C5), 14.92 (CH$_3$ of Et); MS m/z: 319 (M$^+$, 8%; Calcd. for C$_{18}$H$_{25}$N$_2$O$_4$ 319.178, found 319.178), 246 (100), 215 (7), 204 (7), 189 (12); IR (thin film from CH$_2$Cl$_2$): 1717, 1508, 1462, 1265, 1221, 1197, 1101 cm$^{-1}$.

(ii) To 50a (0.308 g, 0.770 mmol) in dry acetonitrile (15 ml) under nitrogen at -45°C was added DBU (0.14 g, 9.2 mmol). The solution was stirred between -45°C and -40°C for 6 h. and then allowed to warm slowly to room temperature. Concentration and then column chromatography of the residue on alumina with dichloromethane/20% light petroleum gave a mixture of the isomers of 52a (0.211 g, 86%, E/Z =19.0).

(iii) To 50a (0.295 g, 0.737 mmol) in dry acetonitrile (15 ml) at reflux, under nitrogen, was added DBU (0.14 g, 9.2 mmol). The solution was refluxed for 1 h. then concentrated and purified as for (i) to give a mixture (0.164 g, 70%) of the isomers E-52a:Z-52a:53a in the ratio 19.3:1.9:1.0.

(iv) To 50a (0.508 g, 1.27 mmol) in dry acetonitrile (20 ml) under nitrogen at room temperature was added DBU (0.13 g, 0.87 mmol). The solution was stirred for 4.5 h. then concentrated. Column chromatographic purification of the residue on alumina with dichloromethane/20% light petroleum gave a mixture of the isomers of 52a (0.251 g, 90%, E/Z =19.0). The column was then eluted with ethanol. Concentration of the ethanol solution gave a residue (0.391 g) which was partitioned between 1% aqueous hydrochloric acid (10 ml) and dichloromethane (10 ml). The aqueous layer was extracted with dichloromethane (2 x 5 ml) and then the organic
extracts were combined, dried, and then concentrated to give cis-50a (0.109 g). Sublimation of the initial mixture of 52a by heating at 95°C for 7 h. under oil-pump vacuum afforded 52a (0.215 g, 86% recovery) as a colourless noncrystalline solid with m.p. 90-92°C, and an unchanged isomer ratio.

(v) To 50a (0.481 g, 1.20 mmol) suspended in dry tetrahydrofuran (30 ml) under nitrogen at room temperature was added DBU (0.18 g, 1.18 mmol). The solution was stirred for 1 h. and then concentrated. Passage of the residue through a silica plug with dichloromethane gave, upon concentration, a mixture of the isomers of 52a (0.283 g, 74%) as a pale oil. The attempted purification of this oil by p.t.l.c. on a silica plate with dichloromethane/4% ethanol gave:

(a) several unidentified impure high R<sub>f</sub> bands of < 3 mg.
(b) at R<sub>f</sub> 0.6, Z-52a (7 mg) as a pale yellow oil.
(c) at R<sub>f</sub><0.3, unidentified polar material.

**Ethyl 3-Benzyl-9,10-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazonine-4-carboxylate 52b**

To 50b (0.519 g, 1.09 mmol) in dry acetonitrile under nitrogen was added DBU (0.18 ml, 1.2 mmol). The mixture was stirred for 3 h. and then concentrated. The column chromatographic purification of the residue on alumina (17 g) with dichloromethane/20% light petroleum gave, on concentration, the E-3-benzyl-3-benzazonine 52b (0.401 g, 93%) as a colourless oil. ¹H NMR δ: 7.47-7.45 (m, 2ArH'), 7.38-7.26 (m, 3ArH'), 6.79 (s, H8), 6.63 (s, H11), 6.57 (d, J 16.2 Hz, H7), 5.56-5.46 (m, H6), 4.19-4.05 (m, CH₂ of Et and H of CH₂Ph), 3.96 (d, J 13.9 Hz, H of CH₂Ph), 3.88 (s, OCH₃), 3.85 (s, OCH₃), 3.52 (dd, J 1.3 Hz, 6.2 Hz, H4), 2.98-2.90 (m, H2'A), 2.76-2.66 (m, H1'A and H5), 2.41-2.34 (m, H1'A), 2.06-2.00 (m, H5), 1.26 (t, CH₃ of Et); ¹³C NMR δ: 173.79 (COO), 147.45 (C9A), 147.25 (C10A), 140.34 (C1'), 134.84 (C7'B), 133.99 (C7a'C), 132.09 (C11a'C), 131.02 (C6'B), 129.66 (2C"'), 128.89 (2C"'), 127.81 (C"'), 113.85 (C11), 110.81 (C8), 62.25 (C4), 60.80 (CH₂ of Et and CH₂Ph), 56.59 (2OCH₃), 55.13 (C2), 38.53 (C1), 36.62 (C5), 15.08
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(\text{CH}_3 \text{ of Et}); \text{ MS m/z: } 395 (M^+, 7\%; \text{ Calcd. for C}_{24}\text{H}_{29}\text{N}_0\text{O}_4 \, 395.209, \text{ found } 395.211), 322 (84), 282 (18), 230 (14), 189 (14), 115 (11), 91 (100).

**Ethyl 7.8-Dimethoxy-3-methyl-1-vinyl-2,3,4,5-tetrahydro-IH-3-benzazepine-4-carboxylate 53**

An 87:9:4 mixture (0.164 g) of \textit{E}-52a, \textit{Z}-52a, and a component attributed to 53, was refluxed in butyronitrile (10 ml) for 11.5 h. to produce, after concentration, a 40:9:51 mixture of the same isomers. Purification of a portion (0.103 g) of this material by p.t.l.c. on silica with dichloromethane/5\% ethanol afforded a mixture (82:18) of the B-ring diastereomers of the 3-benzazepine 53 (0.042 g) as a pale yellow oil. \textit{trans diastereomer} \textsuperscript{1}H NMR \delta: 6.62 (s, ArH), 6.61 (s, ArH), 6.21-6.18 (m, \text{H}1\text{'}), 5.18 (d, \text{J} 10.3 \text{ Hz}, \text{H}2\text{'}), 4.91 (d, \text{J} 17.2 \text{ Hz}, \text{H}2\text{'}), 4.11-3.98 (q, \text{CH}_2 \text{ of Et}), 3.95-3.91 (m, \text{H}1), 3.85 (s, \text{OCH}_3), 3.83 (s, \text{OCH}_3), 3.67 (d, \text{J} 5.7 \text{ Hz}, \text{H}2), 3.38-3.31 (m, \text{H}), 3.19-3.10 (m, \text{H}), 2.77-2.59 (m, \text{H}), 2.54 (s, \text{NCH}_3), 1.17 (t, \text{CH}_3 \text{ of Et}); \textsuperscript{13}C NMR \delta: 171.99 (\text{COO}), 148.03 (C7\text{A}), 147.39 (C8\text{A}), 138.72 (C1\text{'}), 133.90 (C5a\text{B}), 130.91 (C9a\text{B}), 116.77 (C2\text{'}), 114.40 (C6\text{C}), 113.86 (C9\text{C}), 69.28 (C2), 60.45 (\text{CH}_2 \text{ of Et}), 56.59 (2\text{OCH}_3), 52.11 (C1), 51.22 (C2), 46.92 (\text{NCH}_3), 35.40 (C5), 15.08 (\text{CH}_3 \text{ of Et}); \textit{cis diastereomer} \textsuperscript{1}H NMR \delta: 5.82-5.83 (m, \text{H}1\text{'}), 2.58 (s, \text{NCH}_3), 1.23 (t, \text{CH}_3 \text{ of Et}); \textsuperscript{13}C NMR \delta: 173.88 (\text{COO}), 66.95 (C2), 60.71 (\text{CH}_2 \text{ of Et}), 52.87 (C4), 45.37 (\text{NCH}_3), 38.15 (C5); MS m/z: 319 (M^+, 12\%; \text{ Calcd. for C}_{18}\text{H}_{25}\text{N}_0\text{O}_4 \, 319.1783, \text{ found } 319.1786), 246 (100), 230 (3), 204 (4), 189 (6).

**Conversion of 52a to the Proposed Pyrrolo[2,1-a]isoquinolinium Derivative 54**

(i) The reaction of 52a (0.294 g, 0.920 mmol) with iodomethane (0.157 g, 1.11 mmol) in dry butanone (2 ml) at room temperature in a sealed vessel protected from light over 3 days gave the precipitation of colourless needles tentatively attributed to the \textit{3-ethoxycarbonyl-8,9-dimethoxy-4-methyl-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolinium iodide 54} (0.015 g, 3\%) with m.p. 206-207°C. Satisfactory microanalytical results could not be obtained from this material. \textsuperscript{1}H NMR \delta: 6.19 (t,
H10bA), 6.02 (t, H3A), 3.58 (s, NCH3); 1H NMR (d6-DMSO) δ: 6.95 (s, ArH), 6.83 (s, ArH), 5.04 (t, H10bA), 4.84 (t, H3A), 4.34 (q, CH2 of Et), 3.79 (s, OCH3), 3.77 (s, OCH3), 3.71-3.64 (m, 2H), 3.27 (s, NCH3), 3.21-3.17 (m, H), 3.04-2.98 (m, H), 2.77-2.69 (m, H), 2.53-2.43 (m, 2H), 2.03-1.96 (m, H), 1.34 (t, CH3 of Et); 13C (d6-DMSO) NMR δ: 169.05 (COO), 152.73 (C8A), 152.05 (C9A), 125.31 (C6aB), 123.84 (C10aB), 115.59 (C7C), 113.89 (C10C), 78.38 (C10bD), 76.94 (C3D), 66.62 (CH2 of Et), 59.67 (OCH3), 59.56 (OCH3), 51.87 (C5), 50.16 (NCH3), 33.10 (C6), 26.59 (C1E), 26.02 (C2E), 17.75 (CH3 of Et); Anal. Calcd for C18H26N04I: C, 48.33; H, 5.86; N, 3.13%, found: C, 47.19; H, 5.83; N, 3.15%.

(ii) The reaction of 52a (0.231 g, 0.724 mmol) with iodomethane (0.156 g, 1.11 mmol) in refluxing dry butanone (2 ml) for 2 h. afforded, after aging at -5°C, a precipitate which was collected to give 54 (0.027 g, 8%).

6,7-Dimethoxy-2,2-dimethyl-1-vinyl-1,2,3,4-tetrahydroisoquinolinium Iodide 55a

The 1-vinylisoquinoline 49a (0.461 g, 1.98 mmol) was refluxed in acetone (10 ml) with iodomethane (2.1 g, 14 mmol) for 1 h. The solution was then cooled and concentrated. Recrystallisation of the residue from methanol gave the isoquinolinium iodide 55a (0.612 g, 83%) as pale yellow prisms with m.p. 231-232°C. 1H NMR δ: 6.72 (s, ArH), 6.55 (s, ArH), 6.03-5.82 (m, H1' and H2'), 5.66 (d, J 7.9 Hz, H1), 4.13-4.06 (m, H3), 4.00-3.92 (m, H3), 3.89 (s, OCH3), 3.83 (s, OCH3), 3.59 (s, NCH3), 3.36 (s, NCH3), 3.20 (t, H4); 1H NMR (CD3CN) δ: 6.68 (s, ArH), 6.43 (s, ArH), 5.89-5.76 (m, H1'), 5.64-5.59 (m, H2'), 4.88 (d, J 8.8 Hz, H1), 3.65 (s, OCH3), 3.59 (s, OCH3), 3.55-3.41 (m, H3), 2.99-2.92 (m, H4 and NCH3), 2.85 (s, NCH3); 13C NMR δ: 150.04 (C6A), 149.05 (C7A), 129.91 (C1'), 129.36 (C2'), 121.61 (C4aB), 121.44 (C8aB), 111.46 (C5C), 110.97 (C8C), 74.34 (C1), 57.88 (C3), 56.55 (2OCH3), 51.58 (NCH3), 48.37 (NCH3), 24.31 (C4); Anal. Calcd for C15H22N04I: C, 48.01; H, 5.91; N, 3.73%, found: C, 48.13; H, 5.93; N, 3.83%; IR (KBr): 1520, 1238, 1119, 1111, 783 cm⁻¹.
2-Benzyl-6,7-dimethoxy-2-methyl-1-vinyl-1,2,3,4-tetrahydroisoquinolinium Iodide 55b

The 1-vinylisoquinoline 49b (1.012 g, 3.271 mmol) was refluxed in acetone (10 ml) with iodomethane (4.3 g, 31 mmol) for 2 h. The solution was then cooled and concentrated. Recrystallisation of the residue from methanol gave a mixture (54:46) of the B-ring diastereomers of the isoquinolinium iodide 55b (1.146 g, 78%) as pale yellow prisms with m.p. 209-210°C. 1H NMR (superscripts a-b denote those attributed to each diastereomer) δ: 7.79-7.76 (m, 2ArH"b"), 7.64-7.62 (m, 2ArH"a"), 7.50-7.33 (m, 3ArH""), 6.76 (s, ArH"a"), 6.67 (s, ArH"b"), 6.62 (s, ArH"b"), 6.56 (s, ArH"a"), 6.35-6.01 (m, H1' and H2"b"), 5.92-5.82 (m, H2"a"), 5.71 (d, J 9.2 Hz, H1"b"), 5.63 (d, J 8.6 Hz, H1"a"), 5.50 (d, J 12.8 Hz, NCH"b"Ph), 5.30 (d, J 12.8 Hz, NCH"a"Ph), 4.83 (d, J 12.8 Hz, NCH"a"Ph), 4.52 (d, J 12.9 Hz, NCH"b"Ph), 4.27-4.19 (m, H3"a"), 3.90-3.84 (m, 2OCH3 and H3"b"), 3.77-3.61 (m, H), 3.38-3.27 (m, H), 3.20 (s, NCH3"a"), 3.14 (s, NCH3"b"), 3.07-2.98 (m, H4); Anal. Calcd for C211 -126NO2I: C, 55.88; H, 5.81; N, 3.10%, found: C, 55.75; H, 5.82; N, 3.18%; IR (KBr): 1522, 1227, 1119, 1113, 706 cm⁻¹.

N,N-Dimethyl-α-vinyl-4,5-dimethoxy-2-vinylbenzylamine 56a

To 55a (0.475 g, 1.27 mmol) suspended in dry tetrahydrofuran (20 ml) at -20°C under nitrogen was added dropwise a 0.98M solution of lithium diisopropylamide (1.5 ml, 1.5 mmol) in a tetrahydrofuran/hexane mixture. The mixture was stirred at -20°C for 30 min. and then allowed to warm with stirring for a further 30 min. before the addition of water (15 ml) and diethyl ether (25 ml). The aqueous layer was extracted with further diethyl ether (2 x 20 ml) and the ether extracts were then combined and washed with water (10 ml), and then saturated brine (10 ml). Drying and then concentration of the ether solution gave the benzylamine 56a (0.079 mg, 25%) as a yellow oil. 1H NMR δ: 7.19 (dd, J 10.0 Hz, 17.2 Hz, H1""""), 7.00 (s, ArH), 6.93 (s, ArH), 5.90 (m, H1""'), 5.49 (dd, J 1.2 Hz, 17.2 Hz, H2""'), 5.24-5.14 (m, H2' and H2""'), 5.02 (dd, J 1.3 Hz, 10.1 Hz, H2''), 3.89 (s, OCH3), 3.87
(s, OCH₃), 3.76 (d, J 8.7 Hz, H1), 2.19 (s, 2NCH₃); ¹³C NMR δ: 149.34 (C⁴"A), 148.23 (C⁵"A), 141.02 (C²B), 134.13 (C¹"B), 133.50 (C¹"C), 129.34 (C²"C), 115.89 (C²"D), 114.63 (C²"D), 110.88 (C³"E), 109.04 (C⁶"E), 72.16 (Cl), 56.62 (OCH₃), 56.40 (OCH₃), 44.58 (NCH₃); MS m/z: 247 (M⁺, 60%; Calcd. for C₁₅H₂₁NO₂ 247.157, found 247.159), 232 (62), 203 (100), 188 (25), 172 (47), 84 (47), 58 (55).

The aqueous washings were concentrated and the residue was then extracted with hot chloroform. Concentration of these extracts afforded 55a (0.305 g, 64%).

**N-Benzyl-N-methyl-α-vinyl-4,5-dimethoxy-2-vinylbenzylamine 56b**

To 55b (0.518 g, 1.15 mmol) suspended in dry tetrahydrofuran (20 ml) at -20°C under nitrogen was added dropwise a 0.98M solution of lithium diisopropylamide (1.4 ml, 1.4 mmol) in a tetrahydrofuran/hexane mixture. The mixture was stirred at -20°C for 20 min. and then allowed to warm with stirring for a further 40 min. before the addition of water (15 ml) and diethyl ether (25 ml). The aqueous layer was extracted with further diethyl ether (2 x 20 ml) and the extracts were then combined and washed with water (10 ml), and then saturated brine (10 ml). Drying and then concentration of the ether solution gave a yellow oil which was purified by passage through an alumina plug with dichloromethane to give the benzylamine 56b (0.244 mg, 55%) as a pale yellow oil. ¹H NMR δ: 7.39-7.19 (m, 5ArH and H₁"'), 7.16 (s, ArH), 6.99 (s, ArH), 5.99 (m, H₁'), 5.53 (dd, J 1.2 Hz, 17.3 Hz, H₂"'), 5.27-5.20 (m, H₂' and H₂"'), 5.07 (dd, J 1.4 Hz, 10.0 Hz, H₂'), 4.09 (d, J 8.9 Hz, H₁), 3.91 (s, OCH₃), 3.89 (s, OCH₃), 3.56 (d, J 13.3 Hz, NCHPh), 3.33 (d, J 13.3 Hz, NCHPh), 2.12 (s, NCH₃); ¹³C NMR δ: 149.72 (C⁴"A), 148.50 (C⁵"A), 140.51 (C₁'B), 140.38 (C₁+C), 134.98 (C¹"B), 133.30 (C¹"C), 129.94 (C²"C), 129.30 (2C⁺), 128.77 (2C⁺), 127.35 (C⁴⁺), 116.39 (C²"D), 114.57 (C²"D), 111.04 (C₃"E), 109.51 (C₆"E), 70.84 (C₁), 59.92 (NCH₂Ph), 56.58 (OCH₃), 56.44 (OCH₃), 40.58 (NCH₃); MS m/z: 323 (M⁺, 25%; Calcd. for C₂₁H₂₅NO₂ 323.188, found 323.188), 308 (16), 232 (37), 203 (63), 172 (29), 134 (43), 91 (100).
The aqueous solutions were combined and extracted with chloroform (3 x 20 ml). Concentration of the extracts afforded a mixture (70:30) of the B-ring diastereomers of 55b (0.198 g, 38%).

6,7-Dimethoxy-1-vinyl-1,2,3,4-tetrahydroisoquinoline 57

A solution of vinylmagnesium bromide in dry tetrahydrofuran (130 ml) under nitrogen was prepared from vinyl bromide (22.2 g, 0.208 mol). The solution was cooled to 0°C and dry diethyl ether (160 ml) was added prior to the addition of the imine 47 (13.24 g, 69.25 mmol) as a solution in dry tetrahydrofuran (100 ml) over 30 mm. The mixture was allowed to warm to room temperature with stirring for 3.5 h. and then the excess Grignard reagent was hydrolysed by the addition of saturated aqueous ammonium chloride. The organic solvents were decanted and the residual solids were rinsed with diethyl ether (30 ml). The solids were dissolved in 3M aqueous hydrochloric acid (250 ml) and the solution was then basified with 80% aqueous sodium hydroxide. The solids which precipitated were collected by centrifuging the mixture, while the supernatant liquid was decanted and extracted with chloroform (4 x 50 ml); centrifugation was necessary to break the emulsions formed during the extractions. The solid was then dissolved in the chloroform extracts. The resultant solution was washed with water (20 ml) then saturated brine (20 ml), and then dried and concentrated to a dark solid (6.355 g) which was purified by column chromatography on silica with dichloromethane/0-2% methanol to give the secondary amine 57 (5.009, 33%) as a pale tan powder. $^1$H NMR $\delta$: 6.59 (s, ArH), 6.58 (s, ArH), 6.00-5.88 (m, H1'), 5.29-5.22 (m, H2'), 4.40 (d, J 7.8 Hz, H1), 3.85 (s, OCH$_3$), 3.82 (s, OCH$_3$), 3.26-3.20 (m, H), 3.06-2.98 (m, H), 2.88-2.75 (m, H), 2.72-2.62 (m, H), 1.85 (bs, NH); $^{13}$C NMR $\delta$: 148.27 (C6A), 147.72 (C7A), 141.31 (C1'), 129.25 (C4aB), 127.60 (C8aB), 117.71 (C2'), 112.39 (C5C), 110.93 (C8C), 60.60 (C1), 56.49 (2OCH$_3$), 42.25 (C3), 29.78 (C4); MS m/z: 219 (M+, 28%; Calcd. for C$_{13}$H$_{17}$NO$_2$ 219.1259, found 219.1269), 218 (34), 204 (13), 192 (100), 188 (12), 178 (13), 176 (16).
6.7-Dimethoxy-2-trimethylsilylmethyl-1-vinyl-1,2,3,4-tetrahydroisoquinoline 58

The secondary amine 57 (0.926 g, 4.22 mmol) was stirred in dry acetonitrile (5 ml) with trimethylsilylmethyl trifluoromethanesulfonate (0.992 g, 4.20 mmol) under nitrogen for 6 h. at room temperature, then water (5 ml) and diethyl ether (10 ml) were added. The aqueous layer was extracted with further diethyl ether (4 ml) and then the ether extracts were combined and washed with water (3 x 2 ml), and then saturated brine (2 x 2 ml). The ether solution was then dried and concentrated to a tan solid which was purified by column chromatography on alumina (30 g) with hexane/40% dichloromethane. The residual 57 was retained on the column and the 2-trimethylsilylmethylisoquinoline 58 (0.801 g, 63%) was obtained as a pale yellow oil on concentration of the early fractions. ¹H NMR δ: 6.58 (s, ArH), 6.54 (s, ArH), 5.77-5.66 (m, H1'), 5.27-5.17 (m, H2'), 3.79 (s, OCH₃), 3.77 (s, OCH₃), 3.68 (d, J 8.4 Hz, H1), 3.02-2.97 (m, H), 2.85-2.78 (m, H), 2.69-2.62 (m, H), 2.47-2.36 (m, H and H of NCH₂Si), 1.78 (d, J 14.7 Hz, H of NCH₂Si), 0.07 (s, Si(CH₃)₃); ¹³C NMR δ: 147.82 (C₆A), 147.26 (C₇A), 141.30 (C1'), 128.77 (C₄aB), 127.01 (C₈aB), 117.90 (C₂'), 111.53 (C₅ and C₈), 71.15 (C₁), 56.09 (2OCH₃), 50.65 (NCH₂SiC), 46.43 (C₃C), 29.00 (C₄), -0.95 (Si(CH₃)₃).

6.7-Dimethoxy-2-methyl-2-trimethylsilylmethyl-1-vinyl-1,2,3,4-tetrahydroisoquinolinium Iodide 59

The amine 58 (0.682 g, 2.23 mmol) was stirred in dry acetonitrile (4 ml) with iodomethane (1.9 g, 13 mmol) at 60°C for 1 h. Concentration of the mixture and recrystallisation of the residue from methanol/ethyl acetate gave a mixture (51:49) of the B-ring diastereomers of the isoquinolinium salt 59 (0.917 g, 92%) as off-white prisms. ¹H NMR (superscripts a,b denote those attributed to each diastereomer) δ: 6.74 (s, ArH a), 6.73 (s, ArH b), 6.60 (s, ArH a), 6.54 (s, ArH b), 6.09-5.76 (m, 3H and H1 b), 5.49 (d, J 8.6 Hz, H1 a), 4.01-3.92 (m, H), 3.88 (s, OCH₃), 3.82 (s, OCH₃), 3.57 (d, J 14.9 Hz, NCH₃Si), 3.50-3.10 (m, 3H), 3.45 (s, NCH₃ b), 3.31 (s, NCH₃ a), 2.98 (d, J 14.7 Hz, NCH₃Si), 0.37 (s, Si(CH₃)₃ b), 0.35 (s, Si(CH₃)₃ a); ¹³C NMR δ:
150.30 (C6A), 149.35 (C7A), 130.91 (C1'), 129.27 (C2'), 121.83-121.06 (C4a and C8a), 111.75-111.38 (C5 and C8), 76.88 and 76.64 (C1), 58.45 and 57.81 (NCH₂SiB), 56.82 (2OC₃H₃), 55.84 and 54.53 (C3B), 51.32 and 50.51 (NCH₃), 24.92 and 24.73 (C4), 0.83 and 0.68 (Si(CH₃)₃).

9,10-Dimethoxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazonine 61

All traces of moisture were excluded from this procedure. The cesium fluoride was dried immediately prior to use under vacuum at 170-190°C over phosphorus pentoxide. Dry dimethylformamide was obtained by distillation from barium oxide, under reduced pressure, onto 4A molecular sieves and then storage. The glassware was dried at 120°C prior to use.

The salt 59 (0.408 g, 0.912 mmol) was placed in a two-necked flask to which a test-tube containing dry cesium fluoride (0.698 g, 4.60 mmol) was attached by rubber tubing and the apparatus was flushed with nitrogen. Dry dimethylformamide (3 ml) was added via syringe to 59, then the cesium fluoride was added and the mixture was stirred sealed under nitrogen, protected from light, for 44 h. The resultant mixture was treated with 2.5% aqueous sodium bicarbonate (25 ml) and then extracted with diethyl ether (4 x 10 ml). The organic extracts were washed with 2.5% sodium bicarbonate (5 ml), then saturated brine (5 ml), and then dried and concentrated to give the E-3-benzazonine 61 (0.063 g, 30%) as a colourless oil. ¹H NMR δ: 6.69 (s, H8), 6.55 (s, H11), 6.34 (d, J 16.2 Hz, H7), 5.26-5.15 (m, H6), 3.79 (s, OCH₃), 3.76 (s, OCH₃), 2.79-2.57 (m, 4H), 2.39 (s, NCH₃), 2.35-2.16 (m, 4H); ¹³C NMR δ: 147.40 (C9A), 147.21 (C10A), 134.15 (C7aB), 133.56 (C7C), 132.23 (C6C), 134.15 (C11aB), 114.13 (C11), 110.90 (C8), 61.08 (C4D), 57.96 (C2D), 56.58 (2OC₃H₃), 45.38 (NCH₃), 38.31 (C1), 35.76 (C5); MS m/z: 247 (M⁺, 100%; Calcd. for C₁₅H₂₁NO₂ 247.1572, found 247.1578), 246 (35), 232 (29), 204 (15), 189 (13), 149 (14); IR (thin film from CH₂Cl₂): 1508, 1463, 1328, 1264, 1219, 1196, 1104 cm⁻¹.
The various aqueous washings were combined and saturated with sodium chloride then extracted with chloroform (4 x 10 ml). Concentration of these extracts, after drying, afforded 55a (0.201 g, 59%).

2-Cyanomethyl-6.7-dimethoxy-2-methyl-1-vinyl-1,2,3,4-
tetrahydroisoquinolinium Iodide 62a

Iodoacetonitrile was prepared for this synthesis by stirring a mixture of sodium iodide (75.0 g, 0.500 mole), chloroacetonitrile (20.0 ml, 0.316 mole) and dry acetonitrile (150 ml) at room temperature for 24 h. The mixture was filtered and the filtrate was then concentrated at 50°C. The residue was taken up in dichloromethane and the solution was again filtered and then concentrated at 50°C. The vacuum distillation of the residual liquid afforded iodoacetonitrile (19.82 g, 37%) at approximately 110°C. $^1$H NMR δ: 3.54.

The amine 49a (1.022 g, 4.381 mmol) was stirred in dry butanone (3 ml) with iodoacetonitrile (1.10 g, 6.59 mmol) for 40 h. at room temperature protected from light. The mixture was then cooled to -10°C and a first crop of solid (0.548 g) was collected. The concentration of the filtrate afforded a second crop (1.276 g). The solids were combined and recrystallised from methanol/ethyl acetate to give a mixture (trans:cis=53:47) of the B-ring diastereomers of the N-cyanomethyl salt 62a (1.090 g, 62%) as an off-white powder. The characteristic NMR peaks were: trans diastereomer $^1$H NMR δ: 3.51 (s, NCH$_3$); $^{13}$C NMR δ: 132.33 (C2'), 128.77 (C1'), 111.99 (C5A), 111.01 (C8A), 74.66 (C1), 58.19 (NCH$_2$CN), 56.95 (20CH$_3$), 50.88 (C3), 47.14 (NCH$_3$), 24.43 (C4); cis diastereomer $^1$H NMR δ: 3.66 (s, NCH$_3$); $^{13}$C NMR δ: 130.23 (C1'), 130.15 (C2'), 111.87 (C5A), 111.26 (C8A), 74.93 (C1), 56.19 (NCH$_2$CN), 56.95 (20CH$_3$), 51.73 (C3), 48.74 (NCH$_3$), 24.43 (C4).

6.7-Dimethoxy-2-methyl-2-phenacyl-1-vinyl-1,2,3,4-
tetrahydroisoquinolinium Bromide 62b

To the N-methyl base 49a (2.015 g, 8.641 mmol) in dry butanone (6.0 ml) was added phenacyl bromide (2.623 g, 13.18 mmol). The mixture was warmed briefly to
dissolve all the solids and was then stirred at room temperature for 12 h. with the formation of a solid. The mixture was aged at -10°C for 2 h. then filtered while cold. The addition of diethyl ether (10 ml) to the filtrate gave a small second crop of solid. The solids were combined and reslurried with diethyl ether (3 x 30 ml) then dried to give a mixture (trans:cis=78:22) of the B-ring diastereomers of the N-phenacyl salt 62b (3.062 g, 82%) as a pale yellow powder. Trans diastereomer: 1H NMR δ: 8.35-8.31 (m, o-ArH"), 7.66-7.61 (m, p-ArH"), 7.53-7.48 (m, m-ArH"), 6.63 (s, ArH), 6.59 (s, ArH), 6.65-6.58 (m, H2'), 6.25-6.15 (bd, NCHCO), 6.18-6.00 (m, H1' and H2'), 5.84 (d, J 10.8 Hz, H1), 5.60-5.48 (bd, NCHCO), 4.79-4.75 (m, H), 3.93-3.78 (m, H), 3.88 (s, OCH3), 3.85 (s, OCH3), 3.60 (s, NCH3), 3.15-3.11 (m, 2H); 13C NMR δ: 192.10 (CO), 150.05 (C6A), 149.21 (C7A), 135.40 (C1'), 134.53 (Cl''), 129.90 (C2'), 129.54 (2C''), 129.24 (C''), 128.95 (2C''), 121.06 (C4aB), 120.69 (C8aB), 111.27 (C5C), 110.73 (C8C), 73.72 (C1), 62.88 (NCH2CO), 56.47 (2OCH3), 54.93 (C3), 47.71 (NCH3), 24.29 (C4); cis diastereomer: distinguishable peaks 1H NMR δ: 8.01-7.97 (m, o-ArH"), 4.98-4.92 (m, H), 3.69 (s, NCH3); 13C NMR δ: 72.68 (C1), 45.92 (NCH3), 23.59 (C4).

Recrystallisation of this material from methanol gave a mixture (95:5) of the B-ring diastereomers as a cream powder (1.257 g, 34%) with m.p. 198-201°C. Anal. Calcd for C22H26NO3Br: C, 61.12; H, 6.06; N, 3.24%, found: C, 60.80; H, 6.23; N, 3.34%; IR (KBr): 1697, 1519, 1258, 1225, 1115, 860 cm-1.

9,10-Dimethoxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazonine-4-carbonitrile 63a

(i) To the salt 62a (0.395 g, 0.987 mmol) in dry acetonitrile (15 ml) at room temperature under nitrogen was added DBU (0.195 g, 1.28 mmol). After stirring for 5 h. the solution was then concentrated and the residue was purified by column chromatography on alumina (25 g) with dichloromethane/20% light petroleum. Concentration of the early fraction (100 ml) gave a pale yellow oil (0.227 g, 84%) which upon 1H NMR analysis indicated 3 components in the ratio of 11.4:2.3:1.0. The purification of this oil by preparative reverse phase HPLC with acetonitrile/24%
water afforded at 8.89 min. the major component, the E-4-cyano-benzazonine 63a (0.133 g, 49%), as a colourless oil. \(^1\)H NMR \(\delta\): 6.69 (s, H8), 6.58 (s, H11), 6.40 (d, \(J_16.1\) Hz, H7), 5.43-5.33 (m, H6), 3.78 (s, OCH\(_3\)), 3.75 (s, OCH\(_3\)), 3.67-3.64 (m, H4), 2.75-2.54 (m, 6H), 2.46 (s, NCH\(_3\)); \(^1^3\)C NMR \(\delta\): 147.66 (C9 and C10), 137.19 (C7), 133.05 (C11a\(A\)), 131.35 (C7a\(A\)), 128.33 (C6), 118.82 (CN), 114.01 (C11), 110.66 (C8), 57.03 (C2), 56.65 (2OCH\(_3\)), 56.44 (C4), 45.34 (NCH\(_3\)), 39.17 (C1), 37.55 (C5); MS m/z: 272 (M\(^+\)), 257 (17), 245 (100), 230 (65), 204 (37), 189 (53), 188 (66).

(ii) To 62a (0.631 g, 1.58 mmol) in dry acetonitrile (30 ml) at reflux under nitrogen was added DBU (0.337 g, 2.21 mmol). The solution was refluxed for 1 h. Concentration and purification as for (i) gave a pale yellow oil (0.265 g, 62%) which contained the same 3 components as for (i), but in the ratio of 10.0:1.0:1.5.

4-Benzoyl-9,10-dimethoxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazonine 63b

(i) To the salt 62b (1.507 g, 3.486 mmol) suspended in dry acetonitrile (50 ml) under nitrogen at 0°C was added DBU (0.69 g, 4.53 mmol). After stirring at 0°C for 5 h, the solution was then concentrated and the residue was purified by column chromatography on alumina with dichloromethane/20% light petroleum. Concentration of the early fraction gave a yellow oil (1.026 g, 84%). Analysis by \(^1\)H NMR revealed a 91:7:2 mixture of E-63b:Z-63b:64b. Purification of a portion of this mixture by preparative reverse phase HPLC with acetonitrile/20% water gave:

(a) the Z-benzazonine Z-63b as a yellow oil. \(^1\)H NMR \(\delta\): 7.84 (dd, \(J_11.0\) Hz, 7.6 Hz, \(o\)-ArH\(\_n\)), 7.55-7.50 (m, \(p\)-ArH\(\_n\)), 7.45-7.40 (m, \(m\)-ArH\(\_n\)), 6.67 (d, \(J_11.0\) Hz, H7), 6.65 (s, ArH), 6.54 (s, ArH), 6.04-5.95 (m, H6), 4.33 (dd, \(J_3.5\) Hz, 10.9 Hz, H4), 3.88 (s, OCH\(_3\)), 3.83 (s, OCH\(_3\)), 3.14-3.06 (m, H2), 2.76-2.67 (m, H1), 2.53 (s, NCH\(_3\)), 2.43-2.32 (m, H5), 2.18-2.14 (m, H5); \(^1^3\)C NMR \(\delta\): 200.46 (CO), 148.54 (C9\(A\)), 147.70 (C10\(A\)), 137.71 (C11\(a\)\(B\)), 134.28 (C7a\(B\)), 133.30 (C6\(C\)), 132.37 (C7\(C\)), 132.06 (C4\("C\)), 130.11 (C1\("B\)), 129.17 (2C\("\)), 128.77 (2C\("\)), 113.61 (C8\(D\)), 111.83 (C11\(D\)), 65.96 (C4), 56.56 (2OCH\(_3\)), 53.54 (C2), 42.90 (NCH\(_3\)), 36.10 (C1), 30.93
(b) the E-benzazonine E-63b as a yellow oil. The compound showed 2 conformers (51:49) on NMR analysis at room temperature. $^1$H NMR (superscripts$^a,b$ denote signals for each conformer) $\delta$: 7.84-7.77 (m, $o$-ArH$^a$), 7.54-7.51 (m, $p$-ArH$^a$), 7.47-7.37 (m, $m$-ArH$^a$), 6.84 (s, ArH$^a$), 6.78 (s, ArH$^b$), 6.67 (s, ArH$^b$), 6.58 (s, ArH$^b$), 6.41 (d, $J$ 16.4 Hz, H4$^b$), 6.23 (d, $J$ 16.1 Hz, H4$^a$), 5.82-5.71 (m, H6$^b$), 5.42-5.32 (m, H6$^a$), 4.40-4.37 (m, H$^b$), 3.91-3.83 (m, 20CH$_3$ and H), 3.71-3.56 (m, H), 3.11-3.06 (m, H$^a$), 2.84-2.67 (m, 2H), 2.53 (s, NCH$_3$$^b$), 2.50-2.32 (m, 2H), 2.25 (s, NCH$_3$$^b$); $^{13}$C NMR $\delta$: 201.14 and 200.92 (CO), 147.75 and 147.53 (C9$^A$), 147.28 (C10$^A$), 139.07 and 137.68 (C11$^a$), 133.89 (C7$^a$), 135.68 and 133.70 (C6$^C$), 133.31 and 133.02 (C7$^C$), 132.79 and 132.30 (C1$^a$), 131.76 and 130.94 (C4$^a$), 129.07-128.61 (4C$^a$), 114.21 (C8$^D$), 111.06 and 109.81 (C1$^a$), 70.34 and 70.02 (C4), 56.52 (20CH$_3$), 59.62 and 55.56 (C2), 41.40 (NCH$_3$), 35.94 and 34.88 (C1), 33.37 and 33.26 (C5); MS m/z: 349 (M-2+, 2%; Calcd. for C$_{22}$H$_{23}$NO$_3$ 349.1675, found 349.168), 246 (100), 215 (7), 206 (12), 160 (12), 105, (14), 77 (16). IR (thin film from CH$_2$Cl$_2$): 2934, 1678, 1512, 1259, 1221, 1105, 735, 698 cm$^{-1}$.

(ii) To 62b (0.125 g, 0.289 mmol) suspended in dry acetonitrile (5 ml) under nitrogen at -30°C was added DBU (0.053 g, 0.35 mmol). After stirring between -20°C and -30°C for 5 h, the solution was worked up as for (i) to give a 94:6 mixture of E-63b:Z-63b (0.071 g, 71%).

(iii) To 62b (0.521 g, 1.205 mmol) suspended in dry acetonitrile (20 ml) under nitrogen at room temperature was added DBU (0.204 g, 1.34 mmol). After stirring for 3 h, the solution was worked up as for (i) to give a 89:3:8 mixture of E-63b:Z-63b:64b (0.280 g, 66%).
2-Benzoyl-7.8-dimethoxy-3-methyl-1-vinyl-2,3,4,5-tetrahydro-1H-3-benzazepine

64b

(i) To the salt 62b (0.122 g, 0.282 mmol) suspended in dry acetonitrile (5 ml) at 65°C was added DBU (0.052 g, 0.35 mmol), producing the immediate removal of the solid. After stirring at 65°C for 1 h. the solution was then concentrated and the residue was purified by column chromatography on alumina with dichloromethane/20% light petroleum. Concentration of the early fraction gave a yellow oil (0.053 g, 54%). Analysis by ¹H NMR revealed a mixture (3.6:1.0) of the B-ring diastereomers of the 3-benzazepine 64b. P.t.l.c. on silica with dichloromethane/3% methanol failed to separate the diastereomers. trans diastereomer ¹H NMR δ: 7.88-7.83 (m, o-ArH"), 7.57-7.52 (m, p-ArH"), 7.48-7.42 (m, m-ArH"), 6.66 (s, ArH), 6.37 (s, ArH), 6.27-6.16 (m, H1'), 5.12 (dd, J 1.5 Hz, 10.3 Hz, H2'), 4.91 (dd, J 1.5 Hz, 17.7 Hz, H2'), 4.48 (d, J 6.8 Hz, H2), 4.12-4.08 (m, H1), 3.86 (s, OCH₃), 3.76 (s, OCH₃), 3.42-3.35 (m, H3), 3.14-3.07 (m, H3), 2.88-2.80 (m, H4), 2.43 (s, NCH₃); ¹³C NMR δ: 201.97 (CO), 148.05 (C7A), 147.54 (C8A), 138.60 (C1'), 137.35 (C9aB), 133.30 (C4"), 133.13 (C5aB), 131.19 (C1"B), 129.21 (2C"), 128.53 (2C"'), 117.30 (C2'), 113.65 (C6C), 111.38 (C9C), 69.18 (C2), 56.56 (2OCH₃), 51.82 (C4), 50.33 (C1), 45.71 (NCH₃), 34.60 (C5); MS m/z: 351 (M⁺,100%), 335 (26), 322 (33), 247 (20), 217 (24), 161, (20); cis diastereomer ¹H NMR (discernible peaks) δ: 8.00-7.98 (m, o-ArH"), 6.65 (s, ArH), 6.53 (s, ArH), 6.48-6.39 (m, H1'), 4.76 (dd, J 1.5 Hz, 17.7 Hz, H2'), 4.37 (d, J 1.3 Hz, H2), 3.88 (s, OCH₃), 3.80 (s, OCH₃), 2.41 (s, NCH₃); ¹³C NMR δ 138.80 (C1'), 133.74 (C4"), 117.30 (C2'), 114.34 (C6A), 114.18 (C9A), 72.20 (C2), 51.63 (C1), 44.58 (NCH₃).

(ii) The 3-benzazonine E-63b (0.072 g) in dry acetonitrile (10 ml) was refluxed for 75 min. Concentration and then passage of the residue through an alumina plug with dichloromethane/20% light petroleum afforded a mixture (4.8:1.0) of the B-ring diastereomers of 64b (0.043 g, 60%).
E-9,10-Dimethoxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazonine-4-spiro-3'-
tetrahydro-2'-furanone 66

(i) The base 49a (1.049 g, 4.502 mmol) was stirred in dry butanone (4 ml) at 50°C
with α-bromo-γ-butyrolactone (1.40 g, 8.48 mmol) for 40 h. Then the solution was
cooled and diethyl ether (10 ml) was added. The resultant gummy solid was
triturated with diethyl ether (4 x 10 ml) then taken-up and concentrated from
dichloromethane to give a pale tan hygroscopic powder (1.219 g) of crude 65.

A portion of the above solid (0.870 g) in dry acetonitrile (45 ml) at 0°C was
treated with DBU (0.415 g, 2.72 mmol). After stirring at 0°C for 5 h. the solution
was then concentrated and the residue was purified by column chromatography on
alumina (15 g) with dichloromethane/10% light petroleum. Concentration of the
early fraction (100 ml) gave a yellow oil (0.377) which contained mainly 49a. This
fraction was further purified by column chromatography on alumina (20 g) with light
petroleum/15% ethyl acetate to give 49a (0.210 g, 28%) followed by the E-
benzazonine 66 (0.118 g, 12%) as a colourless oil. 1H NMR δ: 6.78 (s, H8), 6.66 (s,
H11), 5.42-5.35 (m, H6), 4.26-4.21 (m, H3'), 3.87 (s, OCH3), 2.96-2.88 (m, H), 2.75-2.72
(m, H), 2.69-2.61 (m, H5), 2.57-2.55 (m, H), 2.49 (s, OCH3), 2.43-2.41 (m, H), 2.37-2.28
(m, H4'), 2.04-1.96 (m, H4'); 13C NMR δ: 178.23 (CO), 147.53 (C9A), 147.46 (C10A),
136.65 (C7), 133.47 (C11aB), 131.32 (C7aB), 128.98 (C6), 113.76 (C11), 110.39 (C8), 68.12
(C4), 65.70 (C3'), 56.54 (2OCH3), 55.77 (C2), 42.22 (C5C), 39.14 (NCH3), 37.18
(C1C), 29.94 (C4'); MS m/z: 317 (M+, 71%; Calcd. for C18H23N04 317.1626, found
317.1640), 258 (16), 204 (53), 189 (50), 173 (26), 126 (100).

(ii) A mixture of α-bromo-γ-butyrolactone (13.29 g, 82.6 mmol) and sodium iodide
(19.0 g, 127 mmol) in acetonitrile was stirred sealed at room temperature for 4 days
protected from light. The solution was then filtered and the acetonitrile was removed
by distillation at atmospheric pressure. The vacuum distillation of the dark residue
provided the removal of residual α-bromo-γ-butyrolactone at 130°C and then α-iodo-
γ-butyrolactone (12.4 g, 72%) as a yellow liquid with b.p. 165-170°C (1 mmHg).
The base 49a (1.007 g, 4.316 mmol) was stirred in dry butanone (3 ml) protected from light with α-iodo-γ-butyrolactone (1.64 g, 7.74 mmol) for 40 h. at 50°C. The solution was then concentrated and the residue was triturated with diethyl ether (2 x 20 ml). Column chromatography of the residue on silica with chloroform/10% acetonitrile afforded unreacted 49a. Elution of the column with chloroform/50% acetonitrile gave crude 65 (0.359, 19%) as a tan powder which was then stirred with DBU (0.171 g, 1.13 mmol) in dry acetonitrile (20 ml) at room temperature for 5 h. Concentration of the solution and then purification of the residue by column chromatography on alumina with dichloromethane/40% hexane afforded 66 (0.075 g, 29%) as a clear oil.

2-(2"-Chloroethoxycarbonyl)methyl-6,7-dimethoxy-1-vinyl-1,2,3,4-tetrahydroisoquinoline 67

2-Chloroethyl bromoacetate was prepared by the reaction of bromoacetic acid (17.2 g, 0.132 mol) with 2-chloroethanol (19.0 g, 0.236 mol) and concentrated sulfuric acid (0.5 ml) in toluene (20 ml). The mixture was refluxed for 5 h. connected to a Dean-Stark condenser then cooled. The organic liquid was extracted with water (40 ml) then 1% aqueous sodium bicarbonate (2 x 20 ml) and water (30 ml) again before drying over sodium sulfate. The residual water and toluene were evaporated from the crude 2-chloroethyl bromoacetate at 150°C under atmospheric pressure, and then the liquid was distilled under reduced pressure to give 2-chloroethylbromoacetate (18.7 g, 75%) as a clear liquid with b.p. 102-104°C (80 mm).

To the secondary amine 57 (3.01 g, 13.7 mmol) in dichloromethane (85 ml) with potassium carbonate (15 g) was added 2-chloroethyl bromoacetate (4.20 g, 20.7 mmol). The mixture was stirred for 16 h. Filtration of the mixture and washing of the solids with dichloromethane (2 x 10 ml) gave an organic filtrate which was extracted with 5% aqueous sodium bicarbonate (40 ml), then dried and concentrated. The residue was purified by column chromatography on silica (60 g), with a gradient
from dichloromethane/25% hexane to dichloromethane/2.5% ethanol, to give 2-(2"-chloroethoxycarbonyl)methylisoquinoline 67 (2.52 g, 54%) as a pale tan oil. 

$^1$H NMR δ: 6.59 (s, ArH), 6.56 (s, ArH), 5.83-5.71 (m, H1'), 5.35-5.29 (m, H2'), 4.39 (H1''), 4.20 (d, H1), 3.85 (s, OCH3), 3.80 (s, OCH3), 3.70 (t, H2''), 3.64 (d, J 17.1 Hz, H of NCH2CO), 3.50 (d, J 17.1 Hz, H of NCH2CO), 3.15-3.09 (m, H), 2.94-2.83 (m, 2H), 2.76-2.70 (m, H); $^{13}$C NMR δ: 171.36 (CO), 148.14 (C6A), 147.59 (C7A), 139.85 (Cl'), 128.07 (C4aB), 126.90 (C8aB), 119.52 (C2'), 111.70 (C5C), 111.34 (C8C), 66.34 (Cl), 64.47 (CH2 of NCH2CO), 56.38 (2OCH3), 56.23 (Cl''D), 48.65 (C3), 42.15 (C2''), 29.26 (C4); MS m/z: 339 (M+, 6%; Calcd. for C17H22N04Cl 339.1233, found 339.1225), 338 (7), 314 (34), 312 (100), 250 (11), 232 (61), 218 (42).

Attempted cyclisation of 67 to the Spiro Salt 68

(i) The amine 67 (0.628 g, 1.84 mmol) was stirred in dry butanone (20 ml) with potassium iodide (0.349 g, 2.10 mmol) under nitrogen at room temperature for 1 h. with no reaction.

(ii) Compound 67 (0.622 g, 1.82 mmol) was stirred in dry acetonitrile (20 ml) with potassium iodide (0.352 g, 2.12 mmol) under nitrogen at room temperature for 12 h., with no reaction. The mixture was heated at 55°C and then concentrated. Extraction of the residue with dichloromethane then concentration of the extracts gave unchanged 67 (0.578 g, 93%).

(iii) Compound 67 (0.550 g, 1.62 mmol) was refluxed in dry acetonitrile (15 ml) with potassium iodide (0.364 g, 2.19 mmol) for 12 h. Concentration and then treatment of the residue on a silica column gave the elution of unchanged 67 with dichloromethane. Elution of the column with acetonitrile afforded a dark powder (0.222 g) containing numerous components.

(iv) Compound 67 (0.623 g, 1.83 mmol) was refluxed in dry acetone (15 ml) with sodium iodide (1.0 g, 6.6 mmol) for 48 h. protected by a drying tube. The solution was then concentrated and the residue was extracted with dichloromethane (3 x 20
The extracts were filtered then concentrated to afford a tan foam (0.688 g) which on analysis by $^1$H NMR indicated many components.

6,7-Dimethoxy-1-isopropenyl-2-methyl-1,2,3,4-tetrahydroisoquinoline 70a

A solution of isopropenylmagnesium bromide was prepared by the slow addition of 2-bromopropene (10.25 g, 84.7 mmol) to magnesium turnings (2.30 g, 94.6 mmol) in dry tetrahydrofuran (100 ml) under nitrogen. The reaction was initiated by heating the solution to reflux in the presence of an iodine crystal. The addition rate was controlled to maintain a gentle reflux. The mixture was refluxed for 30 min. after the completion of the addition.

The solution of isopropenylmagnesium bromide in tetrahydrofuran was cooled to <-50°C in an acetone/liquid nitrogen slush bath, with the deposition of some solid, and then the iminium salt 48a (9.51 g, 28.5 mmol) was added portionwise over 30 min. The mixture was allowed to warm slowly to room temperature with stirring for 20 h. and then warmed to 40°C for 1 h. The mixture was then cooled and ice was added carefully to decompose the excess Grignard reagent. The mixture was basified by the addition of 40% aqueous potassium hydroxide and diethyl ether (100 ml) was added. The organic layer was decanted from the precipitated inorganic salts and washed with water (50 ml). The inorganic salts and aqueous layer were extracted with further portions of diethyl ether (3 x 50 ml). The ether extracts were combined and then concentrated. The residue was taken up in dichloromethane (100 ml) and the organic solution was washed with water (6 x 20 ml). Drying and then concentration of the organic solution gave the 1-isopropenylisoquinoline 70a (6.595 g, 94%) as a pale tan oil of >99% purity by GC-MS analysis. The oil formed a solid on storage at -5°C. $^1$H NMR δ: 6.64 (s, ArH), 6.58 (s, ArH), 5.08 (d, J 1.5 Hz, H2'), 3.84 (s, OCH3), 3.79 (s, OCH3), 3.61 (s, H1), 3.06-3.00 (m, 2H), 2.62-2.56 (m, H), 2.49-2.40 (m, H), 2.32 (s, NCH3), 1.50 (CH3); $^{13}$C NMR δ: 148.02 (C6A), 147.82 (C7A), 147.22 (C1'), 128.32 (C4aB), 127.77 (C8aB), 116.18 (C2'), 111.59 (C5C), 110.25 (C8C), 74.18 (C1), 56.46 (OCH3), 56.35
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(\text{OCH}_3), 53.08 (\text{C3}), 44.66 (\text{NCH}_3), 29.75 (\text{C4}), 17.56 (\text{CH}_3); \text{ MS } m/z: 247 (M^+, 2\%); \text{ Calcd. for C}_{15}H_{21}140_2 247.1570, \text{ found 247.156}, 207 (14), 206 (100), 191 (6), 190 (14), 162 (6); \text{ IR (thin film from CH}_2Cl_2): 2945, 2833, 2781, 1516, 1259, 1219, 1142 \text{ cm}^{-1}.

6.7-Dimethoxy-2-methyl-1-(\alpha\text{-phenylethenyl})-1.2.3.4-tetrahydroisoquinoline 70b

A solution of \alpha\text{-phenylethenylmagnesium} bromide was prepared by the dropwise addition of \alpha\text{-bromostyrene} (15.0 g, 81.9 mmol) to magnesium turnings (2.22 g, 91.3 mmol) in dry tetrahydrofuran (200 ml) under nitrogen over 45 min. The mixture was heated briefly to initiate the reaction at the start of the addition with an iodine crystal present. The reaction temperature was then kept below 35°C. The solution was stirred for 30 min. after the addition had ceased.

The solution of \alpha\text{-phenylethenylmagnesium} bromide in tetrahydrofuran was cooled to < -50°C in an acetone/liquid nitrogen slush bath and then the iminium salt 48a (13.52 g, 40.6 mmol) was added. The mixture was stirred at < -50°C for 90 min. and then allowed to warm slowly to room temperature with stirring for 16 h. before the careful addition of ice to decompose excess Grignard reagent. The mixture was basified by the addition of 40% aqueous potassium hydroxide and diethyl ether (150 ml) was added. The organic layer was decanted from the precipitated inorganic salts then centrifuged to remove any residual solids, washed with water (150 ml), and then concentrated. The residue was dissolved in diethyl ether (240 ml) which had been used, in three portions, to extract the inorganic solids and then the aqueous wash. The ether solution was washed with water (30 ml) then saturated brine (2 x 20 ml), and then dried and passed through a silica plug. Concentration of the solution afforded a solid which recrystallised from ethanol to give the 1-(\alpha\text{-phenylethenyl})isoquinoline 70b (11.11 g, 88%) as a pale yellow powder with m.p. 80-82°C. $^1H$ NMR $\delta$: 7.33-7.28 (m, 2ArH$^+$), 7.22-7.17 (m, 3ArH$^+$), 6.72 (s, ArH), 6.59 (s, ArH), 5.60 (d, J 1.6 Hz, H2'), 5.34 (d, J 1.6 Hz, H2'), 4.09 (s, H1), 3.84 (s, OCH$_3$), 3.72 (s, OCH$_3$), 3.10-3.02 (m, 2H), 2.66-2.45 (m, 2H), 2.33 (s, NCH$_3$); $^{13}C$
NMR δ: 149.93 (C1'), 147.94 (C6A), 147.78 (C7A), 140.30 (C1"B), 128.91 (C4aB), 128.48 (2C"), 128.18 (2C"), 127.96 (C"), 127.23 (C8aB), 119.10 (C2'), 111.63 (C5C), 110.55 (C8C), 73.69 (Cl), 56.34 (2OCH3), 52.98 (C3), 44.74 (NCH3), 29.38 (C4); MS m/z: 308 (M-H+, 0.5%; Calcd. for C20H22NO2 308.1650, found 308.1647), 206 (100), 190 (8), 162 (4), 132 (2), 103 (2), 77 (4); IR (KBr disc): 2768, 1514, 1256, 1217, 1143, 783 cm⁻¹; Anal. Calcd for C20H23NO2: C, 77.64; H, 7.49; N, 4.53%, found : C, 77.67; H, 7.64; N, 4.42%.

6.7-Dimethoxy-2-methyl-1-(1'-trimethylsilylethenyl)-1,2,3,4-tetrahydroisoquinoline 70c

The 1-(bromovinyl)trimethylsilane required for this procedure was prepared¹⁷⁷ from commercial (Aldrich) vinyltrimethylsilane. A solution of 1-trimethylsilyltheneylethynylmagnesium bromide in dry tetrahydrofuran (60 ml) under nitrogen was then prepared from the 1-(bromovinyl)trimethylsilane (9.03 g, 50.4 mmol) by the method of Ottolenghi et. al.¹⁷⁸

The solution of 1-trimethylsilyltheneylethynylmagnesium bromide in tetrahydrofuran was cooled to <-50°C in an acetone/liquid nitrogen slush bath and then additional dry tetrahydrofuran (50 ml) was added followed by the iminium salt 48a (8.404 g, 25.22 mmol). The mixture was allowed to warm slowly to room temperature with stirring for 19 h. The reaction was worked up (as for 70b) to give a solid upon concentration of the ether solution. Recrystallisation of the solid from ethanol afforded 1-(1'-trimethylsilyltheneylethynyl)isoquinoline 70c (6.231 g, 81%) as a colourless solid with m.p. 89-90°C. ¹H NMR δ: 6.55 (s, 2ArH), 5.79 (d, J 3.3 Hz, H2'), 5.62 (d, J 3.1 Hz, H2'), 3.85 (s, OCH3), 3.78 (s, OCH3), 3.67 (s, H1), 3.03-2.95 (m, 2H), 2.62-2.54 (m, H), 2.42-2.36 (m, H), 2.27 (s, NCH3), -0.12 (Si(CH3)3); ¹³C NMR δ: 156.03 (C1'), 147.86 (C6A), 147.42 (C7A), 129.66 (C4aB), 128.95 (C2'), 127.36 (C8aB), 111.53 (C5 and C8), 76.56 (C1), 56.46 (2OCH3), 52.97 (C3), 45.30 (NCH3), 29.70 (C4), 0.44 (Si(CH3)3); MS m/z: 305 (M+, 0.4%), 304 (1), 290 (2), 206 (100), 190 (8), 162
6,7-Dimethoxy-1-(1'-iodoethenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline 70d

(i) To a stirred mixture of sodium iodide (1.301 g, 8.68 mmol) in acetonitrile (6 ml) was added trimethylchlorosilane (0.934 g, 8.60 mmol) then a solution of water (85 mg, 4.7 mmol) in acetonitrile (4 ml). After 10 min. the 1-ethynyl base 71 (0.503 g, 2.17 mmol) was added. The mixture was stirred in an oil bath at 80°C for 4 h. then cooled and treated with 2M aqueous sodium hydroxide (5 ml). The solution was extracted with diethyl ether (3 x 10 ml) and the ether extracts were then combined and washed with water (5 ml), and then saturated brine (5 ml). Drying and then concentration of the extracts gave a tan powder (0.569 g) which contained 71 (41%), the 1-(1'-iodoethenyl) product 70d (27%), and a component tentatively identified as 6,7-dimethoxy-1-(cis-2'-iodoethenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (32%) due to the following signals: \(^1\)H NMR δ: 6.58 (d, \(J 7.4\) Hz, H2'), 6.18 (dd, \(J 7.6\) Hz, 8.8 Hz, H1'), 4.23 (d, \(J 8.8\) Hz, H1), 2.31 (NCH3); \(^{13}\)C NMR δ: 142.31 (C1'), 86.59 (C2'), 68.96 (C1). Purification of this material by p.t.l.c. on silica with hexane/50% ethyl acetate provided, from \(R_f 0.92\), the 1-(1'-iodoethenyl)isoquinoline 70d (0.149 g, 19%) which recrystallised from ethanol as a pale tan powder with m.p. 89-90°C. \(^1\)H NMR δ: 6.59 (s, ArH), 6.57 (s, ArH), 6.53 (d, \(J 0.8\) Hz, H2'), 6.09 (d, \(J 0.8\) Hz, H2'), 3.85 (s, OCH3), 3.82 (s, OCH3), 3.18 (s, H1), 3.12-3.05 (m, 2H), 2.67-2.59 (m, 2H), 2.38 (s, NCH3); \(^{13}\)C NMR δ: 148.43 (C6A), 147.85 (C7A), 128.92 (C2'), 126.70 (C8aB), 120.92 (C1'B), 111.42 (C5C), 110.24 (C8'C), 75.96 (C1), 56.47 (OCH3), 56.23 (OCH3), 51.71 (C3), 44.26 (NCH3), 29.23 (C4); MS m/z: 359 (M+, 4%; Calcd. for C\(_{14}\)H\(_{18}\)NO\(_2\)I 359.0382, found 359.0382), 230 (2), 206 (100), 190 (5), 142 (4); Anal. Calcd for C\(_{14}\)H\(_{18}\)NO\(_2\)I: C, 46.81; H, 5.05; N, 3.90%; found: C, 46.72; H, 5.16; N, 3.94%.

(ii) To a stirred mixture of sodium iodide (15.54 g, 103.7 mmol) in acetonitrile (53 ml) was added trimethylchlorosilane (11.23 g, 103.4 mmol) then a solution of water
(0.938 g, 52.1 mmol) in acetonitrile (35 ml). After 10 min. the 1-ethynyl base 71 (4.046 g, 17.49 mmol) was added. The mixture was stirred in an oil bath at 80°C for 8.5 h. then cooled and concentrated. The residue was partitioned between 2M aqueous sodium hydroxide (50 ml) and diethyl ether (150 ml) and the aqueous layer was then extracted with further diethyl ether (2 x 60 ml). The ether extracts were combined and washed with water (3 x 30 ml) then saturated brine (2 x 30 ml), and then dried and passed through a silica plug, removing much yellow colour. Concentration of the solution gave a yellow solid (3.123 g) which, after applying the material in the minimum of dichloromethane/25% hexane, was purified by column chromatography on silica with hexane/30% ethyl acetate to afford 70d (1.885 g, 30%). Elution of the column with hexane/60% ethyl acetate afforded 71 (1.190 g, 29%).

**Attempted Preparation of 70d, or a 1-(1'-Bromoethenyl)- Analogue, from 70c**

(i) The 1-(1'-trimethylsilylethenyl)isoquinoline 70c (0.646 g, 1.939 mmol) was stirred in dichloromethane (35 ml) with iodine (0.40 g, 1.6 mmol) at room temperature for 4 h. The organic solution was washed with 5% aqueous sodium bicarbonate (2 x 10 ml) then dried and concentrated to give a dark solid (0.548 g). The material contained many components, all with signals between 3.96 δ and 3.65 δ for the N-methyl group in the 1H NMR spectrum.

(ii) To 70c (0.527 g, 1.725 mmol) in dichloromethane (2 ml) at -78°C was added dropwise a solution of bromine (0.294 g, 1.86 mmol) in dichloromethane (2 ml), with the rapid removal of colour and the formation of a colourless precipitate. The mixture was stirred for 40 min. at -78°C then warmed to room temperature. The solid dissolved. Concentration of the solution gave a pale yellow powder comprising two approximately equal components. The compounds were tentatively identified as 6,7-dimethoxy-2-methyl-1-(1'-trimethylsilylethenyl)-3,4-dihydroisoquinolinium bromide and 6,7-dimethoxy-2-methyl-1-(1'-trimethylsilylethenyl)-1,2,3,4-tetrahydroisoquinolinium bromide by NMR analysis of the mixture.
6.7-Dimethoxy-1-ethynyl-2-methyl-1,2,3,4-tetrahydroisoquinoline 71

A commercial (Aldrich) solution of 0.5M ethynylmagnesium bromide in tetrahydrofuran (180 ml, 90 mmol) under nitrogen was cooled in an acetone/liquid nitrogen slush bath to <-50°C and then the iminium salt 48a (15.00 g, 45.04 mmol) was added. The mixture was allowed to warm slowly to room temperature with stirring for 16 h. then worked up (as for 70b) to give a solid upon concentration of the ether solution. Recrystallisation of the solid from ethanol afforded 1-ethynylisoquinoline 71 (6.88 g, 66%) as a pale yellow solid of >99% purity by GC-MS analysis. 1H NMR δ: 6.75 (s, ArH), 6.57 (s, ArH), 4.42 (s, H1), 3.85 (s, OCH3), 3.83 (s, OCH3), 2.94-2.63 (m, 4H), 2.54 (s, NCH3), 2.42 (d, J 2.3 Hz, H2'); 13C NMR δ: 148.75 (C6A), 147.93 (C7A), 127.15 (C4aB), 126.02 (C8aB), 111.79 (C5C), 110.58 (C8C), 82.31 (C2'), 74.57 (C1'D), 56.47 (C1D), 56.34 (OCH3), 56.28 (OCH3), 48.79 (C3), 43.99 (NCH3), 28.89 (C4); MS m/z: 231 (M+, 84%; Calcd. for C14H17NO2 231.1259, found 231.1250), 230 (100), 216 (30), 200 (37), 188 (50), 145 (53), 115 (34); IR (KBr disc): 3239, 2943, 1519, 1256, 1225, 1136, 1010, 702 cm⁻¹.

2-Ethoxycarbonylmethyl-6.7-dimethoxy-1-isopropenyl-2-methyl-1,2,3,4-tetrahydroisoquinolinium Bromide 72a

The base 70a (1.498 g, 6.059 mmol) was stirred in dry butanone (10 ml) under nitrogen with ethyl bromoacetate (2 ml, 18 mmol) for 10 h. at 55°C. Concentration of the solution and trituration of the residue with diethyl ether (4 x 15 ml) gave, after drying, a pale foam (2.452 g) which upon recrystallisation from ethanol/tetrahydrofuran afforded a mixture (trans:cis=46:54) of the B-ring diastereomers of the 2-ethoxycarbonylmethylisooquinolinium salt 72a (1.183 g, 47%) as an off-white powder. trans diastereomer (assignable signals) 1H NMR δ: 6.70 (s, ArH), 6.49 (s, ArH), 5.91 (s, H1), 5.38 (d, J 17.4 Hz, H of NCH2CO), 4.38 (d, J 17.3 Hz, H of NCH2CO), 4.25 (q, CH2 of Et), 3.97-3.88 (m, H), 3.89 (s, OCH3), 3.83 (s, OCH3), 3.60 (s, NCH3), 1.82 (s, CH3), 1.29 (t, CH3 of Et); 13C NMR δ: 137.57 (C1'), 130.00 (C2'), 76.13 (C1), 63.47 (CH2 of Et), 58.28 (NCH2COA), 56.69
(2OCH₃), 54.84 (C₃A), 49.47 (NCH₃), 24.20 (C₄), 22.09 (CH₃), 14.48 (CH₃ of Et); cis diastereomer (assignable signals) ¹H NMR δ: 6.72 (s, ArH), 6.43 (s, ArH), 6.20 (s, H1), 5.37 (d, J 17.3 Hz, H of NCH₂CO), 4.95-4.4.89 (m, H), 4.64 (d, J 17.1 Hz, H of NCH₂CO), 4.25 (q, CH₂ of Et), 3.90 (s, OCH₃), 3.83 (s, OCH₃), 3.78 (s, NCH₃), 1.71 (s, CH₃), 1.33 (t, CH₃ of Et); ¹³C NMR δ: 138.49 (C₁'), 128.05 (C₂'), 76.13 (C₁), 63.47 (CH₂ of Et), 61.52 (NCH₂COA), 56.69 (2OCH₃), 56.10 (C₃A), 47.35 (NCH₃), 23.58 (C₄), 20.83 (CH₃), 14.48 (CH₃ of Et); IR of mixture (thin film from CDCl₃): 1744, 1520, 1257, 1229, 1123 cm⁻¹.

2-Ethoxycarbonylmethyl-6,7-dimethoxy-2-methyl-1-(α-phenylethenyl)-1,2,3,4-tetrahydroisoquinolinium Bromide 72b

The base 70b (2.224 g, 7.188 mmol) was stirred in dry butanone (7 ml) under nitrogen with ethyl bromoacetate (1.81 g, 10.8 mmol) for 10 h. at 50°C. Concentration of the solution and trituration of the residue with diethyl ether (4 x 20 ml) afforded a gum which on concentration from a solution in dichloromethane gave a mixture (trans: cis = 58:42) of the B-ring diastereomers of the 2-ethoxycarbonylmethylisoquinolinium salt 72b (1.183 g, 47%) as a tan hygroscopic powder. trans diastereomer (assignable signals) ¹³C NMR δ: 165.36 (COO), 143.44 (C₁'A), 139.60 (C₁'A), 131.41 (C₂'), 74.2-73.6 (bs, C₁), 63.19 (CH₂ of Et), 61.20 (NCH₂COB), 56.52 (2OCH₃), 53.81 (C₃B), 47.11 (NCH₃), 23.76 (C₄), 14.10 (CH₃ of Et); cis diastereomer (assignable signals) ¹³C NMR δ: 165.17 (COO), 142.49 (C₁'A), 138.60 (C₁'A), 130.65 (C₂'), 74.2-73.6 (bs, C₁), 63.03 (CH₂ of Et), 58.17 (NCH₂COB), 56.52 (2OCH₃), 54.84 (C₃B), 49.79 (NCH₃), 23.05 (C₄), 14.10 (CH₃ of Et).

2-Ethoxycarbonylmethyl-6,7-dimethoxy-2-methyl-1-[(1'-trimethylsilyl)ethenyl]-1,2,3,4-tetrahydroisoquinolinium Bromide 72c

To the base 70c (0.520 g, 1.70 mmol) in dry acetonitrile (4 ml) under nitrogen at 0°C was added a solution of ethoxycarbonylmethyltriflate (0.528 g, 2.24 mmol) in
Acetonitrile (2 ml). Stirring at 0°C for 45 min. and 25°C for 4 h. provided a homogeneous solution which was then concentrated. Trituration of the residue with diethyl ether (4 x 15 ml) afforded a white powder which was stirred in ethanol (10 ml) with potassium bromide (1.43 g) for 3 h. Concentration of the mixture and extraction of the residue with dichloromethane (4 x 10 ml) gave, after concentration of the organic extracts, a single B-ring diastereomer of the 2-ethoxycarbonylmethyl salt 72c (0.781 g, 80%) as a white powder. 

$^1$H NMR $\delta$: 6.67 (s, ArH), 6.30 (s, ArH$^A$), 6.24 (s, H2$^A$), 6.18 (bs, H2$^A$), 5.64 (s, H1), 4.44 (d, J 16.9 Hz, H of NCH$_2$CO), 4.37 (d, J 16.9 Hz, H of NCH$_2$CO), 4.29-4.19 (m, CH$_2$ of Et and H3), 3.85 (s, OCH$_3$), 3.76 (s, OCH$_3$), 3.71-3.56 (m, H3), 3.27 (s, NCH$_3$), 3.17-3.09 (m, H4), 1.25 (t, CH$_3$ of Et), 0.11 (s, Si(CH$_3$)$_3$); $^{13}$C NMR $\delta$: 165.55 (COO), 150.37 (C6$^A$), 149.67 (C7$^A$), 146.64 (C1'), 143.99 (C2'), 122.14 (C4a$^B$), 120.64 (C8a$^B$), 111.19 (C5$^C$), 110.93 (C8$^C$), 74.43 (bs, C1), 63.62 (CH$_2$ of Et), 58.41 (NCH$_2$CO$^D$), 56.62 (2OCH$_3$), 54.52 (C3$^D$), 49.66 (NCH$_3$), 24.00 (C4), 14.32 (CH$_3$ of Et), 0.58 (Si(CH$_3$)$_3$).

2-Ethoxycarbonylmethyl-6.7-dimethoxy-1-iodo-2-methyl-1,2,3,4-tetrahydroisoquinolinium Bromide 72d

To the base 70d (0.602 g, 1.68 mmol) in dry acetonitrile (4 ml) under nitrogen at 0°C was added a solution of ethoxycarbonylmethyltriflate (0.524 g, 2.22 mmol) in acetonitrile (3 ml). Stirring at 0°C for 1 h. and 25°C for 4 h. provided a homogeneous solution which was then concentrated. Trituration of the residue with diethyl ether (3 x 20 ml) afforded a gum which was stirred in ethanol (10 ml) with potassium bromide (1.00 g) for 3 h. Concentration of the mixture and extraction of the residue with dichloromethane (4 x 7 ml) gave, after concentration of the organic extracts, a yellow powder from which residual 70d was then removed by column chromatography on silica with dichloromethane/0-20% ethanol to give a single B-ring diastereomer of the 2-ethoxycarbonylmethyl salt 72d (0.781 g, 89%) as an off-white powder. 

$^1$H NMR $\delta$: 7.46 (s, H2'), 6.71 (s, H2$^A$), 6.63 (s, ArH$^A$), 6.51 (s,
ArHA), 5.56 (s, H1), 4.63-4.56 (m, H3), 4.33-4.20 (m, 5H), 3.90 (s, OCH3), 3.85 (s, OCH3), 3.52 (s, NCH3), 3.15-3.07 (m, H4), 1.28 (t, CH3 of Et); 13C NMR δ: 165.13 (COO), 151.02 (C6A), 150.05 (C7A), 143.53 (C2'), 121.35 (4aB), 120.93 (8aB), 111.29 (C5C), 110.94 (C8C), 100.94 (C1'), 77.44 (C1), 63.90 (CH2 of Et), 59.36 (NCH2CO), 56.83 (OCH3), 56.67 (OCH3), 53.93 (C3), 50.31 (NCH3), 23.93 (C4), 14.38 (CH3 of Et).

1-[2'-{6.7-dimethoxy-2-methyl-1.2.3.4-tetrahydroisoquinoline}ethynyl]-6.7-dimethoxy-2-methyl-1.2.3.4-tetrahydroisoquinoline 73

The crystallisation mother liquor from the formation of 71 was concentrated and the residue was then submitted to column chromatography on alumina (45 g) with a gradient from dichloromethane/5%hexane to dichloromethane/5% methanol. Residual 71 eluted in the early fractions. Concentration of the late fractions provided the title compound 73 (0.76 g, 8%) as a pale yellow powder. Recrystallisation of a portion from dichloromethane/hexane gave off-white needles with m.p. 178-179°C. Two conformers (ratio 71:29) gave the signals marked with superscriptsX,Y in the 1H NMR spectrum of this material. 1H NMR δ: 6.78X and 6.73Y (s, ArH), 6.56 (s, ArH), 4.41 (s, H1), 3.83 (s, OCH3), 3.78X and 3.71Y (s, OCH3), 2.98-2.90 (m, H), 2.83-2.79 (m, 2H), 2.63-2.57 (m, H), 2.56Y and 2.52X (s, NCH3); 13C NMR δ 148.56 (C6A), 147.82 (C7A), 127.94 (C4aB), 126.02 (C8aB), 111.67 (C5C), 110.78 (C8C), 85.02 (C1'), 57.03 (C1), 56.40 (2OCH3), 49.79 (C3), 44.42 (NCH3), 29.02 (C4); MS (LSIMS in a glycerol matrix) m/z: 437 (MH+, 33%), 406 (3), 277 (9), 230 (13), 219 (8), 206 (100), 204 (28); IR (KBr disc): 3239, 2943, 1522, 1254, 1223, 1132, 1009 cm⁻¹.

Attempted Preparation of 1-Cyanoethenylmagnesium Chloride for Synthesis of 74a

(i) To magnesium turnings (1.71 g, 70.2 mmol) in dry tetrahydrofuran under nitrogen was added an iodine crystal and 2-chloroacrylonitrile (5.12 g, 58.5 mmol) portionwise. The mixture was heated to reflux for 10 min. No reaction initiated.
The mixture was cooled and submitted to ultrasound irradiation, then a small amount of iodomethane was added and the mixture was returned to reflux. No reaction occurred.

(ii) Magnesium turnings (3.40 g, 142 mmol) were activated\(^9\) by stirring the turnings vigorously under nitrogen for 2.5 days. The magnesium became very dark and a 'mirror' of metal formed on the glass vessel. Dry tetrahydrofuran (10 ml) was added and the mixture was cooled to 0°C then 2-chloroacrylonitrile (2.20 g, 25.1 mmol) was added as a solution in dry tetrahydrofuran (25 ml) dropwise over 80 min. The mixture was stirred at 0°C for a further 5 h. No reaction occurred.

**Attemped Preparation of 6,7-Dimethoxy-1-(1'-cyclopentenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline 74b**

The method of Braude and Forbes\(^9\) was modified to generate 1-cyclopentenyllithium in tetrahydrofuran rather than diethyl ether. Thus freshly distilled 1-chlorocyclopentene (4.056 g, 39.54 mmol) in dry tetrahydrofuran (8 ml) was added to a stirred suspension of finely cut lithium wire (0.61 g, 88 mmol) in dry tetrahydrofuran (70 ml) under argon. The mixture was heated for 6 h. in an oil bath at 45-50°C then 18 h. at 63-65°C. No reaction occurred at the lower temperature. After heating at the higher temperature the solution was a grey/green colour with a white precipitate. The solution was transferred via cannula to a new reaction vessel, leaving residual lithium (0.31 g), then cooled to -78°C under nitrogen and the iminium salt 48a (6.164 g, 18.50 mmol) was added. After 1 h. at -78°C the mixture was allowed to warm to room temperature with stirring over 18 h. Ice was added cautiously until the vigorous reaction ceased then water (30 ml) and diethyl ether (60 ml) were added. The aqueous layer was made basic with 2M aqueous sodium hydroxide then the layers were separated and the aqueous layer was extracted with diethyl ether (2 x 30 ml) then chloroform (3 x 30 ml). The ether extracts were combined and washed with water (2 x 20 ml) then saturated brine (20 ml), and then dried and concentrated to a yellow oil (0.994 g) which displayed many components
on 1H NMR spectral analysis. Concentration of the chloroform extracts and recrystallisation of the residue from ethanol afforded the recovery of **48a** (3.554 g, 58%).

**Ethyl 9,10-Dimethoxy-3,6-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazonine-4-carboxylate 75a**

(i) The salt **72a** (0.302 g, 0.729 mmol) was stirred in dry acetonitrile (10 ml) under nitrogen at room temperature with **DBU** (0.14 g, 0.94 mmol) for 5 h. then the solution was concentrated. Purification of the residue by column chromatography on alumina (6 g) with dichloromethane/20% light petroleum afforded, from the early fraction (100 ml), a mixture (E/Z = 1.83) of the 3-benzazonine isomers **75a** (0.226 g, 93%) as a pale yellow oil. A portion (148 mg) of this mixture was purified by preparative reverse phase HPLC with acetonitrile/20% water to give:

(a) after 20.8 min., the Z-benzazonine **Z-75a** (37 mg) as a colourless oil. 1H NMR δ:
- 6.56 (s, ArH), 6.53 (s, ArH), 6.38 (s, H7), 4.09 (q, CH2 of Et), 3.86 (s, OCH3), 3.83 (s, OCH3), 3.59 (dd, J 4.0 Hz, 12.6 Hz, H4), 3.06-2.99 (m, H), 2.90-2.82 (m, H), 2.71-2.57 (m, 2H), 2.60 (s, NCH3), 2.27 (dd, J 13.3 Hz, 13.3 Hz, H5), 2.03 (dd, J 3.9 Hz, 14.0 Hz, H5), 1.90 (s, CH3), 1.23 (t, CH3 of Et); 13C NMR δ: 174.31 (COO), 148.07 (C9A), 147.20 (C10A), 138.59 (C7aB), 135.04 (C11aB), 130.70 (C6B), 127.53 (C7), 113.63 (C8C), 112.10 (C11C), 65.04 (C4), 60.65 (CH2 of Et), 56.43 (2OCH3), 52.95 (C2), 45.57 (NCH3), 38.35 (C5), 36.65 (C1), 22.31 (CH3), 15.01 (CH3 of Et); MS m/z: 333 (M+, 21%; Calcd. for C19H27N04 333.1940, found 333.1951), 260 (100), 229 (4), 203 (10), 130 (4).

(b) after 24.5 min., the E-benzazonine **E-75a** (52 mg) as a colourless oil. 1H NMR δ:
- 6.71 (s, ArH), 6.67 (s, ArH), 6.28 (s, H7), 4.12 (q, CH2 of Et), 3.87 (s, OCH3), 3.85 (s, OCH3), 3.54 (d, J 6.3 Hz, H4), 2.88-2.70 (m, 4H), 2.65 (s, NCH3), 2.59-2.53 (m, H5), 1.99-1.94 (m, H5), 1.45 (s, CH3), 1.26 (t, CH3 of Et); 13C NMR δ: 174.34 (COO), 147.29 (C9A), 147.03 (C10A), 133.87 (C7aB), 132.48 (C11aB), 131.64 (C6B), 129.66 (C7), 113.84 (C8C), 111.89 (C11C), 65.92 (C4), 60.82 (CH2 of Et),
56.67 (OCH₃), 56.51 (OCH₃), 55.22 (C₂), 45.64 (NCH₃), 41.56 (C₁D), 39.00 (C₅D), 18.91 (CH₃), 14.99 (CH₃ of Et); MS m/z: 333 (M⁺, 23%; Calcd. for C₁₉H₂₇N0₄ 333.1940, found 333.1922), 276 (10), 260 (100), 217 (5), 203 (10).

(ii) The salt 72a (0.282 g, 0.682 mmol) was stirred in dry acetonitrile (15 ml) under nitrogen (10 ml) with DBU (0.13 g, 0.87 mmol) between -45°C and -40°C for 6 h. then allowed to warm slowly to room temperature before workup as for (i) to afford a mixture (E/Z = 1.72) of the isomers of 75a (0.221 g, 97%).

(iii) The salt 72a (0.290 g, 0.700 mmol) was refluxed in dry acetonitrile (10 ml) with DBU (0.13 g, 0.87 mmol) for 1 h. before workup as for (i) to afford a mixture (E/Z = 3.10) of the isomers of 75a (0.217 g, 93%).

Ethyl 9,10-Dimethoxy-3-methyl-6-phenyl-2,3,4,5-tetrahydro-1H-3-benzazonine-4-carboxylate 75b

(i) The salt 72b (0.307 g, 0.644 mmol) was stirred in dry acetonitrile (15 ml) under nitrogen at room temperature with DBU (0.17 g, 0.84 mmol) for 5 h. then the solution was concentrated. Purification of the residue by column chromatography on alumina with dichloromethane/20% light petroleum afforded a pale yellow oil (0.206 g, 81%). ¹H NMR analysis indicated a mixture of 4 components attributed to E-75b:Z-75b:76b:77 in the ratio of 37:53:8:2. A portion (160 mg) of this mixture was purified by preparative reverse phase HPLC with acetonitrile/36% water to give:

(a) after 27.0 min., a mixture (9 mg) of two components (67:33) attributed to 76b and 77. Compound 76b ¹H NMR δ: 7.42-7.25 (m, 5ArH'), 6.72 (s, ArH), 6.63 (s, ArH), 5.33 (s, H2'), 4.91 (s, H2'), 4.50 (d, J 6.5 Hz, H2), 4.03 (q, CH₂ of Et), 3.86 (s, OCH₃), 3.82 (s, OCH₃), 3.66 (d, J 6.5 Hz, H1), 3.30-3.15 (m, 2H), 2.75-2.65 (m, 2H), 2.29 (s, NCH₃), 1.15 (t, CH₃ of Et); ¹³C NMR δ: 172.61 (COO), 116.52 (C₂'), 66.98 (C2), 60.48 (CH₂ of Et), 53.29 (C1), 50.44 (C4), 46.61 (NCH₃), 35.81 (C5), 15.11 (CH₃ of Et). Compound 77 ¹H NMR δ: 7.64 (dd, J 1.4 Hz, 7.6 Hz, o-ArH'), 7.42-7.25 (m, 3ArH'), 7.06 (s, H), 6.96 (s, H), 6.89 (s, H), 6.80 (dd, J 11.0 Hz, 17.0, H), 5.57 (dd, J 1.0 Hz, 17.0, H), 5.17 (dd, J 1.0 Hz, 11.0, H), 4.03 (q, CH₂ of Et),
3.94 (s, OCH₃), 3.91 (s, OCH₃), 3.61 (s, 2H), 3.15 (s, 2H), 2.25 (s, NCH₃), 1.17 (t, CH₃ of Et); ¹³C NMR δ: 171.60 (COO), 113.83 (=CH₂), 60.81 (CH₂ of Et), 58.25 (NCH₂), 55.19 (NCH₂), 42.72 (NCH₃), 14.79 (CH₃ of Et).

(b) after 32.8 min., the benzazonine isomer* E-75b (50 mg) which recrystallised from ethanol as colourless needles with m.p. 101-102°C. ¹H NMR (d₆-benzene at 75°C) δ: 7.56 (d, J 7.3 Hz, o-ArH"), 7.01-6.91 (m, 3ArH"), 6.74 (s, H₇A), 6.60 (s, H₈A), 6.56 (s, H₁₁A), 4.10-3.82 (bs, CH₂ of Et), 3.53 (s, OCH₃), 3.45 (s, OCH₃), 3.36 (t, H₄), 3.01-2.94 (m, 4H), 2.66-2.57 (bs, H), 2.48 (s, NCH₃), 2.42-2.36 (bs, H), 0.94 (t, CH₃ of Et); ¹³C NMR (d₆-benzene) δ: 173.00 (COO), 150.04 (C₉A), 149.65 (C₁₀A), 141.27 (C₁¹⁺B), 133.40 (C₇aB), 132.62 (C₁₁aB or C₆B), 131.47 (C₇), 117.56 (C₁₁), 114.66 (C₈), 65.95 (C₄), 60.78 (CH₂ of Et), 57.96 (bs, C₂), 57.11 (OCH₃), 56.99 (OCH₃), 41.47 (C₅), 37.53 (bs, C₁), 14.93 (CH₃ of Et), NCH₃ not observed; ¹H NMR (CDCl₃ at -50°C): conformer 1 δ: 6.88 (s, H₇A), 6.54 (s, H₈A), 6.38 (s, H₁₁A), 3.98 (s, OCH₃), 3.83 (s, OCH₃), 2.36 (s, CH₃), 1.38 (t, CH₃ of Et). conformer 2 δ: 6.82 (s, H₇A), 6.67 (s, H₈A), 6.45 (s, H₁₁A), 3.93 (s, OCH₃), 3.64 (s, OCH₃), 2.69 (s, CH₃), 0.84 (t, CH₃ of Et); MS m/z: 395 (M⁺, 27%; Calcd. for C₂₄H₂₉N⁰₄ 395.2096, found 395.2098), 377 (6), 322 (100), 291 (14), 265 (10); Anal. Calcd for C₂₄H₂₉N⁰₄: C, 72.88; H, 7.39; N, 3.54%, found: C, 72.69; H, 7.40; N, 3.36%.

(c) after 38.8 min., the benzazonine isomer* Z-75b (54 mg) which recrystallised from ethanol as colourless prisms with m.p. 124-125°C. ¹H NMR δ: 7.52-7.49 (m, o-ArH"), 7.41-7.31 (m, 3ArH"), 6.78 (s, ArH), 6.61 (s, ArH and H₇), 4.06 (q, CH₂ of Et), 3.88 (s, OCH₃), 3.83 (s, OCH₃), 3.32 (dd, J 3.3 Hz, 12.4 Hz, H₄), 2.96-2.91 (m, 2H), 2.80-2.69 (m, 3H), 2.56-2.46 (m, H), 2.41 (s, NCH₃), 1.21 (t, CH₃ of Et); ¹³C NMR δ: 174.30 (COO), 148.39 (C₉A), 147.41 (C₁₀A), 143.45 (C₁¹⁺B), 141.67 (C₇aB), 134.66 (C₁₁aB), 130.32 (C₆B), 130.00 (C₇C), 129.05 (2C"), 128.04 (C"C), 127.41 (2C"), 113.89 (C₈D), 112.44 (C₁₁D), 65.21 (C₄), 60.67 (CH₂ of Et), 56.51 (2OCH₃), 52.76 (C₂), 45.11 (NCH₃), 38.28 (C₅), 34.83 (C₁), 15.04 (CH₃ of Et); ¹H NMR (d₆-benzene) δ: 7.56 (d, J 8.4 Hz, o-ArH"), 7.30-7.17 (m, 3ArH"), 6.91 (s, H₇), 6.65 (s, H₈), 6.59 (s, H₁₁), 3.92 (q, CH₂ of Et), 3.56 (dd, J 4.1 Hz, 12.0 Hz, H₄),
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3.49 (s, OCH₃), 3.48 (s, OCH₃), 3.35 (dd, J 3.3 Hz, 15.5 Hz, H), 3.07-2.88 (m, 4H), 2.78-2.70 (m, H), 2.47 (s, NCH₃), 0.93 (t, CH₃ of Et); ¹³C NMR (d₆-benzene) δ: 173.81 (C=O), 149.56 (C₉₆), 148.62 (C₁₀₆), 143.45 (C₁¹₆), 142.04 (C₇₆), 134.68 (C₁₁₆ or C₆₆), 130.48 (C₇), 113.89 (C₁₁), 112.44 (C₈), 65.45 (C₄), 60.20 (CH₂ of Et), 55.94 (2OCH₃), 53.15 (C₂), 45.15 (NCH₃), 38.84 (C₅), 35.09 (C₁), 14.70 (CH₃ of Et); MS m/z: 395 (M⁺, 29%; Calcd. for C₂₄H₂₉N⁰₄ 395.2096, found 395.2099), 377 (6), 322 (100), 291 (11), 265 (9); Anal. Calcd for C₂₄H₂₉N⁰₄: C, 72.88; H, 7.39; N, 3.54%, found: C, 72.99; H, 7.58; N, 3.62%.

* For consistency with the other olefinic benzazonines in this work the E and Z isomers of 75b are named according to the structures pictured for 75. IUPAC rules would reverse the naming of these geometric isomers of 75b.

(ii) The salt 72b (0.297 g, 0.623 mmol) was stirred in dry acetonitrile (15 ml) under nitrogen (10 ml) with DBU (0.12 g, 0.81 mmol) between -15°C and -20°C for 6 h. Workup as for (i) afforded a mixture (0.200 g, 81%) of E-75b:Z-75b:76b in the ratio of 38:54:8.

(iii) To the salt 72b (0.401 g, 0.842 mmol) in refluxing dry acetonitrile (15 ml) was added DBU (0.17 g, 1.1 mmol). The solution was refluxed for 1 h. Workup as for (i) afforded a mixture (0.281 g, 84%) of 4 components attributed to E-75b:Z-75b:76b:77 in the ratio of 36:35:11:18. Preparative reverse phase HPLC as for (i) afforded, after 27.0 min., a mixture (45 mg) of two components (37:63) attributed to 76b and 77.

**Ethyl 9,10-Dimethoxy-3-methyl-6-trimethylsilyl-2,3,4,5-tetrahydro-1H-3-benzazonine-4-carboxylate 75c**

(i) The salt 72c (0.306 g, 0.648 mmol) was stirred in dry acetonitrile (10 ml) under nitrogen at room temperature with DBU (0.13 g, 0.84 mmol) for 5 h. then the solution was concentrated. Purification of the residue by column chromatography on alumina with dichloromethane/25% light petroleum afforded the 3-benzazonine E-75c (0.171 g, 67%) as a colourless oil. ¹H NMR δ: 7.2-7.1 (bs, H7), 6.78 (s, ArH),
6.64 (s, ArH), 4.25-4.15 (bs, CH2 of Et), 3.88 (s, OCH3), 3.86 (s, OCH3), 3.1-2.6
(bm, 6H), 2.45-2.25 (bs, 4H), 1.30 (t, CH3 of Et), -0.10 (s, Si(CH3)3); 1H NMR
(C2D2Cl4 at 75°C*) δ: 6.89 (bs, H7), 6.73 (s, ArH), 6.59 (s, ArH), 4.13 (q, CH2 of
Et), 3.79 (s, OCH3), 3.77 (s, OCH3), 3.15-2.91 (bs, 2H), 2.69-2.58 (m, 4H), 2.48-
2.36 (m, H), 2.43 (s, NCH3), 2.24 (t, CH3 of Et), -0.13 (s, Si(CH3)3); 1H NMR (d8-
toluene at -20°C, two conformers in 61:39 ratio) δ: 7.52a and 7.22b (bs, H7), 7.06b
and 6.95a (s, ArH), 6.58a and 6.53b (s, ArH), 4.05a and 3.90b (q, CH2 of Et), 2.60a
and 2.46b (NCH3), 0.25a and 0.04b (s, Si(CH3)3); 13C NMR (d8-toluene at -20°C) δ:
173.89 (COO), 148.41 (C9A), 147.83 (C10A), 147.38 (C7), 136.47 (C7aB), 133.43
(C11aB), 130.36 (C6B), 115.01 and 114.41 (C8C), 112.44 and 111.83 (C11C), 66.23
(C4), 61.29 and 60.89 (CH2 of Et), 55.99 (2OCH3), 53.93 (C2), 44.86 (NCH3), 40.13
(C5D), 38.78 (C1D), 15.34 (CH3 of Et), 1.86 (Si(CH3)3); MS m/z: 391 (M+, 5%;
Calcd. for C21H33NO4Si 391.2170, found 391.2174), 389 (45), 318 (26), 246 (100),
230 (20), 206 (15), 73 (55).

* The rapid collection of spectral data (within 5 min.) was necessary to prevent the
reaction of 75c under these conditions.

(ii) To the salt 72c (0.150 g, 0.317 mmol) in dry acetonitrile (8 ml) at reflux was
added DBU (0.063 g, 0.41 mmol). The solution was refluxed for 1 h. then
concentrated. Purification of the residue by column chromatography on alumina
with dichloromethane/20% light petroleum afforded an unidentified mixture (0.012
g).

**Attempted Base-Promoted Rearrangement of 72d to 75d**

The salt 72d (0.336 g, 0.639 mmol) was stirred in dry acetonitrile (10 ml)
under nitrogen and protected from light for 5 h. at room temperature with DBU (0.13
g, 0.85 mmol). The solution was then concentrated and the residue was purified by
column chromatography on alumina. Elution with dichloromethane/25% light
petroleum afforded only the precursor base 70d (0.008 g). Elution with
dichloromethane/5-10% ethanol afforded a mixture (0.300 g) which was found to
contain protonated DBU salts (~75%) and impure material inconsistent with either 72d, 75d or 76d upon 1H NMR spectral analysis.

Degradation of 75c to the Proposed Pyrrolo[2,1-a]isoquinolinium Salt 78

The NMR analysis of 75c in C2D2Cl4 at 75°C afforded, after 115 min., the total removal of 75c and the formation of signals tentatively attributed to a mixture (58:42) of the diastereomers of 3-ethoxycarbonyl-8,9-dimethoxy-4-methyl-1-trimethylsilyl-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolinium chloride 78. major diastereomer 1H NMR* δ: 6.15 (d, J 11.6 Hz, H10b), 4.95-4.87 (m, H3), 3.42 (s, NCH3), -0.29 (s, Si(CH3)3); 13C DEPT NMR* δ: 113.30 (C7A), 111.62 (C10A), 74.70 (C10bB), 73.85 (C3B), 63.29 (CH2 of Et), 56.58 (2OCH3), 48.03 (C5), 45.86 (NCH3), 27.98 (C6C), 27.29 (C1), 23.25 (C2C), 14.30 (CH3 of Et), -1.21 (Si(CH3)3); minor diastereomer 1H NMR* δ: 5.56 (d, J 7.8 Hz, H10b), 5.34 (d, J 8.6 Hz, H3), 3.28 (s, NCH3), -0.26 (s, Si(CH3)3); 13C DEPT NMR* δ: 113.30 (C7A), 112.02 (C10A), 73.76 (C10bB), 72.99 (C3B), 63.57 (CH2 of Et), 56.58 (2OCH3), 54.46 (C5), 43.28 (NCH3), 29.79 (C6C), 29.21 (C1), 23.45 (C2C), 14.30 (CH3 of Et), -1.21 (Si(CH3)3).

* in C2D2Cl4 at 75°C.

6,7-Dimethoxy-1-[2'-(3,4-dimethoxyphenyl)ethenyl]-3,4-dihydroisoquinoline 79

Homoveratrylamine (5.30 g, 29.2 mmol) and 3,4-dimethoxycinnamic acid (7.45 g, 35.8 mmol) were heated at 170°C under nitrogen for 3 h. The solid product was taken up in chloroform (100 ml) and the organic solution was washed with 2.5 M sodium hydroxide (30 ml), 2.5 M hydrochloric acid (30 ml), water (30 ml) and then saturated brine (30 ml). The solution was then concentrated to give crude N-(3,4-dimethoxyphenethyl)-3,4-dimethoxycinnamide97 (9.39 g) as a yellow solid.

The crude amide was refluxed in dry toluene (80 ml) with phosphorus oxychloride (14.8 g, 96.6 mmol) for 2 h. then the solution was allowed to cool to room temperature. The yellow precipitate was collected by filtration and rinsed with
light petroleum then dried briefly under vacuum. Recrystallisation of this solid from methanol gave the hydrochloride salt$^97$ of the title compound (6.56 g). The salt was dissolved in chloroform (200 ml) and then 2 M sodium hydroxide (30 ml) was added and the mixture was stirred vigorously for 5 min. The organic layer was then separated and washed with water (2 x 30 ml). Drying and concentration of the solution afforded $1$-$[2'$-$($3,4$-$dimethoxyphenyl$)$ethenyl$]$isoquinoline 79 (4.56 g, 44%) as a pale yellow solid. $^1$H NMR $\delta$: 7.36 (d, $J$ 16.0 Hz, H1$^A$), 7.15-7.10 (m, 3ArH), 7.07 (d, $J$ 16.0 Hz, H2$^A$), 6.68 (d, $J$ 8.8 Hz, H4$^a$), 6.76 (s, ArH), 3.91 (s, OCH$_3$), 3.88 (s, OCH$_3$), 3.87 (s, OCH$_3$), 3.86 (s, OCH$_3$), 3.74 (t, H3), 2.67 (t, H4); $^{13}$C NMR $\delta$: 163.67 (Cl), 151.45 (C6$^A$), 150.42 (C7$^A$), 149.72 (C3$^a$A), 147.98 (C4$^a$A), 136.74 (C1$^B$), 132.89 (C1$^a$C), 130.15 (C4a$^C$), 124.45 (C2$^B$), 122.63 (C8a$^C$), 121.61 (C6$^D$), 111.72 (C5$^a$D), 111.01 (C2$^a$D), 110.33 (C5$^D$), 110.00 (C8$^D$), 57.03-56.59 (4OCH$_3$), 48.01 (C3), 26.76 (C4); MS m/z: 353 (M$^+$, 38%), 352 (100), 338 (23), 336 (16), 322 (11).

6.7-Dimethoxy-1-$[2'$-$($3,4$-$dimethoxyphenyl$)$ethenyl$]$ -2-methyl-3,4-
dihydroisoquinolinium Iodide 80

The imine 79 (3.96 g, 11.2 mmol) was heated at 70°C in dry butanone (20 ml) with iodomethane (22.8 g, 161 mmol) for 30 min. The removal of the solvents in vacuo and then recrystallisation of the residue twice from methanol gave the isoquinolinium salt 80 (3.87 g, 70%) as yellow needles with m.p. 193-195°C. $^1$H NMR $\delta$: 7.62 (d, $J$ 16.0 Hz, H1$^A$), 7.48 (d, $J$ 1.8 Hz, H2$^a$), 7.29-7.18 (m, 2ArH), 7.13 (s, ArH), 6.99 (s, ArH), 6.91 (d, $J$ 8.3 Hz, H4$^a$), 4.12 (t, H3), 4.08 (s, OCH$_3$), 4.06 (s, OCH$_3$), 4.04 (s, OCH$_3$), 3.94 (s, OCH$_3$), 3.80 (NCH$_3$), 3.26 (t, H4); $^{13}$C NMR $\delta$: 171.03 (Cl), 156.47 (C6$^A$), 153.58 (C7$^A$), 151.79 (Cl$^B$), 150.41 (C3$^a$A), 148.65 (C4$^a$A), 134.43 (C1$^a$C), 127.24 (C4a$^C$), 125.58 (C2$^B$), 119.72 (C8a$^C$), 116.04 (C6$^D$ and C5$^a$D), 111.63 (C2$^a$D and C2$^a$D), 110.77 (C5$^D$), 57.97-56.75 (4OCH$_3$), 53.24 (C3), 47.38 (NCH$_3$), 26.76 (C4).
A solution of 2-methylpropenylmagnesium bromide was prepared by the slow addition of 1-bromo-2-methylpropene (9.711 g, 71.93 mmol) to magnesium turnings (1.90 g, 78.0 mmol) in dry tetrahydrofuran (100 ml) under nitrogen. The reaction was initiated by heating the solution to reflux in the presence of an iodine crystal and was then maintained at a gentle reflux for 90 min., with the slow consumption of the magnesium.

The solution of 2-methylpropenylmagnesium bromide in tetrahydrofuran was cooled to <-50°C in an acetone/liquid nitrogen slush bath and then additional dry tetrahydrofuran (50 ml) was added, followed by 48a (9.855 g, 29.58 mmol). The mixture was allowed to warm slowly to room temperature with stirring for 21 h. before workup (as for 70b) to give, upon concentration of the ether solution, the 1-(2-methylpropenyl)isoquinoline 81a (4.731 g, 61%) as a pale oil of >99% purity by GC-MS analysis. The oil formed a solid, which melted on exposure to room temperatures, when stored at -5°C. 1H NMR δ: 6.48 (s, ArH), 6.41 (s, ArH), 5.06 (d, J 9.7 Hz, H1'), 3.84 (d, J 9.6 Hz, H1), 3.74 (s, OCH3), 3.70 (s, OCH3), 2.97-2.93 (m, 2H), 2.59-2.53 (m, H), 2.47-2.40 (m, H), 2.29 (s, NCH3), 1.75 (CH3), 1.74 (CH3); 13C NMR δ: 147.91 (C6A), 147.53 (C7A), 135.28 (C4aB), 130.07 (C2'B), 127.54 (C1'), 126.83 (C8aB), 111.59 (C5C), 111.05 (C8C), 63.55 (C1), 56.33 (OCH3), 56.29 (OCH3), 52.55 (C3), 44.42 (NCH3), 29.45 (C4), 26.38 (E-CH3), 18.89 (Z-CH3); MS m/z: 261 (M+, 18%; Calcd. for C16H23NO2 261.1728, found 261.1730), 260 (16), 246 (5), 218 (12), 206 (100), 203 (19), 190 (7); IR (thin film from CH2Cl2): 1510, 1259, 1217, 1139, 829 cm⁻¹.

The methiodide salt of 81a crystallised from methanol as pale yellow needles with m.p. 207-209°C. 1H NMR δ: 6.72 (s, ArH), 6.46 (s, ArH), 5.56 (d, J 10.3 Hz, H1), 5.21 (d, J 10.3 Hz, H1'), 4.39-4.32 (m, H3), 4.16-4.08 (m, H3), 3.88 (s, OCH3), 3.82 (s, OCH3), 3.56 (s, NCH3), 3.21-3.15 (m, NCH3 and H4), 2.13 (CH3), 1.98 (CH3); Anal. Calcd for C17H26NO2I: C, 50.63; H, 6.50; N, 3.47%, found: C, 50.76; H, 6.54; N, 3.53%.
Mixture of 6,7-Dimethoxy-2-methyl-1-propenyl-1,2,3,4-tetrahydroisoquinoline 81b Isomers

A solution of propenylmagnesium bromide was prepared by the slow addition of 1-bromo-1-propene (28.97 g, 239.4 mmol, a mixture of Z and E isomers) to magnesium turnings (6.45 g, 265 mmol) in dry tetrahydrofuran (180 ml) under nitrogen. The reaction was initiated by heating the solution to reflux in the presence of an iodine crystal. The addition rate was controlled to maintain a gentle reflux. The mixture was refluxed for 30 min. after the completion of the addition.

The solution of propenylmagnesium bromide in tetrahydrofuran was cooled to <-50°C in an acetone/liquid nitrogen slush bath and then 48a (20.00 g, 60.03 mmol) was added. The mixture was allowed to warm slowly to room temperature with stirring for 21 h. before workup (as for 70b) to give, upon concentration of the ether solution, a mixture (Z:E=3:1) of the isomers of 1-propenylisoquinoline 81b (12.72 g, 86%) as a tan oil with >99% purity upon GC-MS analysis. ¹H NMR* δ: 6.55 (s, ArH), 6.51 (s, ArH), 5.82-5.78 (m, H2X), 5.20-5.12 (m, H2Y), 5.39-5.31 (m, H1'), 4.02 (d, J 9.7 Hz, H1X), 3.81 (s, OCH3), 3.77 (s, OCH3), 3.63 (d, J 8.6 Hz, H1Y), 3.03-2.97 (m, 2H), 2.65-2.59 (m, H), 2.51-2.47 (m, H), 2.37 (s, NCH3), 1.81 (dd, J 1.8 Hz, 6.9 Hz, CH3X), 1.76 (dd, J 1.6 Hz, 6.4 Hz, CH3Y); ¹³C NMR* δ: 147.99 (C6A), 147.62 (C7A), 133.41 (C1'BX), 133.15 (C1'BX), 129.70 (C2'BY), 129.31 (C5'B), 126.83 (C8aC), 126.91 (C2'BX), 126.65 (C5D), 110.85 (C8D), 68.89 (C1Y), 62.15 (C1X), 56.36 (2OCH3), 52.71 (C3X), 51.85 (C3Y), 44.54 (NCH3), 29.54 (C4X), 29.31 (C4Y), 18.23 (CH3Y), 13.91 (CH3X); MS m/z: 247 (M+, 14%; Calcd. for C₁₅H₂₁NO₂ 247.1572, found 247.1565), 246 (11), 246 (5), 232 (5), 206 (100), 190 (12), 189 (15).

* Signals attributed to the Z and E isomers are marked with superscripts X and Y respectively.
6,7-Dimethoxy-1-[2'-[3,4-dimethoxyphenyl]ethenyl]-2-methyl-1,2,3,4-tetrahydroisoquinoline 81c

The methiodide salt 80 (3.83 g, 7.73 mmol) was suspended in ethanol (100 ml) at 0°C and then treated with sodium borohydride (0.84 g, 22 mmol) portionwise over 30 min. The mixture was stirred for 1 h, then concentrated and the residue was partitioned between 5% aqueous sodium bicarbonate (50 ml) and dichloromethane (50 ml). The organic layer was separated and washed with water (2 x 10 ml), then dried and concentrated. Column chromatographic purification of the residue on silica (35 g) with a gradient from dichloromethane/5% light petroleum to dichloromethane/8% methanol gave:

(a) the desired 1-[2'-[3,4-dimethoxyphenyl]ethenyl]isoquinoline 81c (2.495 g, 86%) as a pale yellow powder from the late fractions. ¹H NMR 8: 7.01 (d, J 1.4 Hz, H2''), 6.96 (dd, J 1.4 Hz, 8.6 Hz, H6''), 6.83 (d, J 8.6 Hz, H5''), 6.64 (s, ArH), 6.62 (s, ArH), 6.57 (d, J 15.7 Hz, H2'), 6.02 (dd, J 8.9 Hz, 15.7 Hz, H1''), 3.88 (s, 2OCH3), 3.86 (s, OCH3), 3.81 (d, J 8.9 Hz, H1), 3.76 (s, OCH3), 3.10-3.03 (m, 2H), 2.76-2.66 (m, H), 2.58-2.54 (m, H), 2.48 (s, NCH3); ¹³C NMR 8: 149.57 (C6A), 149.33 (C7A), 148.16 (C3'a), 147.62 (C4'a), 133.41 (C1''c), 130.37 (C1''C), 130.11 (C2'b), 128.92 (C4'aC), 126.99 (C8aC), 120.26 (C2''D), 111.70 (C5''D), 111.58 (C6''D), 111.44 (C5''D), 109.04 (C8''D), 69.09 (C1), 56.45-56.34 (4OCH3), 51.92 (C3), 44.73 (NCH3), 29.42 (C4); MS m/z: 369 (M⁺, 47%); Calcld. for C22H27N04 369.1939, found 369.1930; IR (thin film from CH2Cl2): 2936, 2833, 2783, 1516, 1265, 1142, 1028 cm⁻¹.

(b) an unidentified isomer of 81c (0.123 g, 4%) as a pale yellow oil from an early fraction. The material showed two sets of signals (a/b=1.21) on NMR analysis. ¹H NMR 8: 6.98-6.91 (m, 2ArH''), 6.85-6.81 (m, H2''), 6.67-6.65 (m, ArH), 6.62-6.57 (m, H1''a and H2''b), 6.55-6.52 (m, ArH), 6.10 (d, J 15.9 Hz, H2''a), 6.04 (dd, J 9.4 Hz, 15.6 Hz, H1''b), 4.61 (d, J 9.4 Hz, H1''b), 4.34 (d, J 7.5 Hz, H1''b), 3.90-3.87 (m, 3OCH3), 3.82 (s, OCH3), 3.37-2.85 (m, 8H), 2.72 (s, NCH3a), 2.64 (s, NCH3b); ¹³C NMR 8: 150.21-148.34 (6 peaks; C7, C8, C3'', and C4''); 137.07 and 136.61 (C1''A),
2-Ethoxycarbonylmethyl-6,7-dimethoxy-2-methyl-1-(2'-methylpropenyl)-1,2,3,4-tetrahydroisoquinolinium Bromide 82a

To the base 81a (1.295 g, 4.955 mmol) in dry acetonitrile (3 ml) at 0°C was added ethyl bromoacetate (1.06 g, 6.34 mmol). The mixture was stirred at room temperature for 24 h. and then concentrated to afford a gum which was triturated with diethyl ether (3 x 10 ml), then taken-up in dichloromethane and reconcentrated. Further trituration of the resultant powder with diethyl ether (3 x 10 ml) and drying afforded a mixture (trans: cis = 58:42) of the B-ring diastereomers of the 2-ethoxycarbonylmethylisoquinolinium salt 82a (1.869 g, 88%) as an off-white powder. 

trans diastereomer (assignable signals) 1H NMR δ: 6.72 (s, ArH), 6.43 (s, ArH), 6.10 (d, J 10.2 Hz, H1'), 5.31 (d, J 10.7 Hz, H1), 3.41 (s, NCH3), 2.14 (s, CH3), 1.97 (s, CH3); 13C NMR δ: 165.39 (COO), 149.78 (C6A), 148.90 (C7A), 122.34 (C4aB), 120.88 (C8aB), 116.52 (C2'), 111.47 (C5C), 110.71 (C8C), 69.21 (C1), 62.96 (CH2 of Et), 58.53 (NCH2CO), 56.31 (2OCH3), 55.39 (C3A), 46.88 (NCH3), 26.75 (CH3), 23.86 (C4), 20.16 (CH3), 14.09 (CH3 of Et);
cis diastereomer (assignable signals) 1H NMR δ: 6.74 (s, ArH), 6.44 (s, ArH), 5.86 (d, J 10.5 Hz, H1'), 5.42 (d, J 10.5 Hz, H1), 3.70 (s, NCH3), 2.04 (s, CH3), 1.91 (s, CH3); 13C NMR δ: 164.89 (COO), 148.28 (C6A), 146.04 (C7A), 122.46 (C4aB), 120.68 (C8aB), 117.30 (C2'), 111.31 (C5C), 110.30 (C8C), 69.81 (C1), 62.85 (CH2 of Et), 58.53 (NCH2CO), 56.31 (2OCH3), 55.39 (C3A), 45.63 (NCH3), 26.75 (CH3), 23.44 (C4), 19.91 (CH3), 14.21 (CH3 of Et).
2-Ethoxycarbonylmethyl-6,7-dimethoxy-2-methyl-1-propenyl-1,2,3,4-tetrahydroisoquinolinium Bromide 82b

(i) To the base 81b (0.860 g, 3.48 mmol, 3:1 mixture of the Z and E olefinic isomers) was added ethyl bromoacetate (0.72 ml, 6.47 mmol). The mildly exothermic reaction was cooled and the solution was then left to sit for 16 h. at room temperature. Trituration of the resultant gel with diethyl ether (5 x 20 ml) afforded a mixture (A:B:C:D=51:18:19:12) of the four possible isomers of the 2-ethoxycarbonylmethylisoquinolinium salt 82b (1.42 g, 98%) as a tan powder. Isomers A and B were attributed to the Z-olefinic diastereomers and isomers C and D to the E-olefinic diastereomers. Isomer A $^1$H NMR δ: 3.37 (s, NCH$_3$), 2.07 (d, $J$=7.1 Hz, CH$_3$); Isomer B $^1$H NMR δ: 3.69 (s, NCH$_3$), 1.96 (d, $J$=7.0 Hz, CH$_3$); Isomer C $^1$H NMR δ: 3.60 (s, NCH$_3$), 1.82 (d, $J$=6.3 Hz, CH$_3$); Isomer D $^1$H NMR δ: 3.45 (s, NCH$_3$), 1.77 (d, $J$=6.5 Hz, CH$_3$).

(ii) To 81b (1.984 g, 8.023 mmol, a 3:1 mixture of the Z and E olefinic isomers) in dry acetonitrile (3.5 ml) at room temperature was added ethyl bromoacetate (1.7 ml, 15 mmol). The solution was stirred for 24 h. then concentrated and the residue was triturated with diethyl ether (5 x 20 ml) to afford a mixture (A:B:C:D=55:18:17:9) of the isomers of 82b (3.19 g, 96%).

2-Ethoxycarbonylmethyl-6,7-dimethoxy-1-[2'-(3,4-dimethoxyphenyl)ethenyl]-2-methyl-1,2,3,4-tetrahydroisoquinolinium Iodide 82c

Potassium iodide (1.38 g, 8.31 mmol), dry acetonitrile (50 ml) and ethyl bromoacetate (0.90 ml, 8.1 mmol) were combined and stirred under nitrogen, protected from light, for 24 h. Filtration of the mixture afforded a solution, assumed to contain ethyl iodoacetate, which was added to 81c (1.00 g, 2.71 mmol). The mixture was heated in a sealed tube at 100-110°C for 3.5 h. then concentrated. The residue was dissolved in chloroform and the solution was filtered then reconcentrated. Trituration of the residue with diethyl ether (3 x 20 ml) and then recrystallisation of the gum from ethanol/tetrahydrofuran gave a mixture
(trans:cis=46:54) of the B-ring diastereomers of the 2-ethoxycarbonylmethylisoquinolinium salt 82c (0.977 g, 62%) as a pale yellow powder. trans diastereomer 1H NMR δ: 6.37 (d, J 9.4 Hz, H1), 3.59 (s, NCH3); cis diastereomer 1H NMR δ: 7.30 (d, J 15.4 Hz, H2'), 5.84 (d, J 9.6 Hz, H1), 3.66 (s, NCH3); 13C NMR of mixture δ: 165.14 (COO), 142.71 and 140.70 (C2'A), 122.60 and 122.35 (C1'A), 118.36 and 117.49 (C6''A), 78.19 and 74.53 (C1), 63.60 and 63.47 (CH2 of Et), 60.99 and 58.29 (NCH2CO), 56.17 and 55.02 (C3A), 48.35 and 46.70 (NCH3), 24.16 and 23.84 (C4), 14.64 and 14.54 (CH3 of Et).

Ethyl N-{2-[4',5'-Dimethoxy-2'-(3"-methyl-1"E,3"-butadienyl)phenyl]ethyl}-N-methyl-aminoethanoate 83a

To the base 81a (1.710 g, 4.955 mmol) in dry butanone (5 ml) was added ethyl bromoacetate (1.06 g, 6.34 mmol). The solution was stirred at 50°C for 10 h. then concentrated. The residue was triturated with diethyl ether (3 x 15 ml) then taken-up in dichloromethane. Concentration and then further trituration of the residue with diethyl ether (3 x 10 ml) afforded a gum which, upon purification by column chromatography on silica (30 g) with dichloromethane/0-4% ethanol, gave the title compound 83a (1.407 g, 62%) as a yellow oil. 1H NMR δ: 7.03 (s, ArH), 6.72 (s, H1''A), 6.71 (s, H2''A), 6.68 (s, ArH), 5.10 (s, H4"'), 5.05 (s, H4"'), 4.17 (q, CH2 of Et), 3.89 (s, OCH3), 3.87 (s, OCH3), 3.30 (s, NCH2CO), 2.88-2.83 (m, 2H), 2.69-2.64 (m, 2H), 2.48 (s, NCH3), 2.00 (s, CH3), 1.26 (t, CH3 of Et); 13C NMR δ: 171.12 (COO), 149.00 (C4'A), 147.98 (C5'A), 142.60 (C3''), 131.68 (C1''B), 130.76 (C1'C), 128.56 (C2'C), 125.91 (C2''B), 116.92 (C4''), 113.33 (C3'D), 108.75 (C6'D), 60.73 (CH2 of Et), 58.89 (NCH2CO and C1), 56.20 (2OCH3), 42.68 (NCH3), 31.66 (C2), 19.05 (CH3), 14.58 (CH3 of Et). 1H NMR (d6-benzene) δ: 7.35 (s, ArH), 7.23 (d, J 15.9 Hz, H1''A), 7.10 (d, J 15.9 Hz, H2''A), 6.68 (s, ArH).
Ethyl N-[2-[4',5'-Dimethoxy-2'-[(1',3''-butadienyl)phenyl]ethyl]-
N-methylamino-ethanoate 83b

(i) To 81b (5.20 g, 21.0 mmol, a 3:1 mixture of the Z and E olefinic isomers) in dry acetone (3.5 ml) was added ethyl bromoacetate (5.3 ml, 48 mmol). The solution was refluxed for 5 h. then concentrated. The oily residue was purified by column chromatography on silica with dichloromethane/0-6% ethanol to give successively:

(a) the 1E,3-butadienyl isomer of 83b (0.88 g, 13%) as a yellow oil. 1H NMR δ:
7.02 (s, ArH), 6.77 (d, J 14.6 Hz, H1"), 6.68 (s, ArH), 6.63-6.52 (m, H2" and H3"),
5.31 (d, J 17.4 Hz, H4"), 5.16 (d, J 9.1 Hz, H4"), 4.20 (q, CH2 of Et), 3.90 (s, OCH3),
3.88 (s, OCH3), 3.37 (s, NCH2CO), 2.90-2.85 (m, 2H), 2.75-2.70 (m, 2H),
2.52 (s, NCH3), 1.28 (t, CH3 of Et); 13C NMR δ: 170.98 (COO), 149.48 (C4'A),
148.38 (C5'A), 138.10 (C1'B), 130.67 (C1'C), 130.21 (C2'' and C3''B), 128.64 (C2'C),
117.53 (C4''), 113.65 (C3'D), 108.87 (C6'D), 61.44 (CH2 of Et), 58.99 (NCH2COE),
58.79 (C1'E), 56.60 (20CH3), 42.97 (NCH3), 31.72 (C2), 14.92 (CH3 of Et); MS m/z: 333 (M+, 12%; Calcld. for C19H27N04 333.1940, found 333.194), 260 (7), 190 (2), 130 (100), 102 (10).

(b) the 1Z,3-butadienyl isomer of 83b (3.88 g, 55%) as a yellow oil. 1H NMR δ:
6.99 (s, ArH), 6.86-6.80 (m, ArH and H1"), 6.68-6.60 (m, H2" and H3"), 5.32 (d, J
17.4 Hz, H4"), 5.17 (d, J 9.1 Hz, H4"), 4.26 (q, CH2 of Et), 3.97 (s, NCH2CO), 3.97
(s, 2OCH3), 3.40-3.37 (m, 2H), 3.27-3.23 (m, 2H), 3.01 (s, NCH3), 1.30 (t, CH3 of
Et); 13C NMR δ: 165.57 (COO), 149.68 (C4'A), 149.07 (C5'A), 137.98 (C1'B),
131.21 (C2''B), 129.27 (C3''B), 129.01 (C1'C), 128.64 (C2'C), 118.20 (C4''), 113.79
(C3'D), 108.96 (C6'D), 63.26 (CH2 of Et), 56.78 (NCH2COE), 56.57 (2OCH3), 54.56
(C1'E), 41.72 (NCH3), 29.24 (C2), 14.62 (CH3 of Et); MS m/z: 333 (M+, 13%;
Calcld. for C19H27N04 333.1940, found 333.194), 260 (7), 190 (2), 130 (100), 102
(13).

(c) a mixture (A:B:C:D=4:6:25:65) of the isomers of 82b (0.77 g, 9%).
A mixture (A:B:C:D=55:18:17:9) of the isomers of $82b$ (0.273 g, 0.659 mmol) was refluxed in dry acetone for 7 h. then worked-up as for (i) to afford a mixture (Z/E=8.8) of the isomers of $83b$ (0.137 g, 62%).

**N-(3,4-dimethoxyphenylethyl)crotonamide $84a$**

Homoveratrylamine (10.00 g, 55.2 mmol) and crotonic acid (5.70 g, 66.2 mmol) were heated at 170°C, under a slow flow of nitrogen to remove water, for 2 h. The mixture was allowed to cool to 80°C then chloroform (150 ml) was added; preventing the formation of a difficult to dissolve glassy solid. The organic solution was washed with 2.0 M sodium hydroxide (2 x 30 ml), 2.5 M hydrochloric acid (4 x 30 ml) and water (2 x 30 ml) then dried and concentrated. The residue was purified by column chromatography on silica (80 g) with dichloromethane/2-4% methanol, leaving residual homoveratrylamine on the column. The eluant was concentrated and the residue was recrystallised from ethyl acetate to give the crotonamide $84a$ (2.59 g, 19%) as an off-white powder. $^1$H NMR $\delta$: 6.85-6.71 (m, 3ArH and NH), 5.96-5.89 (m, H3), 5.78 (dd, $J$ 1.6 Hz, 15.2 Hz, H2), 3.85 (s, 2OCH3), 3.57-3.50 (m, 2H), 2.78 (t, 2H), 1.82 (dd, $J$ 1.6 Hz, 6.9 Hz, CH3); $^{13}$C NMR $\delta$: 166.55 (CO), 149.51 (C3"A), 147.814 (C4"A), 140.14 (C2B), 132.05 (C1"), 125.70 (C3B), 121.15 (C6"B), 112.48 (C2"C), 111.90 (C5"C), 56.41 (2OCH3), 41.27 (C1'), 35.77 (C2'), 18.19 (C4); MS m/z: 249 (M+, 5%; Calcd. for C14H19NO3 249.1363, found 249.137), 164 (100), 151 (33), 149 (10), 69 (37); IR (thin film from CH2Cl2): 3306, 2940, 1516, 1263, 1236 cm$^{-1}$.

**Attempted N-[2-(3,4-Dimethoxyphenyl)ethyl]fumaramide Ethyl Ester $84b$**

Homoveratrylamine (3.409 g, 18.81 mmol) and fumaric acid monoethyl ester (4.027 g, 27.94 mmol) were heated at 155°C under a slow flow of nitrogen, to remove water, for 4 h. Some solid was present throughout the reaction. Upon cooling the mixture was taken up in chloroform (50 ml) and washed with 2M sodium hydroxide (4 x 10 ml) then 5% hydrochloric acid (3 x 10 ml) and water (10 ml).
Drying and then concentration of the solution gave a tan solid (2.755 g). Analysis by GC-MS showed fumaric acid monoethyl ester (86%) and a second component (14%) with MS m/z: 261 (M⁺, 15%), 164 (43), 151 (100), 149 (9), 107 (17).

(ii) To fumaric acid monoethyl ester (1.515 g, 10.50 mmol) as a melt at 90°C under nitrogen was added homoveratrylamine (2.093 g, 11.55 mmol). The mixture was then heated to 185-190°C. A solid formed rapidly in the liquid melt and then dissolved as the temperature exceeded 170°C. After 20 min. at 185-190°C under a steady flow of nitrogen the evolution of water from the brown liquid mixture ceased. The reaction was allowed to cool slowly to room temperature under oil pump vacuum and the solid was taken up in chloroform (30 ml). The solution was washed with 1M sodium hydroxide (4 x 6 ml), 1M hydrochloric acid (3 x 6 ml), and then water (10 ml). Drying and then concentration of the solution gave a tan solid (2.360 g). Analysis by GC-MS showed 3 components with molecular ions at 261 (65%, as for (i)), 429 (17%) and 442 (18%).

**Attempted Preparation of 6,7-Dimethoxy-1-(1'-propenyl)-3,4-dihydroisoquinoline 85**

(i) The technique of Markaryan and Airapetyan,98 reported to provide the hydrochloride of 85 in 75-87% yield via 85 as a crude oil, was followed. A mixture of the amide 84a (11.79 g, 47.27 mmol) in dry benzene (150 ml) with phosphorus oxychloride (76.0 g, 496 mmol) was refluxed for 6.5 h. then cooled to room temperature. The mixture was then concentrated and the residue was dissolved in water (150 ml). The solution was cooled and 10% aqueous sodium carbonate was added carefully to provide a pH of 9-10. The mixture which resulted was extracted with benzene (3 x 100 ml) and the extracts were then combined and washed with water (2 x 50 ml). Drying and then concentration of the organic solution afforded a dark yellow powder (6.735 g). Analysis by t.l.c., GC-MS and 1H NMR techniques showed many components.

(ii) Compound 84a (0.614 g, 2.46 mmol) was refluxed in dry toluene (12 ml) with phosphorus oxychloride (3.29 g, 21.5 mmol) for 2.5 h. then the mixture was cooled
and the dark toluene layer was decanted from the resultant oil. The toluene was extracted with water (5 ml) while ice/water (30 g) was added to the oil. The aqueous layers were combined and washed with diethyl ether then cooled and basified to pH 9-10 by the slow addition of 80% aqueous sodium hydroxide. The mixture was extracted with chloroform (4 x 20 ml) and the extracts were then dried and concentrated to a dark film (0.606 g). Analysis by t.l.c., GC-MS and $^1$H NMR techniques showed many components.

(iii) Compound 84a (0.944 g, 3.79 mmol) was refluxed in dry toluene (25 ml) with phosphorus pentoxide (5.12 g, 36.1 mmol) for 1.5 h. then the mixture was cooled to room temperature. The dark toluene layer was decanted and extracted with water (5 ml), while the solid was dissolved in ice/water (30 g). The aqueous layers were combined and washed with diethyl ether (3 x 10 ml) then cooled and basified to pH 9-10 by the slow addition of 80% aqueous sodium hydroxide. The mixture was extracted with diethyl ether (3 x 20 ml) and the extracts were then dried and concentrated to give a yellow oil. Analysis by t.l.c., GC-MS and $^1$H NMR techniques showed many components.

(iv) Compound 84a (0.605 g, 2.43 mmol) was refluxed in dry acetonitrile (20 ml) with phosphorus oxychloride (3.29 g, 21.5 mmol) for 2 h. over 4A molecular sieves. The molecular sieves were removed by filtration and the solution was then washed with light petroleum (3 x 10 ml), and then concentrated. The residue was treated with methanol (30 ml) and sodium cyanoborohydride portionwise until the yellow colour was removed, then stirred for 3 h. The mixture was then concentrated and 5% aqueous sodium bicarbonate was added to produce an alkaline solution which was extracted with dichloromethane (30 ml). The dichloromethane extracts were washed with 5% aqueous sodium bicarbonate (3 x 10 ml) then dried and concentrated. Analysis of the residual powder (0.519 g) by t.l.c. and GC-MS showed many components inconsistent with 6,7-dimethoxy-1-(1'-propenyl)-1,2,3,4-tetrahydroisoquinoline.
Attempted Preparation of 2-Chloroethenylmagnesium Chloride and 1-(trans-2'-Chloroetheny1)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline 86

A solution of trans-1,2-dichloroethene (7.59 g, 78.3 mmol) in dry tetrahydrofuran (10 ml) was added to magnesium turnings (1.96 g, 80.6 mmol) in dry tetrahydrofuran (70 ml) under nitrogen. An iodine crystal was added and the mixture was refluxed for 2.5 h. The magnesium was consumed and a pale tan solid formed in the dark solution. The mixture was cooled to -50°C and then the iminium salt 48a (6.01 g, 18.0 mmol) was added. The mixture was allowed to warm to room temperature with stirring for 16 h. then worked up (as for 70b) to provide an ether solution which on concentration gave a yellow oil (0.43 g). The oil contained many components.

Ethyl 9.10-Dimethoxy-3,5,5-trimethyl-2,3,4,5-tetrahydro-1H-3-benzazonine-4-carboxylate 87a

(i) The salt 82a (0.104 g, 0.243 mmol) was stirred in dry acetonitrile (10 ml) under nitrogen at -20°C with DBU (0.048 g, 0.32 mmol) for 5 h. then the solution was concentrated. Purification of the residue by column chromatography on alumina with dichloromethane/20% light petroleum afforded a mixture (0.053 g, 65%) of the isomers E-87a:t-88a:c-88 a in the ratio 70:27:3 as a colourless oil. The E-benzazonine E-87a could not be isolated separately. NMR signals attributed to 87a were: $^1$H NMR (d$_6$-benzene) δ: 7.08 (s, ArH), 6.82 (s, ArH), 6.73 (d, J 16.6 Hz, H6A), 6.73 (d, J 16.6 Hz, H7A), 4.18 (q, CH$_2$ of Et), 3.76 (s, OCH$_3$), 3.68 (s, OCH$_3$), 3.22-3.13 (m, H), 3.12 (s, H4), 3.05-2.98 (m, H), 2.82-2.71 (m, H), 2.80 (s, NCH$_3$), 2.64-2.57 (m, H), 1.52 (s, CH$_3$), 1.42 (s, CH$_3$), 1.19 (t, CH$_3$ of Et); $^{13}$C NMR (CDCl$_3$) δ: 170.87 (COO), 147.44 (C9A), 147.02 (C10A), 139.18 (C6B), 134.34 (C7aC), 132.17 (C11aC), 130.62 (C7B), 113.74 (C8D), 110.81 (C11D), 77.18 (C4), 60.14 (CH$_2$ of Et), 56.54 (OCH$_3$), 54.97 (C2), 46.39 (NCH$_3$), 41.71 (C5), 38.22 (C1), 25.57 (CH$_3$), 24.80 (CH$_3$), 15.18 (CH$_3$ of Et).
(ii) The salt 82a (0.433 g, 1.011 mmol) was stirred in dry acetonitrile (15 ml) under nitrogen at room temperature with DBU (0.048 g, 0.32 mmol) for 5 h. then worked-up as for (i) to give a mixture (0.293 g, 86%) of the isomers E-87a:t-88a:c-88a in the ratio 58:37:5 as a colourless oil.

**Ethyl 9.10-Dimethoxy-3,5-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazonine-4-carboxylate 87b**

(i) A mixture (A:B:C:D=55:18:17:9) of the isomers of 82b (2.450 g, 5.913 mmol), in dry acetonitrile (100 ml) under nitrogen at 0°C, was treated with DBU (1.08 g, 7.09 mmol) then allowed to warm to room temperature with stirring for 12 h. Concentration and then purification of the residue by column chromatography on alumina with dichloromethane/40% light petroleum afforded a colourless oil (1.578 g, 80%) containing a mixture of the isomers* E-87bA:E-87bB:Z-76bA:Z-87bB:88bA:88bB in the ratio 42:23:3:3:27:2.

A portion (1.26 g) of the above oil was purified by column chromatography on alumina (57 g) with light petroleum/0-50% dichloromethane to afford successively:

(a) a fraction (0.712 g) enriched in E-87bA. Purification of a portion (0.150 g) of this material by preparative reverse phase HPLC with acetonitrile/26% water gave, after 20.7 min., the *E-benzazonine E-87bA* (0.102 g) as a colourless oil. H NMR δ: 6.81 (s, ArH), 6.61 (s, ArH), 6.41 (d, J 16.1 Hz, H7), 5.51 (dd, J 9.9 Hz, 16.1 Hz, H6), 4.18-4.10 (m, CH2 of Et), 3.86 (s, OCH3), 3.83 (s, OCH3), 3.32 (d, J 5.8 Hz, H4), 2.74-2.57 (m, 4H), 2.63 (s, NCH3), 2.41-2.32 (m, H), 1.24 (t, CH3 of Et), 1.16 (d, J 7.0 Hz, CH3); 13C NMR δ: 171.00 (COO), 147.44 (C9A), 147.13 (C10A), 135.75 (C7B), 133.83 (C11aC), 132.73 (C6B), 132.01 (C7aC), 113.78 (C8D), 110.69 (C11D), 72.08 (C4), 60.19 (CH2 of Et), 56.52 (2OCH3), 54.58 (C2), 45.47 (NCH3E), 43.93 (C5E), 38.18 (C1), 15.83 (CH3F), 15.19 (CH3 of EtF); MS m/z: 333 (M+, 4%; Calcd. for C19H27N04 333.1940, found 333.1939), 260 (100), 203 (12), 189 (6), 115 (4).
(b) a mixture (0.130 g) of E-87bA, Z-87bB and 88bA.

(c) a fraction which when crystallised from ethanol afforded 88bA (0.219 g).

(d) a mixture (0.068 g) of 88bA, 88bB and Z-87bA.

(ii) A mixture (A:B:C:D=55:18:17:9) of the isomers of 82b (0.100 g, 0.241 mmol) in dry acetonitrile (100 ml) at reflux was treated with DBU (0.10 ml, 0.67 mmol). The solution was refluxed for 50 min. A preliminary work-up as for (i) afforded a colourless oil (0.058 g, 72%) with E-87bA:E-87bB:Z-87bA:Z-87bB:88bA:88bB in the ratio 39:14:2:3:37:5.

(iii) A mixture (A:B:C:D=4:6:25:65) of the isomers of 82b (0.198 g, 0.478 mmol) in dry acetonitrile (100 ml) under nitrogen at 0°C, was treated with DBU (0.10 ml, 0.67 mmol) then allowed to warm to room temperature with stirring for 12 h. A preliminary work-up as for (i) afforded a colourless oil (0.104 g, 65%), with E-87bA:E-87bB:Z-87bA:Z-76bB:88bA:88bB in the ratio 40:30:13:11:4, which was purified by preparative reverse phase HPLC with acetonitrile/26% water to give:

(a) after 11.4 min., the Z-benzazonine Z-87bA (0.010 g), attributed to the cis B-ring diastereomer, as a colourless oil.  1H NMR δ: 6.61 (s, ArH), 6.56 (d, J 10.5 Hz, H7), 6.54 (s, ArH), 6.41 (dd, J 10.5 Hz, 10.6 Hz, H6), 4.26 (q, CH2 of Et), 3.89 (s, OCH3), 3.85 (s, OCH3), 3.34-3.26 (m, H), 2.96 (d, J 4.2 Hz, H4), 2.89-2.79 (m, 2H), 2.63-2.44 (m, 2H), 2.41 (s, NCH3), 1.32 (t, CH3 of Et), 0.90 (d, J 7.0 Hz, CH3);  13C NMR δ: 172.82 (COO), 148.23 (C9A), 147.53 (C10A), 137.00 (C7B), 133.42 (C11aC), 130.63 (C7aC), 129.77 (C6B), 113.94 (C8D), 111.87 (C11D), 75.56 (C4), 60.94 (CH2 of Et), 56.59 (2OCH3), 55.61 (C2), 46.93 (NCH3), 37.08 (C1), 36.93 (C5), 19.38 (CH3), 15.16 (CH3 of Et); MS m/z: 333 (M+, 5%; Calcd. for C19H27N04 333.1940, found 333.1951), 260 (100), 203 (11), 189 (5), 115 (3).

(b) after 13.4 min., the Z-benzazonine, Z-87b (0.004 g), attributed to the trans B-ring diastereomer, as a colourless oil.  1H NMR δ: 6.59 (d, J 10.5 Hz, H7), 6.57 (s, ArH), 6.56 (s, ArH), 5.60 (dd, J 10.5 Hz, 10.6 Hz, H6), 4.13 (q, CH2 of Et), 3.87 (s, OCH3), 3.85 (s, OCH3), 3.28-3.22 (m, H), 3.06 (d, J 11.4 Hz, H4), 2.71-2.57 (m, 3H), 2.54 (s, NCH3), 2.43-2.33 (m, H5), 1.25 (t, CH3 of Et), 0.81 (d, J 6.5 Hz, CH3);
$^{13}$C NMR $\delta$: 173.29 (COO), 148.33 (C9A), 147.40 (C10A), 138.71 (C7B), 134.80 (C11aC), 129.79 (C7aC and C6B), 113.96 (C8D), 111.97 (C11D), 73.04 (C4), 60.49 (CH$_2$ of Et), 56.55 (20CH$_3$), 51.98 (C2), 45.75 (NCH$_3$), 38.48 (C1), 36.35 (C5), 18.17 (CH$_3$), 15.22 (CH$_3$ of Et); MS m/z: 333 (M$^+$, 9%; Calcd. for C$_{19}$H$_{27}$N$_2$O$_4$ 333.1940, found 333.1954), 260 (100), 203 (9), 189 (5), 115 (4).

* suffixes A and B denote B-ring diastereomers. Compound $E$-$87bB$ could not be isolated. $^1$H NMR $\delta$: 5.65 (dd, $J$ 5.3 Hz, 16.8 Hz, H6), 2.68 (s, NCH$_3$).

**Ethyl 7,8-Dimethoxy-3-methyl-1-(2'-methyl)propenyl-2,3,4,5-tetrahydro-$I$-$H$-3-benzazepine-4-carboxylate $88a$**

(i) To a solution of DBU (0.048 g, 0.32 mmol) in refluxing dry acetonitrile (10 ml) was added a solution of $82a$ (0.105 g, 0.245 mmol) in acetonitrile (1 ml). The solution was refluxed for 1 h. then concentrated. Purification of the residue by column chromatography on alumina with dichloromethane/20% light petroleum afforded a mixture (84:16) of the B-ring diastereomers of the 3-benzazepine $88a$ (0.058 g, 71%) as a colourless oil. Characteristic $^1$H NMR signals were: trans-$88a$

$^1$H NMR (d$_6$-benzene) $\delta$: 7.08 (s, ArH), 6.73 (s, ArH), 6.38 (d, $J$ 8.3 Hz, H1'), 4.61 (t, H2), 2.77 (s, NCH$_3$), 1.92 (s, CH$_3$), 1.85 (s, CH$_3$), 1.15 (t, CH$_3$ of Et); cis-$88a$ $^1$H NMR (d$_6$-benzene) $\delta$: 7.18 (s, ArH), 6.78 (s, ArH), 6.52 (d, $J$ 8.1 Hz, H1'), 4.68 (d, $J$ 7.5 Hz, H2), 2.73 (s, NCH$_3$), 2.02 (s, CH$_3$), 1.72 (s, CH$_3$), 1.07 (t, CH$_3$ of Et).

(ii) The trans B-ring diastereomer of $88a$ was isolated from the synthesis of 101c. $^1$H NMR $\delta$: 6.69 (s, ArH), 6.64 (s, ArH), 5.70 (d, $J$ 9.1 Hz, H1'), 4.13-4.06 (m, CH$_2$ of Et and H1), 3.84 (s, OCH$_3$), 3.83 (s, OCH$_3$), 3.30 (d, $J$ 7.4 Hz, H2), 3.26-3.23 (m, H), 3.03-2.92 (m, 2H), 2.69-2.59 (m, H), 2.43 (s, NCH$_3$), 1.78 (d, $J$ 0.8 Hz, CH$_3$), 1.63 (d, $J$ 1.1 Hz, CH$_3$), 1.21 (t, CH$_3$ of Et); $^{13}$C NMR $\delta$: 172.74 (COO), 147.78 (C7A), 147.42 (C8A), 134.80 (C2B), 133.18 (C5aB), 132.98 (C9aB), 123.85 (C1'), 113.37 (C6C), 112.79 (C9C), 70.65 (C2), 60.44 (CH$_2$ of Et), 56.65 (OCH$_3$), 56.42 (OCH$_3$), 51.61 (C4), 46.25 (C1), 45.38 (NCH$_3$), 34.71 (C5), 26.63 (CH$_3$), 18.82
Ethyl 7,8-Dimethoxy-3-methyl-1-propenyl-2,3,4,5-tetrahydro-1H-
3-benzazepine-4-carboxylate 88b

The synthesis and purification described for 87b afforded the 3-benzazepine,
88bA (0.219 g), attributed to the diastereomer* with the Z-geometry of the double
bond, as an off-white solid with m.p. 83-84°C. 1H NMR δ: 6.71 (s, ArH), 6.64 (s,
ArH), 5.98-5.92 (m, H1'), 5.70-5.66 (m, H2'), 4.23 (dd, J 7.3 Hz, 7.9 Hz, H1), 4.16-
4.03 (m, CH2 of Et), 3.87 (s, OCH3), 3.86 (s, OCH3), 3.35 (d, J 7.7 Hz, H2), 3.28-
3.23 (m, H), 3.00-2.92 (m, 2H), 2.72-2.63 (m, H), 2.45 (s, NCH3), 1.62 (dd, J 1.7 Hz,
6.8 Hz, CH3), 1.22 (t, CH3 of Et); 13C NMR δ: 172.37 (COO), 147.65 (C7A),
147.27 (C8A), 133.05 (C5aB), 132.20 (C9aB), 129.69 (C2C), 123.85 (C1C), 113.21
(C6D), 112.50 (C9D), 70.10 (C2), 60.43 (CH2 of Et), 56.45 (OCH3), 56.27 (OCH3),
51.37 (C4), 46.24 (C1E), 44.19 (NCH3E), 34.63 (C5), 14.94 (C3'), 13.71 (CH3 of Et);
MS m/z: 333 (M+, 5%; Calcd. for C19H27N04 333.1940, found 333.1945), 260
(100), 203 (10), 189 (4), 115 (3).
* The isomer 88bB could not be isolated. 1H NMR δ: 6.21-6.15 (m, H), 2.51 (s,
NCH3), 1.58 (dd, J 1.7 Hz, 6.8 Hz, CH3), 1.10 (t, CH3 of Et).

Ethyl 7,8-Dimethoxy-1-(2',3,4-dimethoxyphenyl)ethenyl]-3-methyl-2,3,4,5-
tetrahydro-1H-3-benzazepine-4-carboxylate 88c

(i) The salt 82c (0.215 g, 0.368 mmol) as a suspension in dry tetrahydrofuran (13
ml) under nitrogen at room temperature was treated with DBU (0.073 g, 0.48 mmol).
After 45 min. the solution was then concentrated. Purification of the residue by
p.t.l.c. on silica with dichloromethane/3% ethanol gave:
(a) at Rf 0.91, compound 89 (0.007 g, 4%).
(b) at Rf 0.56, the trans B-ring diastereomer of the 3-benzazepine 88c (0.081 g, 48%)
which crystallised from ethanol as colourless needles with m.p. 106-108°C. 1H
NMR δ: 6.90 (d, J 1.8 Hz, H2"), 6.89 (dd, J 1.8 Hz, 8.3 Hz, H6"), 6.79 (d, J 8.3 Hz H5"), 6.66 (s, H9), 6.64 (s, H6), 6.50 (dd, J 5.8 Hz, 15.9 Hz, H1'), 6.16 (dd, J 1.3 Hz, 15.9 Hz, H2'), 4.12-3.96 (m, H1 and CH2 of Et), 3.89 (s, OCH3), 3.87 (s, 2OCH3), 3.84 (s, OCH3), 3.74 (d, J 5.8 Hz, H2), 3.39-3.33 (m, H4), 3.21-3.14 (m, H4), 2.76-2.62 (m, H5), 2.56 (s, NCH3), 1.16 (t, CH3 of Et); 13C NMR δ: 172.20 (COO), 149.56 (C7A), 149.10 (C8A), 148.03 (C3"A), 147.41 (C4"A), 134.07 (C1"B), 131.64 (C5aB), 131.28 (C1'C), 131.16 (C9aB), 128.89 (C2'C), 119.83 (C2"D), 114.50 (C5"D), 113.96 (C6"D), 113.72 (C6D), 109.65 (C9D), 69.61 (C2), 60.48 (CH2 of Et), 56.69-56.51 (4OCH3), 51.54 (C1), 51.34 (C4), 46.89 (NCH3), 35.53 (C5), 15.10 (CH3 of Et); MS m/z: 455 (M+, 23%), 383 (38), 382 (100), 366 (4), 309 (3), 151 (6); Anal. Calcd for C26H33N06: C, 68.55; H, 7.30; N, 3.08%; found: C, 68.61; H, 7.32; N, 3.04%.

(c) at Rf 0.42, the cis B-ring diastereomer of the 3-benzazepine 88c (0.019 g, 11%) as a colourless solid. 1H NMR δ: 6.96 (d, J 1.9 Hz, H2"), 6.95 (dd, J 1.9 Hz, 6.2 Hz, H6"), 6.86-6.79 (m, H1' and H5"), 6.70 (s, H9), 6.66 (s, H6), 6.38 (d, J 15.8 Hz, H2'), 4.13 (d, J 8.1 Hz, H1), 4.09-4.00 (q, CH2 of Et), 3.91 (s, OCH3), 3.88 (s, OCH3), 3.86 (s, OCH3), 3.82 (s, OCH3), 3.61 (s, H2'), 3.36-3.30 (m, H), 3.13-3.08 (m, H), 2.89-2.82 (m, H), 2.76-2.70 (m, H), 2.52 (s, NCH3), 1.21 (t, CH3 of Et); 13C NMR δ: 172.23 (COO), 149.64 (C7A), 149.34 (C8A), 148.02 (C3"A), 147.54 (C4"A), 133.92 (C1"B), 133.29 (C5aB), 132.13 (C1'C), 131.17 (C9aB), 128.30 (C2'C), 120.00 (C2"D), 113.56 (C5"D), 112.67 (C6"D), 111.82 (C6D), 109.76 (C9D), 70.85 (C2), 60.61 (CH2 of Et), 56.87-56.58 (4OCH3), 53.23 (C4), 50.85 (C1), 45.89 (NCH3), 35.28 (C5), 14.99 (CH3 of Et); MS m/z: 455 (M+, 25%), 383 (36), 382 (100), 366 (5), 309 (4), 151 (6).

(ii) To 82c (0.299 g, 0.513 mmol) in dry acetonitrile (15 ml) under nitrogen at -45°C was added DBU (0.094 g, 0.62 mmol). The solution was stirred between -45°C and -40°C for 6 h. then allowed to warm slowly to -10°C over 1.5 h. Concentration and then column chromatography of the residue on alumina with dichloromethane/20% light petroleum gave a mixture (trans/cis=4.8) of the isomers of 88c (0.168 g, 72%).
Methyl 7,8-Dimethoxy-1-[2'-(3,4-dimethoxyphenyl)ethenyl]-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-4-carboxylate 89

(i) A portion of 82c was crystallised from methanol/diethyl ether to afford a pale yellow powder (0.080 g, 0.14 mmol) which was treated, as a suspension in dry tetrahydrofuran (5 ml) under nitrogen at room temperature, with DBU (0.027 g, 0.18 mmol). After 30 min. the solution was then concentrated. Purification of the residue by p.t.l.c. on silica with dichloromethane/4% methanol gave:

(a) at Rf 0.94, the trans B-ring diastereomer of the 3-benzazepine 89 (0.039 g, 65%) which crystallised from methanol as colourless needles with m.p. 123-124°C. 1H NMR δ: 6.90-6.87 (m, H2" and H6"), 6.79 (d, J 8.8 Hz H5"), 6.66 (s, H9), 6.64 (s, H6), 6.50 (dd, J 5.9 Hz, 15.9 Hz, H1'), 6.16 (dd, J 1.4 Hz, 15.9 Hz, H2'), 4.12-4.08 (m, H1), 3.90 (s, OCH3), 3.87 (s, 2OCH3), 3.85 (s, OCH3), 3.75 (d, J 5.9 Hz, H2), 3.57 (CO2CH3), 3.36-3.29 (m, H4), 3.20-3.16 (m, H4), 2.74-2.65 (m, H5), 2.55 (s, NCH3); 13C NMR δ: 172.53 (COO), 149.51 (C7A), 149.08 (C8A), 148.03 (C3"A), 147.41 (C4"A), 133.95 (C1"B), 131.59 (C5aB), 131.28 (C1'C), 131.07 (C9aB), 128.70 (C2'C), 119.79 (C2"D), 114.25 (C5"D), 113.65 (C6"D), 111.66 (C6D), 109.57 (C9D), 69.70 (C2), 56.72 (OCH3), 56.49 (4OCH3), 51.49 (C1), 51.45 (C4), 46.86 (NCH3), 35.43 (C5); MS m/z: 441 (M+, 39%; Calcd. for C25H31N06 441.215, found 441.214), 382 (100), 309 (9), 206 (13), 189 (8), 151 (23).

(b) at Rf 0.86, the cis B-ring diastereomer of the 3-benzazepine 89 (0.010 g, 16%) as a pale yellow oil. 1H NMR δ: 6.97-6.94 (m, H2" and H6"), 6.81 (d, J 8.0 Hz H5"), 6.78 (dd, J 7.9 Hz, 15.8 Hz, H1'), 6.69 (s, H9), 6.65 (s, H6), 6.34 (d, J 15.8 Hz, H2'), 4.12-4.06 (m, H1), 3.91 (s, OCH3), 3.88 (s, OCH3), 3.87 (s, OCH3), 3.83 (s, OCH3), 3.62 (d, J 6.2 Hz, H2); 3.61 (CO2CH3), 3.36-3.28 (m, H4), 3.10-3.02 (m, H4), 2.91-2.84 (m, H5), 2.76-2.70 (m, H5), 2.51 (s, NCH3); 13C NMR δ: 172.73 (COO), 149.60 (C7A), 149.32 (C8A), 147.98 (C3"A), 147.55 (C4"A), 133.83 (C1"B), 133.22 (C5aB), 132.23 (C1'C), 131.10 (C9aB), 128.08 (C2'C), 119.99 (C2"D), 113.50 (C5"D), 112.73 (C6"D), 111.74 (C6D), 109.91 (C9D), 70.95 (C2), 56.91 (OCH3), 56.59 (3OCH3), 53.53 (C4), 51.94 (CO2CH3), 50.92 (C1), 45.79 (NCH3), 34.90 (C5); MS
m/z: 441 (M+, 37%; Calcd. for C_{25}H_{31}NO_{6} 441.215, found 441.215), 382 (100), 309 (10), 206 (18), 189 (11), 151 (36).

3-Ethoxycarbonyl-2-(3,4-dimethoxy)phenyl-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-alisoquinoline 90

The preparation of 88c described above afforded the pyrrolo[2,1-]

alisoquinoline 90 (0.007 g, 4%) as a pale yellow oil. \(^1\)H NMR \(\delta\): 7.06 (s, H10), 7.01-6.98 (m, H2' and H6'), 6.88 (d, \(J = 8.3\) Hz, H5'), 6.75 (s, H7), 6.45 (s, H1), 4.61 (t, H5), 4.16 (q, CH\(_2\) of Et), 3.92 (s, 3OCH\(_3\)), 3.90 (s, OCH\(_3\)), 3.05 (t, H6), 1.11 (t, CH\(_3\) of Et); \(^1\)C NMR \(\delta\): 162.20 (C00), 149.47 (C8A), 148.94 (C9A), 148.62 (C31A and C41A), 147.41 (C4'A), 135.57 (C2aB), 135.00 (C3aB), 130.35 (C1'C), 125.46 (C10bB), 122.48 (C1), 121.38 (C6aB), 118.83 (C10aB), 113.88 (C7C), 111.59 (C10C), 111.04 (C2'C), 107.49 (C5'C), 106.57 (C6'C), 60.44 (CH\(_2\) of Et), 56.71 (4OCH\(_3\)), 43.54 (C5), 29.35 (C6), 14.77 (CH\(_3\) of Et); MS m/z: 437 (M+, 100%; Calcd. for C_{25}H_{27}NO_{6} 437.1837, found 437.184), 422 (15), 364 (8), 218 (8), 204 (6); IR (thin film from CH\(_2\)Cl\(_2\)): 1684, 1504, 1418, 1265, 1134, 1055, 1028 cm\(^{-1}\).

2-Ethoxycarbonylmethyl-6,7-dimethoxy-1-ethynyl-2-methyl-1,2,3,4-tetrahydrossoquinolinium Bromide 91

The reaction of the base 71 (1.515 g, 6.551 mmol) with ethyl bromoacetate (1.81 g, 10.8 mmol) in dry butanone (5 ml) at 50°C for 3 h. afforded a solid which was collected, after aging at 5°C for 1 h., to give a mixture (trans:cis=78:22) of the B-ring diastereomers of the 2-ethoxycarbonylmethylisoquinolinium salt 91 (2.172 g, 83%) as an off-white powder. trans diastereomer \(^1\)H NMR \(\delta\): 6.94 (d, \(J = 1.7\) Hz, H1), 6.90 (s, ArH), 6.75 (s, ArH), 5.14 (q, NCH\(_2\)CO), 4.71-4.62 (m, H3), 4.40-4.34 (m, H3), 4.29 (q, CH\(_2\) of Et), 3.89 (s, OCH\(_3\)), 3.88 (s, OCH\(_3\)), 3.59 (s, NCH\(_3\)), 3.40 (d, \(J = 2.2\) Hz, H2', 3.28-3.10 (m, H4), 1.32 (s, CH\(_3\)); \(^1\)C NMR \(\delta\): 165.13 (COO), 150.69 (C6A), 149.40 (C7A), 120.92 (C4aB), 118.58 (C8aB), 111.51 (C5'C), 110.82 (C8'C), 84.42 (C1), 74.52 (C1'), 64.55 (C2'), 63.55 (CH\(_2\) of Et), 59.31 (NCH\(_2\)CO), 56.60
(2OCH3), 55.94 (C3), 46.07 (NCH3), 24.08 (C4), 14.27 (CH3 of Et); cis
diastereomer (assignable signals) 1H NMR δ: 6.80 (s, ArH), 6.57 (s, H1), 3.79 (s, NCH3); 13C NMR δ 84.56 (C1), 64.33 (C2'), 46.75 (NCH3), 23.75 (C4).

Ethyl 7,8-Dimethoxy-1-ethynyl-3-methyl-2,3,4,5-tetrahydro-1H-
3-benzazepine-4-carboxylate 92

(i) To the salt 91 (0.323 g, 0.811) in refluxing dry acetonitrile (10 ml) was added
DBU (0.160 g, 1.05 mmol). The mixture was refluxed for 1 h. Concentration and
then purification of the residue by column chromatography on alumina with
dichloromethane/20% light petroleum afforded a yellow oil (0.090 g, 35%) which
was further purified by preparative reverse phase HPLC with H2O/44% acetonitrile
to give:

(a) at 15.9 min, the 3-benzazepine 92 (0.018 g, 7%) as a yellow oil. 1H NMR δ: 6.89
(s, ArH), 6.64 (s, ArH), 4.34 (dd, J 2.6 Hz, 7.0 Hz, H1), 4.11 (q, CH2 of Et), 3.86 (s, 2OCH3), 3.62 (d, J 6.9 Hz, H2), 3.25-3.20 (m, 2H), 2.83-2.72 (m, 2H), 2.53 (s, NCH3), 2.43 (d, J 2.6 Hz, CH3), 1.22 (t, CH3 of Et); 13C NMR δ: 171.26 (COO),
148.23 (C7A), 147.62 (C8A), 133.58 (C5aB), 128.25 (C9aB), 113.48 (C6C), 113.15
(C9C), 83.25 (C1'), 73.66 (C2D), 69.45 (C2'D), 60.97 (CH2 of Et), 56.63 (OCH3),
56.53 (OCH3), 51.45 (C4), 46.47 (NCH3E), 39.99 (C1E), 34.60 (C5), 15.03 (CH3 of
Et); MS m/z: 317 (M+, 56%; Calcd. for C18H23N04 317.1627, found 317.1633),
302 (31), 288 (9), 244 (100), 228 (11), 201 (21), 115 (14).

(b) at 18.2 min, compound 93 (0.018 g, 7%).

(c) at 29.1 min, compound 94 (0.007 g, 3%).

(ii) To 91 (0.534 g, 1.34 mmol) suspended in dry acetonitrile (5 ml) at 0°C was
added DBU (0.35 g, 2.3 mmol). The mixture was stirred for 80 min. while allowed
to warm to room temperature. Water (10 ml) and dichloromethane (15 ml) were then
added. The layers were partitioned and the aqueous layer was extracted with further
dichloromethane (2 x 5 ml). Drying and then concentration of the organic extracts
afforded a dark oil (0.099 g) in which no rearrangement products were detected by t.l.c. or $^1$H NMR analysis.

1-Ethoxycarbonyl-6,7-dimethoxy-1-ethynyl-2-methyl-1,2,3,4-tetrahydroisoquinoline 93

The preparation of 92 described above afforded the 1-ethoxycarbonylmethyl-isoquinoline 93 (0.018 g) as a yellow oil. $^1$H NMR (d$_6$-benzene) $\delta$: 7.04 (s, ArH), 6.31 (s, ArH), 3.92-3.74 (m, CH$_2$ of Et), 3.49 (s, OCH$_3$), 3.39 (s, OCH$_3$), 3.26 (d, J 14.0 Hz, H of CH$_2$COO), 3.13 (d, J 13.9 Hz, H of CH$_2$COO), 2.98-2.83 (m, H3 and H4), 2.62 (s, NCH$_3$), 2.60-2.55 (m, H3), 2.30-2.25 (m, H4), 2.20 (s, H$_2'$), 0.78 (t, CH$_3$ of Et); $^{13}$C NMR (d$_6$-benzene) $\delta$: 169.01 (COO), 149.85 (C6A), 149.38 (C7A), 130.96 (C4aB), 129.01 (C8aB), 112.77 (C5C), 112.49 (C8C), 84.38 (C1'), 75.40 (C2'), 61.14 (C1), 60.40 (CH$_2$ of Et), 56.60 (OCH$_3$), 56.15 (OCH$_3$), 50.12 (C3), 46.78 (CH$_2$CO$_2$), 40.91 (NCH$_3$), 30.28 (C4), 14.63 (CH$_3$ of Et); MS m/z: 317 (M$^+$, 2%; Calcd. for C$_{18}$H$_{23}$N$_2$O$_4$ 317.1627, found 317.1649), 291 (3), 244 (3), 230 (100), 214 (8), 115 (6).

1-[E-3-Ethoxycarbonyl-Z-2-propenylidene]-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline 94

The preparation of 92 described above afforded an intensely yellow coloured oil tentatively attributed to the isoquinoline 94 (0.007 g). $^1$H NMR $\delta$: 7.97 (dd, J 12.1 Hz, 14.5 Hz, H2'), 7.15 (s, ArH), 6.68 (s, ArH), 5.57 (d, J 14.5 Hz, H3' A), 5.37 (d, J 12.1 Hz, H1' A), 4.13 (q, CH$_2$ of Et), 3.92 (s, 2OCH$_3$), 3.35 (t, H3), 3.11 (s, CH$_3$), 2.75 (t, H4), 1.24 (t, CH$_3$ of Et); $^{13}$C NMR $\delta$: 169.60 (COO), 152.23 (C3' A), 150.32 (C7 A), 147.50 (C6 A), 147.09 (C1'), 131.12 (C8a B), 123.56 (C4a B), 114.78 (C2 C), 110.86 (C8 C), 108.46 (C5 C), 94.51 (C3'), 59.83 (CH$_2$ of Et), 56.86 (OCH$_3$), 56.67 (OCH$_3$), 51.01 (C3), 40.72 (NCH$_3$), 30.49 (C4), 15.27 (CH$_3$ of Et); MS m/z: 317 (M$^+$, 49%; Calcd. for C$_{18}$H$_{23}$N$_2$O$_4$ 317.1627, found 317.1624), 302 (11), 288 (6), 272 (31), 244 (100), 230 (60), 214 (20), 199 (12).
Attempted Preparation of 6,7-Dimethoxy-2-methyl-1-(1'-propynyl)-1,2,3,4-tetrahydroisoquinoline 96

(i) A solution of the 1-ethynyl base 71 (3.019 g, 13.05 mmol) in dry tetrahydrofuran (25 ml) was added dropwise to a suspension of sodium amide (0.584 g, 90% technical grade, ≥ 13.5 mmol) in dry tetrahydrofuran (25 ml) at -78°C under nitrogen. The mixture was allowed to warm to room temperature with stirring over 1 h. then the resultant solution was cooled to -78°C and iodomethane (1.86 g, 13.2 mmol) was added dropwise. The solution was maintained at -70°C for 15 min. then allowed to warm to room temperature and stirred for 2 h. with the deposition of a tan solid. Ammonium chloride (0.5 g) and water (30 ml) were added cautiously and the solution was extracted with diethyl ether (4 x 20 ml). The ether extracts were combined and washed with water (2 x 10 ml) then saturated brine (10 ml), and then dried and passed through a silica plug. Concentration afforded 71 (1.501 g, 50%). The original aqueous layer was then concentrated and extracted with chloroform (3 x 25 ml). Concentration of the chloroform extracts afforded a dark powder (2.326 g) which was taken up in hot methanol. Ethyl acetate was added and the mother liquor was decanted from the resultant dark oil. The concentration of the mother liquor gave a tan powder tentatively identified as crude 6,7-Dimethoxy-1,2,2-trimethyl-1-(1'-propynyl)-1,2,3,4-tetrahydro-isoquinolinium iodide 97 (1.424 g). ¹H NMR δ: 6.93 (s, ArH), 6.70 (s, ArH), 4.50-4.42 (s, H), 4.13-4.01 (m, H), 3.91 (s, OCH₃), 3.89 (s, OCH₃), 3.56 (s, NCH₃), 3.47 (s, NCH₃), 3.32-3.21 (m, 2H), 2.06 (s, CH₃), 2.05 (s, CH₃); ¹³C NMR δ: 149.95 (C₆A), 148.87 (C₇A), 125.46 (C₈aB), 111.35 (C₅C), 110.00 (C₈C), 90.07 (C₁D), 74.42 (C₁¹D), 71.75 (C₂¹D), 56.51 (OCH₃), 56.23-(OCH₃), 56.06-(C₃), 49.81-(NCH₃), 49.01-(NCH₃), 29.01 (CH₃), 23.80 (C₄), 4.50 (C₃'); MS (LSIMS) m/z: 274 (M-I⁺, 100%), 258 (5), 246 (5), 232 (6), 220 (9).

(ii) Compound 71 (0.964 g, 4.17 mmol) was added to a suspension of sodium amide (0.197 g, 90% technical grade, ≥ 4.54 mmol) in dry tetrahydrofuran (25 ml) at -78°C under nitrogen. The mixture was allowed to warm to 0°C with stirring over 1 h. then
stirred at this temperature for 8 h. The brown solution was cooled to -78°C and a solution of iodomethane (0.604 g, 4.28 mmol) in dry tetrahydrofuran (20 ml) was added dropwise over 1 h. The solution was then stirred at 25°C for 24 h. Work up as for (i) gave, from the ether solution, 71 (0.342 g, 35%).

3-Ethoxycarbonylmethyl-8,9-dimethoxy-3-methyl-5-trimethylsilyl-1,2,3,4-tetrahydro-3-benzazocinium Bromide 98

(i) A solution of the base 70c (0.506 g, 1.66 mmol) and ethyl bromoacetate (0.75 g, 4.5 mmol) in dry butanone (8 ml) under nitrogen was stirred for 24 h. at 60-70°C then aged at 0°C for 12 h. Collection of the precipitate and recrystallisation of this material from dichloromethane/butanone afforded the 3-benzazocinium salt 98 (0.254 g, 32%) as a pale yellow powder with m.p. 140-142°C. 1H NMR δ: 7.25 (s, H6), 6.64 (s, H10), 6.39 (s, H7), 5.08 (d, J 17.0 Hz, H of NCH2CO), 4.73 (d, J 17.0 Hz, H of NCH2CO), 4.40-4.28 (m, H2), 4.13 (d, J 13.0 Hz, H4), 3.79 (d, J 13.3 Hz, H4), 4.02 (m, CH2 of Et), 3.71 (s, OCH3), 3.68-3.59 (m, H2), 3.66 (s, OCH3), 3.37 (s, NCH3), 2.95-2.87 (m, H1), 2.78-2.69 (m, H1), 1.07 (t, CH3 of Et), 0.15 (s, Si(CH3)3); 13C NMR δ: 164.93 (COO), 151.74 (C6), 150.21 (C8A), 148.10 (C9A), 132.85 (C5), 129.09 (C6aB), 127.56 (C10aB), 112.92 (C7C), 110.89 (C10C), 64.12 (CH2 of EtD), 63.83 (NCH2CO), 62.82 (C4D), 62.38 (C2D), 56.31 (OCH3), 56.19 (OCH3), 48.26 (NCH3), 28.25 (C1), 14.10 (CH3 of Et), 0.05 (Si(CH3)3); Anal. Calcd for C21H34NO4SiBr: C, 53.38; H, 7.25; N, 2.97%, found: C, 53.30; H, 7.30; N, 3.06%.

(ii) A solution of the base 70c (0.498 g, 1.63 mmol) and ethyl bromoacetate (0.75 g, 4.5 mmol) in dry butanone (2.5 ml) under nitrogen was stirred for 48 h. at room temperature. Concentration of the solution and trituration of the residue with diethyl ether (3 x 20 ml) afforded a 60:40 mixture (0.125 g, 16%) of 98 and 72c. The diethyl ether washings contained unchanged 70c.

(iii) A solution of the salt 72c (0.196 g, 0.415 mmol) in dry butanone (6 ml) was refluxed for 24 h. Concentration and then 1H NMR spectral analysis of the residue
indicated a 2:1:1 mixture of 72c, 98, and a component attributed to the previously unobserved B-ring diastereomer of 72c with the following characteristic NMR signals: $^1\text{H NMR } \delta$: 5.44 (s, H1), 3.30 (s, NCH$_3$), -0.01 (s, Si(CH$_3$)$_3$); $^{13}\text{C NMR } \delta$: 142.62 (C2'), 46.99 (NCH$_3$).

$N$-{[2-[4,5-Dimethoxy-2-(4-ethoxycarbonyl-4-iodo-1(E)-buteny]phenyl]ethyl]}-$N,N,N$-trimethylammonium iodide 100

(i) Treatment of 52a (0.246 g, 0.771 mmol) with iodomethane (0.156 g, 3.47 mmol) in dry butanone (2 ml) at reflux for 3 h. gave the precipitation of a solid which, after cooling, was collected and recrystallised from butanone to afford the title compound 100 (0.170 g, 37%) as a colourless powder with m.p. 167-169°C. $^1\text{H NMR } \delta$: 6.95 (s, ArH), 6.73 (d, $J$ 15.6 Hz, H1"), 6.63 (s, ArH), 6.08-5.98 (m, H2"), 4.79 (dd, $J$ 3.9 Hz, 10.8 Hz, H4"), 4.26 (q, CH$_2$ of Et), 3.91 (s, OCH$_3$), 3.88 (s, OCH$_3$), 3.67 (s, 3NCH$_3$), 3.30-3.23 (m, 3H), 3.18-3.13 (m, 2H), 2.95-2.84 (m, H), 1.22 (t, CH$_3$ of Et); $^{13}\text{C NMR } \delta$: 167.40 (COO), 149.76 (C4'A), 148.81 (C5'A), 133.13 (C1"B), 131.60 (C1'C), 127.47 (C2'C), 120.74 (C2"B), 113.31 (C3'D), 109.65 (C6'D), 74.51 (C4"), 63.87 (CH$_2$ of Et), 56.93 (OCH$_3$), 56.60 (OCH$_3$), 53.92 (3NCH$_3$), 37.76 (C1), 31.96 (C2), 14.78 (CH$_3$ of Et), 6.41 (C3"); MS (LSIMS) m/z: 476 ([M-I]$^+$, 100%), 417 (26), 366 (11), 348 (7); IR (thin film from CHCl$_3$): 1740, 1512, 1271, 1215, 731 cm$^{-1}$.

(ii) The reaction of 52a (0.183 g, 0.573 mmol) in iodomethane (2.0 ml, 32 mmol) at room temperature under nitrogen over 16 h. gave a solid which was collected and recrystallised three times from dichloromethane/toluene to afford 100 (0.107 g, 31%) as a colourless powder with m.p. 163-164°C. Anal. Calcd for C$_{20}$H$_{31}$NO$_4$I$_2$: C, 39.82; H, 5.18; N, 2.32%; found: C, 40.23; H, 5.22; N, 2.47%.
Ethyl 9,10-Dimethoxy-3-methyl-2,3,4,5,6,7-hexahydro-1H-3-benzazonine-4-carboxylate 101a

Compound 52a (0.178 g, 0.558 mmol, E/Z=19) was refluxed in ethanol (15 ml) under hydrogen at atmospheric pressure with 5% Pd-C (0.025 g) for 3 h. Concentration and then purification of the residue by p.t.l.c. on silica with dichloromethane/3% ethanol afforded:

(a) at Rf 0.95, the hexahydro-3-benzazonine 101a (0.102 g, 66% from unrecovered 52a) as a colourless oil. \(^1\)H NMR δ: 6.63 (s, ArH), 6.54 (s, ArH), 4.08 (q, CH₂ of Et), 3.85 (s, 20CH₃), 3.55-3.45 (m, H), 3.23 (dd, J 2.8 Hz, 12.1 Hz, H₄), 2.87-2.73 (m, 3H), 2.61-2.57 (m, H), 2.57 (s, NCH₃), 2.48-2.40 (m, H), 1.83-1.76 (m, 2H), 1.54-1.47 (m, H), 1.22 (t, CH₃ of Et), 1.18-1.11 (m, H); \(^13\)C NMR δ: 174.07 (COO), 147.90 (C9A), 147.23 (Cl0A), 135.00 (C7aB), 133.24 (C11aB), 114.15 (C8C), 113.19 (C11C), 68.75 (C4), 60.41 (CH₂ of Et), 56.50 (20CH₃), 53.40 (C2), 44.05 (NCH₃), 36.78 (C7D), 32.08 (Cl1D), 31.91 (C5D), 26.27 (C6D), 15.06 (CH₃ of Et); MS m/z: 321 (M⁺, 2%); Calcd. for C₁₈H₂₇N₂O₄ 321.1939, found 321.1948), 248 (100), 205 (13), 164 (4), 124 (5).

(b) at Rf 0.88, compound Z-52a (0.024 g).

Ethyl 9,10-Dimethoxy-3-methyl-6-phenyl-2,3,4,5,6,7-hexahydro-1H-3-benzazonine-4-carboxylate 101b

A 38:54:8 mixture of the isomers E-75b, Z-75b, and 76b (0.200 g, 0.504 mmol) was refluxed in ethanol (15 ml) under hydrogen at atmospheric pressure with 5% Pd-C (0.030 g) for 3 h. and was then concentrated. The residue was passed through an alumina plug with dichloromethane/5% light petroleum to give a colourless oil (0.143 g). Purification of a portion (0.067 g) of this oil by preparative reverse phase HPLC with acetonitrile/29% water gave:

(a) after 30.0 min., unchanged Z-75b (0.011 g).

(b) after 37.5 min., the hexahydro-3-benzazonine 101b (0.029 g) as a colourless oil. \(^1\)H NMR δ: 7.39-7.36 (m, 4ArH'), 7.27-7.25 (m, ArH'), 6.70 (s, ArH), 6.59 (s, ArH),
4.15 (t, H7), 4.13 (q, CH2 of Et), 3.87 (s, OCH3), 3.86 (s, OCH3), 3.18-3.12 (m, H6), 3.02-2.97 (m, H4 and H1), 2.81-2.78 (m, H2), 2.72 (dd, J 4.3 Hz, 12.3 Hz, H7), 2.55 (s, NCH3), 2.54-2.50 (m, H1), 1.67-1.60 (m, H5), 1.15 (t, CH3 of Et); 13C NMR δ: 174.23 (COO), 148.09 (C9A), 147.63 (C10A), 145.31 (C1'B), 134.93 (C7aB), 132.98 (C11aB), 129.05 (2C'), 128.73 (2C'), 126.93 (C'), 114.41 (C8C), 113.49 (C11C), 63.07 (C4), 60.47 (CH2 of Et), 56.61 (2OCH3), 54.09 (C2), 46.91 (C6), 43.86 (NCH3), 38.86 (C7D), 36.13 (C1D), 33.02 (C5), 15.09 (CH3 of Et); MS m/z: 397 (M+, 3%; Calcd. for C24H31N04 397.2253, found 397.2281), 324 (100), 267 (9), 220 (4), 165 (5), 91 (6), 70 (6).

(c) after 42.5 min., an unidentified isomer of 101b as a colourless oil (0.008 g). 1H NMR δ: 7.37-7.26 (m, 2ArH'), 7.22-7.19 (m, ArH'), 7.07-7.05 (m, 2ArH'), 6.54 (s, ArH), 5.52 (s, ArH), 4.14-4.00 (m, CH2 of Et and H), 3.83 (s, OCH3), 3.40-3.34 (m, OCH3 and H), 3.28-3.20 (m, H), 3.04-2.99 (m, H), 2.85-2.77 (m, 3H), 2.66 (s, NCH3), 2.55-2.50 (m, H), 1.86-1.81 (m, H), 1.66-1.57 (m, H), 1.23 (t, CH3 of Et); MS m/z: 397 (M+, 7%; Calcd. for C24H31N04 397.2253, found 397.2247), 324 (100), 267 (10), 220 (5), 165 (8), 91 (12), 70 (5).

Ethyl 9,10-Dimethoxy-3,5,5-trimethyl-2,3,4,5,6,7-hexahydro-1H-3-benzazonine-4-carboxylate 101c

A 58:37:5 mixture of the isomers E-87a, trans-88a, and cis-88a (0.259 g, 0.772 mmol) was refluxed in ethanol (15 ml) under hydrogen at atmospheric pressure with 5% Pd-C (0.030 g) for 3 h. and was then concentrated. The residue was passed through an alumina plug with dichloromethane/5% light petroleum to give a pale yellow oil (0.236 g). Purification of the oil by preparative reverse phase HPLC with acetonitrile/36% water gave:

(a) after 17.2 min., unchanged trans-88a (0.057 g).

(b) after 34.7 min., the hexahydro-3-benzazonine 101c (0.088 g, 58% based on original E-87a) as a colourless oil. 1H NMR δ: 6.62 (s, ArH), 6.60 (s, ArH), 4.18 (q, CH2 of Et), 3.85 (s, 2OCH3), 3.60 (s, H4), 3.09-3.04 (m, H1 and H2), 2.50-2.42 (m,
Ethyl 9,10-Dimethoxy-3-methyl-6-methylene-2,3,4,5,6,7-hexahydro-1H-3-benzazonine-4-carboxylate 102

A 66:34 mixture of E-75a and Z-75a (0.185 g, 0.555 mmol) was refluxed in ethanol (10 ml) under hydrogen at atmospheric pressure with 5% Pd-C (0.030 g) for 2.5 h. Concentration and then purification of the residue by p.t.l.c. on silica with dichloromethane/5% methanol afforded, at Rf 0.55, compound 103 (0.007 g) and, at Rf 0.92, a mixture (0.131 g) which was further purified by p.t.l.c. on silica with dichloromethane to give:

(a) at Rf 0.12, a mixture with predominantly Z-75a (0.044 g).

(b) at Rf 0.23, a mixture (0.054 g) attributed to compounds 101d and 102.

Purification by preparative reverse phase HPLC with acetonitrile/20% water gave, after 22.15 min., the 6-methylene-3-benzazonine 102 (0.030 g) as a colourless oil.

\(^1\)H NMR 8: 6.63 (s, ArH), 6.55 (s, ArH), 4.99 (s, H of =CH\(_2\)), 4.79 (s, H of =CH\(_2\)), 4.20 (d, J 13.2 Hz, H7), 4.10 (q, CH\(_2\) of Et), 3.85 (s, OCH\(_3\)), 3.83 (s, OCH\(_3\)), 3.32-2.25 (H4 and H7), 2.89-2.80 (m, 3H), 2.55 (s, NCH\(_3\)), 2.51-2.45 (m, H), 2.18 (dd, J 3.2 Hz, 14.0 Hz, H5), 1.90 (dd, J 13.1 Hz, 14.0 Hz), 1.24 (t, CH\(_3\) of Et); \(^{13}\)C NMR 8: 173.50 (CO), 150.65 (C6), 147.81 (C9\(_A\)), 147.69 (C10\(_A\)), 134.19 (C7\(_A\)), 131.60 (C11\(_A\)), 114.12 (C8\(_C\)), 113.51 (C11\(_C\)), 112.60 (NCH\(_3\)), 67.92 (C4), 60.64 (CH\(_2\) of Et), 56.50 (OCH\(_3\)), 53.63 (C2), 43.74 (NCH\(_3\)), 41.91 (C7\(_D\)), 36.65 (C1\(_D\)), 36.05 (C5\(_D\)), 15.15 (CH\(_3\) of Et); MS m/z: 333 (M\(^+\), 12%; Calcd. for C\(_{19}\)H\(_{27}\)NO\(_4\) 333.1940, found 333.1950), 260 (100), 217 (13), 203 (4), 168 (3), 130 (5).
Ethyl 9,10-Dimethoxy-3,6-dimethyl-2,3,4,7-tetrahydro-1H-3-benzazonine-4-carboxylate 103

The synthesis described for the preparation of 102 afforded the 2,3,4,7-tetrahydro-3-benzazonine 103 (0.007 g) as a colourless oil. ¹H NMR δ: 6.70 (s, ArH), 6.55 (s, ArH), 5.21 (d, J 9.8 Hz, H5), 4.50 (d, J 9.9 Hz, H4), 4.23 (q, CH₂ of Et), 4.18 (d, J 13.2 Hz, H7), 3.87 (s, OCH₃), 3.84 (s, OCH₃), 3.14-3.08 (m, 2H), 2.97-2.91 (m, H), 2.75 (d, J 13.3 Hz, H7), 2.49-2.23 (m, H), 2.39 (s, NCH₃), 1.82 (d, J 1.2 Hz, CH₃), 1.32 (t, CH₃ of Et); ¹³C NMR δ: 173.79 (CO), 148.10 (C9A), 147.64 (C10A), 140.34 (C6), 134.00 (C7aB), 129.15 (C11aB), 119.88 (C5), 115.54 (C8C), 114.14 (C11C), 63.89 (C4), 61.89 (CH₂ of Et), 56.80 (OCH₃), 56.58 (OCH₃), 54.70 (C2), 40.63 (NCH₃), 37.42 (C7D), 26.42 (C1D), 24.15 (CH₃), 14.95 (CH₃ of Et); MS m/z: 333 (M⁺, 28%); Calcd. for C₁₉H₂₇N⁰₄ 333.1940, found 333.1917, 290 (30), 260 (100), 246 (13), 217 (47), 206 (31), 202 (23).

Ethyl 9,10-Dimethoxy-2,3,4,5,6,7-hexahydro-1H-3-benzazonine-4-carboxylate 104b

(i) Compound 52b (0.193 g) was refluxed in ethanol (10 ml) under hydrogen at atmospheric pressure with 5% Pd-C (0.020 g) for 16 h. Samples analysed by GC-MS after 1.5 h., 3.5 h. and 16 h. showed mixtures attributed to 52b, 104a, and 104b in the ratios 8:88:4, 1:88:11, and 0:77:23.

(ii) Compound 105 (0.101 g, 0.233 mmol) was stirred in methanol (5 ml) at room temperature with 5% Pd-C (0.015 g) under hydrogen for 3 h. The solution was filtered and then concentrated. Treatment of the residue with 1M aqueous sodium hydroxide (5 ml) and extraction of the aqueous mixture with diethyl ether (3 x 5 ml) afforded, after drying and then concentration of the ether extracts, the hexahydro-3-benzazonine 104b (0.051 g, 71%) as a colourless oil. ¹H NMR δ: 6.63 (s, ArH), 6.57 (s, ArH), 4.13 (q, CH₂ of Et), 3.85 (s, 2OCH₃), 3.83-3.74 (m, H), 3.45 (dd, J 4.4 Hz, 7.9 Hz, H4), 2.98-2.63 (m, 5H), 1.97 (bs, NH), 1.81-1.69 (m, 2H), 1.62-1.48 (m, 2H), 1.24 (t, CH₃ of Et); ¹³C NMR δ: 175.53 (COO), 148.05 (C9A), 147.48 (C10A), 134.43 (C7aB), 133.15 (C11aB), 113.68 (C8C), 112.94 (C11C), 61.19 (CH₂ of Et),
60.82 (C4), 56.45 (2OCH3), 48.02 (C2), 37.83 (C7D), 31.77 (C1D), 28.66 (C5D),
27.54 (C6D), 14.85 (CH3 of Et); MS m/z: 307 (M+, 20%; Calcd. for C17H25N04
307.1782, found 307.1787), 234 (100), 217 (11), 165 (17), 117 (7).

(iii) Compound 105 (0.101 g, 0.233 mmol) was stirred in methanol (5 ml) at 0°C
with 5% Pd-C under hydrogen. Samples analysed by GC-MS after 10 min., 30 min.,
1 h. and 2 h. showed mixtures attributed to 52b, 104a, and 104b in the ratios 46:53:1,
0:84:16, 0:7:93, and 0:0:100.

3-Benzyl-9,10-Dimethoxy-4-ethoxycarbonyl-2,3,4,5-tetrahydro-1H-
3-benzazoninium Hydrochloride 105

Hydrogen chloride gas from a Kipps' apparatus was passed through a solution
of 52b (1.123 g, 2.839 mmol) in diethyl ether (20 ml) for 5 min. The precipitate was
collected and recrystallised from methanol/diethyl ether to give the title compound
105 (0.613 g, 50%) as fine colourless prisms with m.p. 102-103°C. 1H NMR δ:
11.70 (s, NH), 8.08 (s, 2ArH'), 7.49 (bs, 3ArH'), 6.71 (s, ArH), 6.34 (s, ArH), 5.51-
5.42 (m, H6), 5.03-4.98 (m, H7), 4.45-4.29 (m, CH2 of Et and NCH2), 3.89 (s,
OCH3), 3.75 (s, OCH3), 3.30-3.11 (m, 3H), 1.78-1.72 (m, H), 1.36 (t, CH3 of Et);
13C NMR δ: 167.66 (COO), 148.15 (C9A), 147.61 (C10A), 137.82 (C6B), 133.26
(C7 and C4'B), 132.80 (C7aC), 130.68 (2C'), 130.00 (C11aC), 129.61 (2C'), 128.77
(C1C), 113.37 (C8D), 110.22 (C11D), 69.05 (C4), 63.51 (CH2 of Et), 62.56 (NCH2),
58.09 (C2), 56.48 (2OCH3), 33.40 (C1E), 33.16 (C5E), 14.60 (CH3 of Et).

7,8-Dimethoxy-5-isopropionitrile-3-methyl-2,3-dihydro-1H-3-benzazepine 106

A pale yellow oil (0.265 g) containing 3 components in the ratio 10.0:1.0:1.5,
with 63a the major component (from the rearrangement of 62a in refluxing
acetonitrile), was refluxed in dry butyronitrile (20 ml) for 66 h. Concentration and
then purification of the residue by passage through an alumina plug with
dichloromethane/25% light petroleum afforded an oil (109 mg). A portion of the oil
(0.074 mg) was purified by preparative reverse phase HPLC with acetonitrile/41%
water to give the 5-isopropionitrile-3-benzazepine 106 (0.037 g) as a yellow oil. \[1^H\]

NMR δ: 6.69 (s, ArH), 6.57 (s, ArH), 6.31 (s, H4), 3.87 (s, OCH3), 3.86 (s, OCH3),
3.78 (q, H2'), 3.41 (t, H2), 2.88 (t, H1), 2.86 (s, NCH3), 1.50 (d, J 7.1 Hz, CH3); \[13^C\]
NMR δ: 148.03 (C7A), 146.88 (C8A), 137.19 (C4), 133.89 (C9aB), 129.74 (C5aB),
123.95 (CN), 113.09 (C6D), 109.23 (C9D), 102.16 (C5C), 57.54 (C2), 56.72
(OCH3), 56.55 (OCH3), 45.64 (NCH3), 36.13 (C1), 31.55 (C2'), 21.23 (C3'); MS
m/z: 272 (M+, 75%; Calcd. for C16H20N202 272.1524, found 272.1517), 257 (100),
243 (7), 230 (3), 218 (10), 199 (4), 175 (4).

**Attempted Preparation of E-9,10-Dimethoxy-3-methyl-2,3,4,5-tetrahydro-1H-
3-benzazonine-4-methanol 107**

A suspension of lithium aluminium hydride (0.289 g, 7.61 mmol) in dry
diethyl ether (6 ml) was refluxed for 10 min. and then a solution of 52a (1.029 g,
3.222 mmol, E/Z = 19) in diethyl ether (10 ml) was added dropwise to maintain
reflux. Substantial solid formed. After refluxing for 30 min. the mixture was stirred
for 1 h. at 25°C and then cooled and water was added cautiously until the hydrogen
evolution ceased. Diethyl ether (10 ml) was added and the solution was filtered. The
solid was extracted with further diethyl ether (2 x 10 ml) and then the ether solutions
were combined and washed with water (5 ml), and then saturated brine (5 ml).
Drying and then concentration of the extracts afforded a colourless solid tentatively
attributed to 107 (0.864 g, 95%). \[1^H\]NMR (CDCl3 at 60°C) δ: 6.72 (s, ArH), 6.63 (s,
ArH), 6.32 (bs, H7), 5.53 (bs, H6), 3.82 (s, OCH3), 3.81 (s, OCH3), 3.46 (bs, 3H),
3.11 (bs, 2H), 2.70 (bs, 2H), 2.55 (dd, J 15.8 Hz, 7.8 Hz, H), 2.44 (s, NCH3), 2.32-
2.05 (m, 2H).

Purification of a portion (0.260 g) of the above solid by p.t.l.c. on alumina
with ethyl acetate/5% hexane gave:

(i) at Rf 0.92, the pyrrolidine 108b (0.113 g, 36%).

(ii) at Rf 0.40, the pyrrolidine 108a (0.034 g, 12%).
5-(2-Ethenyl-4,5-dimethoxyphenyl)-1-methyl-2-pyrrolidinemethanol 108a

The procedure described for the preparation of 107 afforded the title compound 108a (0.034 g, 12%) as a colourless oil. \(^1\)H NMR \(\delta: 7.08 \text{ (dd, } J 17.3 \text{ Hz, } 10.9 \text{ Hz, } H1''), 6.99 \text{ (s, } ArH'), 6.83 \text{ (s, } ArH''), 5.51 \text{ (dd, } J 17.3 \text{ Hz, } 1.3 \text{ Hz, } H2''), 5.22 \text{ (dd, } J 10.9 \text{ Hz, } 1.3 \text{ Hz, } H2''), 4.36 \text{ (t, } H5), 3.88 \text{ (s, OCH}_3), 3.86 \text{ (s, OCH}_3), 3.67 \text{ (t, CH}_2 \text{ of CH}_2\text{OH}), 3.30-3.26 \text{ (m, } H2), 2.23 \text{ (s, NCH}_3), 2.29-2.11 \text{ (m, } 2H), 1.87-1.74 \text{ (m, } 2H); \(^1^3\)C NMR \(\delta: 149.52 \text{ (C4'A), 148.26 \text{ (C5'A), 134.84 \text{ (C1'), 133.73 \text{ (C1'B), 130.25 \text{ (C2'B), 114.72 \text{ (C2''), 110.20 \text{ (C3'C), 109.44 \text{ (C6'C), 65.04 \text{ (C5D), 63.35 \text{ (C2D), 62.74 \text{ (CH}_2\text{OH), 56.60 \text{ (OCH}_3), 56.48 \text{ (OCH}_3), 35.85 \text{ (NCH}_3), 32.98 \text{ (C4E), 27.60 \text{ (C3E); MS m/z: 277 (M+, 12%; Calcd. for C}_{16}H_{23}NO_3 277.1677, found 277.1669), 246 (100), 215 (13), 189 (32), 70 (30).}

5-(2-Ethenyl-4,5-dimethoxyphenyl)-1-methyl-2-pyrrolidinemethanol acetate 108b

The procedure described for the preparation of 107 afforded the title compound 108b (0.113 g, 36%) as a colourless oil. \(^1\)H NMR \(\delta: 7.05 \text{ (dd, } J 17.3 \text{ Hz, } 10.9 \text{ Hz, } H1''), 7.00 \text{ (s, } ArH'), 6.97 \text{ (s, } ArH''), 5.51 \text{ (dd, } J 17.3 \text{ Hz, } 1.3 \text{ Hz, } H2''), 5.20 \text{ (dd, } J 10.9 \text{ Hz, } 1.3 \text{ Hz, } H2''), 4.26 \text{ (dd, } J 11.2 \text{ Hz, } 4.9 \text{ Hz, H of CH}_2\text{OAc), 4.15-4.06 \text{ (m, H5 and H of CH}_2\text{OAc), 3.90 \text{ (s, } 2\text{OCH}_3), 3.59-3.53 \text{ (m, } H2), 2.32 \text{ (s, NCH}_3), 2.29-2.24 \text{ (m, } H), 2.12 \text{ (s, CH}_3), 2.10-2.01 \text{ (m, } H), 1.72-1.53 \text{ (m, } 2H); \(^1^3\)C NMR \(\delta: 171.51 \text{ (CO), 149.71 \text{ (C4'A), 148.05 \text{ (C5'A), 134.42 \text{ (C1'), 129.58 \text{ (C1' and C2'), 114.34 \text{ (C2''), 109.54 \text{ (C3'C), 109.16 \text{ (C6'C), 64.60 \text{ (CH}_2 \text{ of CH}_2\text{OAc), 63.10 \text{ (C5D), 61.68 \text{ (C2D), 56.43 \text{ (OCH}_3), 56.34 \text{ (OCH}_3), 35.43 \text{ (NCH}_3), 33.78 \text{ (C4E), 27.42 \text{ (C3E), 21.60 \text{ (CH}_3); MS m/z: 319 (M+, 17%; Calcd. for C}_{18}H_{25}NO_4 319.1783, found 317.1775), 246 (100), 215 (12), 189 (26), 70 (24).}
6.3 Experimental for Chapter Three

6.7-Dimethoxy-2-methyl-1-vinyl-1,2,3,4-tetrahydroisoquinoline N-oxide 123a

To 49a (2.116 g, 9.07 mmol) in dichloromethane (40 ml) at 0°C was added a solution of m-CPBA (1.9 g, 11 mmol) in dichloromethane (30 ml). The solution was allowed to warm to room temperature and stirred for 24 h. before the addition of 5% aqueous sodium bicarbonate (40 ml) and removal of the organic solvent in vacuo. The aqueous solution was washed with diethyl ether (3 x 15 ml) then made acidic to litmus with 3M aqueous hydrochloric acid and washed with further diethyl ether (3 x 15 ml). The solution was basified with saturated aqueous sodium bicarbonate then saturated with sodium chloride and extracted with chloroform (3 x 25 ml). Drying and then concentration of the organic extracts afforded a mixture (65:35) of the B-ring diastereomers of 1-vinyltetrahydroisoquinoline N-oxide 123a (1.647 g, 73%) as a tan hygroscopic solid. \(^1\)H NMR δ: 6.68 (s, H5), 6.55 (s, H8a), 6.60-6.51 (m, H4a), 6.48 (s, H8b), 5.93-5.81 (m, H1b), 5.67 (d, J 10.1 Hz, H2a), 5.57 (d, J 17.8 Hz, H2b), 5.52 (d, J 10.1 Hz, H2'c), 5.28 (d, J 16.8 Hz, H2h), 4.75 (d, J 9.0 Hz, H1h), 4.67 (d, J 7.5 Hz, H1h), 3.87 (s, OCH3), 3.73 (s, OCH3), 3.74-3.38 (m, 3H), 3.28 (s, NCH3a), 3.22 (s, NCH3b), 2.93-2.81 (m, H); \(^13\)C NMR δ: 149.31 (C6A), 148.38 (C7A), 134.51 and 134.03 (C1'), 124.33 and 124.56 (C2'), 123.68 (C4a and C8a), 111.57 (C5B), 111.67 and 111.14 (C8B), 78.41 and 77.95 (C1), 63.26 and 60.89 (C3), 58.13 and 57.23 (NCH3), 56.51 (2OCH3), 26.02 and 25.66 (C4); MS m/z: 249 (M+, 24%; Calcd. for C14H19NO3 249.136, found 249.135), 232 (7), 203 (12), 190 (100), 175 (43), 159 (24).

2-Benzyl-6,7-dimethoxy-1-vinyl-1,2,3,4-tetrahydroisoquinoline N-oxide 123b

To 49b (2.109 g, 6.817 mmol) in dichloromethane (40 ml) at 0°C was added a solution of m-CPBA (1.42 g, 8.26 mmol) in dichloromethane (30 ml). The solution was allowed to warm to room temperature and stirred for 24 h. before the addition of 5% aqueous sodium bicarbonate (40 ml) and removal of the organic solvent in
The aqueous solution was washed with diethyl ether (3 x 15 ml) then made acidic to litmus with 3M aqueous hydrochloric acid and washed with further diethyl ether (3 x 15 ml). The solution was basified with saturated aqueous sodium bicarbonate then saturated with sodium chloride and extracted with chloroform (3 x 25 ml). Drying and then concentration of the organic extracts afforded a mixture (81:19) of the B-ring diastereomers of 1-vinyltetrahydroisoquinoline N-oxide 123b (1.778 g, 80%) as a tan hygroscopic solid. 1H NMR δ: 7.57-7.26 (m, 5ArH"), 6.73-6.62 (m, H5 and H1a), 6.53 (s, H8a), 6.44 (s, H8b), 6.11-5.98 (m, H1b), 5.67 (d, J 10.4 Hz, H2a), 5.57 (d, J 10.3 Hz, H2b), 5.48 (d, J 10.1 Hz, H2b), 5.19 (d, J 17.5 Hz, H2a), 5.03 (d, J 9.1 Hz, H1b), 4.85 (d, J 6.5 Hz, H1a), 4.69-4.51 (m, NCH2Ph), 3.88 (s, OCH3a), 3.86 (s, OCH3b), 3.77 (s, OCH3a), 3.71 (s, OCH3), 3.73-3.32 (m, 3H), 2.99-2.74 (m, H); 13C NMR δ: 149.55 (C6A), 148.51 (C7A), 134.16-128.28 (6C", C1', C4a and C8a), 123.97 and 125.26 (C2'), 111.57 (C8B), 111.35 (C8b), 74.69 and 79.40 (C1), 71.46 and 70.21 (NCH2Ph), 59.21 and 57.17 (C3), 56.68 (2OCH3), 26.04 and 25.38 (C4).

Mixture of 6,7-Dimethoxy-2-methyl-1-propenyl-1,2,3,4-tetrahydroisoquinoline N-oxide isomers 123c

To a mixture (Z:E=3:1) of the 1-propenyl isomers of 81b (1.282 g, 5.18 mmol) in dichloromethane (25 ml) at 0°C was added a solution of m-CPBA (1.079 g, 6.27 mmol) in dichloromethane (25 ml). The solution was allowed to warm to room temperature and stirred for 20 h. before the addition of 5% aqueous sodium bicarbonate (25 ml) and removal of the organic solvent in vacuo. The aqueous solution was washed with diethyl ether (3 x 10 ml) then made acidic to litmus with 3M aqueous hydrochloric acid and washed with diethyl ether (3 x 10 ml). The solution was basified with saturated aqueous sodium bicarbonate then saturated with sodium chloride and extracted with chloroform (3 x 25 ml). Drying and then concentration of the organic extracts afforded a mixture (51:24:16:9) attributed to the two Z and two E B-ring diastereomers of 1-propenyltetrahydroisoquinoline N-oxide
123c (1.243 g, 91%) as a tan hygroscopic solid. 1H NMR characteristic peaks δ: 6.54c, 6.52a, 6.48d and 6.42b (s, H8), 5.14b, 5.08a, 4.70d and 4.63c (d, J 9.6 Hz, H1), 3.27a, 3.25c, 3.21b and 3.19d (s, NCH3).

6,7-Dimethoxy-1-[2'-[3,4-dimethoxyphenyl]ethenyl]-2-methyl-1,2,3,4-tetrahydroisoquinoline N-oxide 123d

To 81c (0.301 g, 0.781 mmol) in dichloromethane (10 ml) at 0°C was added a solution of m-CPBA (0.263 g, 1.53 mmol) in dichloromethane (15 ml). The solution was allowed to warm to room temperature and stirred for 21 h. then washed with 0.5M aqueous sodium bicarbonate (3 x 5 ml). Drying and then concentration of the organic layer afforded a residue which was purified by p.t.l.c. on silica with dichloromethane/10% methanol to afford a mixture (68:32) of the B-ring diastereomers of tetrahydroisoquinoline N-oxide 123d (0.259 g, 82%) as a tan hygroscopic solid. 1H NMR δ: 7.10-6.74 (m, 3ArH"), H1'a, and H2'b), 6.72 (s, H5), 6.60 (s, H8a), 6.52 (s, H8b), 6.41 (d, J 16.1 Hz, H2'a), 6.01 (dd, J 15.5 Hz, 9.3 Hz, H1'b), 4.98 (d, J 9.3 Hz, H1b), 4.87 (d, J 7.5 Hz, H1a), 3.89-3.88 (m, 3OCH3), 3.78 (s, OCH3), 3.72-3.49 (m, 3H), 3.34 (s, NCH3a), 3.32 (s, NCH3b), 2.94-2.85 (m, H); 13C NMR δ: 138.24 and 138.47 (Cl'), 122.76 (C2'A), 121.17 (C6A), 78.09 and 80.70 (C1), 63.02 and 59.83 (C3), 57.78 and 57.41 (NCH3), 56.42-56.25 (4OCH3), 25.82 and 25.28 (C4); MS m/z: 385 (M+, 43%), 354 (43), 326 (16), 206 (100), 204 (45), 151 (53).

7,8-Dimethoxy-3-methyl-1-vinyl-1,3,4,5-tetrahydro-2,3-benzoxazepine 124a

(i) The N-oxide 123a (1.647 g) was refluxed in dry acetonitrile (50 ml) for 1 h. Concentration and then purification of the residue by column chromatography on alumina with dichloromethane/2% light petroleum afforded the 2,3-benzoxazepine 124a (1.197 g, 73%) as a pale tan oil. 1H NMR δ: 6.67 (s, ArH), 6.58 (s, ArH), 6.01-6.10 (m, H1'), 5.45 (d, J 6.8 Hz, H1), 5.29 (d, J 17.9 Hz, H2'), 5.24 (d, J 10.8 Hz, H2'), 3.86 (s, OCH3), 3.83 (bs, OCH3 and H), 3.28-3.24 (m, H), 3.10-3.02 (m, H),
2.92-2.85 (m, H), 2.72 (s, NCH₃); $^{13}$C NMR δ: 148.03 (C7A), 147.89 (C8A), 137.17 (C1'), 132.81 (C5aB), 129.63 (C9aB), 117.78 (C2'), 114.39 (C6C), 111.16 (C9C), 87.12 (C1), 60.69 (C4), 56.57 (20CH₃), 47.39 (NCH₃), 33.25 (C5); MS m/z: 249 (M⁺, 22%; Calcd. for C₁₄H₁₉NO₃ 249.1363, found 249.135), 232 (10), 203 (11), 190 (100), 175 (44), 159 (22), 147 (17).

(ii) A solution of 123a (0.219 g) in acetonitrile (15 ml) was stored sealed under nitrogen and protected from light at 20-25°C for 3.5 months. $^1$H NMR analysis indicated a 79:21 mixture of 124a:123a.

(iii) A solution of 123a (0.419 g) in dichloromethane (30 ml) was refluxed for 6 days. $^1$H NMR analysis indicated a 64:36 mixture of 124a:123a.

(iv) A solution of 123a (0.109 g) in mesitylene (10 ml) was refluxed for 25 min. then concentrated. The residue was purified by passage through an alumina plug with dichloromethane to give 124a (0.016 g, 15%).

3-Benzyl-7,8-dimethoxy-1-vinyl-1,3,4,5-tetrahydro-2,3-benzoxazepine 124b

The N-oxide 123b (1.778 g) was refluxed in dry acetonitrile (50 ml) for 1 h. Concentration and then purification of the residue by column chromatography on alumina with dichloromethane/2% light petroleum afforded the 2,3-benzoxazepine 124b (1.260 g, 71%) as a pale yellow oil. $^1$H NMR δ: 7.45-7.25 (5ArH"), 6.66 (s, ArH), 6.49 (s, ArH), 5.97-5.85 (m, H1'), 5.12-5.00 (m, 2H2' and H1), 3.92-3.77 (m, 2OCH₃ and NCH₂Ph), 3.37-3.29 (m, H), 3.21-3.13 (m, H), 3.04-2.96 (m, H), 2.79-2.71 (m, H); $^{13}$C NMR δ: 147.86 (C7A), 147.70 (C8A), 138.25 (C1"), 136.94 (C1'), 133.20 (C5aB), 132.54 (C9aB), 130.11 (2C"), 128.60 (2C"), 127.68 (C4"), 117.61 (C2'), 114.33 (C6C), 111.09 (C9C), 87.40 (C1), 63.96 (C4), 58.69 (NCH₂Ph), 56.55 (2OCH₃), 33.42 (C5); MS m/z: 325 (M⁺, 14%; Calcd. for C₂₀H₂₃NO₃ 325.1677, found 325.1692), 308 (10), 282 (14), 203 (15), 190 (100), 175 (30), 159 (16), 147 (11), 91 (61); IR: 2934, 2832, 1516, 1258, 1109, 1030, 700 cm⁻¹; UV: 286, 240, 215 nm.
7,8-Dimethoxy-3-methyl-1-propenyl-1,3,4,5-tetrahydro-2,3-benzoxazepine 124c

(i) A mixture (Z:E=3:1) of the isomers of the 1-propenyl-N-oxide 123c (0.411 g) was refluxed in dry acetonitrile (25 ml) for 1 h. Concentration and then purification of the residue by column chromatography on alumina with dichloromethane/2% light petroleum afforded a mixture (Z:E=3:1) of the isomers of the 2,3-benzoxazepine 124c (0.358 g, 87%) as a colourless oil. The isomers could not be separated by p.t.l.c. or HPLC techniques. Z-isomer ¹H NMR δ: 6.67 (s, ArH), 6.59 (s, ArH), 5.82 (d, J 8.6 Hz, H1), 5.75-5.68 (m, H1' and H2'), 3.86 (s, OCH₃), 3.82 (s, OCH₃), 3.32-3.22 (m, H), 3.12-3.04 (m, H), 2.90-2.86 (m, 2H), 2.71 (s, NCH₃), 1.83 (dd, J 6.6 Hz, 1.4 Hz, CH₃); ¹H NMR (d₆ Benzene) δ: 6.00 (d, J 8.7 Hz, H1), 5.93-5.87 (m, H1), 5.61-5.57 (m, H2'), 1.61 (dd, J 6.9 Hz, 1.6 Hz, CH₃); ¹³C NMR (d₆ benzene) δ: 149.13 (C7A), 149.07 (C8A), 135.61 (C5aB), 131.52 (C9aB), 131.04 (C1'), 126.92 (C2'), 116.26 (C6C), 112.56 (C9C), 81.57 (C1), 61.13 (C4), 56.68 (2OCH₃), 47.82 (NCH₃), 34.93 (C5), 14.30 (CH₃). Signals attributed to the E-isomer ¹H NMR δ: 6.65 (s, ArH), 6.55 (s, ArH), 5.41 (d, J 7.0 Hz, H1), 2.70 (s, NCH₃), 1.73 (d, J 5.3 Hz, CH₃); ¹³C NMR (d₆ benzene) δ: 87.21 (C1), 62.83 (C4), 56.36 (2OCH₃), 47.53 (NCH₃), 34.01 (C5), 18.48 (CH₃).

(ii) A mixture (Z:E=3:1) of the isomers of 123c (0.221 g) was refluxed in dichloromethane (12 ml) for 5 days then worked up as for (i) to give a mixture (Z:E=3:1) of the isomers of 124c (0.118 g, 53%).

(iii) A mixture (Z:E=3:1) of the isomers of 123c (0.033 g) was absorbed onto 60HF₂₅₄ basic alumina type E (0.22 g) from dichloromethane. The residual solvent was removed under vacuum. The solid was irradiated on medium power for 5 min. in a standard microwave (high power=750W) then extracted with dichloromethane to give a mixture (Z:E=1.9:1) of the isomers of 124c (0.023 g, 70%).
7.8-Dimethoxy-1-[2'-(3,4-dimethoxyphenyl)ethenyl]-3-methyl-1,3,4,5-tetrahydro-2,3-benzoxazepine 124d

(i) The N-oxide 123d (0.192 g) was refluxed in dry acetonitrile (10 ml) for 1 h. Concentration and then purification of the residue by p.t.l.c. with dichloromethane/5% methanol afforded:

(a) at Rf 0.15, recovered 123d (0.042 g, 22%).

(b) at Rf 0.40, the precursor amine 81c (0.003 g, 2%).

(c) at Rf 0.80, the 2,3-benzoxazepine 124d (0.112 g, 58%) as a pale yellow oil. 1H NMR δ: 6.97-6.92 (m, o-ArH"), 6.80 (d, J 8.2 Hz, H5"), 6.69 (s, H6), 6.61 (s, H9), 6.57 (d, J 15.9 Hz, H2'), 6.26 (dd, J 15.8 Hz, 7.5 Hz, H1'), 5.62 (d, J 7.4 Hz, H1), 3.88 (s, 3OCH3), 3.82 (s, OCH3), 3.46-3.38 (m, m, H), 3.14-3.07 (m, m, H), 2.96-2.90 (m, m, H), 2.75 (s, NCH3), 2.73-2.67 (m, m); 13C NMR δ: 149.55 (C7 and C2"A), 148.07 (C8 and C3"A), 133.11 (C1''), 132.94 (C5aB), 130.15 (C1"B), 129.04 (C9aB), 126.16 (C2'), 120.83 (C6'C), 114.32 (C6'C), 111.47 (C9'C), 111.27 (C5"C), 109.36 (C2"C), 87.29 (C1), 60.66 (C4), 56.56 (4OCH3), 47.28 (NCH3), 32.88 (C5); MS m/z: 385 (M+, 9%; Calcd. for C22H27N05 385.189, found 385.188), 369 (62), 354 (50), 326 (16), 206 (100), 204 (25), 190 (12), 151 (43); IR: 1516, 1464, 1265, 1227, 1140, 1026, 914, 802, 731 cm⁻¹.

(ii) Photolysis of 123d (0.259 g) in dry acetonitrile (200 ml) at ≥225 nm for 30 min. afforded a mixture with numerous components.

6,7-Dimethoxy-1-methyl-1,3,3a,4,9,9a-hexahydroisoxazolo[3,4-b]naphthalene 126a

The benzoxazepine 124a (1.050 g) was heated in an evacuated sealed tube at an internal temperature of 210°C for 30 min. Passage of the resultant oil through an alumina plug with dichloromethane afforded a colourless residue (0.868 g). Purification of this residue by column chromatography on silica, with a gradient from dichloromethane/5% light petroleum to dichloromethane/1% methanol, afforded 124a (0.070 g, 7%) followed by the isoxazolo[3,4-b]naphthalene 126a (0.450 g, 43%) as a colourless oil. 1H NMR δ: 6.68 (s, ArH), 6.67 (s, ArH), 4.09 (t,
H3), 3.83 (s, OCH3), 3.82 (s, OCH3), 3.40 (t, H3), 2.97-2.92 (m, H3a and H), 2.80-
2.72 (m, H), 2.70 (s, NCH3), 2.66-2.45 (m, 3H); 13C NMR δ: 147.66 (C6A), 147.51
(C7A), 129.10 (C4aB), 128.81 (C8aB), 111.90 (C5 and C8), 71.23 (C3), 68.18 (C9a),
56.23 (OCH3), 56.05 (OCH3), 43.92 (C3aC), 43.44 (NCH3C), 31.70 (C9D), 30.83
(C4D); MS m/z: 249 (M+, 100%; Calcd. for C14H19NO3 249.1364, found
249.1378), 232 (16), 218 (52), 204 (55), 189 (56), 164 (63); IR: 1514, 1464, 1452,
1258, 1229, 1115.

1-Benzyl-6,7-Dimethoxy-1,3,3a,4,9,9a-hexahydroisoxazolo[3,4-b]naphthalene 126b

The benzoxazepine 124b (0.890 g) was heated in an evacuated Buchi bulb-to-
bulb apparatus at an internal temperature of 180°C for 150 min. with the distillation
of a 67:25:8 mixture of 124b:127:126 (0.190 g, 21%). The residual dark oil was
purified by passage through a silica plug with dichloromethane to afford a pale
yellow oil (0.508 g) which was then further purified by preparative reverse phase
HPLC with acetonitrile/41% H2O to give:

(a) at 21.9 min., the isoxazolo[3,4-b]naphthalene 126b (0.210 g, 24%) as a
colourless oil. 1H NMR δ: 7.39-7.25 (m, 5ArH'), 6.66 (s, ArH), 6.59 (s, ArH), 4.13
(t, H3), 3.98 (d, J 3.9 Hz, NCH2Ph), 3.82 (s, 2OCH3), 3.48 (t, H3), 3.19-3.13 (m,
H9a), 2.93-2.85 (m, H3a), 2.72-2.62 (m, H4 and H9), 2.56-2.45 (m, H4 and H9);
13C NMR δ: 147.81 (C6A), 147.75 (C7A), 137.86 (C1'), 129.74 (C4aB), 129.51
(2C'), 129.32 (C8aB), 128.74 (2C'), 127.78 (C4'), 112.19 (C5C), 111.83 (C8C), 71.63
(C3), 66.41 (C9a), 61.58 (NCH2Ph), 56.48 (2OCH3), 43.69 (3C3a), 32.83 (C9D),
31.65 (C4D); MS m/z: 325 (M+, 46%; Calcd. for C14H19NO3 249.1364, found
249.1378), 294 (20), 204 (35), 189 (60), 165 (41), 106 (22), 91 (100); IR: 1516,
1464, 1452, 1223, 1113.

(b) at 42.5 min., compound 124b (0.005 g, 1%)

(c) at 45.9 min., compound 127 (0.076 g, 9%).
2-Benzylxyloxy-6,7-dimethoxy-1-vinyl-1,2,3,4-tetrahydroisoquinoline 127

The preparation of 126b described above gave the 2-benzyloxyisoquinoline 127 (0.076 g, 9%) which crystallised from methanol as a colourless solid with m.p. 67-68°C. $^1$H NMR $\delta$: 7.40-7.24 (m, 5ArH"), 6.60 (s, ArH), 6.57 (s, ArH), 5.98-5.87 (m, H1"), 5.39 (dd $J$ 9.7 Hz, H2"), 5.35 (d, $J$ 15.7 Hz, H2"), 4.78 (d, $J$ 10.7 Hz, H of OCH$_2$Ph), 4.73 (d, $J$ 10.7 Hz, H of OCH$_2$Ph), 4.34 (d, $J$ 7.8 Hz, H1), 3.83 (s, OCH$_3$), 3.80 (s, OCH$_3$), 3.44-3.36 (m, H), 3.04-2.93 (m, 2H), 2.85-2.77 (m, H); $^{13}$C NMR $\delta$: 148.47 (C6A), 147.91 (C7A), 139.44 (C1"'), 138.19 (C1"), 129.56 (2C"), 128.88 (2C"'), 128.45 (C"'), 127.70 (C4aB), 126.35 (C8aB), 119.83 (C2'), 111.43 (C5C), 111.30 (C8C), 75.85 (OCH$_2$Ph), 56.50 (2OCH$_3$), 52.07 (C3), 28.81 (C4); MS m/z: 325 (M+, 18%; Calcd. for C$_{20}$H$_{23}$NO$_2$ 325.1677, found 325.1670), 308 (9), 254 (32), 234 (77), 204 (13), 189 (100), 176 (27), 91 (71).

6,7-Dimethoxy-1-isopropenyl-2-methyl-1,2,3,4-tetrahydroisoquinoline N-oxide 128a

To 70a (1.020 g, 4.378 mmol) in dichloromethane (30 ml) at 0°C was added a solution of m-CPBA (0.904 g, 5.25 mmol) in dichloromethane (30 ml). The solution was stirred for 30 h, while allowed to warm to room temperature then 5% aqueous sodium bicarbonate (25 ml) was added and the organic solvent was removed in vacuo. The aqueous solution was washed with diethyl ether (3 x 10 ml) then made acidic to litmus with 3M aqueous hydrochloric acid and washed with further diethyl ether (3 x 15 ml). The solution was basified with saturated aqueous sodium bicarbonate then saturated with sodium chloride and extracted with chloroform (3 x 25 ml). Drying and then concentration of the organic extracts afforded a mixture (50:50) of the B-ring diastereomers of 1-isopropenyltetrahydroisoquinoline N-oxide 128a (0.693 g, 64%) as a tan hygroscopic solid. trans isomer* $^1$H NMR $\delta$: 6.60 (s, ArH), 6.36 (s, ArH), 5.25 (m, H2"'), 4.84 (s, H1), 3.79 (s, OCH$_3$), 3.72 (s, OCH$_3$), 3.61-3.45 (m, 2H), 3.42-3.31 (m, H), 3.16 (s, NCH$_3$), 2.73-2.66 (m, H), 1.61 (s, CH$_3$); $^{13}$C NMR $\delta$: 148.84 (C6A), 148.46 (C7A), 141.43 (C1"'), 124.03 (C4aB), 123.93 (C2'), 123.31 (C8aB), 111.24 (C5C), 110.83 (C8C), 84.83 (C1), 60.62 (C3),
58.28 (NCH₃), 56.40 (2OCH₃), 24.96 (C4), 20.49 (CH₃); IR: 1520, 1256, 1229, 1124, 918, 729. *Peaks attributed to the cis isomer* ¹H NMR δ: 6.40 (s, ArH), 5.48 (s, H2'), 5.09 (s, H2'), 4.76 (s, H1), 3.29 (s, NCH₃), 2.03 (s, CH₃); ¹³C NMR δ: 80.75 (C1), 63.79 (C3), 58.49 (NCH₃), 25.87 (C4), 22.26 (CH₃).

* The *trans* isomer was obtained separately as described in the formation of 129a.

6.7-Dimethoxy-2-methyl-1-(α-phenylethenyl)-1,2,3,4-tetrahydroisoquinoline *N*-oxide 128b

Whenever possible solutions were cooled in ice throughout this procedure. To 70b (1.486 g, 4.803 mmol) in dichloromethane (25 ml) at 0°C was added a solution of *m*-CPBA (1.021 g, 5.936 mmol) in dichloromethane (25 ml). The solution was stirred at 0°C for 20 h. then 5% aqueous sodium bicarbonate (30 ml) was added and the organic solvent was removed *in vacuo*. The cooled aqueous solution was washed with diethyl ether (3 x 10 ml) then made acidic to litmus with 3M aqueous hydrochloric acid and washed with further diethyl ether (3 x 15 ml). The solution was basified with saturated aqueous sodium bicarbonate then saturated with sodium chloride and extracted with chloroform (3 x 25 ml). Drying and then concentration of the organic extracts afforded a 4:1 mixture of 128b and 129b (1.525 g). Purification of a portion (1.161 g) of this mixture by column chromatography on alumina with dichloromethane/0-10% methanol gave:

(a) a 78:22 mixture of 129b and 130b (0.156 g, 14%).

(b) the *trans*-B-ring diastereomer of the *tetrahydroisoquinoline N-oxide* 128b (0.547 g, 47%) as a cream hygroscopic solid. ¹H NMR δ: 7.30 (s, 3ArH"), 7.07 (bs, o-ArH"), 6.71 (s, ArH), 6.62 (s, ArH), 5.61 (s, H1₁), 5.30 (s, 2H2'ₐ), 3.91 (s, OCH₃), 3.83 (s, OCH₃), 3.73-3.60 (m, 2H), 3.18-3.11 (m, H), 3.12 (s, NCH₃), 2.65-2.58 (m, H); ¹³C NMR δ: 149.28 (C6₁), 148.92 (C7₁), 147.83 (C1₁), 140.53 (C1"), 129.43 (2C"), 129.03 (2C"), 127.95 (C4"), 126.14 (C2'), 124.75 (C4aB), 124.28 (C8aB), 111.56 (C5 and C8), 82.45 (C1), 59.76 (NCH₃), 58.66 (C3), 56.67 (OCH₃), 56.56 (OCH₃), 24.91 (C4).
6.7-Dimethoxy-2-methyl-1-(1'-trimethylsilylthienyl)-1,2,3,4-tetrahydroisoquinoline 
N-oxide 128c

To 70c (0.506 g, 1.66 mmol) in dichloromethane (10 ml) at 0°C was added a solution of m-CPBA (0.310 g, 1.80 mmol) in dichloromethane (10 ml). The solution was allowed to warm to room temperature and stirred for 20 h. then washed with 5% aqueous sodium bicarbonate (2 x 7 ml). Drying and then concentration of the organic solution afforded a hygroscopic foam that was purified by column chromatography on alumina, with a gradient from dichloromethane/5% hexane to dichloromethane/10% methanol, to give:

(a) a 74:26 mixture (0.134 g) of 70c (20%) and 129c (6%).

(b) a mixture (trans:cis=66:34) of the B-ring diastereomers of the tetrahydroisoquinoline N-oxide 128c (0.325 g, 61%) as a yellow oil. 1H NMR δ: 6.49 (s, H5a), 6.47 (s, H5b), 6.26 (s, H8b), 6.15 (s, H8a), 5.83-5.78 (m, 2H2ta and H2tb), 5.62 (d, J 2.5 Hz, H2b) 4.88 (s, H1a), 4.58 (s, H1b), 3.69 (s, OCH3), 3.60 (s, OCH3), 3.48-3.32 (m, 2H), 3.24-3.17 (m, H), 2.99 (s, NCH3b), 2.96 (s, NCH3a), 2.64-2.53 (m, H), 1.03 (s, Si(CH3)a), -0.17 (s, Si(CH3)b); 13C NMR δ: 138.08 and 134.58 (C2'), 111.49-110.95 (C5 and C8), 82.67 and 82.24 (C1), 59.70 and 63.42 (C3), 57.88 and 58.66 (NCH3), 56.30 (2OCH3), 25.25 and 25.39 (C4), 0.50 and 1.87 (Si(CH3)3).

6.7-Dimethoxy-1-(1'-iodoethenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline N-oxide 128d

To 70d (0.953 g, 2.65 mmol) in dichloromethane (20 ml) at 0°C was added a solution of m-CPBA (0.545 g, 3.17 mmol) in dichloromethane (15 ml). The solution was allowed to warm to room temperature and stirred for 26 h. then 5% aqueous sodium bicarbonate (25 ml) was added and the organic solvent was removed in vacuo. The aqueous solution was washed with diethyl ether (3 x 10 ml). Concentration of the ether washings gave 70d (0.129 g, 14%). The aqueous solution was made acidic to litmus with 3M aqueous hydrochloric acid and washed with diethyl ether (3 x 10 ml) then basified with saturated aqueous sodium bicarbonate.
Saturation of the solution with sodium chloride and extraction with chloroform (3 x 25 ml), then drying and concentration of the extracts, afforded a single B-ring diastereomer of \(1-(1'\text{-iodoethenyl})\text{tetrahydroisoquinoline N-oxide 128d}\) (0.814 g, 82%) as a red hygroscopic solid. \(^1\text{H NMR} \delta: 7.46 (s, H2'), 6.66 (ArH^A), 6.52 (s, ArH^A), 6.47 (s, H2'A), 5.34 (s, H1), 4.23-4.10 (m, H), 3.91 (s, OCH_3), 3.83 (s, OCH_3), 3.70-3.62 (m, H), 3.52 (s, NCH_3), 3.45-3.33 (m, H), 2.89-2.84 (m, H); \(^1\text{C NMR} \delta: 141.34 (C2'), 111.18 (C8^A), 110.87 (C4a^A), 83.25 (C1), 60.45 (C3), 57.36 (NCH_3^B), 57.01 (OCH_3^B), 56.64 (OCH_3^B), 24.74 (C4).

**Z-9,10-Dimethoxy-3,6-dimethyl-1,2,3,5-tetrahydro-4,3-benzoxazonine 129a**

A mixture (50:50) of the diastereomers of N-oxide 128a (0.544 g) was refluxed in dry dichloromethane (25 ml) for 34 h. Concentration and then purification of the residue by passage through an alumina column with dichloromethane afforded the 4,3-benzoxazonine 129a (0.223 g, 41%) as a colourless oil. \(^1\text{H NMR} \delta: 6.67 (s, ArH), 6.52 (s, ArH), 6.46 (s, H7), 4.06 (bs, H5), 3.86 (s, OCH_3), 3.82 (s, OCH_3), 2.88 (bs, 2H), 2.57 (s, NCH_3), 1.90 (s, CH_3), 2H of CH_2CH_2 not detected; \(^1\text{C NMR} \delta: 148.25 (C9^A), 147.13 (C10^A), 138.68 (C7a^B), 133.58 (C11a^B), 131.10 (C6), 127.93 (bs, C7), 111.58 (C8^C), 111.16 (C11^C), 74.77 (bs, C5), 62.81 (C2), 56.28 (OCH_3), 56.20 (OCH_3), 47.41 (bs, NCH_3), 33.24 (bs, C1), 24.36 (CH_3); MS m/z: 263 (M^+, 12%; Calcd. for C_{15}H_{21}NO_3 263.1521, found 263.1532), 246 (5), 204 (100), 189 (37), 175 (11); IR: 1516, 1258, 1231, 1117, 986, 871, 763 cm\(^{-1}\); UV: 290, 221 nm.

NMR analyses at -30°C displayed two conformers in a 50:50 ratio. Assignable signals were: \(^1\text{H NMR} \delta: 6.78 and 6.65 (s, ArH^A), 6.56 and 6.54 (s, ArH^A), 6.49 (s, H7), 4.25-3.95 (4 d, J 12.4 Hz, H5), 3.92 and 3.89 (s, OCH_3), 3.85 (s, OCH_3), 2.67 and 2.57 (s, NCH_3), 1.98 and 1.87 (s, CH_3); \(^1\text{C NMR} \delta: 147.95 and 146.98 (C9^A), 146.59 and 146.13 (C10^A), 139.25 and 137.30 (C7a^B), 133.65 and 132.08 (C11a^B), 130.48 (C6), 129.37 and 126.18 (C7), 110.66 and 110.49 (C8^C), 110.11 and 109.85 (C11^C), 77.25 and 72.46 (C5), 62.80 and 62.20 (C2),
55.99 (2OCH₃), 48.64 and 46.29 (NCH₃), 34.44 and 31.35 (C1), 24.64 and 24.24 (CH₃).

Elution of the alumina column with dichloromethane/20% methanol afforded the recovery of the pure trans diastereomer of N-oxide 128a (0.117 g, 22%).

Z-9,10-Dimethoxy-3-methyl-6-phenyl-1,2,3,5-tetrahydro-4,3-benzoxazonine 129b

To 70b (2.056 g, 6.626 mmol) in dichloromethane (40 ml) at 0°C was added a solution of m-CPBA (1.40 g, 8.14 mmol) in dichloromethane (60 ml). The solution was stirred at 0°C for 40 h. then 5% aqueous sodium bicarbonate (40 ml) was added and the organic solvent was removed in vacuo. The aqueous solution was washed with diethyl ether (3 x 25 ml) then made acidic to litmus with 3M aqueous hydrochloric acid and washed with further diethyl ether (3 x 15 ml). The solution was basified with saturated aqueous sodium bicarbonate then saturated with sodium chloride and extracted with chloroform (3 x 25 ml). Drying and then concentration of the organic extracts, then column chromatography of the residue on alumina with dichloromethane/0-10% methanol, gave a 44:56 mixture of 129b and 130b (0.522 g, 24%) and the trans diastereomer of N-oxide 128b (1.142 g, 53%). Preparative reverse phase HPLC of this mixture with acetonitrile/37% H₂O gave:

(a) at 14.3 min., the 2,3-benzoxazepine 130b.

(b) at 17.1 min., the 4,3-benzoxazonine 129b as colourless prisms from methanol with m.p. 111-112°C. ¹H NMR δ: 7.55-7.52 (m, o-ArH'), 7.40-7.24 (3ArH'), 7.00 (s, H7), 6.75 (s, ArH), 6.63 (s, ArH), 4.51 (bs, H5), 3.89 (s, OCH₃), 3.85 (s, OCH₃), 2.94 (bs, 2H), 2.65 (s, NCH₃), 2H of CH₂CH₂ not detected; ¹³C NMR δ: 148.84 (C9A), 147.49 (C10A), 142.39 (C6B), 142.05 (C1'B), 133.56 (C7aC), 131.32 (C7), 130.75 (C11aC), 129.06 (2C'), 127.88 (C4'), 126.82 (2C'), 111.75 (C8D), 111.06 (C11D), 74.55 (C5), 63.00 (C2), 56.51 (OCH₃), 56.35 (OCH₃), 47.94 (NCH₃), 32.91 (C1); MS m/z: 325 (M⁺, 13%; Calcld. for C₂₀H₂₃NO₃ 325.1677, found 325.1670), 266 (93), 251 (18), 235 (7), 206 (100), 178 (12), 165 (17); Anal. Calcld for
C_{20}H_{23}NO_{3}: C, 73.87; H, 7.13; N, 4.31%, found: C, 73.84; H, 7.10; N, 4.44%; UV: 293, 235, 220 nm.

NMR analyses at -30°C displayed two conformers in a 78:22 ratio. Assignable signals were: \(^1\)H NMR \(\delta\): 7.11 and 6.92 (s, H\(_7\)), 6.83 and 6.70 (s, ArH), 6.67 and 6.63 (s, ArH), 4.87 (d, \(J = 12.7\) Hz, H5\(^a\)), 4.47 (s, 2H5\(^b\)), 4.32 (d, \(J = 12.7\) Hz, H5\(^a\)), 2.73 and 2.63 (s, NCH\(_3\)); \(^13\)C NMR \(\delta\): 132.44 and 131.66 (C7), 75.76 and 71.74 (C5), 63.02 and 62.98 (C2), 48.77 and 46.53 (NCH\(_3\)), 31.71 and 34.34 (C1).

**Z-9,10-Dimethoxy-3-methyl-6-trimethylsilyl-1,2,3,5-tetrahydro-4,3-benzoxazonine 129c**

A mixture (trans:cis=66:34) of the diastereomers of N-oxide 128c (0.325 g, 1.01 mmol) was refluxed in dichloromethane (20 ml) for 36 h. Concentration and then purification of the residue by passage through an alumina column with dichloromethane/5% hexane gave a 62:38 mixture of 129c and 130c (0.262 g, 81%). The components were not separated by HPLC. Recrystallisation twice from methanol, with the collection of the early solid, afforded the 4,3-benzoxazonine 129c (0.044 g, 14%) as colourless prisms with m.p. 132-133°C. \(^1\)H NMR (50°C) \(\delta\): 6.95 (s, H7), 6.66 (s, ArH), 6.49 (s, ArH), 4.17 (s, H5), 3.84 (s, OCH\(_3\)), 3.80 (s, OCH\(_3\)), 2.82-2.73 (m, 4H), 2.51 (s, NCH\(_3\)), 0.17 (s, Si(CH\(_3\))\(_3\)); \(^13\)C NMR (50°C) \(\delta\): 148.75 (C9\(^A\)), 147.58 (C10\(^A\)), 145.11 (C6), 141.83 (C7), 133.42 (C7\(^aB\)), 132.87 (C11\(^aB\)), 112.53 (C8\(^C\)), 110.95 (C11\(^C\)), 71.42 (C5), 62.87 (C2), 56.63 (OCH\(_3\)), 56.48 (OCH\(_3\)), 47.29 (NCH\(_3\)), 33.44 (C1), -1.17 (Si(CH\(_3\))\(_3\)); MS m/z: 321 (M\(^+\), 3%; Calcd. for C\(_{17}\)H\(_{27}\)NO\(_3\)Si 321.1759, found 321.1761), 290 (4), 262 (10), 247 (30), 206 (100), 178 (16); Anal. Calcd for C\(_{17}\)H\(_{27}\)NO\(_3\)Si: C, 63.51; H, 8.47; N, 4.36%, found: C, 63.53; H, 8.44; N, 4.33%.

NMR analyses at -30°C displayed two conformers in a 74:26 ratio. Assignable signals were: \(^13\)C NMR \(\delta\): 143.15 and 139.33 (C7), 110.06 and 110.68 (C8\(^A\)), 109.65 and 108.52 (C11\(^A\)), 73.50 and 69.17 (C5), 62.76 and 62.04 (C2),
55.95 (2OCH₃), 48.64 and 46.15 (NCH₃), 31.48 and 34.24 (C1), -1.27 and -1.50 (Si(CH₃)₃).

Z-9,10-Dimethoxy-6-iodo-3-methyl-1,2,3,5-tetrahydro-4,3-benzoxazonine 129d

The N-oxide 128d (0.301 g, 0.803 mmol) was refluxed in dichloromethane (13 ml) for 24 h. Concentration and then purification of the residue by passage through an alumina column with dichloromethane/25% hexane gave an oil (0.084 g). Analysis of the oil by HPLC at 254 nm indicated a 90:10 mixture of 70d and 129d. Preparative reverse phase HPLC purification of this mixture with acetonitrile/33% H₂O gave:

(a) at 12.9 min., the precursor amine 70d (0.055 g, 19%).
(b) at 15.4 min., the 4,3-benzoxazonine 129d (0.005 g, 2%) as a yellow oil. ¹H NMR δ: 7.44 (s, H7), 6.66 (s, ArH), 6.51 (s, ArH), 4.50 (s, H5), 3.87 (s, OCH₃), 3.83 (s, OCH₃), 2.92 (bs, 3H), 2.57 (bs, NCH₃ and H); MS m/z: 375 (M⁺, 2%; Calcd. for C₁₄H₁₈NO₃I 375.0331, found 375.0353), 358 (4), 316 (15), 248 (10), 206 (100), 189 (90).

7,8-Dimethoxy-1-isopropenyl-3-methyl-1,3,4,5-tetrahydro-2,3-benzoxazepine 130a

(i) The benzoxazonine 129a (0.027 g) was refluxed in dry xylene (5 ml) for 1 h. Concentration and then purification of the residue by passage through an alumina plug with dichloromethane gave a 5:95 mixture (0.023 g, 85%) of 129a and the 2,3-benzoxazepine 130a as a pale tan oil. ¹H NMR δ: 6.65 (s, ArH), 6.53 (s, ArH), 5.39 (s, H1A), 4.97 (s, H2'A), 4.94 (s, H2'A), 3.86 (s, OCH₃), 3.81 (s, OCH₃), 3.47-3.42 (m, H), 3.14-3.06 (m, H), 2.95-2.88 (m, H), 2.72 (s, NCH₃), 2.62-2.55 (m, H); ¹³C NMR δ: 147.98 (C7A), 145.47 (C8 and C1'A), 132.71 (C5aB), 129.72 (C9aB), 115.18 (C6C), 114.12 (C9C), 111.34 (C2'), 90.49 (C1), 60.81 (C4), 56.63 (OCH₃), 56.55 (OCH₃), 47.25 (NCH₃), 33.29 (C5), 19.46 (CH₃); IR: 1516, 1258, 1227, 1209, 1119, 1036, 905, 864, 781 cm⁻¹; UV: 286, 240, 220 nm.
(ii) The trans-N-oxide 128a (0.028 g) was refluxed in dry acetonitrile (5 ml) for 50 min. Concentration and then purification of the residue by passage through an alumina column with dichloromethane/5% hexane gave a 34:66 mixture of 129a and 130a (0.023, 82%).

(iii) A mixture (50:50) of the diastereomers of N-oxide 128a (0.076 g) was treated as for (ii) to give a 58:42 mixture of 129a and 130a (0.067, 88%).

7.8-Dimethoxy-3-methyl-1-(α-phenylethenyl)-1,3,4,5-tetrahydro-2,3-benzoxazepine 130b

The preparation of 129b described above afforded the 2,3-benzoxazepine 130b as colourless prisms from methanol with m.p. 96-97°C. 1H NMR δ: 7.48-7.45 (m, o-ArH"), 7.33-7.25 (m, 3ArH"), 6.65 (s, ArH), 6.50 (s, ArH), 5.98 (s, H2'), 5.53 (s, H2'), 5.15 (s, H1), 3.85 (s, OCH3), 3.69 (s, OCH3), 3.45-3.37 (m, m, H), 3.12-3.04 (m, H), 2.91-2.86 (m, m, H), 2.72-2.67 (m, H), 2.66 (s, NCH3); 13C NMR δ: 148.14 (C7A), 147.86 (C8A), 147.61 (C1A), 140.58 (C1"), 132.81 (C5aB), 130.43 (C9aB), 128.69 (2C"), 128.01 (C4"), 127.31 (2C"), 117.25 (C2'), 114.21 (C6C), 111.71 (C9C), 87.18 (C1), 60.64 (C4), 56.46 (OCH3), 56.30 (OCH3), 47.24 (NCH3), 33.74 (C5); MS m/z: 325 (M+, 12%; Calcd. for C20H23NO3 325.1677, found 325.1670), 308 (3), 266 (100), 251 (16), 237 (10), 206 (47); Anal. Calcd for C20H23NO3: C, 73.87; H, 7.13; N, 4.31%, found: C, 73.98; H, 7.29; N, 4.48%; UV: 284, 237, 220 nm.

7.8-Dimethoxy-1-(1' trimethylsilyl ethenyl)-3-methyl-1,3,4,5-tetrahydro-2,3-benzoxazepine 130c

The preparation of 129c described above afforded a 62:38 mixture (81%) of 129c and 130c. Compound 130c could not be isolated separately. The signals attributed to 130c were: 1H NMR δ: 6.65 (s, ArH), 6.46 (s, ArH), 5.66 (s, H1), 5.56 (d, J 2.6 Hz, H2'), 5.50 (d, J 2.6 Hz, H2'), 3.84 (s, OCH3), 3.82 (s, OCH3), 3.38-3.12
(m, 2H), 2.95-2.87 (m, H), 2.70 (s, NCH₃), 2.2.68-2.62 (m, H); ¹³C NMR δ: 128.37 (C2'), 89.26 (C1).

7,8-Dimethoxy-1-(1'-iodoethenyl)-3-methyl-1,3,4,5-tetrahydro-2,3-benzoxazepine

The N-oxide 128d (0.210 g, 0.560 mmol) was refluxed in dry acetonitrile (12 ml) for 50 min. Concentration and then purification of the residue by passage through an alumina column with dichloromethane/25% hexane gave an oil (0.056 g). Analysis by HPLC at 254 nm indicated a 59:30:11 mixture of 70d, 130d and 129d. Preparative reverse phase HPLC purification of this mixture with acetonitrile/33% H₂O gave, at 11.9 min., the 2,3-benzoxazepine 130d (0.010 g, 5%) as a yellow oil. ¹H NMR δ: 6.66 (s, ArH), 6.57 (s, ArH), 6.27 (bs, H1), 6.00 (s, H2'), 5.30 (s, H2'), 3.88 (s, OCH₃), 3.83 (s, OCH₃), 3.63-3.52 (m, H), 3.12-3.03 (m, H), 2.99-2.92 (m, H), 2.78 (s, NCH₃), 2.65-2.57 (m, H); ¹³C NMR δ: 148.59 (C7A), 148.06 (C8A), 130.99 (C5aB), 130.58 (C9aB), 129.53 (C2'), 114.66 (C6C), 111.85 (C9C), 110.79 (C1'), 91.83 (C1), 60.65 (C4), 56.66 (2OCH₃), 47.60 (NCH₃), 33.73 (C5); MS m/z: 375 (M⁺, 2%; Calcd. for C₁₄H₁₈NO₃I 375.0331, found 375.0344), 358 (2), 316 (11), 248 (12), 206 (19), 189 (100), 145 (23), 115 (16), 60 (28).

6,7-Dimethoxy-1-(3"-fluorophenyl)-2-methyl-1-vinyl-1,2,3,4-tetrahydroisoquinoline

6,7-Dimethoxy-1-(3'-fluorophenyl)-3,4-dihydroisoquinoline (7.70 g, 27.9 mmol) was refluxed for 1.5 h. in dry acetone (60 ml) with iodomethane (16.0 g, 112 mmol). The solution was then cooled and the yellow solid was collected, washed with cold acetone, and then dried to give 6,7-dimethoxy-1-(3'-fluorophenyl)-2-methyl-3,4-dihydroisoquinolinium iodide 131 (11.52, 99%). m.p. 215-217°C.

A solution of vinylmagnesium bromide in dry tetrahydrofuran (120 ml) under nitrogen was prepared from vinyl bromide (5.02 g, 47.0 mmol). The solution was cooled to 0°C and the imine salt 131 (5.02 g, 11.7 mmol) was then added portionwise
over 30 min. The mixture was refluxed for 3.5 h. then stirred at room temperature for 12 h. before workup (as for 70b) to give, upon concentration of the ether solution, the 1-(3"-fluorophenyl)isoquinoline 132 (3.73 g, 97%) as a pale yellow oil. 

1H NMR δ: 7.28-7.22 (m, 3ArH"), 6.95-6.88 (m, H2"'), 6.56 (s, ArH), 6.34 (dd, J 10.6 Hz, J 17.2 Hz, H1"'), 6.04 (s, ArH), 5.54 (dd, J 1.7 Hz, J 10.6 Hz, H2"'), 4.67 (dd, J 1.7 Hz, J 17.2 Hz, H2"'), 3.84 (s, OCH3), 3.58 (s, OCH3), 3.13-3.05 (m, H), 2.82-2.63 (m, 3H), 2.16 (s, NCH3); 13C NMR displayed two conformers δ: 165.13 and 161.89 (C3"), 150.01 (C6A), 148.01 and 147.04 (C7A), 138.32 (C1'), 131.44 (C4aB), 129.70 (C6C), 128.07 (C8aB), 126.05 (C1"B), 124.78 (C5C), 121.54 (C2'), 116.36 and 116.06 (C4'D), 114.50 and 114.21 (C2"D), 113.89 (C5E), 111.13 (C8E), 71.10 and 69.45 (C1), 56.38 (2OCH3), 47.36 (C3), 39.77 (NCH3), 29.90 (C4); MS m/z: 327 (M+, 12%; Calcd. for C20H22NO2F 327.1634, found 327.1615), 300 (100), 286 (23), 284 (10), 232 (53), 218 (12).

Z-9.10-Dimethoxy-3-methyl-7-(3'-fluorophenyl)-1,2,3,5-tetrahydro-4,3-benzoxazonine 134

To the amine 132 (0.771 g, 2.35 mmol) in dichloromethane (23 ml) at 0°C was added a solution of m-CPBA (0.485 g, 2.82 mmol) in dichloromethane (20 ml). The solution was allowed to warm to room temperature and stirred for 40 h. then 5% aqueous sodium bicarbonate (20 ml) was added and the organic solvent was removed in vacuo. The aqueous solution was extracted with diethyl ether (10 ml and 3 x 5 ml). The ether extracts were washed with saturated brine (5 ml) then dried and concentrated to afford a tan solid (0.567 g). Purification of a portion (0.371 g) of this material by p.t.l.c. on silica with dichloromethane/7% methanol afforded a band, at Rf 0.95, which was collected (0.220 g) and subjected to further p.t.l.c. on silica with two developments by dichloromethane/1% methanol. The front third of the resultant broad band, at Rf 0.69, gave the 4,3-benzoxazonine 134 (0.125 g, 24%) as colourless prisms from methanol with m.p. 131-132°C. 1H NMR δ: 7.24-7.17 (m, H6'), 7.05 (d, J 7.8 Hz, H2"'), 6.94-6.88 (m, 2ArH"), 6.78 (s, ArH), 6.52 (t, H6), 6.45 (s, ArH), 4.35
(dd, J 13.4 Hz, 5.9 Hz, H5), 3.99 (dd, J 13.7 Hz, 6.0 Hz, H5), 3.92 (s, OCH3), 3.76 (s, OCH3), 3.01-2.94 (m, H), 2.92-2.85 (m, 2H), 2.66-2.61 (m, H), 2.57 (s, NCH3); 

13C NMR δ: 165.04 and 161.78 (C3'), 149.00 (C9A), 147.65 (C10A), 144.80 (C1'B), 144.06 (C7B), 134.30 (C7aC), 131.07 (C11aC), 130.07 (C6'D), 127.61 (C5'D), 122.71 (C6D), 114.89 and 114.61 (C8D), 114.10 and 113.81 (C11D), 111.48 (C2' and C4D), 69.37 (C5), 62.62 (C2), 56.41 (OCH3), 56.19 (OCH3), 47.35 (NCH3), 33.15 (C1); MS m/z: 343 (M+, 18%; Calcd. for C20H22NO3F, 343.1583, found 343.1600), 326 (14), 297 (20), 284 (100), 271 (15), 253 (12); Anal. Calcd for C20H22NO3F: C, 69.95; H, 6.46; N, 4.08%, found: C, 69.90; H, 6.58; N, 4.12%.

NMR analysis at -30°C displayed two conformers in a 69:31 ratio. Assignable signals were: 13C NMR δ: 66.26 and 73.01 (C5), 61.96 and 62.81 (C2), 46.43 and 48.78 (NCH3), 33.93 and 30.94 (C1).

6.4 Experimental for Chapter Four

8-Chloro-1,2-dimethyl-6-phenyl-2,4-dihydro-1H-s-triazolo[4,3-a]-[1,4]benzodiazepine 145

Alprazolam 136 (0.216 g, 0.701 mmol) in dry butanone (10 ml) at 50°C was stirred with iodomethane (0.11 g, 0.80 mmol) under nitrogen for 20 h. The solution was then concentrated to a pale yellow solid. 1H NMR analysis of the material indicated two isomers (2.24:1) were present with characteristic peaks for: (a) compound 144.140 1H NMR δ: 5.42 (d, J 13.3 Hz, H4), 4.25 (d, J 13.4 Hz, H4), 4.11 (s, NCH3), 3.19 (s, CH3); (b) an unknown isomer 1H NMR δ: 5.46 (d, J 14.4 Hz, H4), 4.66 (d, J 14.4 Hz, H4), 4.18 (s, NCH3), 2.77 (s, CH3).

The crude solid above in dry ethanol (10 ml) at 0°C was treated with sodium borohydride (0.025 g, 0.66 mmol) added portionwise over 1 h. The solution was then concentrated and the residue was extracted with dichloromethane (3 x 5 ml). Concentration of the extracts afforded a pale yellow powder which was purified by p.t.l.c. on silica with dichloromethane/10% methanol to give the triazolo[4,3-
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[1,4]benzodiazepine $^{140}$ 145 (0.058 g, 26%). $^1$H NMR $\delta$: 7.53-7.39 (m, 6ArH), 7.17 (d, $J$ 2.5 Hz, H7), 6.86 (d, $J$ 8.8 Hz, H10), 4.85 (d, $J$ 12.4 Hz, H4), 4.75 (q, H1), 3.92 (d, $J$ 12.4 Hz, H4), 2.77 (s, NCH$_3$), 1.52 (d, $J$ 5.2 Hz, CH$_3$).

8-Chloro-1-methyl-6-phenyl-5,6-dihydro-4H-s-triazolo[4,3-a][1,4]benzodiazepine $^{146}$

A solution of alprazolam 136 (1.976 g, 6.399 mmol) in methanol (40 ml) was acidified to a pH of 3 to 4 with a mixture of concentrated hydrochloric acid/methanol (1:4) and then sodium cyanoborohydride (0.46 g, 7.3 mmol) was added. A solid precipitated after 2 min. The solution was returned to a pH of 3 to 4 by the further addition of the acid mixture and then stirred for 20 min. Aqueous 0.5 M sodium bicarbonate (40 ml) was added and the mixture was then extracted with dichloromethane (4 x 40 ml), with poor separation. The extracts were combined and washed with water (4 x 15 ml). The aqueous washings were combined and back-extracted with dichloromethane (2 x 20 ml). All the dichloromethane layers were then combined, dried, and concentrated to give the 5,6-dihydrotriazolo-benzodiazepine $^{142-145}$ 146 (1.872 g, 94%) as a colourless solid. $^1$H NMR $\delta$: 7.46 (dd, $J$ 2.4 Hz, 8.4 Hz, H9), 7.35-7.28 (m, 5ArH), 7.26 (d, $J$ 8.4 Hz, H10), 6.95 (d, $J$ 2.3 Hz, H7), 4.95 (s, H6), 4.27 (d, $J$ 15.0 Hz, H4), 3.77 (d, $J$ 15.0 Hz, H4), 2.54 (s, CH$_3$), 2.50-2.25 (bs, NH); $^{13}$C NMR $\delta$: 153.88 (C1A), 150.65 (C3aA), 140.03 (C1'B), 138.35 (C6aB), 135.57 (C10aB), 132.84 (C8B), 131.71 (C7C), 129.70 (C9C), 129.37 (2C'), 129.03 (C'C), 128.46 (2C'), 124.97 (C10C), 60.35 (C6), 40.71 (C4), 12.07 (CH$_3$); MS m/z: 310 (M$^+$, 73%; Calcd. for C$_{17}$H$_{15}$N$_4$Cl 310.0984, found 310.098), 294 (8), 282 (20), 232 (100), 205 (36), 179 (22).

Other Attempted Reductions of 136 to 146

(i) To 136 (0.263 g, 0.850 mmol) in dry ethanol (35 ml) was added sodium borohydride (0.033 g, 0.88 mmol). After 90 min. additional sodium borohydride
(0.037 g, 0.98 mmol) was added. After a further 30 min. t.l.c. analysis confirmed that 136 remained unchanged.

(ii) To 136 (0.263 g, 0.850 mmol) in dry methanol (25 ml) with glacial acetic acid (1.25 ml) was added sodium cyanoborohydride (0.053 g, 0.84 mmol). After 1 h. t.l.c. analysis confirmed that 136 remained unchanged.

(iii) To 136 (0.263 g, 0.850 mmol) in glacial acetic acid (12 ml) was added sodium cyanoborohydride (0.214 g, 3.41 mmol). After 18 h. t.l.c. analysis indicated that 136 remained almost unchanged. The solution was then warmed to 50°C for 3 h. The solution was cooled and water (30 ml) and concentrated aqueous ammonia were added to afford a basic mixture which was then extracted with dichloromethane (4 x 30 ml). The extracts were washed with saturated brine (15 ml) then dried and concentrated. Analysis of the residual yellow solid by GC-MS indicated the presence of 146 (64%) and components attributed to: (a) 148a (25%), MS m/z: 338 (M^+ , 71%), 323 (41), 282 (63), 261 (100), 207 (14); and (b) 148b (11%), MS m/z: 352 (M^+ , 36%), 337 (100), 295 (29), 282 (45), 275 (36). Purification of this material by p.t.l.c. on silica with dichloromethane/4% methanol gave 146 (0.083 g, 36%).

8-Chloro-1.5-dimethyl-6-phenyl-5.6-dihydro-4H-s-triazolo[4.3-a][1.4]benzodiazepine 147

(i) A solution of dihydroalprazolam 146 (1.872, 6.024 mmol) in methanol (80 ml) was treated with 37% aqueous formaldehyde (0.80 ml, 10 mmol) then stirred for 15 min., and then acidified to a pH of 4 with a concentrated hydrochloric acid/methanol (1:1) mixture. After 5 min. sodium cyanoborohydride (0.475 g, 7.56 mmol) was added and the solution was then stirred for 4 h. The pH was then readjusted to 4 with the acid mixture and the stirring was continued for 1 h. Aqueous 0.25 M potassium hydroxide (40 ml) was then added and the organic solvent was removed in vacuo. The extraction of the aqueous mixture with dichloromethane (70 ml, 3 x 40 ml), then drying and concentration of the extracts gave the 1,5-dimethyl-5,6-
dihydro-triazolobenzodiazepine 147 (1.950 g, 100%) as a colourless solid of purity >99% upon GC-MS analysis. $^1$H NMR δ: 7.47 (dd, $J$ 2.3 Hz, 8.4 Hz, H9), 7.30 (bs, 5ArH'), 7.25 (d, $J$ 8.4 Hz, H10), 7.01 (d, $J$ 2.3 Hz, H7), 4.18 (s, H6), 3.96 (d, $J$ 14.1 Hz, H4), 3.67 (d, $J$ 14.1 Hz, H4), 2.48 (s, NCH$_3^A$), 2.42 (s, CH$_3^A$); $^{13}$C NMR δ: 150.88 (C$_1^A$), 150.18 (C$_3^A$), 139.90 (C$_1^B$), 137.66 (C$_6^B$), 135.03 (C$_{10a}^B$), 132.86 (C$_8^B$), 132.48 (C$_7^C$), 129.69 (C$_9^C$), 129.16 (2C'), 128.61 (C$_C^C$), 128.26 (2C'), 125.07 (C$_{10}^C$), 69.45 (C6), 48.75 (C4), 44.42 (NCH$_3$), 11.94 (CH$_3$); MS m/z: 324 (M$^+$, 41%; Calcd. for C$_{18}$H$_{17}$N$_4$C$_1$324.1142, found 324.1140), 282 (16), 247 (100), 219 (21), 193 (15); IR (KBr): 1491, 1105, 1094, 723, 536 cm$^{-1}$.

(ii) A solution of 146 (0.192 g, 0.619 mmol) in methanol (35 ml) and 37% aqueous formaldehyde (10 ml) was stirred for 1 h. and then cooled to 0°C. Sodium borohydride (0.45 g, 12 mmol) was added portionwise over 1.5 h. The solution was then concentrated to a gummy residue which was partitioned between dichloromethane (25 ml) and 0.5 M aqueous sodium bicarbonate (10 ml). The aqueous layer was extracted with further dichloromethane (2 x 25 ml) and the extracts were then dried and concentrated to afford a pale yellow oil which displayed a single major spot on t.l.c. analysis. The purification of this oil by p.t.l.c. on silica with dichloromethane/10% methanol gave a single band. The recovery of this material from the silica with dichloromethane/10% methanol afforded a white powder (0.210 g) which displayed four components on t.l.c. analysis.

**Attempted One-Pot Reduction of 136 to 147 with Formic Acid and Sodium Borohydride**

(i) To 136 (0.299 g, 0.970 mmol) and powdered sodium borohydride (0.206 g, 5.45 mmol) in dry tetrahydrofuran (4 ml) at 0°C under nitrogen was added freshly distilled formic acid (2.8 ml, 80 mmol). A vigorous reaction ensued. The mixture was allowed to warm slowly to room temperature with stirring for 12 h. then cooled to 0°C and water (7 ml) was added. The mixture was made basic with 50% aqueous sodium hydroxide and then extracted with dichloromethane (4 x 10 ml). The
extracts were washed with saturated brine (7 ml) then dried and concentrated to give a white powder (0.296 g). Analysis of this material by GC-MS, with peak integration, indicated the presence of 147 (7%) and the formamide 149 (93%). Compound 149 displayed the following characteristic peaks with 2 conformers at approximately equal levels in CDCl₃ at room temperature. ¹H NMR δ: 8.47 and 8.34 (s, CHO), 7.80-6.65 (m, 8ArH), 6.62 and 5.92 (s, H6), 5.69 (d, J 15.3 Hz) and 5.18 (d, J 14.2 Hz, H4), 4.20 (d, J 14.2 Hz) and 3.87 (d, J 15.3 Hz, H4), 2.08 and 2.03 (s, CH₃); ¹³C NMR δ: 162.28 and 161.68 (CHO), 63.25 and 58.46 (C6), 41.07 and 37.49 (C4), 11.30 and 11.06 (CH₃); MS m/z: 338 (M⁺, 71%; Calcd. for C₁₈H₁₅N₄OCl 338.0932, found 338.095), 309 (95), 295 (100), 207 (54), 206 (63).

(ii) To 136 (0.203 g, 0.659 mmol) and powdered sodium borohydride (0.230 g, 6.07 mmol) in dry tetrahydrofuran (4 ml) at 0°C under nitrogen was added freshly distilled formic acid (1.9 ml, 54 mmol) dropwise over 3 h. The mixture was allowed to warm slowly to room temperature with stirring for 8 h. and then worked up as for (i) to afford a white powder (0.233 g). Analysis of this material by GC-MS, with peak integration, indicated the presence of 147 (47%), 136 (6%) and 149 (47%).

Investigation of the Proposed N-alkylation of 147 to 150

(i) The base 147 (99.2 mg, 0.305 mmol) was refluxed in acetone (3 ml) with ethylbromoacetate for 12 h. The solution was then cooled and concentrated. The residue was triturated with diethyl ether (4 x 2 ml) and dried to give a white powder (10.0 mg) which remained at the origin upon t.l.c. analysis with dichloromethane/10% methanol on silica. This material was unchanged when treated with DBU in acetonitrile.

(ii) The base 147 (0.623 g, 1.92 mmol) in dry dimethylformamide (20 ml) at 0°C was treated with ethoxycarbonylmethyltriflate (0.596 g, 2.51 mmol) dropwise. The solution was stirred for 1 h. at 0°C and then for 5 days at room temperature sealed and protected from light. The removal of the solvent under oil pump vacuum and trituration of the residue with hexane (4 x 5 ml) gave a white waxy oil which was
taken up in ethanol (7 ml) and stirred with potassium bromide (1.28 g, 10.8 mmol) for 2 h. Filtration of this mixture and concentration of the filtrate gave an off-white powder (0.921 g) which on $^1$H NMR analysis displayed many peaks between 2.96 and 2.40 $\delta$.

**Attempted N-oxidation of 147 to 152 with m-Chloroperoxybenzoic Acid.**

To the base 147 (53.0 mg, 0.163 mmol) in dichloromethane (5 ml) at 0°C was added a solution of m-chloroperoxybenzoic acid (51.7 mg, 0.300 mmol) in dichloromethane (2 ml) portionwise over 1 h. The solution was allowed to warm slowly to room temperature with stirring for 40 h. and then washed with 0.5M aqueous sodium bicarbonate (3 x 3 ml). The aqueous washings were concentrated and the residue was extracted with dichloromethane (5 ml). The dichloromethane solutions were then combined, dried, and concentrated to give a pale yellow powder (42.5 mg). The analysis of this material by GC-MS revealed many components. The major components had molecular ions at 322 (attributed to 151), 325, 296, 338 and 354 mass units.

8-Chloro-1,5-dimethyl-6-phenyl-5,6-dihydro-4H-s-triazolo[4,3-a]-[1,4]benzodiazepine N-Oxide 152 and 9-Chloro-1,5-dimethyl-7-phenyl-4,5-dihydro-7H-s-triazolo[4,3-a][5,1,4]benzoxadiazocine 153

To the base 147 (0.611 g, 1.88 mmol) in ethanol (50 ml) at 0°C was added a solution of monomagnesiumperoxyphthalate hexahydrate (0.71 g, 80% technical grade, 1.15 mmol) in water (20 ml). The solution was allowed to warm slowly with stirring for 35 h. and then 0.5M aqueous sodium bicarbonate (30 ml) was added. The mixture was then concentrated and the residue was extracted with dichloromethane (3 x 25 ml). The extracts were dried, filtered, and then concentrated to afford a mixture (65:35) of N-oxide 152 and triazolo[4,3-a][5,1,4]benzoxadiazocine 153, as a colourless hygroscopic solid (0.525 g). Compound 152 displayed the following discernible characteristic peaks. $^1$H NMR
δ: 5.61 (bs, H6), 4.38-4.31 (m, H4), 3.72-3.64 (m, H4), 2.87 (bs, NCH3), 2.45 (CH3); ¹³C NMR δ: 80.86 (C6), 57.27 (C4), 47.86 (NCH3), 12.26 (CH3).

The solid above was refluxed in dry acetonitrile (50 ml) for 50 min. Concentration and then purification of the residue by p.t.l.c. on silica with dichloromethane/10% methanol gave triazolo[4,3-a][5,1,4]benzoxadiazocine 153 (0.304 g, 50%) as a colourless solid. ¹H NMR δ: 7.46 (d, J 2.4 Hz, H8), 7.37 (dd, J 2.3 Hz, 8.3 Hz, H10), 7.20-7.17 (m, 3ArH'), 7.02 (d, J 8.3 Hz, H11), 6.78-6.75 (m, 2ArH'), 5.97 (s, H7), 4.43 (d, J 14.1 Hz, H4), 4.22 (d, J 14.1 Hz, H4), 2.80 (s, NCH3), 1.80 (s, CH3); ¹³C NMR δ: 152.75 (C1A), 151.99 (C3aA), 142.35 (C1'B), 138.68 (C7aB), 136.10 (C11aB), 130.80 (C9B), 130.23 (C8C), 129.85 (C10C), 129.14 (2C'), 128.89 (C'C), 128.69 (C11C), 125.83 (2C'), 86.43 (C7), 58.33 (C4), 46.60 (NCH3), 11.22 (CH3); MS m/z: 340 (M⁺, 15%; Calcd. for C₁₈H₁₇N₄OCl 340.1091, found 340.1080), 323 (24), 310 (22), 295 (36), 281 (100), 253 (51), 233 (39), 218 (78).

10b-Cyano-8,9-dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline 155

To a solution of the pyrrolo[2,1-a]isoquinolinium iodide¹⁵¹ 154 (15.13 g, 42.12 mmol) in methanol (100 ml) and water (200 ml), made slightly alkaline with sodium bicarbonate, was added sodium cyanide (7.0 g, 143 mmol). The solution was heated for 2 h. with slow evaporation to a volume of 190 ml then cooled and extracted with diethyl ether (3 x 100 ml) and chloroform (3 x 100 ml). The ether and chloroform solutions were each dried and evaporated to provide the 10b-cyanopyrrolo[2,1-a]isoquinoline derivative 155 (5.07 g and 5.01 g respectively, total 93%) as an oil. ¹H NMR δ: 6.70 (s, ArH), 6.62 (s, ArH), 3.88 (s, OCH3), 3.85 (s, OCH3), 3.22-3.16 (m, 2H), 3.17-2.93 (m, 2H), 2.85-2.70 (m, 3H), 2.08-2.00 (m, 3H); ¹³C NMR δ: 149.59 (C8A), 148.34 (C9A), 127.23 (C6aB), 126.96 (C10aB), 120.24 (CNB), 112.12 (C10C), 109.02 (C7C), 64.12 (C10b), 56.63 (OCH3), 56.43 (OCH3), 50.96 (C5D), 45.07 (C3D), 37.69 (C6), 27.66 (C1), 21.27 (C2); MS m/z: 231 (M⁺-HCN, 64%), 230 (100), 219 (28), 199 (15), 187 (11).
11b-Cyano-9.10-dimethoxy-1,2,3,4,5,6,7,11b-octahydrobenzo[a]quinolizine 157

The benzo[a]quinolizinium iodide\textsuperscript{152} 156 (X=I) (2.324 g, 6.227 mmol) was dissolved in water (60 ml) made slightly alkaline with sodium bicarbonate by mild warming, and potassium cyanide (1.42 g, 21.8 mmol) was then added. The solution was allowed to cool while stirring for 2 h. A precipitate was observed after 5 min. The suspension was extracted with diethyl ether (3 x 50 ml). Drying and then concentration of the ether extracts gave a solid which was recrystallised from ethanol/H\textsubscript{2}O to give the 11b-cyanobenzo[a]quinolizine 157 (1.094 g, 64%) as an off-white powder. \textsuperscript{1}H NMR \(\delta: 6.80\) (s, ArH), 6.58 (s, ArH), 3.86 (s, OCH\textsubscript{3}), 3.84 (s, OCH\textsubscript{3}), 3.12-3.00 (m, H), 2.89-2.50 (m, 6H), 1.87-1.58 (m, 5H); \textsuperscript{13}C NMR \(\delta: 149.28\) (C9A), 148.10 (C10A), 127.47 (C7aB), 126.90 (C11aB), 118.86 (CNB), 111.91 (C11C), 108.22 (C8C), 62.00 (C11b), 56.43 (OCH\textsubscript{3}), 56.21 (OCH\textsubscript{3}), 52.93 (C6D), 50.11 (C4D), 36.48 (C7), 28.84 (C1E), 25.09 (C3E), 22.34 (C2E); MS m/z: 245 (M\textsuperscript{+}-HCN, 95%), 244 (100), 230 (35), 216 (10), 123 (12).

8.9-Dimethoxy-10b-vinyl-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline 158a

A solution of vinylmagnesium bromide in dry tetrahydrofuran (90 ml) was prepared from vinyl bromide (9.9 g, 93 mmol). To this solution at 0°C under nitrogen was added dropwise a solution of the cyano derivative 155 (5.98 g, 23.1 mmol) in tetrahydrofuran (50 ml). The mixture was stirred for 24 h. at room temperature then treated with ice and basified with 40% aqueous potassium hydroxide. The supernatant liquor was decanted from the deposited solids which were then extracted with tetrahydrofuran (3 x 75 ml). The tetrahydrofuran extracts were centrifuged to remove the solids then concentrated. The residue was treated with 0.5 M aqueous sodium hydroxide (50 ml) and extracted with diethyl ether (3 x 100 ml). The ether extracts were washed with saturated brine (30 ml) then dried and concentrated. Purification of the residue by column chromatography on silica with dichloromethane/5% methanol gave the 10b-vinylpyrrolo[2,1-a]isoquinoline 158a (3.54 g, 59%) as a pale yellow oil. \textsuperscript{1}H NMR \(\delta: 6.59\) (s, ArH), 6.55 (s, ArH), 5.95
(dd, J 17.2 Hz, 10.3 Hz, H1'), 5.07 (dd, J 10.3 Hz, 1.5 Hz, H2'), 4.73 (dd, J 17.2 Hz, 1.5 Hz, H2'), 3.85 (s, OCH3), 3.84 (s, OCH3), 3.15-3.08 (m, 1H), 3.05-2.86 (m, H3 and 2H), 2.46-2.38 (m, 1H), 2.22-2.13 (m, H1), 1.92-1.81 (m, 1H2), 1.72-1.64 (m, 1H2); 13C NMR δ: 147.79 (C8A), 147.61 (C9A), 146.15 (C1'), 131.52 (C6aB), 127.66 (C10aB), 115.00 (C2'), 111.61 (C10C), 111.52 (C7C), 67.55 (C10b), 56.49 (OCH3), 56.26 (OCH3), 50.04 (C5D), 42.84 (C3D), 39.20 (C6), 23.82 (C1E), 23.13 (C2E); MS m/z: 259 (M+, 7%; Calcd. for C16H21NO2 259.1572, found 259.1565), 244 (4), 232 (100), 230 (18), 216 (12).

9,10-Dimethoxy-11b-vinyl-1,2,3,4,5,6,7,11b-octahydrobenzo[a]quinolizine 158b

A solution of vinylmagnesium bromide in dry tetrahydrofuran (80 ml) was prepared from vinyl bromide (15.9 g, 149 mmol). To this solution at 0°C under nitrogen was added dry tetrahydrofuran (70 ml) and the iminium salt 156 (X=Cl) (10.02 g, 35.6 mmol). The mixture was refluxed for 5 h. then cooled, treated with ice, and then basified with 40% aqueous potassium hydroxide. The supernatant tetrahydrofuran solution was decanted from the deposited solids then treated with water (30 ml) and diethyl ether (100 ml). The organic layer was separated and diethyl ether (3 x 100 ml) then used to further extract the solids and the aqueous solution. The organic extracts were combined and then concentrated. The residue was taken up in diethyl ether (100 ml) and washed with water (4 x 20 ml), saturated brine (20 ml), and then dried. Concentration and then column chromatography of the residue on silica with dichloromethane/5% methanol gave the 11b-vinylbenzo[a]quinolizine 158b (1.60 g, 16%) as a pale yellow oil. 1H NMR δ: 6.66 (s, ArH), 6.57 (s, ArH), 6.08 (dd, J 17.4 Hz, 10.7 Hz, H1'), 5.16 (dd, J 10.7 Hz, 1.5 Hz, H2'), 4.63 (dd, J 17.4 Hz, 1.5 Hz, H2'), 3.84 (s, OCH3), 3.82 (s, OCH3), 3.28-3.18 (m, H), 3.04-2.93 (m, H), 2.83-2.77 (m, H4 and H), 2.70-2.60 (m, H4), 2.55-2.47 (m, H), 2.00-1.96 (m, 2H), 1.73-1.58 (m, H3 and H), 1.52-1.46 (m, H); 13C NMR δ: 148.25 (C9A), 147.46 (C10A), 144.67 (C1'), 131.54 (C7aB), 127.88 (C11aB), 117.12 (C2'), 112.12 (C11C), 110.94 (C8C), 62.22 (C11b), 56.67 (OCH3),
56.33 (OCH₃), 49.41 (C₆D), 47.01 (C₄D), 35.59 (C₇), 26.64 (CIE), 25.87 (C₃E),
21.45 (C₂E); MS m/z: 273 (M⁺, 39%; Calcd. for C₁₇H₂₃NO₂ 273.1727, found
273.174), 272 (38), 246 (100), 244 (40), 230 (35), 205 (18).

Attempted Preparation of 8,9-Dimethoxy-10b-phenyl-1,2,3,5,6,10b-hexahydro-
pyrrolo[2,1-a]isoquinoline 159a

To a solution of phenylmagnesium bromide [from bromobenzene (9.8 ml, 94
mmol)], in dry tetrahydrofuran (30 ml) and dry diethyl ether (60 ml), under nitrogen
at 0°C, was added dropwise a solution of 155 (5.85 g, 22.6 mmol) in tetrahydrofuran
(50 ml). The mixture was allowed to warm to room temperature with stirring
overnight then worked-up as for 158a. Examination of the crude product by GC-MS
indicated many components were present. None had the desired molecular weight
for 159a.

Attempted Preparation of 9,10-Dimethoxy-11b-phenyl-1,2,3,4,5,6,7,11b-octahydro-
benzof[alquinolizine 159b

(i) To a solution of phenylmagnesium bromide [from bromobenzene (3.5 g, 22
mmol)], in dry tetrahydrofuran (25 ml), under nitrogen at 0°C, was added dropwise a
solution of 157 (1.520 g, 5.581 mmol) in tetrahydrofuran (50 ml). The mixture was
allowed to warm to room temperature with stirring overnight then worked-up as for
158b. The cyano compound was recovered. No other products were evident.
(ii) The procedure of (i) was repeated, but with the reaction mixture instead refluxed
for 4 h. The GC-MS analysis of the product residue indicated only traces of a
compound with the desired molecular weight.
(iii) To 157 (0.965 g, 3.54 mmol) in tetrahydrofuran (30 ml) under nitrogen was
added a solution of phenyl lithium (4 equiv.) in diethyl ether (20 ml). The mixture
was stirred for 2 h. then ice water (20 ml) and diethyl ether (50 ml) were added. The
ether layer was washed with water (4 x 20 ml) and saturated brine (2 x 15 ml) then
dried and concentrated to an oil which was triturated with hexane to remove
bromobenzene. The residue was purified by column chromatography on silica to provide a fraction containing the major product. The GC-MS analysis of this fraction suggested the major product was the reduced compound 9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-benzo[a]quinolizine.156

8,9-Dimethoxy-4-ethoxycarbonylmethyl-10b-vinyl-1,2,3,5,6,10b-hexahydro-pyrrolo[2,1-a]isoquinolinium Bromide 160a

To the base 158a (0.665 g, 2.56 mmol) in dry acetonitrile (3 ml) at 0°C under nitrogen was added dropwise a solution of ethoxycarbonylmethyltriflate (0.78 g, 3.3 mmol) in dry acetonitrile (3 ml). The solution was stirred for 1 h. at 0°C then 4 h. at room temperature, then concentrated. The residue was triturated with hexane (4 x 5 ml) then taken up in ethanol (6 ml) and stirred with potassium bromide (1.50 g, 12.6 mmol) for 2 h. before the addition of activated charcoal and filtration of the solution. The filtrate was concentrated and the residue then redissolved in dichloromethane and the filtration was repeated. Concentration of the filtrate gave the 4-ethoxycarbonylmethylpyrrolo[2,1-a]isoquinolinium salt 160a (1.014 g, 93%) as a tan solid. $^1$H NMR $\delta$: 6.74 (s, ArH), 6.47 (s, ArH), 6.17 (dd, $J_{17.1}$ Hz, 10.6 Hz, H1'), 5.91 (d, $J_{10.6}$ Hz, H2'), 5.69 (d, $J_{17.1}$ Hz, H2'), 4.35 (d, $J_{16.5}$ Hz, H of CH$_2$CO), 4.27 (q, CH$_2$ of Et), 4.13-3.92 (m, 5H), 3.88 (s, OCH$_3$), 3.81 (s, OCH$_3$), 3.20-3.13 (m, 2H), 2.92-2.84 (m, H), 2.58-2.50 (m, H), 2.42-2.32 (m, H), 2.30-2.22 (m, H), 1.72-1.64 (m, 1H2), 1.31 (t, CH$_3$ of Et); $^{13}$C NMR $\delta$: 164.73 (CO), 149.59 (C8A), 148.99 (C9A), 133.43 (C1'), 126.38 (C2'), 124.45 (C6aB), 121.18 (C10aB), 111.27 (C10C), 110.24 (C7C), 83.88 (C10b), 63.24 (CH$_2$ of EtD), 59.94 (NCH$_2$CO$_3$D), 56.84 (C3D), 56.30 (OCH$_3$), 56.24 (OCH$_3$), 51.96 (C5D), 34.23 (C6), 23.55 (C1E), 20.21 (C2E), 13.86 (CH$_3$ of Et).
9,10-Dimethoxy-5-ethoxycarbonylmethyl-11b-vinyl-1,2,3,4,5,6,7,11b-octahydro-benzo[a]quinolizinium Bromide 160b

To the base 158b (0.700 g, 2.56 mmol) in dry acetonitrile (3 ml) at 0°C under nitrogen was added dropwise a solution of ethoxycarbonylmethyl triflate (0.80 g, 3.4 mmol) in dry acetonitrile (3 ml). The solution was stirred for 1 h. at 0°C then 4 h. at room temperature, then concentrated. The residue was tritutated with hexane (4 x 5 ml) then taken up in ethanol (6 ml) and stirred with potassium bromide (1.58 g, 13.3 mmol) for 2 h. before the addition of activated charcoal and filtration of the solution. The filtrate was concentrated then the residue redissolved in dichloromethane and refiltered. Concentration of the filtrate gave the 5-ethoxycarbonylmethyl-benzo[a]quinolizinium salt 160b (0.908 g, 80%) as a tan solid. Two conformationally flexible diastereomers (ratio 3.3:1.0) were evident in the NMR spectra of this material. Discernible NMR peaks were: \(^1\)H NMR \(\delta\): 6.80 and 6.78 (s, ArH), 6.62 and 6.53 (s, ArH), 4.32-4.27 (m, CH\(_2\) of Et'), 3.91 and 3.90 (s, OCH\(_3\)), 3.87-3.83 (s, OCH\(_3\)), 1.36-1.30 (m, CH\(_3\) of Et); \(^13\)C NMR \(\delta\): 164.91 (CO), 150.49 and 150.17 (C\(_9\)A), 149.63 and 149.20 (C\(_{10}\)A), 135.25 and 133.54 (C1'), 128.46 and 127.90 (C2'), 112.14 and 112.02 (C11B), 110.11 and 109.38 (C8B), 623.75 (CH\(_2\) of Et), 56.83 (OCH\(_3\)), 56.58 (OCH\(_3\)), 14.25 (CH\(_3\) of Et).

Ethyl 9,10-Dimethoxy-7-vinyl-1,2,4,5,6,7-hexahydro-3,7-methano-3-benzazonine-12-carboxylate 161a

To the salt 160a (0.961, 2.25 mmol) in dry acetonitrile (30 ml) was added DBU (0.54 g, 3.5 mmol). The solution was refluxed for 20 h. then cooled and concentrated. Purification of the residue by column chromatography on alumina (25 g) with dichloromethane/33% hexane gave an impure yellow oil (36 mg) from the first eluted fraction. Further purification of this oil by preparative reverse phase HPLC with acetonitrile/20% water gave a colourless oil tentatively attributed to the 3,7-methano-3-benzazonine 161a (8 mg, 1%). \(^1\)H NMR \(\delta\): 7.51 (s, ArH), 7.10 and 7.01 (m, H1' and ArH), 5.52 (dd, \(J\) 17.2, 1.1 Hz, H2'), 5.18 (dd, \(J\) 10.9, 1.1 Hz, H2'),
4.19 (q, CH$_2$ of Et), 3.90 (s, OCH$_3$), 3.89 (s, OCH$_3$), 3.94-3.84 (m, 2H), 3.09-3.03 (m, H), 2.86-2.77 (m, H), 2.38-2.30 (m, H), 2.17-1.93 (m, 5H), 1.70-1.62 (m, H), 1.29 (t, CH$_3$ of Et); $^{13}$C DEPT NMR δ: 136.70 (C1''), 112.83 (C2''), 111.42 (C8A), 110.13 (C11A), 64.48 (C12), 61.02 (CH$_2$ of Et), 56.62 (2OCH$_3$), 48.71 (C2), 41.91 (C4B), 40.24 (C6B), 32.35 (C1C) 28.60 (C5C), 15.02 (CH$_3$ of Et).

**Attempted Base-Promoted Rearrangement of 160b to 161b**

(i) To the salt 160b (0.323, 0.733 mmol) in dry acetonitrile (20 ml) was added DBU (0.15 g, 0.99 mmol). The solution was stirred at 45°C for 18 h. then cooled and concentrated. The non-polar fraction of the residue was obtained by column chromatography on alumina (25 g) with dichloromethane/10% light petroleum and then purified by passage of the crude oil through an alumina plug with diethyl ether. Concentration of the ether solution gave an impure oil (5 mg) found to contain the precursor 158b as the major component (≥50%) upon GC-MS and $^1$H NMR spectral analysis.

(ii) To the salt 160b (0.203, 0.461 mmol) in dry acetonitrile (20 ml) at reflux under nitrogen was added DBU (0.10 g, 0.66 mmol). The solution was refluxed for 10 h. then cooled and concentrated. Workup as for (i) gave an impure oil (11 mg). GC-MS analysis of the oil revealed the presence of 158b (33%) and three isomers (10%, 36%, and 11%) possessing almost identical mass spectra, and consistent with the desired 3,8-methano-benzazecine 161b. MS m/z: 359 (M$^+$, 24%), 316 (15), 305 (69), 286 (100, M-CO$_2$Et), 246 (13), 188 (40).

(iii) To the salt 160b (0.147, 0.334 mmol) in dry butyronitrile (25 ml) at reflux under nitrogen was added DBU (0.080 g, 0.052 mmol). The solution was refluxed for 4 h. then cooled and concentrated to a dark residue. Workup as for (i) gave an impure oil (16 mg). GC-MS analysis of the oil gave a similar result to (ii).
8.9-Dimethoxy-10b-vinyl-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline N-Oxide 162a

The pyrrolo[2,1-a]isoquinoline 158a (3.54 g, 13.7 mmol) in dichloromethane (50 ml) at 0°C was treated with m-CPBA (3.28 g, 19.1 mmol) in dichloromethane (50 ml). The resultant solution was stirred for 40 h., while allowed to warm to 20°C, then water (100 ml) was added and the dichloromethane was removed in vacuo. The aqueous solution was basified with solid potassium carbonate and washed with diethyl ether (3 x 30 ml), then acidified with 3 M aqueous hydrochloric acid and again washed with diethyl ether (3 x 30 ml). The solution was rebasified and saturated with sodium chloride then extracted with chloroform (3 x 40 ml). The extracts were dried and then concentrated. Elution of the residue through an alumina plug with chloroform/20% methanol gave the pyrrolo[2,1-a]isoquinoline N-oxide 162a (2.92 g, 78%) as a mixture of the B-ring diastereomers (13.3:1) with the following diagnostic peaks. Major diastereomer: 1H NMR δ: 6.68 (dd, J 17.5 Hz, 10.6 Hz, H1'), 6.60 (s, ArH), 6.55 (s, ArH), 5.46 (d, J 10.6 Hz, H2'), 4.78 (d, J 17.5 Hz, H2'), 3.88 (s, OCH3), 3.84 (s, OCH3), 3.66-3.46 (m, 4H), 3.12-2.93 (m, 3H), 2.44-2.39 (m, 2H), 1.81-1.70 (m, H); 13C NMR δ: 149.08 (C8A), 148.27 (C9A), 139.78 (Cl'), 127.28 (C6aB), 123.48 (C10aB), 121.67 (C2'), 111.06 (C7 and C10), 82.24 (C10b), 63.96 (C5C), 57.29 (C3C), 56.44 (OCH3), 56.28 (OCH3), 34.80 (C6), 26.83 (C1), 19.87 (C2). Minor diastereomer: 1H NMR δ: 6.02 (dd, J 17.5 Hz, 10.6 Hz, H1'), 5.29 (d, J 10.6 Hz, H2').

9.10-Dimethoxy-11b-vinyl-1,2,3,4,5,6,7,11b-octahydrobenzo[a]quinolizine N-Oxide 162b

The benzo[a]quinolizine 158b (0.827 g, 3.03 mmol) in dichloromethane (30 ml) at 0°C was treated with m-CPBA (0.632 g, 3.67 mmol) in dichloromethane (15 ml). The resultant solution was stirred for 40 h., while allowed to warm to 20°C, then washed with 0.5 M aqueous sodium bicarbonate (3 x 10 ml). Drying and then concentration gave the crude benzo[a]quinolizine N-oxide 162b (0.723 g, 83%) as a
mixture of the B-ring diastereomers (5.7:1) with the following diagnostic peaks. Major diastereomer: $^1$H NMR $\delta$: 5.35 (d, $J$ 10.7 Hz, H2'), 4.49 (d, $J$ 15.5 Hz, H2'); $^{13}$C NMR $\delta$: 141.01 (C1'), 121.88 (C2'), 111.98 (C8A), 110.70 (C11A), 77.69 (C11b). Minor diastereomer: $^1$H NMR $\delta$: 5.50 (d, $J$ 10.7 Hz, H2'), 4.87 (d, $J$ 12.4 Hz, H2'); $^{13}$C NMR $\delta$: 136.52 (C1'), 125.10 (C2'), 111.66 (C8A), 109.83 (C11A), 76.09 (C11b).

9,10-Dimethoxy-7-vinyl-1,2,4,5,6,7-hexahydro-3,7-epoxy-3-benzazonine 163a

A solution of the N-oxide 162a (0.365 g, 1.33 mmol) in dry butyronitrile (20 ml) was refluxed for 1 h, then concentrated and the residue was extracted with diethyl ether. Concentration of the extracts and $^1$H NMR analysis of the residue (41 mg) indicated a mixture (1.9:1) of the 3,7-epoxy-3-benzazonine 163a and pyrrolo[2,1-c]isoquinoline 158a. Preparative reverse-phase HPLC purification of the mixture with methanol/20%water afforded the 3,7-epoxy-3-benzazonine 163a (22 mg, 6%) as a pale yellow oil. $^1$H NMR $\delta$: 6.56 (s, ArH), 6.49 (s, ArH), 5.94 (dd, $J$ 17.4 Hz, 10.7 Hz, H1'), 5.11 (dd, $J$ 17.4 Hz, 1.1 Hz, H2'), 5.05 (dd, $J$ 10.7 Hz, 1.1 Hz, H2'), 3.87 (s, OCH$_3$), 3.81 (s, OCH$_3$), 3.80-3.70 (m, H2A), 3.59-3.47 (m, H4 and H2A), 3.20-3.12 (m, H1A), 2.86-2.79 (m, H4), 2.51-2.42 (m, H1A), 2.32-2.25 (m, H6), 2.12-2.01 (m, H6), 1.81-1.66 (m, H5), 1.39-1.30 (m, H5); $^{13}$C NMR $\delta$: 147.78 (C9A), 147.37 (C10A), 145.03 (C1'), 135.06 (C7aB), 132.69 (C11aB), 113.81 (C2'), 113.58 (C8C), 112.53 (C11C), 82.87 (C7), 57.97 (C2D), 56.63 (OCH$_3$), 56.43 (OCH$_3$), 53.39 (C4D), 35.83 (C1E), 31.71 (C6E), 13.04 (C5); MS m/z: 275 (M$^+\ast$, 5%); Calcd. for C$_{16}$H$_{21}$NO$_3$ 275.1521, found 275.1513, 258 (27), 245 (6), 232 (100), 215 (35), 199 (14).

Other Thermolyses of 162a and 163a

(i) To dimethyl sulfoxide (10 ml) at 130°C was added 162a (105 mg). The solution was stirred for 50 min at 130°C then cooled and extracted with diethyl ether (3 x 15 ml). The combined ether extracts were washed with water (2 x 7 ml) and saturated
brine (5 ml), then dried and concentrated. $^1$H NMR analysis of the residue (29 mg) indicated a mixture (7.3:1) of 158a and 163a.

(ii) The N-oxide 162a (273 mg) was heated in an evacuated sealed tube for 1 h. at 120°C, then cooled and the residue was extracted with diethyl ether (5 x 2 ml). Concentration of the extracts and $^1$H NMR analysis of the residue (104 mg) indicated a mixture (2.9:1.4:1.0) of 158a and 162a and 163a.

(iii) The 3,7-epoxy-3-benzazonine 163a (12 mg) was refluxed in dry butyronitrile (2 ml) for 1 h. then the solution was cooled and concentrated. $^1$H NMR analysis of the residue showed the majority of the material was unchanged 163a (≥90%) although some 158a (≤10%) was detected.

10,11-Dimethoxy-8-vinyl-1,4,5,6,7,8-hexahydro-2H-3,8-epoxy-3-benzazecine 163b

A solution of the N-oxide 162b (0.846 g, 2.92 mmol) in dry butyronitrile (40 ml) was refluxed for 2 h. then cooled and concentrated. The residue was purified by column chromatography on silica with dichloromethane/0-2% methanol to give 2H-3,8-epoxy-3-benzazecine 163b (46 mg, 5%) as a colourless oil. $^1$H NMR $\delta$: 6.63 (s, ArH), 6.50 (s, ArH), 5.97 (dd, $J$ 17.4 Hz, 10.7 Hz, H1'), 5.12 (dd, $J$ 17.4 Hz, 1.5 Hz, H2'), 5.07 (dd, $J$ 10.7 Hz, 1.5 Hz, H2'), 3.86 (s, OCH3), 3.83 (s, OCH3), 3.58-3.47 (m, H2A), 3.11-3.05 (m, H2A and H1A), 2.86-2.82 (m, H4), 2.51-2.38 (m, H7 and H1A), 2.25-2.16 (m, H7), 1.80-1.60 (m, H5 and H6); $^{13}$C NMR $\delta$: 148.22 (C10A), 147.38 (C11A), 141.63 (C1'), 138.99 (C8aB), 128.57 (C12aB), 115.21 (C9C), 114.57 (C2'), 111.62 (C12C), 87.89 (C8), 56.85 (C2D), 56.52 (2OCH3), 56.07 (C4D), 43.16 (C1E), 33.53 (C7E), 30.74 (C5), 22.86 (C6); MS m/z: 289 (M+, 7%; Calcd. for C17H23NO3 289.1678, found 289.1684), 272 (100), 256 (5), 246 (7), 244 (7), 230 (6).
9,10-Dimethoxy-11b-cyano-1,2,3,4,5,6,7,11b-octahydrobenzo[a]quinolizine

**N-Oxide 164**

The 11b-cyanobenzo[a]quinolizine 157 (0.961 g, 3.53 mmol) in dichloromethane (20 ml) at 0°C was treated with a solution of m-CPBA (0.760 g, 4.42 mmol) in dichloromethane (15 ml). The resultant solution was stirred for 24 h. while allowed to warm to 20°C. The organic solution was washed with 5% aqueous sodium bicarbonate (5 x 20 ml) then dried and concentrated to a residual solid. The aqueous washings were combined and saturated with sodium chloride then back-extracted with chloroform (4 x 15 ml). Drying and then concentration of the extracts gave a second crop of solid. The solids were combined and then purified by column chromatography on alumina with dichloromethane/10% methanol to give the benzo[a]quinolizine N-oxide 164 (0.741 g, 73%) as a light tan powder. $^1$H NMR $\delta$: 6.70 (s, ArH), 6.69 (s, ArH), 4.14-4.04 (m, H), 3.92-3.78 (m, 2H), 3.88 (s, OCH$_3$), 3.85 (s, OCH$_3$), 3.50-3.44 (m, H), 3.39-3.34 (m, H), 2.88-2.73 (m, 3H), 2.49-2.44 (m, H), 2.04-1.96 (m, 2H), 1.74-1.70 (m, H); $^{13}$C NMR $\delta$: 150.49 (C9A), 149.07 (C10A), 125.49 (C7aB), 122.56 (CNB), 119.02 (C11aB), 112.60 (C11C), 109.06 (C8C), 69.75 (C11b), 66.69 (C4D), 63.32 (C6D), 56.91 (OCH$_3$), 56.67 (OCH$_3$), 29.55 (C7), 25.21 (C1E), 20.86 (C3E), 19.95 (C2E); MS m/z: 288 (M$^+$, 6%; Calcd. for C$_{16}$H$_{20}$N$_2$O$_3$ 288.1472, found 288.149), 271 (50), 245 (56), 244 (100), 230 (20), 164 (12); IR (thin film from CDCl$_3$): 2940, 2864, 2837, 1524, 1263, 1140, 729 cm$^{-1}$.

**Thermolyses of Compound 164**

(i) The N-oxide 164 (214 mg) was refluxed in dry acetonitrile (20 ml) for 18 h. then the solution was cooled and concentrated. Analysis of the residue by t.l.c. showed the majority of the N-oxide remained. The residue was partitioned between diethyl ether (30 ml) and water (10 ml) and the ether layer then washed with further water (2 x 5 ml). Drying and then concentration gave an impure oil (2 mg).

(ii) The N-oxide 164 (201 mg) was refluxed in dry butyronitrile (20 ml) for 10 h. then the solution was cooled and concentrated. Analysis of the residue by t.l.c. with
dichloromethane/10% methanol showed mainly material at the origin. The treatment of the residue as for (i) gave an orange oil (75 mg). Analysis of this material by GC-MS revealed two components (82% and 18%) with molecular ions at 246 and 272 mass units.

(iii) The N-oxide 164 (187 mg) was refluxed in dry dimethylformamide (20 ml) for 1 h. then the solution was cooled and concentrated. Treatment of the residue as for (i) gave a dark oil (100 mg). Analysis of this material by GC-MS revealed numerous minor components with a single significant component (40%) with MS: 272 (96%), 256 (31), 232 (100), 203 (32), 82 (69).

6.5 Experimental for Chapter Five

Investigation of the Epoxidation of 1-Vinylisoquinoline 49a and Derivatives with m-CPBA

(i) To 49a (117 mg, 0.501 mmol) in dichloromethane (10 ml) was added m-CPBA (258 mg, 1.50 mmol). The solution was stirred for 48 h. then extracted with 0.5 M aqueous sodium bicarbonate (2 x 5 ml). The aqueous washings were concentrated and the residue was extracted with dichloromethane (5 ml). The dichloromethane portions were combined then dried and concentrated to afford a yellow solid (97 mg). The NMR spectra confirmed the material was the N-oxide 123a.

(ii) To 49a (93 mg, 0.40 mmol) in chloroform (10 ml) was added m-CPBA (206 mg, 1.20 mmol). The solution was refluxed for 12 h. before workup as for (i) to afford a solid residue. The NMR spectra confirmed the material was the N-oxide 123a contaminated with some m-chlorobenzoic acid.

(iii) To 49a (113 mg, 0.484 mmol) in chloroform (10 ml) was added m-CPBA (250 mg, 1.45 mmol). The solution was refluxed for 1 h. before the addition of further m-CPBA (250 mg, 1.45 mmol) and continuation of reflux for 5 h. Workup as for (i) gave a dark solid residue. The NMR spectra confirmed the material was the N-oxide 123a contaminated with some m-chlorobenzoic acid.
(iv) To the hydrochloride salt 49a.HCl (54 mg, 0.20 mmol) in chloroform (6 ml) was added m-CPBA (79 mg, 0.46 mmol). The solution was stirred for 16 h. before workup as for (i) to afford a solid residue. The NMR spectra confirmed the material was the N-oxide 123a.

(v) To the methiodide salt 55a (147 mg, 0.392 mmol) suspended in chloroform (10 ml) was added a solution of m-CPBA (191 mg, 0.702 mmol) in chloroform (5 ml) dropwise, providing dissolution of the initial salt. After stirring for 15 h. a sample was withdrawn and then concentrated for analysis. The NMR spectra confirmed that 55a remained, along with m-chlorobenzoic acid.

(vi) To the methiodide salt 55a (53 mg, 0.14 mmol) in 1,2-dichloroethane (5 ml) at reflux was added m-CPBA (74 mg, 0.43 mmol). After refluxing for 3 h. a sample was withdrawn and then concentrated for analysis. The NMR spectra confirmed that 55a remained, along with m-chlorobenzoic acid.

Investigation of the Epoxidation of 1-Vinylisoquinoline 49a and Derivatives with Urea-Hydrogen Peroxide

(i) To the trifluoroacetic acid salt of 49a (379 mg, 1.09 mmol) with disodium hydrogen phosphate (1.352 g, 9.52 mmol) and urea-hydrogen peroxide (1.040 g, 11.1 mmol) in dry dichloromethane (8 ml) under nitrogen was added trifluoroacetic anhydride (0.40 ml, 2.83 mmol) dropwise. The mixture, with solid present, was refluxed for 1 h. then saturated aqueous sodium bicarbonate was added carefully to give a basic mixture. The organic layer was separated and the aqueous layer was extracted with dichloromethane (4 x 10 ml). The organic extracts were combined and washed with 5% aqueous sodium bicarbonate (5 ml) then water (5 ml). Drying and then concentration of the organic solution afforded only the free base 49a (98 mg, 39%).

(ii) To 49a (345 mg, 1.48 mmol) in dry acetonitrile (5 ml) under nitrogen was added trifluoroacetic acid (169 mg, 1.48 mmol) then a solution of urea-hydrogen peroxide (561 mg, 5.96 mmol) and trifluoroacetic anhydride (0.40 ml, 2.83 mmol) in dry
dichloromethane (8 ml). The mixture was stirred for 5 h. then saturated aqueous sodium bicarbonate (10 ml) and dichloromethane (15 ml) were added. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 x 5 ml). The organic extracts were combined and washed with 5% aqueous sodium bicarbonate (5 ml) then water (5 ml). Drying and then concentration of the organic solution afforded only 49a (268 mg, 78%).

Investigation of the Simmons-Smith Cyclopropanation of 1-Vinyltetrahydroisoquinoline 49a

A zinc-copper couple was prepared\textsuperscript{179} by the addition of zinc dust (3.0 g, 45.9 mmol) to a hot rapidly stirred solution of cupric acetate monohydrate (0.173 g, 0.866 mmol) in glacial acetic acid (5 ml), followed by stirring for 1 min. The mixture was briefly allowed to settle and then the acetic acid was decanted. The solid was washed with glacial acetic acid (2 x 5 ml) then diethyl ether (3 x 10 ml) and was used immediately.

To the zinc-copper couple (0.30 g, 4.6 mmol) and 49a (0.418 mg, 1.80 mmol) in dry diethyl ether (5 ml) under nitrogen was added a crystal of iodine. Methylene iodide (0.997 g, 3.72 mmol) was then added in three portions over 50 min. while the solution was brought to reflux. The mixture was refluxed for 10 h. with the deposition of a tan precipitate. Saturated aqueous ammonium chloride (5 ml) was then added. The supernatant liquor was decanted from the solids, which were then extracted with diethyl ether (3 x 5 ml). The ether extracts were washed with saturated aqueous sodium bicarbonate (2 x 5 ml) then dried and concentrated to afford only a trace of material (0.1 mg). The ether insoluble solid was extracted with chloroform (4 x 5 ml). These extracts were filtered then washed with saturated aqueous sodium bicarbonate (2 x 5 ml). Drying and concentration of the extracts afforded a tan powder assumed to be the methiodide salt 55a (0.468 g, 70%).
N-[2-(3,4-Dimethoxyphenyl)ethyl]cyclopropyl carboxamide 174a

Homoveratrylamine (30.03 g, 165.7 mmol) and cyclopropane carboxylic acid 173a (20.40 g, 237.0 mmol) were combined and stirred as a melt at 160°C for 4.25 h. under a slow stream of nitrogen to remove water vapour, then allowed to cool to a solid which was taken up in chloroform (300 ml). This solution was washed with 2M sodium hydroxide (3 x 80 ml), 3M hydrochloric acid (2 x 80 ml), 0.5M hydrochloric acid (3 x 60 ml), and water (60 ml) then dried and concentrated. The residue was recrystallised from ethyl acetate to give the cyclopropyl carboxamide 174a (28.59 g, 69%) as a colourless powder, m.p. 94-95°C. \(^1H\) NMR \(\delta\): 6.82 (d, \(J \) 8.4 Hz, ArH), 6.74 (d, \(J \) 8.2 Hz, ArH), 6.73 (s, ArH), 5.84 (bs, NH), 3.87 (s, OCH\(_3\)), 3.86 (s, OCH\(_3\)), 3.50 (q, H1), 2.77 (t, H2), 1.32-1.27 (m, H1'), 0.98-0.93 (m, 2H'), 0.74-0.67 (m, 2H'); \(^13\)C NMR \(\delta\): 174.15 (CO), 149.63 (C3"A), 148.26 (C4"A), 132.12 (C1"), 121.24 (C6"B), 112.55 (C2"B), 111.95 (C5"A), 56.50 (2OCH\(_3\)), 41.55 (C1), 35.96 (C2), 15.31 (C1'), 7.63 (C2', C3'); MS m/z: 249 (M\(^+\), 9%; Calcd. for C\(_{14}\)H\(_{19}\)NO\(_3\) 249.1364, found 249.1357), 165 (11), 164 (100), 151 (25), 149 (10), 69 (17); Anal. Calcd for C\(_{14}\)H\(_{19}\)NO\(_3\): C, 67.44; H, 7.68; N, 5.62%, found: C, 67.66; H, 7.85; N, 5.72%; IR (thin film from CDC\(_3\)): 3309 (NH), 1636 (CO), 1028 cm\(^{-1}\).

N-[2-(3,4-Dimethoxyphenyl)ethyl]-trans-2'-phenylcyclopropyl carboxamide 174b

Homoveratrylamine (12.2 g, 67.3 mmol) and trans-2'-phenylcyclopropane carboxylic acid 173b (13.14 g, 81.02 mmol) were combined and stirred as a melt between 140°C and 160°C for 5 h. under a slow stream of nitrogen to remove water vapour, then allowed to cool to a solid which was taken up in chloroform (150 ml). This solution was washed with 2M sodium hydroxide (3 x 35 ml), 3M hydrochloric acid (3 x 30 ml), water (20 ml), and saturated aqueous sodium chloride (20 ml) then dried and concentrated. The residue was recrystallised from ethyl acetate to give the t-phenylcyclopropyl carboxamide 174b (16.51 g, 75%) as a colourless powder, m.p. 116-117°C. \(^1H\) NMR \(\delta\): 7.27-7.17 (m, 3ArH), 7.06-7.03 (m, 2ArH), 6.80-6.70 (m, 3ArH), 5.85 (bs, NH), 3.84 (s, OCH\(_3\)), 3.82 (s, OCH\(_3\)), 3.50 (q, H1), 2.76 (t, H2),
2.48-2.42 (m, H2'), 1.60-1.52 (m, H1' and 1H3'), 1.23-1.17 (m, 1H3'); $^{13}$C NMR $\delta$: 172.53 (CO), 149.58 (C3"A), 148.23 (C4"A), 141.43 (C1"B), 131.92 (C1"B), 129.03 (2C"C), 126.84 (1C"C), 126.55 (2C"C), 121.21 (C6"D), 112.43 (C2"D), 111.91 (C5"D), 56.47 (OCH3), 56.39 (OCH3), 41.64 (C1), 35.87 (C2), 27.31 (C2E), 25.58 (C1'E), 16.52 (C3'); MS m/z: 325 (M+, 15%; Calcd. for C20H11NO3 325.1677, found 325.1674), 165 (12), 164 (100), 151 (16), 91 (6); IR (KBr disk): 3323 (NH), 1638 (CO), 1028 cm$^{-1}$.

1-Cyclopropyl-6,7-dimethoxy-3,4-dihydroisoquinoline 175a

The carboxamide 174a (32.44 g, 130.1 mmol) was refluxed in dry acetonitrile (500 ml) with phosphorus oxychloride (48 ml, 510 mmol) for 3 h. Ice was then added to decompose the excess reagent. The resultant solution was concentrated in vacuo until the majority of the organic solvent was removed, then water (700 ml) was added and the aqueous solution was washed with diethyl ether (3 x 100 ml). The aqueous solution was made basic with concentrated ammonia and then extracted with chloroform (4 x 300 ml). The extracts were dried and then concentrated to give the crude 1-cyclopropylimine 175a (26.50 g, 88%) as a grey solid. Recrystallisation of a portion of this material from ethanol gave a colourless powder, m.p. 80-81°C. $^1$H NMR $\delta$: 7.31 (s, ArH), 6.70 (s, ArH), 3.94 (s, OCH3), 3.93 (s, OCH3), 3.56 (t, H3), 2.60 (t, H4), 2.02-1.90 (m, H1'), 1.01-0.97 (m, H2'), 0.91-0.86 (m, H3'); $^{13}$C NMR $\delta$: 167.22 (C1), 151.33 (C6A), 148.09 (C7A), 131.80 (C4aB), 123.59 (C8aB), 110.74 (C5C), 109.52 (C8C), 56.83 (OCH3), 56.58 (OCH3), 47.41 (C3), 26.48 (C4), 15.24 (C1'), 7.66 (C2', C3'); MS m/z: 231 (M+, 88%; Calcd. for C14H17NO2 231.1259, found 231.1241), 230 (100), 216 (28), 214 (14), 200 (37), 184 (13); IR (thin film from CDCl3): 3001, 2936, 2832, 1512, 1281, 1142 cm$^{-1}$.

6,7-Dimethoxy-1-(t-2-phenylcyclopropyl)-3,4-dihydroisoquinoline 175b

The carboxamide 174b (16.50 g, 50.70 mmol) was refluxed in dry acetonitrile (300 ml) with phosphorus oxychloride (20 ml) for 3 h. Ice (50 g) was then added to
decompose the excess reagent. The resultant solution was concentrated until the majority of the organic solvent was removed, then water (300 ml) was added and the aqueous solution was washed with diethyl ether (3 x 75 ml). The solution was made basic with concentrated ammonia and then extracted with chloroform (3 x 75 ml). The yellow extracts developed a red colour. The extracts were dried and then concentrated to afford the crude \(1-(2'-\text{phenylcyclopropyl})\text{imine} \ 175b\) (15.50 g, 98%) as a red oil which was used without further purification. \(^1\text{H NMR} \delta: 7.32-7.16 \text{ (m, 5ArH")}, 7.07 \text{ (s, ArH)}, 6.68 \text{ (s, ArH)}, 3.89 \text{ (s, OCH}_3\text{)}, 3.81-3.74 \text{ (m, 1H3)}, 3.64 \text{ (s, OCH}_3\text{)}, 3.51-3.42 \text{ (m, 1H3)}, 2.68-2.58 \text{ (m, H4)}, 2.29-2.19 \text{ (m, 2H')}, 1.86-1.80 \text{ (m, 1H')}, 1.39-1.33 \text{ (m, 1H'); } ^{13}\text{C NMR} \delta: 165.90 \text{ (Cl)}, 151.29 \text{ (C6A)}, 148.05 \text{ (C7A)}, 142.60 \text{ (C4aB)}, 131.56 \text{ (C8aB)}, 129.03 \text{ (2C")}, 127.94 \text{ (C4"), 126.39 (2C")}, 123.23 \text{ (Cl"B)}, 110.69 \text{ (C5C)}, 109.36 \text{ (C8C)}, 56.52 \text{ (OCH}_3\text{)}, 56.39 \text{ (OCH}_3\text{)}, 47.58 \text{ (C3)}, 28.32 \text{ (C1'D), 26.68 (C2'D), 26.39 (C4'), 15.55 (C3'); MS m/z: 307 (M^+ 50%)}; \text{Calcd. for C}_{20}\text{H}_{22}\text{NO}_3 ~307.1572, \text{found 307.1586), 306 (83), 305 (100), 304 (63), 290 (21), 276 (12), 201 (18).}

1-Cyclopropyl-6.7-dimethoxy-2-methyl-3.4-dihydroisoquinolinium Iodide \(176a\)

To the crude 1-cyclopropylimine \(175a\) (21.3 g, 92.1 mmol) in dry acetone (140 ml) was added iodomethane (39.0 g, 280 mmol). The solution was refluxed for 3 h. with the formation of a yellow precipitate. A further portion of iodomethane (11.5 g, 81.6 mmol) was then added and the refluxing was continued for 1 h. The mixture was then cooled and concentrated to approximately 100 ml. The precipitate was collected and rinsed with cold acetone, then recrystallised from ethanol to afford the \(1\)-cyclopropylmethiodide salt \(176a\) (32.04 g, 93%) as yellow prisms, m.p. 212-213°C. \(^1\text{H NMR} \delta: 7.58 \text{ (s, ArH)}, 6.89 \text{ (s, ArH)}, 4.09 \text{ (t, H3)}, 4.03 \text{ (s, NCH}_3\text{)}, 4.00 \text{ (s, OCH}_3\text{)}, 3.94 \text{ (s, OCH}_3\text{)}, 3.30 \text{ (t, H4)}, 2.57-2.48 \text{ (m, H1')}, 1.52-1.44 \text{ (m, H2')}, 1.21-1.13 \text{ (m, H3'); } ^{13}\text{C NMR} \delta: 176.21 \text{ (C1)}, 156.48 \text{ (C6A)}, 148.47 \text{ (C7A)}, 133.56 \text{ (C4aB)}, 120.03 \text{ (C8aB)}, 113.81 \text{ (C5C)}, 111.06 \text{ (C8C)}, 57.32 \text{ (OCH}_3\text{)}, 57.05 \text{ (OCH}_3\text{)}, 53.07 \text{ (C3)}, 46.21 \text{ (NCH}_3\text{)}, 26.31 \text{ (C4)}, 14.42 \text{ (C1')}, 9.89 \text{ (C2', C3'); Anal. Calcd. for}
C_{15}H_{20}NO_{2}I: C, 48.27; H, 5.40; N, 3.75%, found: C, 48.24; H, 5.57; N, 3.85%; IR (thin film from CDCl₃): 2941, 1602, 1560, 1521, 1394, 1007, 920, 731 cm⁻¹.

6,7-Dimethoxy-2-methyl-1-(t-2-phenylcyclopropyl)-3,4-dihydroisoquinolinium Iodide 176b

Heating must be avoided at all stages in this preparation. The crude 1-(2'-phenylcyclopropyl) imine 175b (0.664 g, 2.16 mmol) was stirred at room temperature in dry acetone (6 ml) with iodomethane (0.32 g, 2.3 mmol), protected from light, for 3 days. Concentration and then recrystallisation of the residue from acetone/ethyl acetate gave the 1-(2'-phenylcyclopropyl) methiodide salt 176b (0.498 g, 51%) as yellow needles, m.p. 159-160°C. ¹H NMR δ: 7.35-7.22 (m, 5 ArH⁺, ArH), 6.85 (s, ArH), 4.11 (t, H3), 3.99 (s, NCH₃), 3.98 (s, OCH₃), 3.60 (s, OCH₃), 3.51-3.39 (m, 1H'), 3.37-3.25 (m, 1H'), 2.67 (t, H4), 2.02-1.96 (m, 1H'), 1.86-1.78 (m, 1H'); ¹³C NMR δ: 174.84 (Cl), 156.74 (C₆A), 148.76 (C₇A), 141.67 (C₅B), 139.16 (C₄aB), 133.67 (C₈aB), 129.54 (2C⁺), 127.81 (1C⁺), 126.51 (2C⁺), 120.44 (C₁"B), 113.67 (C₅C), 111.23 (C₈C), 57.45 (OCH₃), 56.68 (OCH₃), 53.38 (C₃), 47.00 (NCH₃), 27.67 (C₁¹D), 26.48 (C₄), 24.78 (C₂¹D), 20.23 (C₃⁺); Anal. Calcd for C_{21}H_{24}NO_{2}I: C, 56.13; H, 5.38; N, 3.12%, found: C, 56.41; H, 5.40; N, 3.02%; IR (KBr disc): 2932, 1603, 1563, 1521, 1292, 1265, 1219, 1010 cm⁻¹.

1-Cyclopropyl-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline 177a

To the 1-cyclopropyl imine salt 176a (30.45 g, 81.59 mmol) suspended in ethanol (600 ml) at 0°C was added sodium borohydride (8.74 g, 230 mmol) portionwise over 35 min. The solution was allowed to warm to room temperature with stirring over 2 h, then concentrated. The residue was partitioned between water (100 ml) and chloroform (400 ml). The chloroform layer was separated and washed with water (3 x 50 ml), then dried and concentrated to give the 1-cyclopropyltetrahydroisoquinoline 177a (19.24 g, 95%) as a colourless solid. Recrystallisation of a portion of this solid from 2-methyl-1-propanol gave a
colourless powder, m.p. 70-71°C. $^1$H NMR $\delta$: 6.92 (s, ArH), 6.58 (s, ArH), 3.85 (s, 2OCH$_3$), 3.22-3.17 (m, H1), 2.83-2.72 (m, H3, H4), 2.55 (s, NCH$_3$), 1.02-0.96 (m, H1'), 0.71-0.66 (m, H2'), 0.48-0.44 (m, H3'); $^{13}$C NMR $\delta$: 148.10 (C6A), 147.37 (C7A), 130.63 (C4aB), 126.85 (C8aB), 111.78 (C5C), 111.12 (C8C), 67.86 (C1), 56.47 (OCH$_3$), 56.34 (OCH$_3$), 49.66 (C3), 43.23 (NCH$_3$), 26.80 (C4), 15.76 (C1'), 5.21 (C2'), 4.47 (C3'); MS m/z: 247 (M+, 1%; Calcd. for C$_{15}$H$_{21}$NO$_2$ 247.1572, found 247.1579), 207 (13), 206 (100), 190 (8), 162 (3), 145 (2); Anal. Calcd for C$_{15}$H$_{21}$NO$_2$: C, 72.84; H, 8.56; N, 5.66%, found: C, 72.59; H, 8.51; N, 5.69%; IR: 2932, 1516, 1256, 1016 cm$^{-1}$. The methiodide salt of 177a recrystallised from methanol with m.p. 212-213°C. Anal. Calcd for C$_{16}$H$_{24}$NO$_2$I: C, 49.37; H, 6.21; N, 3.60%, found: C, 49.36; H, 6.34; N, 3.70%.

6,7-Dimethoxy-2-methyl-1-((t-2-phenylcyclopropyl)-1,2,3,4-tetrahydroisoquinoline 177b

The 1-((2'-phenylcyclopropyl) imine 175b (1.140 g, 3.709 mmol) was stirred at room temperature in dry acetone (10 ml) with iodomethane (0.576 g, 4.06 mmol) protected from light for 3 days. Concentration of the solution gave a dark residue which was suspended in dry ethanol (20 ml) at 0°C and treated with sodium borohydride (0.42 g, 11 mmol) portionwise over 30 min. The solution was allowed to warm with stirring over 2 h. then concentrated. The residue was partitioned between water (7 ml) and chloroform (30 ml). The chloroform layer was separated and washed with water (3 x 6 ml), then dried and concentrated to give a tan oil (1.121 g). Purification of this oil by column chromatography on silica with chloroform/0-2% methanol gave a mixture (55:45) of the $SSS$ and $RSS$ diastereomers of 177b (0.628 g, 52%). Further purification of a portion (268 mg) of this mixture by p.t.l.c. on silica with dichloromethane/10% methanol gave:

(a) $SSS$-1-((2'-phenylcyclopropyl)tetrahydroisoquinoline 177b (87 mg) as colourless needles from hexane, with m.p. 109-110°C. $^1$H NMR $\delta$: 7.27-7.22 (m, 2ArH$^+$), 7.17-7.14 (m, ArH$^+$), 7.07-7.03 (m, 2ArH$^+$), 6.90 (s, ArH), 6.59 (s, ArH), 3.85 (s,
OCH₃), 3.84 (s, OCH₃), 3.10-3.06 (m, 1H, H1), 2.79 (t, 2H), 2.81-2.77 (m, 1H), 2.53 (s, NCH₃), 1.97-1.92 (m, H2'), 1.47-1.40 (m, H1'), 1.17-1.11 (m, H3'); ¹³C NMR δ: 148.25 (C6A), 147.42 (C7A), 143.09 (C8aB), 130.43 (C4aB), 128.86 (2C'), 126.99 (C1''B), 126.14 (3C''), 111.86 (C5C), 110.98 (C8C), 67.15 (C1), 56.53 (OCH₃), 56.32 (OCH₃), 49.79 (C3), 43.81 (NCH₃), 27.81 (C4), 27.44 (C1''D), 23.75 (C2''D), 15.34 (C3'); MS m/z: 323 (M⁺, 2%; Calcd. for C₂₁H₂₅NO₂ 323.1885, found 323.1879), 305 (8), 219 (14), 206 (100), 190 (8); Anal. Calcd for C₂₁H₂₅NO₂: C, 77.98; H, 7.79; N, 4.33 %, found: C, 78.33; H, 7.77; N, 4.26.

(b) RSS-I-(2'-phenylcyclopropyl)tetrahydroisoquinoline 177b (69 mg) as colourless needles from hexane, with m.p. 100-101°C. ¹H NMR δ: 7.26-7.20 (m, 2ArH''), 7.15-7.13 (m, ArH''), 7.10-7.06 (m, 2ArH''), 6.88 (s, ArH), 6.55 (s, ArH), 3.82 (s, OCH₃), 3.57 (s, OCH₃), 3.19-3.14 (m, 1H), 3.03 (d, J 8.6 Hz, H1), 2.83-2.74 (m, 3H), 2.58 (s, NCH₃), 2.01-1.97 (m, H2'), 1.37-1.33 (m, H1'), 1.21-1.10 (m, H3'); ¹³C NMR δ: 148.14 (C6A), 147.53 (C7A), 143.01 (C8aB), 129.90 (C4aB), 128.97 (2C''), 126.78 (C1''B), 126.42 (3C''), 111.79 (C5C), 110.82 (C8C), 67.74 (C1), 56.36 (OCH₃), 56.24 (OCH₃), 50.72 (C3), 42.98 (NCH₃), 27.85 (C1''D), 26.83 (C4), 23.51 (C2''D), 16.24 (C3'); MS m/z: 323 (M⁺, 1%; Calcd. for C₂₁H₂₅NO₂ 323.1885, found 323.1875), 305 (3), 219 (8), 206 (100), 190 (9); Anal. Calcd for C₂₁H₂₅NO₂: C, 77.98; H, 7.79; N, 4.33 %, found: C, 78.24; H, 7.82; N, 4.34.

1-Cyclopropyl-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline N-oxide 178a

To the 1-cyclopropyltetrahydroisoquinoline 177a (1.46 g, 5.90 mmol) in dichloromethane (25 ml) at 0°C was added a solution of m-CPBA (1.40 g, 8.14 mmol) in dichloromethane (15 ml) dropwise. The solution was allowed to warm and stirred for 21 h. before the addition of 5% aqueous sodium bicarbonate (45 ml) and removal of the organic solvent in vacuo. The aqueous solution was washed with diethyl ether (3 x 20 ml) then concentrated to 10 ml and extracted with chloroform (3 x 30 ml). Drying and then concentration of the ether extracts provided a yellow
solid (32.6 mg). Drying and then concentration of the chloroform extracts gave a mixture (53:47) of the B-ring diastereomers of 1-cyclopropyltetrahydroisoquinoline N-oxide 178a (1.38 g, 89%) as a pale yellow hygroscopic solid. 1H NMR δ: 3.42 and 3.24 (s, NCH3); 13C NMR δ: 149.71 and 149.19 (C6A), 148.14 and 147.94 (C7A), 125.68 (C4aB), 123.35 and 123.08 (C8aB), 111.62 (C5C), 111.49 (C8C), 81.43 and 78.12 (C1), 60.79 and 60.30 (C3), 56.87 (NCH3), 56.61 (OCH3), 56.48 (OCH3), 26.95 and 25.78 (C4), 15.58 and 11.45 (C1'), 7.42 and 4.84 (C2'), 2.88 and 2.74 (C3').

6.7-Dimethoxy-2-methyl-1-(r-2-phenylcyclopropyl)-1,2,3,4-tetrahydroisoquinoline N-oxide 178b

To a mixture (SSS/RSS=0.47) of the 1-(2'-phenylcyclopropyl)tetrahydroisoquinoline diastereomers of 177b (0.947 g, 2.93 mmol) in dichloromethane (30 ml) at 0°C was added a solution of m-CPBA (0.70 g, 4.1 mmol) in dichloromethane (25 ml) dropwise. The solution was allowed to warm and stirred for 40 h. before the addition of water (20 ml) and the removal of the organic solvent in vacuo. The residual aqueous mixture was basified with potassium carbonate then washed with diethyl ether (4 x 10 ml). Drying and then concentration of the ether washes provided a yellow solid (0.041 g) containing mainly 177b. The aqueous layer was made just acidic to litmus with 3M aqueous hydrochloric acid and washed with diethyl ether (4 x 10 ml), then rebasified with potassium carbonate, saturated with sodium chloride, and extracted with chloroform (4 x 10 ml). The extracts were dried and then concentrated to give a crude mixture of the four possible diastereomers of the 1-(2'-phenylcyclopropyl) N-oxide 178b (0.834 g, 84%) as a pale yellow hygroscopic solid. 13C NMR δ: four peaks between 81-76 ppm (C1), four peaks between 65-60 ppm (C3), four peaks between 17-12 ppm (C2').
1-Cyclopropyl-6,7-dimethoxy-2-ethoxycarbonylmethyl-2-methyl-1,2,3,4-tetrahydroisoquinolinium Bromide 179a

To the 1-cyclopropyltetrahydroisoquinoline 177a (2.027 g, 8.195 mmol) in dry acetone (15 ml) was added ethyl bromoacetate (4.2 g, 25 mmol). The solution was refluxed for 8 h, then concentrated. The gummy residue was triturated with diethyl ether (3 x 10 ml) then dissolved in ethanol (20 ml), concentrated, and triturated with further diethyl ether (2 x 10 ml). The residue was dried at 80°C under oil pump vacuum to afford a mixture (55:45) of the B-ring diastereomers of the isoquinolinium salt 179a (2.95 g, 87%), as an off-white powder. 1H NMR δ: 3.82 and 3.59 (s, NCH₃); 13C NMR δ: 165.75 and 165.46 (CO), 150.05 (C₆A), 148.72 and 148.51 (C₇A), 122.53 and 121.98 (C₄Aᵢ), 121.06 and 120.84 (C₈Aᵢ), 111.35 (C₅ and C₈), 75.16 and 74.65 (C₁), 63.18 (CH₂ of CH₂CH₃), 60.36 and 56.79 (CH₂C of CH₂CO), 56.45 (2OCH₃), 55.13 and 54.28 (C₃ᵢ), 49.03 and 47.19 (NCH₃), 24.12 and 23.60 (C₄), 14.28 (CH₃ of CH₂CH₃), 13.87 and 13.43 (C₁'), 8.67 and 7.81 (C₂'), 4.66 and 4.47 (C₃').

6,7-Dimethoxy-2-ethoxycarbonylmethyl-2-methyl-1-(t-2-phenylcyclopropyl)-1,2,3,4-tetrahydroisoquinolinium Bromide 179b

To the predominantly SSS diastereomer of 177b (172 mg, 0.532 mmol, SSS/RSS=19) in dry acetone (2 ml) was added ethyl bromoacetate (0.75 g, 4.5 mmol). The solution was refluxed for 6 h, then concentrated. The gummy residue was triturated with diethyl ether (3 x 3 ml) then dissolved in water (5 ml). The aqueous solution was washed with diethyl ether (2 x 3 ml), removing some yellow colour. The aqueous solution was then saturated with sodium chloride and extracted with chloroform (3 x 3 ml). Drying and then concentration of the extracts gave the crude isoquinolinium salt 178b (225 mg, 90%), as a tan powder. 1H and 13C NMR analyses generally supported the presence of two B-ring diastereomers, however, the peaks were broad and often overlapping, preventing their assignment.
8.9-Dimethoxy-4-methyl-3-phenyl-2,3,5,6-tetrahydropyrrolo[2,1-a]isoquinolinium Iodide 180

(i) To the crude 1-(2'-phenylcyclopropyl) imine 175b (8.11 g, 26.4 mmol) in dry acetone (70 ml) was added iodomethane (11.2 g, 79.4 mmol). The mixture was refluxed for 4 h. The resultant yellow precipitate was collected and washed with cold acetone, then dried to give the tetrahydropyrrolo[2,1-a]isoquinolinium salt 180 (3.82 g, 32%). Concentration of the filtrate afforded crude 176b (7.37 g, 62%). The recrystallisation of 180 gave colourless needles from methanol, m.p. 168-170°C, or pale yellow prisms from acetonitrile, m.p. 175-178°C. Satisfactory elemental microanalysis results could not be obtained from either crystal type. 1H NMR δ (d6-DMSO): 7.58-7.49 (m, 5ArH'), 7.44 (s, H10), 7.18 (s, H1), 6.90 (s, H7), 5.52 (d, J 7.2 Hz, H3), 3.87 (s, OCH3), 3.80 (s, OCH3), 3.87-3.76 (m, H2), 3.50-3.43 (m, H5), 3.43 (s, NCH3), 3.32-3.22 (m, H6), 3.15 (dd, J 3.8 Hz, 18.4 Hz, H2), 3.00 (dd, J 4.1 Hz, 18.3 Hz, H6), 2.55-2.46 (m, H5); 13C NMR δ (d6-DMSO): 156.39 (C8A), 154.40 (C9A), 146.19 (C10bB), 138.90 (C10aB), 136.50 (C'), 135.08 (4C'), 129.04 (C1B), 123.72 (C10), 121.14 (C6aB), 116.95 (C1), 114.08 (C7), 85.01 (C3), 61.85 (OCH3), 61.52 (OCH3), 60.58 (C5), 54.83 (NCH3), 39.76 (C2), 29.51 (C6); MS m/z: 322 (M+I, 5%), 321 (25), 307 (M+-CH3I, 88; Calcd. for C20H21NO2 307.1572, found 307.1565), 306 (100), 290 (13), 230 (27), 142 (33); IR (KBr disc): 1609, 1512, 1265, 1018 cm⁻¹.

(ii) The 1-(t-2-phenylcyclopropyl)isoquinoline salt 176b (110 mg) was refluxed in dry acetone (5 ml) for 24 h. then the solution was cooled. Collection of the precipitate afforded 180 (74 mg, 64%).

Investigation of the Cloke Rearrangement of the 1-(2'-Phenylcyclopropyl) Imine 175b to 181

(i) To crude 175b (0.890 g, 2.89 mmol) in dry xylene (50 ml) was added ammonium chloride (2.0 g, 38 mmol). The mixture was refluxed for 2.6 h. then cooled and water (10 ml) and solid potassium carbonate were added to afford a basic aqueous
layer. The xylene layer was separated and washed with water (2 x 5 ml) then saturated aqueous sodium chloride (5 ml). Concentration of the xylene solution afforded a tan film (0.582 g) which, when analysed by t.l.c. and GC-MS, showed the presence of numerous compounds.

(ii) A mixture of crude 175b (0.355 g, 1.15 mmol) and ammonium chloride (0.090 g, 1.7 mmol) was heated at 160-170°C for 3 h. under a slow flow of nitrogen. The residue was then extracted with dichloromethane. The extracts were filtered and then concentrated to afford a film which, when analysed by t.l.c. and GC-MS, showed the presence of numerous unidentified compounds.

(iii) A mixture of crude 175b (0.371 g, 1.21 mmol) and ammonium chloride (0.090 g, 1.7 mmol) was heated at 195-200°C for 40 min. in a sealed tube under nitrogen. Work-up of the reaction as for (ii) afforded an unidentified mixture of numerous compounds.

1-Cyclopropyl-7,8-dimethoxy-3-methyl-1,3,4,5-tetrahydro-2,3-benzoxazepine 182a

A solution of N-oxide 178a (188 mg, 0.714 mmol) in butyronitrile/mesitylene (1:5 mixture, 25 ml) was refluxed at 143°C for 12 h. then concentrated. Passage of the residue through an alumina plug as a diethyl ether solution afforded, after concentration, a yellow oil (147 mg) which was purified by p.t.l.c. on silica with dichloromethane/5% ethanol to give the 1-cyclopropyl-2,3-benzoxazepine 182a (96 mg, 51%) as a colourless oil. 1H NMR δ: 6.77 (s, ArH), 6.67 (s, ArH), 4.35 (d, J 8.5 Hz, H1), 3.87 (s, OCH3), 3.85 (s, OCH3), 3.30-3.27 (m, 1H), 3.09-3.01 (m, 1H), 2.89-2.74 (m, 2H), 2.70 (s, NCH3), 1.26-1.19 (m, H1'), 0.69-0.60 (m, 2H'), 0.56-0.50 (m, 1H'), 0.45-0.41 (m, 1H'); 13C NMR δ: 148.00 (C7a), 147.71 (C8a), 134.35 (C9aB), 129.81 (C5aB), 114.38 (C6C), 110.99 (C9C), 89.93 (C1), 60.54 (C4), 56.66 (OCH3), 56.60 (OCH3), 47.25 (NCH3), 33.72 (C5), 15.74 (C1'), 4.11 (C2D), 3.78 (C3D); MS m/z: 263 (M+, 57%; Calcd. for C15H20NO3 263.1521, found 263.1516), 246 (18), 217 (14), 204 (100), 189 (75), 173 (57).
Investigation of the Conditions Necessary for the Rearrangement of \(N\)-Oxide 178a

(i) A solution of 178a (310 mg) in dry acetonitrile (25 ml) was refluxed under nitrogen for 3 h. then concentrated. Examination of the residue by t.l.c. and \(^1\)H NMR techniques showed the material was unchanged 178a.

(ii) A solution of 178a (310 mg) in dry acetonitrile (25 ml) was heated in a sealed tube at 111°C for 6 h. then concentrated. The residue was extracted with diethyl ether (3 x 10 ml). The ether extracts were washed with water (2 x 5 ml) then dried and concentrated to afford 182a (7 mg, 2%).

(iii) Compound 178a (303 mg) was heated in a butyronitrile (4 ml) and xylene (20 ml) mixture at 130°C for 5 h. Workup as for (ii) gave 182a (54 mg, 18%).

(iv) Compound 178a (110 mg) was heated at 215°C in an evacuated sealed tube for 15 min. The resultant dark oil was taken up in diethyl ether and eluted through an alumina plug. Concentration of the eluant afforded an oil (0.047 g, 42%) which contained 182a and an unidentified isomer (ratio 60:40) with the following distinctive spectral peaks. \(^1\)H NMR \(\delta\): 6.87 (s, ArH), 6.55 (s, ArH), 4.93 (d, \(J = 4.7\) Hz, 1H), 2.52 (s, NCH\(_3\)); \(^{13}\)C NMR \(\delta\): 15.20 (Cl'), 5.01 (C2A), 4.51 (C3A); MS m/z: 263 (M\(^+\), 1%), 248 (3), 206 (100), 190 (16), 162 (4), 103 (2).

(v) A solution of 178a (159 mg) in acetonitrile (200 ml) was irradiated with UV light passed through a duran glass sleeve (≥300 nm) for 1 h. Concentration and then examination of the residue by t.l.c. and \(^1\)H NMR analysis showed the original material was unchanged.

(vi) A solution of 178a (159 mg) in acetonitrile (220 ml) was irradiated with UV light passed through a vycor glass sleeve (≥230 nm) for 50 min. then concentrated. The resultant dark solid was taken up in diethyl ether and eluted through an alumina plug. Concentration afforded a solid (24 mg, 15%) which contained 182a (18%) and two other components detected by GC-MS analysis. The major component (65%) had a MS pattern identical to that of 175a.
7.8-Dimethoxy-3-methyl-1-(t-2-phenylcyclopropyl)-1,3,4,5-tetrahydro-2,3-benzoxazepine 182b

A solution of N-oxide 178b (303 mg, 0.894 mmol) in butyronitrile (5 ml) and mesitylene (25 ml) was refluxed at 143°C for 90 min. then concentrated and the dark residue taken up in diethyl ether (30 ml). The organic solution was washed with water (3 x 7 ml) then saturated aqueous sodium chloride (7 ml). Drying and then concentration of the ether solution afforded a mixture (55:33:12) of three components (0.256 g). Purification of this mixture by preparative reverse phase HPLC with acetonitrile/25% water gave:

(a) at 17.04 min., the SSS 1-(2'-phenylcyclopropyl)-2,3-benzoxazepine 182b (71 mg, 23%) as a colourless solid which crystallised from methanol, m.p. 102-103°C. 1H NMR δ: 7.28-7.23 (m, 2ArH''), 7.17-7.11 (m, 3ArH''), 6.78 (s, ArH), 6.68 (s, ArH), 4.78 (d, J 6.7 Hz, H1), 3.86 (s, OCH3), 3.71 (s, OCH3), 3.20-3.10 (m, 1H), 3.08-2.98 (m, 1H), 2.96-2.86 (m, 1H), 2.85-2.78 (m, 1H), 2.67 (s, NCH3), 2.08-2.01 (m, H2'), 1.62-1.54 (m, H1'), 1.17-1.06 (m, 2H3'); 13C NMR δ: 148.05 (C7A), 147.66 (C8A), 143.37 (C1''), 134.34 (C5aB), 130.89 (C9aB), 128.95 (2C''), 126.53 (2C''), 126.21 (1C''), 114.46 (C6C), 110.90 (C9C), 86.97 (C1), 60.67 (C4), 56.64 (OCH3), 56.42 (OCH3), 47.43 (NCH3), 34.47 (C5), 26.99 (C2D), 21.54 (C1D), 14.07 (C3'); MS m/z: 339 (M+, 3%), 305 (4), 280 (98), 249 (15), 206 (44), 189 (100); Anal. Calcd for C21H25NO3: C, 74.31; H, 7.42; N, 4.13%, found: C, 74.21; H, 7.35; N, 4.37%.

(b) at 19.34 min., the RSS 1-(2'-phenylcyclopropyl)-2,3-benzoxazepine 182b (83 mg, 27%) as a colourless solid which crystallised from methanol, m.p. 90-91°C. 1H NMR δ: 7.25-7.20 (m, 2ArH''), 7.15-7.05 (m, 3ArH''), 6.76 (s, ArH), 6.66 (s, ArH), 4.53 (d, J 8.6 Hz, H1), 3.84 (s, OCH3), 3.55 (s, OCH3), 3.12-2.89 (m, 3H), 2.88-2.79 (m, 1H), 2.74 (s, NCH3), 1.97-1.94 (m, H2'), 1.60-1.50 (m, H1'), 1.27-1.16 (m, 2H3'); 13C NMR δ: 147.91 (C7A), 147.58 (C8A), 142.62 (C1''), 134.35 (C5aB), 130.56 (C9aB), 128.98 (2C''), 126.38 (3C''), 114.40 (C6C), 110.66 (C9C), 88.78 (C1), 60.59 (C4), 56.58 (OCH3), 56.10 (OCH3), 47.61 (NCH3), 34.61 (C5), 27.95
(C2^D), 22.72 (C1^D), 14.89 (C3'); Anal. Calcd for C21H25NO3: C, 74.31; H, 7.42; N, 4.13%, found: C, 74.30; H, 7.33; N, 4.37%.

(c) at 26.98 min., the 4,3-benzoxazecine 183b (27 mg, 9%) described below.

**10,11-Dimethoxy-3-methyl-5-phenyl-1H-2,3,5,6-tetrahydro-4,3-benzoxazecine 183b**

The preparation of 182b described above gave the 4,3-benzoxazecine 183b (27 mg, 9%) as a colourless solid which crystallised from methanol, m.p. 146-148°C. 

1H NMR δ: 7.42-7.26 (m, 5ArH'), 6.78 (s, ArH), 6.69 (s, ArH), 6.65 (d, J 16.0 Hz, H8), 5.80-5.65 (m, H7), 4.52 (dd, J 3.2 Hz, 11.1 Hz, H5), 3.88 (s, OCH3), 3.86 (s, OCH3), 3.45-3.35 (m, 1H), 3.12-3.04 (m, 2H), 2.62 (s, NCH3), 2.59-2.39 (m, 1H and 2H6); 13C NMR δ: 148.00 (C10A), 147.86 (C11A), 143.90 (C1'), 134.45 (C8B), 132.69 (C8aC), 132.48 (C12aC), 132.25 (C7B), 128.97 (2C'), 127.83 (1C'), 126.59 (2C'), 113.84 (C9D), 111.48 (C12D), 84.16 (C5), 59.34 (C2), 56.66 (2OCH3), 45.52 (NCH3), 41.80 (C6), 28.01 (C1); MS m/z: 339 (M+, 6%; Calcd. for C21H25NO3 339.1834 found 339.1815), 322 (2), 280 (54), 232 (10), 206 (100), 189 (73); Anal. Calcd for C21H25NO3: C, 74.31; H, 7.42; N, 4.13%, found: C, 74.27; H, 7.41; N, 4.33%; IR (thin film from CDCl3): 1508, 1109, 700 cm⁻¹.

**Other Thermolyses of the N-Oxide 178b**

(i) A solution of 178b (288 mg) in dry acetonitrile (25 ml) was refluxed under nitrogen for 60 h. then concentrated. The residue was taken up in diethyl ether (30 ml) and the solution was washed with water (3 x 7 ml) and saturated aqueous sodium chloride (7 ml) then dried and concentrated to afford a yellow oil (141 mg, 49%). 

1H NMR analysis confirmed the oil contained RSS-182b, SSS-182b and 183b (56:33:11).

(ii) A solution of 178b (267 mg) in dry butyronitrile (25 ml) was refluxed under nitrogen for 2.5 h. Workup as for (i) afforded a yellow oil (129 mg, 48%) which contained RSS-182b, SSS-182b and 183b (52:35:13).
Thermolysis of the 1-(2'-Phenylcyclopropyl)-2,3-benzoxazepine 182b

A diastereomeric mixture (SRR/SSS=1.5) of 182b (0.168 g, 0.495 mmol) was heated in an evacuated sealed tube at 210°C for 30 min. $^1$H NMR analysis of the resultant oil confirmed the original material was unchanged.

Ethyl 1-Cyclopropyl-7,8-dimethoxy-3-methyl-1,2,4,5-tetrahydro-3H-3-benzazepine-2-carboxylate 184a

To the 1-cyclopropyl salt 179a (243 mg, 0.586 mmol) in butyronitrile (25 ml) at reflux was added DBU (0.13 ml, 0.87 mmol). The solution was refluxed for 8.5 h. then concentrated. Application of the residue to an alumina column and elution with dichloromethane/10% light petroleum (100 ml) gave, upon concentration, a dark oil (176 mg). Purification of this oil by p.t.l.c. on silica with dichloromethane/5% ethanol gave:

(a) the trans-butadiene isomer of 83b (9 mg, 5%).

(b) the major B-ring diastereomer of the 1-cyclopropyl-3-benzazepine 184a (88 mg, 45%) as a white waxy solid. $^1$H NMR $\delta$: 6.75 (s, ArH), 6.64 (s, ArH), 4.08 (q, CH$_2$ of CH$_2$CH$_3$), 3.85 (s, 2OCH$_3$), 3.51 (d, J 6.9 Hz, H2), 3.24-3.18 (m, 1H), 3.03-2.94 (m, 1H), 2.86-2.78 (m, 1H), 2.74-2.66 (m, 1H), 2.49 (s, NCH$_3$), 2.36-2.28 (m, 1H), 1.43-1.38 (m, H1'), 1.22 (t, CH$_3$ of CH$_2$CH$_3$), 0.68-0.64 (m, H2'), 0.59-0.52 (m, H2'), 0.30-0.50 (m, H3'), 0.17-0.10 (m, H3'); $^{13}$C NMR $\delta$: 173.01 (CO), 147.89 (C7A), 147.50 (C8A), 133.17 (C9aB), 132.89 (C5aB), 113.43 (C6C), 113.18 (C9C), 70.06 (C2), 60.51 (CH$_2$ of CH$_2$CH$_3$), 56.74 (OCH$_3$), 56.51 (OCH$_3$), 53.00 (C1), 51.05 (C4), 46.47 (NCH$_3$), 34.76 (C5), 15.18 (CH$_3$ of CH$_2$CH$_3$), 13.84 (C1'), 6.76 (C2'D), 5.44 (C3'D); MS m/z: 333 (M+, 5%; Calcd. for C$_{19}$H$_{27}$N$_2$O$_4$ 333.1940, found 333.1929), 260 (100), 204 (5), 189 (4), 130 (8).

(c) the cis-butadiene isomer of 83b (28 mg, 14%).

(d) the minor B-ring diastereomer of the 1-cyclopropyl-3-benzazepine 184a (34 mg, 17%) as a white waxy solid. $^1$H NMR $\delta$: 7.00 (s, ArH), 6.63 (s, ArH), 3.89 (q, CH$_2$ of CH$_2$CH$_3$), 3.86 (bs, 2OCH$_3$ and 1H), 3.31 (t, 1H), 3.06 (t, 1H), 2.79-2.72 (m, 1H),
2.65-2.56 (m, 1H), 2.54 (s, NCH₃), 2.41 (d, J 10.3 Hz, 1H), 1.71-1.64 (m, H₁'), 1.07 (t, CH₃ of CH₂CH₃), 0.77-0.72 (m, H₂'), 0.47-0.43 (m, H₃'), 0.18-0.13 (m, H₃');

¹³C NMR δ: 171.99 (CO), 147.74 (C⁷A), 147.46 (C⁸A), 134.03 (C⁹aB), 133.13 (C⁵aB), 113.00 (C⁶C), 111.62 (C⁹C), 70.04 (C₂), 60.28 (CH₂ of CH₂CH₃), 56.83 (OCH₃), 56.55 (OCH₃), 52.33 (C₁), 51.19 (C⁴), 45.76 (NCH₃), 35.92 (C⁵), 15.06 (CH₃ of CH₂CH₃), 14.58 (C¹'), 7.06 (C²D), 6.60 (C³D); MS m/z: 333 (M⁺, 4%; Calcd. for C₁⁹H₂₇N₀₄ 333.1940, found 333.1929), 260 (100), 204 (5), 189 (10).

Other Treatments of the 1-Cyclopropyl-2-ethoxycarbonylmethyl Salt 179a by Base

(i) To 179a (347 mg, 0.837 mmol) in dry acetonitrile (25 ml) under nitrogen was added DBU (0.15 ml, 1.0 mmol). The solution was stirred for 60 h. then concentrated. Analysis of the residue by t.l.c. and GC-MS techniques confirmed no reaction had occurred.

(ii) To 179a (360 mg, 0.869 mmol) in dry acetonitrile (25 ml) under nitrogen at 40°C was added dropwise a solution of 1.6M butyl lithium in hexane (0.70 ml, 1.1 mmol). A small amount of solid formed. The mixture was stirred for 44 h. at 40°C then concentrated and the residue was extracted with diethyl ether (4 x 10 ml). Concentration of the extracts gave a dark oil (72 mg, 26%). Analysis of the oil by \(^1\)H NMR and GC-MS techniques confirmed that only the diastereomers of 184a and 83b were present.

(iii) To 179a (303 mg, 0.731 mmol) in dry acetonitrile (25 ml) at 40°C was added DBU (0.52 ml, 3.4 mmol). The solution was stirred for 48 h. at 40°C before workup as for (ii) to give a dark oil (30 mg, 12%). Analysis of the oil by \(^1\)H NMR and GC-MS techniques confirmed that only the diastereomers of 184a and 83b were present.

(iv) To 179a (265 mg, 0.639 mmol) in chloroform (25 ml) at reflux under nitrogen was added DBU (0.12 ml, 0.83 mmol). The solution was refluxed for 67 h. before workup as for (ii) to give a dark oil (107 mg, 50%). Analysis of the oil by \(^1\)H NMR
and GC-MS techniques confirmed that only the diastereomers of 184a and 83b were present.

(v) To 178a (317 mg, 0.765 mmol) in dry acetonitrile (25 ml) at reflux under nitrogen was added DBU (0.15 ml, 0.99 mmol). The solution was refluxed for 5 h. then concentrated. Application of the residue to an alumina column and elution with dichloromethane/10% light petroleum (100 ml) gave, after concentration, a colourless oil (123 mg). Purification of this oil by p.t.l.c. on silica with dichloromethane/5% ethanol gave the diastereomers of 184a (82 mg, 32%; 23 mg, 9%) and 83b (21 mg, 8%; 10 mg, 4%).

**Ethyl 7,8-Dimethoxy-3-methyl-1-(t-2-phenylcyclopropyl)-1,2,4,5-tetrahydro-3H-3-benzazepine-2-carboxylate 184b**

To the 1-(2'-phenylcyclopropyl) salt 179b (225 mg, 0.459 mmol) in dry butyronitrile (25 ml) at reflux was added DBU (0.10 g, 0.66 mmol). The solution was refluxed for 8.5 h. then concentrated. Application of the residue to an alumina column and elution with dichloromethane/10% light petroleum (130 ml) gave, upon concentration, a dark oil (132 mg, 67%). Purification of this oil by preparative reverse phase HPLC with acetonitrile/25% water gave:

(a) at 14.12 min., a colourless film (2 mg, 1%) approximately 90% pure. The material was not identified. The $^1$H NMR spectrum was inconsistent with that expected for 185b.

(b) at 19.20 min., a mixture (1.66:1) of the B-ring diastereomers of 1-(2'-phenylcyclopropyl)-3-benzazepine 184b (60 mg, 31%) as a colourless oil with the following distinguishable NMR peaks. $^1$H NMR δ: 7.27-7.11 (m, 4ArH"), 7.02-7.01 (m, ArH"), 6.82 and 6.66 (s, ArH), 6.64 (s, ArH), 3.88 and 3.86 (s, OCH$_3$), 3.84 (s, OCH$_3$), 2.43 and 2.42 (s, NCH$_3$), 1.32 and 1.08 (t, CH$_3$ of CH$_2$CH$_3$); $^{13}$C NMR δ: 173.15 and 172.89 (CO), 147.77 (C7A), 147.60 (C8A), 133.02 and 132.75 (C9aB), 143.38 (C1"), 132.49 and 132.33 (C5aB), 128.92 (2C"), 126.87 (C"), 126.19 (2C"), 113.41 and 113.00 (C6C), 112.84 and 112.01 (C9C), 70.55 and 69.86 (C2), 60.79
and 60.64 (CH$_2$ of CH$_2$CH$_3$), 56.78 and 55.96 (OCH$_3$), 56.48 (OCH$_3$), 52.06 (C1), 51.21 and 50.80 (C4), 46.29 and 45.92 (NCH$_3$), 34.59 and 33.94 (C5), 26.98 and 25.59 (C2"D), 25.08 and 23.59 (C1"D), 17.85 and 16.15 (C3"), 15.22 and 14.92 (CH$_3$ of CH$_2$CH$_3$).

(c) at 29.94 min., a colourless film (4 mg, 2%) approximately 90% pure. The material was not identified. The $^1$H NMR spectrum was inconsistent with that expected for 185b.

(d) at 37.70 min., a colourless film (9 mg, 4%) approximately 90% pure. The material was not identified. The $^1$H NMR spectrum was inconsistent with that expected for 185b.
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APPENDIX

1. Conformational Modelling of the \textit{E-2,3,4,5-Tetrahydro-1H-3-Benzazonines}

The molecular modelling of the parent \textit{E-2,3,4,5-tetrahydro-1H-3-benzazonine} derivative (Section 2.3.4) afforded five low energy conformations, described in Table 2.4. The structures determined for conformers 2, 3, and 5 are shown below, with three perspectives of each conformation.

[Conformer 2 diagrams]
2. Conformational Modelling of the Z-2,3,4,5-Tetrahydro-1H-3-Benzazonines

The molecular modelling of the parent Z-2,3,4,5-tetrahydro-1H-3-benzazonine derivative (Section 2.3.4) afforded five low energy conformations, described in Table 2.5. The structures determined for conformers 4 and 5 are shown below, with three perspectives of each conformation.
3. Molecular Modelling of the Z-1,2,3,5-Tetrahydro-4,3-Benzoxazonine System

The molecular modelling of the parent Z-1,2,3,5-tetrahydro-4,3-benzoxazonine derivative (Section 3.7) afforded five low energy conformations, described in Table 3.9. The structures determined for conformers 3, 4, and 5 are shown below, with three perspectives of each conformation.
4. Conformational Modelling of the \(E\)-2,3,5,6-Tetrahydro-1\(H\)-4,3-Benzoxazecine 183b

The molecular modelling of the substituted \(E\)-2,3,5,6-1\(H\)-4,3-benzoxazecine derivative 183b (Section 5.6) afforded four low energy conformations, described in Table 5.4. The structures determined for conformers 2, 3 and 4 are shown below, with three perspectives of each conformation.

![conformer 2 diagram]
conformer 3

conformer 4