Asymmetric Aziridination of Alkenes

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by

Garfield Cecil Tughan B.Sc.

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To Mum and Dad
STATEMENT

The accompanying thesis submitted for the degree of Doctor of Philosophy entitled "Asymmetric Aziridination of Alkenes" is based on work conducted by the author in the Department of Chemistry of the University of Leicester between the period January 1984 and December 1986.

All the work recorded in this thesis is original unless acknowledged in the text or by references. None of the work has been submitted for another degree in this or any other university.

Date: 7th July 1987  Signed: C. Tughan
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Asymmetric Aziridination of Alkenes
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ABSTRACT

The work contained in this thesis is essentially concerned with the
development of methods for the asymmetric aziridination of prochiral
alkenes using N-nitrenes. The studies carried out are a necessary
first step in a strategy directed towards the enantiospecific
functionalization of alkenes.

The addition of the N-nitrenes derived by oxidation of the chiral
1-amino-2-(1,2,2-trimethylpropyl)benzimidazole and chiral 3-amino-
2-(1,2,2-trimethylpropyl)quinazolin-4(3H)-one (in the presence of
TFA) to prochiral alkenes are found to proceed with moderate to
high diastereoselectivities. The asymmetric inductions obtained
are rationalized in most cases by a transition state geometry for
the addition of the N-nitrene to the alkene.

A method of carrying out chiral oxoquinazolinyl nitrene additions
to alkenes both at low temperature (-60°C) (with the expected
increase in diastereoselectivity) and with ~ molar equivalents of
the alkene (with little loss of yield of the aziridine) is also
developed.

Conformational studies on the 7-(3,4-dihydro-2-(1,2,2-trimethyl-
propyl)-4-oxoquinazolin-3-yl)-2-oxa-7-aza-spiro[4,2]-heptane-1-one
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ABBREVIATIONS

Ac - acetyl
Ar - aryl
B.p. - boiling-point
Bu^t - tertiary butyl (Me₃C)
DMSO - dimethylsulphoxide
Et - ethyl
Ether - diethyl ether
Het. - heterocycle
HOS - hydroxylamine-O-sulphonic acid
LTA - lead tetra-acetate
Me - methyl
M.p. - melting-point
Nuc. - nucleophile
Ph - phenyl
iPr - isopropyl
TFA - trifluoroacetic acid
T.S. - transition state
T.S.G. - transition state geometry
CHAPTER 1
Introduction to Asymmetric Synthesis

1.1 Asymmetric synthesis and, in particular, the phenomenon of asymmetric induction, have evoked much current interest in the field of modern Organic Chemistry. This introductory chapter will deal primarily with the latter phenomenon and will review examples of asymmetric induction at nitrogen and in additions to carbon-carbon double bonds, i.e. examples relevant to the work contained in this thesis.

1.1.1 Enantiotopic and Diastereotopic Groups and Faces

In for example acetaldehyde (1), attack by an achiral reagent 'A' at one face of the carbonyl group gives a transition state (T.S.) and product which are the enantiomers of those arising from attack at the other face. Such faces are enantiotopic and, in this case, must give rise to a racemic mixture. However, attack at an enantiotopic face by

\[
\begin{align*}
\text{H} &\quad \text{Me} \\
\text{Me} &\quad \text{A}
\end{align*}
\]

\[
(1)
\]

a chiral reagent will give rise to diastereoisomers which will not be necessarily formed in equal amounts.

In (2) the two faces of the carbonyl group are obviously not equivalent: attack of an achiral reagent 'A' at one face will give rise to a product which is the diastereoisomer of that arising from attack at the other face. The two faces are diastereotopic.

\[
\begin{align*}
\text{Ph} &\quad \text{Me} \\
\text{Me} &\quad \text{A}
\end{align*}
\]

\[
(2)
\]
Enantiotopic and Diastereotopic Substituents

In the case of ethanol, if one of the hydrogens in the methylene group is replaced by a group Z one enantiomer (3) is obtained, while replacement of the other hydrogen gives the other enantiomer (4) (Figure 1): the hydrogens are enantiotopic.

Where two atoms or groups in a molecule are in such positions that replacing each of them in turn by a group Z gives rise to diastereoisomers, the atoms or groups are diastereotopic. An example of this is the methylene group of chlorocyclopropanone (5): one hydrogen from the methylene group is cis to the chlorine while the other is trans, and therefore are obviously different.

1.1.2

An asymmetric synthesis, in its broadest interpretation, includes a reaction or reactions of the substrate molecule in which an achiral unit (which must have enantiotopic or diastereotopic groups or faces) is converted by the reactant into a chiral unit in such a manner that the products (enantiomeric or diastereoisomeric) are produced in unequal amounts. It is, therefore, a process which converts a prochiral unit into a chiral unit such that unequal amounts of stereoisomeric
products result.

If a new chiral centre is created in a molecule, which is already chiral and a single enantiomer, the two diastereoisomers obtained are not (except fortuitously) necessarily formed in equal amounts. The reason is that the configuration of the new chiral centre may be determined by the chiral centre already there. This phenomenon has been termed asymmetric (or chiral) induction. Asymmetric induction, however, can also be brought about by the addition of a chiral reagent to an achiral (but prochiral) substrate. For example, in the Sharpless epoxidation an optically active epoxide is produced from a prochiral allylic alcohol via a chiral transition metal complex catalyst [see section 1.4.2].

Although the pioneering work on the concept of asymmetric induction was carried out by McKenzie and Ritchie, it was not, however, until the studies of Cram and Abd Elhafez on the stereochemistry of addition reactions of aldehydes and ketones having a chiral centre adjacent to the carbonyl group, that a rational interpretation using steric arguments was laid down. From these investigations came Cram's rule (see below). Furthermore, since this early work, most attempts to predict or rationalize the sense of asymmetric induction have, in fact, used the concept, devised by Cram, of large, medium and small groups on the pre-existing chiral centre.

Cram's rule predicts the predominant diastereoisomer in addition reactions to the carbonyl group of aldehydes and ketones containing an asymmetric α-carbon. For example, if such a molecule is observed along its axis, it may be represented by (6) (Figure 2). The oxygen of the carbonyl orientates itself so as to be between the small and medium-sized groups. The rule is that the incoming group preferentially
attacks on the side of the carbonyl bearing the small group.

Apart from the use of asymmetric induction as a means of obtaining certain optically active compounds, it may also be used to elucidate the factors (both steric and electronic) which control the relative energies of the two diastereoisomeric transition states and hence provide an insight into the geometry of the latter. This information, in turn, may allow changes to be made, which maximize the degree of asymmetric induction. For example, a reaction involving the asymmetric Grignard reduction of a ketone was investigated and employed as a tool for studying the factors involved in the transition state for the asymmetric reduction process. Thus, in the reduction of methyl t-butyl ketone (7) by the Grignard reagent (8) (Figure 3) it was proposed that the latter can attack either enantiotopic face of the carbonyl group via T.S.'s represented by (9a) and (9b). Since the T.S.'s are diastereoisomeric, the rates of the two reactions to give either (10a) or (10b) may be different. Common starting materials are used in both processes and the products differ only in the chirality of the products. Thus, the ground state energies of starting materials for the competing processes are identical and are also identical.
for the products. Therefore, in energy terms, the two processes can only differ significantly in their energies of activation [see section 1.2.2]. In (9a) the two larger groups are side by side in front of the plane of the 6-membered cyclic T.S., while the two smaller groups are side by side behind the plane of the T.S. On the other hand, in (9b), one large and one small group from the substrate and reagent oppose each other both in front and in back. Since this latter situation offers a better "fit" of the groups during the hydrogen transfer process, it would be predicted that (9b) represents the T.S. of lower energy and hence (10b) the preferred product. In practice this prediction is realised [12% e.e. of (10b) isomer].

1.2.1 Thermodynamically Controlled Asymmetric Transformations

These processes involve a molecule containing a stereolabile centre. For example, when a chiral sulphoxide is heated it undergoes unimole-
cular racemization via a planar or near planar T.S. (Figure 4). When R and R' equal phenyl and p-tolyl the energy barrier is 39 kcal mol$^{-1}$. \textsuperscript{8a}

\begin{center}
\begin{tikzpicture}

\node at (0,0) {\text{Transition State}};

\node at (-2,0) {\text{R}};
\node at (2,0) {\text{R'}};
\node at (0,1) {\text{O}};
\node at (0,-1) {\text{S}};
\node at (-2,1) {\text{R'}};
\node at (-2,-1) {\text{R}};
\node at (2,1) {\text{O}};
\node at (2,-1) {\text{S}};

\draw[->] (-2,1) -- (0,0) -- (2,-1);
\draw[->] (0,1) -- (2,0) -- (-2,-1);

\end{tikzpicture}
\end{center}

Figure 4

However, in this thesis the stereolabile centre which results in asymmetric transformation is inversion at the aziridine ring nitrogen: the nitrogen inveromers may be related as enantiomers (Figure 5A) or diastereoisomers (Figure 5B).

\begin{center}
\begin{tikzpicture}

\node at (0,0) {A}
\node at (2,-2) {\textbf{R = achiral}}
\node at (2,0) {R = achiral and $X \neq Y$}
\node at (2,2) {or}
\node at (2,4) {R = chiral and $X = Y$ or $X \neq Y$}

\node at (-2,0) {B}
\node at (0,-2) {R = achiral}
\node at (0,0) {R = achiral and $X \neq Y$}
\node at (0,2) {or}
\node at (0,4) {R = chiral and $X = Y$ or $X \neq Y$}

\end{tikzpicture}
\end{center}

Figure 5

Physical separation of nitrogen invertomers (by virtue of an absence of inversion at the aziridine ring) has only been achieved, however,
when the aziridine ring nitrogen has been substituted with a halogen\(^7\) [inversion barrier >23 kcal mol\(^{-1}\); see Chapter 2, Table 1].

All of the N-heterocyclic substituted aziridines described subsequently in this thesis have the diastereoisomeric invertomers in equilibrium at room temperature [inversion barrier ca. 18-22 kcal mol\(^{-1}\); see section 2.4.2] and are not separable at room temperature.

In such processes with low energy barriers the composition of the reaction mixture depends only on the free energy of the ground states of the two invertomers (\(\Delta G^0\)) and is independent of the pathway for interconversion;

\[
\text{i.e. } \Delta G^0 = G_\text{Invertomer A} - G_\text{Invertomer B} = -RT \ln K
\]

where: \(R\) = gas constant, \(T\) = absolute temperature, \(K\) = equilibrium constant for the process.

This may be described as in Figure 6 by an energy-reaction co-ordinate diagram where the invertomers are connected by a pathway which allows them to equilibrate under the conditions of the experiment. Since the interconverting species are diastereoisomers, in which there is one stereolabile centre, then this process represents epimerization (where \(\Delta G^0 \neq 0\)).
1.2.2 Kinetically Controlled Asymmetric Induction

The relative energy of two diastereoisomeric T.S.'s is usually the factor which determines the magnitude and sense of asymmetric induction. Figure 7 is an idealized energy profile diagram representing two types of kinetically controlled asymmetric induction in which the reactants are separated from the products by two diastereoisomeric T.S.'s. Type A represents the case where the kinetically most favoured product is also the thermodynamically most favoured one and type B the case where the kinetically most favoured product is the thermodynamically disfavoured one.

For all kinetically controlled asymmetric inductions, the reactants have the same ground state free energy. Only the free energies of activation (ΔG°) of the two pathways differ; the extent of asymmetric induction depends only upon the differences in free energy (ΔΔG°) of the competing pathways [Figure 7]. For a stereospecific reaction this difference in free energies is of the order of ca. 3 kcal mol⁻¹.

It should be noted that this analysis applies not only to the more familiar case where induction is brought about by a chiral centre within the same molecule but also where a chiral reagent is added to an achiral (but prochiral) substrate.
Moreover, it also applies to the case where a racemic substrate 
(-A) (+A) reacts with a limited amount (less than one mole equivalent) of a chiral reagent (R*) via two competing diastereoisomeric T.S.'s; 
i.e. A(-) + R* → [(-A)R]* → products 
A(+) + R* → [(+A)R]* → products 
When preferential reaction of one enantiomer of a racemic substrate with a chiral reagent occurs then this is termed a kinetic resolution.  
For incomplete reaction of the racemic substrate, the remaining unconverted substrate is enriched in the less reactive isomer.

1.3 Double Asymmetric Induction  
This concept concerns the interaction of two enantiomerically pure reactants: a substrate and a reagent. The concept is demonstrated in the following example of an aldol reaction in which either the asymmetry-inducing factors between a chiral enolate (12) and chiral aldehyde (13) augment each other to form a "matched-pair", or counteract each other to form a "mismatched-pair" (Scheme 1). Clearly the asymmetric induction is brought about by the combined influences of both chiral centres.

1.4 Asymmetric Additions to Alkenes  
Asymmetric induction in additions to carbon-carbon double bonds falls into two general categories. Either the reagent is chiral and the alkene has enantiotopic faces or the alkene has diastereotopic faces and the reagent is achiral.

The work contained in this thesis is concerned only with the former, and therefore a number of relevant examples concerning this type will be reviewed here.
Me-SiO
S-(13)  S-(12)

"matched-pair"

Scheme 1

SiMe3

R-(12)

S-(13)

"mismatched-pair"

(14a): (14b) = 8:1

(15a)

(15a): (15b) = 1:1.5
1.4.1 Asymmetric Epoxidation of Alkenes with (+)-Monopercamphoric acid

(+)-Monopercamphoric acid (16) delivers an epoxide oxygen to the two enantiotopic faces of styrene to give optically active styrene oxide\textsuperscript{18,19} (17) [Figure 8]. Predominant formation of the (-)-enantiomer of (17) is rationalized by the authors using a simple transition state model\textsuperscript{18,19} [Figure 9]. However, it is not clear from such a model what is actually determining the formation of the major enantiomer.

Furthermore, inspection of the probable transition state geometry (T.S.G.) depicted in Figure 9 suggests that it would be difficult to design a worse case for realizing asymmetric induction in the oxygen transfer step. The approach of the alkene is as far away from the chiral group as it can get, and in keeping with expectation the observed asymmetric induction is abysmal.
1.4.2 High Asymmetric Induction in Metal-Catalyzed Asymmetric Epoxidations of Allylic Alcohols

Sharpless et al.\textsuperscript{20} have devised a method of enantioselectively epoxidising prochiral allylic alcohols in high enantiomeric excess, using a titanium tetraisopropoxide catalyst in the presence of tert-butyl hydroperoxide and the (+) or (-) enantiomer of diethyl tartrate [Figure 10]. Depending on which tartrate enantiomer was employed, selective epoxidation of the "top" or the "bottom" face of the (prochiral) allylic alcohol resulted. This reaction was not only enantioselective, but also regioselective: only allylic alcohol double bonds were epoxidized in a substrate molecule that also contained other isolated double bonds.

1.4.3 Asymmetric Induction in Carbenoid Reactions

High enantioselectivity has been achieved by a carbenoid type reaction between an olefin and a diazoalkane, catalyzed by a chiral metal complex\textsuperscript{21} [Figure 11].

Approximately equal amounts of cis (19) and trans (19a) isomers are
formed. It is suggested that the enantioface selectivity is brought about by two cobalt-diazoalkane complexes, which convert to two diastereoisomeric cobalt-carbene-alkene complexes. Due to steric interactions one complex is favoured over the other, leading to the formation of an excess of one enantiomer.

1.5 Asymmetric Induction at Nitrogen

1.5.1 The reaction of imines (20) with chiral peracids yields optically active oxaziridines\textsuperscript{11,23} (21) [Figure 12]. Two types of

\begin{align*}
\text{R''} & \quad \text{N} \sim \text{R} \\
\text{R'} & \quad \text{C} \quad \text{O} \\
\text{C} & = \text{N} \sim \text{R}
\end{align*}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig12}
\caption{Optically active products have been obtained; those having both asymmetry at the ring nitrogen and at the ring carbon\textsuperscript{23} and those whose activity is due entirely to asymmetry at nitrogen.\textsuperscript{11}}
\end{figure}

1.5.2 The optically active aziridine (23), whose chirality depends on the absence of inversion at the aziridine ring nitrogen atom, has been obtained by asymmetric chlorination of the aziridine (22) by the
asymmetric chlorinating agent (24) [Figure 13] and isolated in 65% yield.

1.6 Further Examples of Reactions Resulting in Chiral Aziridines

1.6.1

Treatment of the optically active tosylate (25) with sodium ethoxide results in conversion to the corresponding optically active aziridine (26) [Figure 14]. This reaction, of course, is not an asymmetric induction.

1.6.2 Diastereoisomeric alkyl 1-alkylaziridine-2-carboxylates (30) have been synthesized from alkyl α,β-dibromopropionates (27) and chiral benzyamines (28) in the presence of base; invariably, low diastereoselectivities were obtained [Scheme 2]. Conversion of the aziridine (30) to chiral serine (31), allowed an optical rotation to be determined on the latter.

-14-
The epoxidation of double bonds using peracids is a widely used method in synthesis. The epoxide is invariably prepared only to be ring-opened and the derived product further transformed. Epoxidation of prochiral alkenes that can be directed to produce either enantiomer of the chiral epoxide has not yet been achieved, although Sharpless et al. have achieved epoxidation of allylic alcohols in high enantio-meric excess [see section 1.4.2].

The nitrogen analogue of epoxidation - 'aziridination' is, by contrast, an unfamiliar term in the Organic Chemist's vocabulary, even though aziridines themselves have the same useful features as epoxides as synthetic relay intermediates viz susceptibility to ring-opening in a controlled way. The recent work of Sharpless et al. serves as a reminder of the absence of useful methods for direct aziridination let alone methods which result in the formation of chiral aziridines.†

† Refer to the preceding sections [1.5 and 1.6] for the formation of chiral aziridines via alternative means [Refs. 25-27].
Direct aziridination can be achieved by nitrene addition to $\pi$-bonds although the intermolecular version of this reaction is possible with relatively few nitrenes. The characteristic reactivity of the latter nitrene class does not, in any case, commend them for useful synthesis of aziridines; their highly reactive nature often results in competitive insertion into $\sigma$ and $\pi$-bonds and their discrimination in reacting with different $\pi$-bonds is poor. Moreover, insertion into $\pi$-bonds at low concentration of the latter may be complicated by intervention of the triplet state of the nitrene and consequent non-stereospecific formation of aziridines.

However, there is a group of N-nitrenes whose members show almost complementary behaviour to that more commonly associated with nitrenes as reactive intermediates.

A method for asymmetric aziridination of prochiral alkenes using N-nitrenes would be the necessary first step in a strategy directed towards enantiospecific functionalization of the former [Scheme 3]. Scheme 3, of course, illustrates the ideal case in which a single enantiomer of (32) is produced, which is a chiral functionalized version of the original prochiral alkene. Moreover, in this strategy the chiral auxiliary, which has been cleaved off the ring-opened product, might be retrievable for amination and subsequently re-cycled to generate more of the N-nitrene.

Although N-N bond cleavage of these N-heterocyclic substituted aziridines has not been previously achieved, there are, however, numerous methods for the ring-opening of both unactivated [e.g. (33)] and activated [e.g. (34)] aziridines by both hetero (e.g. amines, thiol) and carbon nucleophiles (e.g. Grignard reagents, organocuprates, enolates, enediolates, malonates and related com-
pounds, \textsuperscript{30} and Wittig reagents \textsuperscript{37}). Moreover, methods have been reported
\begin{align*}
\ce{\begin{array}{|c|}
\hline 
\ce{N} \\
\hline 
\end{array}} 
\text{X} = \text{H, alkyl, aryl} \\
\text{for the regioselective ring-opening of activated aziridine-2-carboxylates}
\end{align*}
e.g. (35)] to provide substituted α-amino acids using heteroatomic
nucleophiles (e.g. \text{P(OMe)}_3, \text{thiols and thioacids}, \text{alcohols}, \text{amines}, \text{halides})..

Previous work carried out in these laboratories \textsuperscript{43} has shown that the
addition of optically active \text{N}-nitrenes to prochiral alkenes proceeded
with some asymmetric induction, although invariably the diastereoselectivities obtained were low. The ability of a chiral reactive
intermediate to bring about any asymmetric induction was considered a
remarkable phenomenon and prompted more studies to be undertaken in
this area.

The work contained in the following chapters is a record of the
investigations carried out in this field and is essentially concerned
with the development of effective methods for bringing about the first
step of the strategy in Scheme 3.
SCHEME 3

Strategy for Enantiospecific Functionalisation of Prochiral Alkenes.
CHAPTER 2
Introduction to the Chemistry of N-Nitrenes that Commends them as Agents for Asymmetric Aziridination of Alkenes

2.1 Nitrenes are the nitrogen analogues of carbenes. They are reactive intermediates containing a nitrogen atom with an incomplete electron shell, R-N. The species can exist as the electrophilic singlet state (36) or the diradical triplet state (37) [Figure 15].

![Figure 15](image)

There are several types of nitrene with differing properties and behaviour: R-N (alkyl nitrenes); Ar-N (aryl nitrenes); RO₂C-N (alkoxycarbonyl nitrenes); NC-N (cyano nitrenes) and R₂N-N (amino nitrenes). This thesis will be concerned only with amino nitrenes, and more specifically heterocyclic N-nitrenes, where the electron deficient nitrogen is bonded to another nitrogen and the substituents (R₁R₂) on this adjacent nitrogen form a heterocyclic ring.

The heterocyclic N-nitrenes may be conveniently generated by the oxidation of the corresponding N-amino compounds, using lead tetaacetate as an oxidising agent [Figure 16]. Iodosobenzene diacetate and peracids have also been used as the oxidising agents, although less commonly. This oxidative route in Figure 16 is
specifically used for producing N-, S- and O-nitrenes: the two principal methods for generating other nitrenes are, in fact, analogous to those used to form carbenes, i.e. α-elimination and the thermal or photolytic decomposition of azides.

N-Aminoheterocycles show a fascinating diversity of behaviour on oxidation. It is convenient to group the derived nitrenes according to the preferred type of reaction they undergo. The three main classes are:

a) rigid N-Nitrenes: these show little or no tendency to fragment or rearrange and when presented with a suitable reagent ('trap') undergo nitrene addition reactions, e.g. forming aziridines with alkenes and sulfoximines with sulfoxides. Without added nitrene traps, the above oxidations usually result simply in de-amination.

b) fragmenting N-Nitrenes: in these cases nitrene generation is followed by extrusion of dinitrogen. The remaining fragments may recombine, or undergo disproportionation or further fragmentation. Dimerization to form tetrazenes is frequently observed as a side reaction both of the fragmenting nitrenes and also of the rigid types. In most cases this will not be a true nitrene dimerization but a trapping of the nitrene by the unchanged amine, followed by further oxidation of the tetrazen so formed.

c) rearranging N-Nitrenes: these undergo ring enlargement by migration of a group attached to the adjacent substituted nitrogen atom (N-α) to the nitrene nitrogen.

Nitrenes derived from aromatic N-aminoheterocycles are represented in all three classes and it is not obvious what factors decide which pathway is taken. For example, the 1-aminobenzimidazole (38) forms a rigid nitrene (39) which does not rearrange to 1,2,4-benzotriazine.
aminoindazole (41) rearranges to form 1,2,3-benzotriazine (43) [Scheme 5] while the N-nitrenes (45) and (48), derived from 1-amino (44) and 2-aminobenzotriazole (47) respectively, fragment in different ways to produce benzyne (46) and mucononitrile (49) [Schemes 6 and 7].
However, sometimes one nitrene will show more than one type of reaction: the nitrene (62) derived from N-aminophthalimide (50) (NAP) is such an example, although it is predominantly a 'rigid' nitrene. On oxidation of NAP in the presence of moderate to high concentrations of alkene, good yields of aziridine are produced. However, on oxidation of NAP in the absence of a nitrene trap, a range of products are produced. These arise mostly from attack of the nitrene (62) on unoxidised NAP, although a small yield of benzocyclobutanedione (51) is obtained by extrusion of nitrogen.\textsuperscript{53} [Figure 17].

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Figure17.png}
\caption{Figure 17}
\end{figure}

Obviously, the characteristic reactivity of N-nitrenes in the two classes (b and c) above does not commend them for use in the synthesis of aziridines. However, a group of N-aminoheterocycles examined by Rees et al. on oxidation gave N-nitrenes whose intramolecular decay was sufficiently retarded for them to be trapped intermolecularly.\textsuperscript{54,55} N-Aminoheterocycles that fall into this class include those illustrated
in Figure 18, and characteristically they yield aziridines when oxidised in the presence of alkenes. Inspection of these heterocycles show that they all contain features that will reduce the availability of the substituted nitrogen (N-α)\textsuperscript{†} lone pair for stabilization of the nitrene; one or both of the N-substituents is a carbonyl or imino function or else the N-α lone pair is part of an aromatic ring. The effect of competition for the N-α lone pair is two-fold: nitrene behaviour (57) is made manifest [with the consequent suppression of the 1,1-diazene resonance hybrid\textsuperscript{84} (58)] and the tendency for elimination of nitrogen is reduced since the N=N bond order is effectively reduced.

\[ \text{N} \equiv \text{N} \leftrightarrow \text{N} \equiv \bar{\text{N}} \]  

(57) (58)

The nitrene derived by oxidation of the N-aminotriazole (59) is not a typical representative of this class of rigid N-nitrenes since it

\[ ^{\dagger} \text{N-α refers to the nitrogen in } \text{\textsuperscript{\alpha}N-N} : \]
shows characteristics of the fragmenting nitrenes (class b) also: it undergoes intramolecular fragmentation in competition with addition to the alkene\textsuperscript{57} [Scheme 8].

\begin{equation}
\begin{array}{c}
\text{Ph} - N - N - \text{Ph} \\
\text{NH}_2
\end{array}
\xrightarrow{\text{LTA or Ph(OAc)}_2}
\begin{array}{c}
\text{Ph} - N - N - \text{Ph} \\
: N:
\end{array}
\xrightarrow{R}
\begin{array}{c}
\text{PhCN} + \text{N}_2
\end{array}
\text{PhCN} + \text{N}_2

\text{Scheme 8}

\section{2.2 Alternative Methods for Aziridine Preparation}

\subsection{2.2.1 Aziridines from $\beta$-Amino alcohols and $\beta$-Haloamines}

The most obvious and oldest approaches to aziridine synthesis involve internal (neighbouring group) cyclisation of an amino group situated beta to a leaving group. The best known of these procedures are the Gabriel\textsuperscript{58} and Wenker\textsuperscript{59} syntheses [Scheme 9]. These reactions

\begin{equation}
\begin{array}{c}
\text{R} - N - \text{H} \\
\xrightarrow{X}
\end{array}
\xrightarrow{\text{base}}
\begin{array}{c}
\text{R} - N - \text{H}
\end{array}
\text{X} = \text{Br, Cl, I} \quad (\text{Gabriel}) \\
\text{X} = \text{OSO}_3^- \quad (\text{Wenker})

\text{Scheme 9}
show the expected stereospecificity and generally fail when the appropriate trans co-planar geometry cannot be assumed.

2.2.2 Aziridines from Oximes and Excess Grignard Reagents

The reaction between oximes and Grignard reagents\textsuperscript{60,61} gives aziridines: a reaction mechanism which includes nitrene formation, cyclisation to an intermediate azirine and Grignard addition to the strained imine bond of the azirine [Scheme 10] has been postulated though with little supporting evidence.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\text{Scheme 10}};
\end{tikzpicture}
\end{center}

2.2.3 Aziridines from Lithium Aluminium Hydride Reduction of Oximes

The reduction of oximes with lithium aluminium hydride yields aziridines, the reaction being stereospecific in that only cis-aziridine is formed\textsuperscript{62} [Figure 19].
2.2.4 Aziridines from 1,2,3-Triazolines

![Figure 20](image)

The formation of aziridines from triazolines [Figure 20] may be accomplished thermally (>100°C) or photochemically. Side reactions include imine formation, isomerization of the aziridine once formed and tar formation.

2.3 Addition of N-Nitrenes to Alkenes

The group of 'rigid' N-nitrenes examined by Rees et al. show almost complementary behaviour to that more commonly associated with nitrenes as reactive intermediates. This is illustrated quite clearly in their properties:

a) They have singlet ground states and hence always insert stereospecifically into π-bonds.

b) They do not insert into σ-bonds.

c) They insert into π-bonds substituted by either electron-donating or electron-withdrawing groups - they are ambiphilic in nature.

d) They show stereospecific formation of a single pyramid at the aziridine ring nitrogen in addition to monosubstituted alkenes (syn-selectivity).

e) They show selectivity in competitive insertion into different π-bonds.

2.3.1 Stereospecific Insertion into π-Bonds

The addition of these 'rigid' N-nitrenes to alkenes is stereospecific (even at low alkene concentration) and hence it is known that N-nitrenes
react in the singlet state. This conclusion comes from an extension of Skell's postulate\(^\text{68}\) for carbenes to nitrenes: concerted and hence stereospecific addition should be observed with singlet species and stepwise non-stereospecific addition with triplet species.

Nitrenes which have been most extensively studied (\(^\text{:\text{N-}CO_2\text{R, :N-C=N}}\)) do not possess substituents which can stabilize the singlet state and thus have triplet ground states. The question is therefore posed: why do \(\text{N}-\text{nitrenes}\) react in the singlet ground state? Clearly, the singlet state must have a particular stabilizing feature that overrides the expected stability\(^\text{83}\) of the triplet [Figure 21]. The simple explanation is that in the singlet state of \(\text{N}-\text{nitrenes}\) there is resonance stabilization by the adjacent nitrogen, due to the availability of an empty p-orbital on the singlet nitrene nitrogen [Figure 21]. However, this explanation does not completely suffice for this particular group of 'rigid' \(\text{N}-\text{nitrenes}\) as they all have features which severely limit the availability of the same lone pair; this consequently makes the proposed resonance stabilization a less important feature.

An alternative explanation is that the conversion from the singlet to the triplet may be very slow compared to the speed of the reaction, although proven stereospecific addition at low alkene concentration does make this explanation a less satisfactory one.
2.3.2 Ambiphilic Nature of N-Nitrenes

These 'rigid' N-nitrenes react with both electron-rich (e.g. styrene) and electron-deficient (e.g. methyl acrylate) alkenes. This ambiphilic nature has been rationalized in frontier molecular orbital terms using the HOMO_{Alkene} - LUMO_{Nitrene} or HOMO_{Nitrene} - LUMO_{Alkene} as the dominant interacting frontier orbitals [see (69) and (70)].

2.3.3 'Syn-Selectivity' of N-Nitrenes

Addition of these 'rigid' heterocyclic N-nitrenes to monosubstituted alkenes, bearing π-electron-containing substituents in conjugation with the double bond, gives a single nitrogen pyramid which, unexpectedly, has the substituent and heterocycle syn. However, the barrier to inversion at nitrogen dictates that this kinetically-formed syn-pyramid (60) inverts to the thermodynamically more favoured anti-pyramid (61) at temperatures >0°C [Scheme 11]. This syn-selectivity

\[
\text{Het - NH}_2 \rightarrow [\text{Het} - \ddot{\text{N}}] \rightarrow \text{Het} \begin{array}{c} \text{R} \end{array} \stackrel{\text{R}}{\text{H}} \\
\text{(60)}
\]

Where: R=Ph, CO₂Me, CH=CH₂ etc.

\[
\text{Het} \begin{array}{c} \text{R} \\
\text{(61)}
\]

\[
\downarrow^{>0\,^\circ\text{C}}
\]

is exhibited by all the N-nitrenes derived from the N-aminoheterocycles in Figure 18 that have been examined, and vinyl, alkoxycarbonyl and phenyl groups have been shown to exhibit a similar propensity for a syn-relationship in the kinetically-formed product. It has also been
shown that hydrogen has a negligible syn-selectivity effect when compared with the π-electron-containing substituents previously listed and that alkyl groups have a greater propensity for a syn relationship than hydrogen but less than π-electron-containing substituents. This is illustrated for the particular case of phthalimidonitrene (62) addition to both styrene and β-methylstyrene [Scheme 12]. In the

![Scheme 12](image)

addition of phthalimidonitrene (62) to styrene at <-20°C, the syn-invertomer (63a), which is formed exclusively, inverts completely to the thermodynamically more stable anti-invertomer (63b) at temperatures >0°C. The use of β-methylstyrene under the same conditions, however, results in a 94:6 mixture of (64a) to (64b) respectively showing that the methyl group has a syn-selectivity that is superior to that of hydrogen.

To account for this syn-selectivity in the formation of the thermodynamically unfavourable syn-product, an attractive secondary interaction
has been proposed between the heterocycle and the alkene substituent in the transition state for addition of the nitrene to the alkene: this attractive interaction is evidently replaced by a steric repulsive interaction in the aziridine to which the transition state leads. The nature of this attractive interaction is unclear. It is not known whether it is a secondary orbital interaction, i.e. one resulting from the favourable overlap of orbitals (but not leading to bonding) whose symmetry is directly related to the primary interaction (which leads to bonding and aziridine ring formation), or whether it is some electrostatic interaction. However, what is known is that an s-cis conformation for the diene or α,β-unsaturated ester is mandatory: thus, in this work, it has been shown that, e.g. phthalimidonitrene (62) reacts normally with α-methylene-γ-butyrolactone (65) whereas using the 2-butenolide (66), in which the α,β-unsaturated lactone is fixed in the s-trans conformation, no aziridine was isolated or detected in the crude reaction mixture [see Chapter 3]. The absence of reactivity of (66) also suggests that the interaction that brings about this syn-selectivity cannot be dismissed as a normal "secondary" one, if its absence results in no reactivity at all.

This syn-selectivity effect was of prime importance when these N-nitrenes were first considered as potential agents to carry out asymmetric aziridination reactions: without such an effect the expectation of achieving any asymmetric induction would have been small [see later].
2.3.4 Selectivity in Competitive Insertion of N-Nitrenes into π-Bonds

An illustration of the selectivity of these nitrenes in an intermolecular reaction is in the oxidation of N-aminophthalimide (50) in the presence of equimolar quantities of α-methylene-γ-butyrolactone (65) and methyl methacrylate. This gives the corresponding aziridines in a ratio of 2.3:1 respectively [see Chapter 3] and this may be rationalized in terms of the greater concentration of the lactone present in the s-cis conformation (100%) compared with the methyl methacrylate (<100%).

Furthermore, studies on the competitive intramolecular trapping of the N-nitrenes (67) and (68) by phenyl-substituted and unsubstituted double bonds have revealed different selectivities of the nitrene for the two double bonds. Whereas the addition of the N-nitrene (67) results in little selectivity for phenyl substituted vs. unsubstituted double bonds (1.5:1 respectively) the corresponding selectivity of the nitrene (68) was 5.8:1 respectively. This change in ratio has been interpreted in terms of a change in mechanism from non-concerted to concerted nitrene addition.

† I.r. studies (Ref. 24) on methyl acrylate have shown the s-trans conformation in solution to be more stable than the s-cis conformation by ΔH = 315 ± 45 cal mol⁻¹.
2.3.5 Transition State Geometry (T.S.G.) for the Addition of N-Nitrenes to Alkenes

At the root of the lack of understanding of the secondary interaction described previously, is an ignorance of the exact geometry of the T.S. for concerted nitrene addition to alkenes.

Examination of models of possible T.S.G.'s for this addition (using an s-cis conformation for the \( \alpha, \beta \)-unsaturated ester, diene, etc.) which would lead to the formation of a single nitrogen pyramid from monosubstituted alkenes as the kinetically formed product, led to the proposed T.S.G. shown in Figure 22. The T.S.G. depicted in Figure 22 shows the heterocycle and alkene contained in parallel planes, the \( N-N \) (nitrene) bond orthogonal to the plane containing the alkene \( \pi \)-electrons and an attractive secondary interaction between the substituent \( CR=CH_2 \) on the alkene and the starred carbon (C*) on the heterocycle. The assumption of this geometry can be justified in frontier molecular orbital terms by (69) and (70) (assuming sp-hybridisation for the nitrene N). If the nitrene approaches the alkene in this way, it is clear that the interactions are bonding and all that is required is that the electrons reorganize themselves into new bonds as the nitrene moves into place. The assumption made in this well-defined geometry, that the occupied p-orbital on the nitrene nitrogen...
is orthogonal to the filled p-orbital on the heterocyclic (N-α) ring nitrogen, is the arrangement which minimizes electron repulsion between electron pairs.

Further support for the T.S.G. illustrated in Figure 22 comes from studies on intramolecular N-nitrene additions to alkenes; the results agree with an orthogonal approach of the N-N bond of the nitrene to the C=C bond of the alkene.

If this picture of the T.S. has any validity, then it is clear that the substituent R on the prochiral alkene must approach closely to the substituent R¹ on the starred carbon C* on the heterocycle [Figure 22]. Furthermore, if the substituent (R¹) on C* were chiral, then its close approach to the substituent R on the prochiral alkene might lead to a distinction between the two faces of the latter and hence determine the configuration of the developing chiral centre of the aziridine ring [Figure 23]: this is no more than a particular case of asymmetric induction. If the N-nitrene were optically pure and if the discrimination between the two enantiotopic faces of the prochiral alkene was sufficient, a single optically active aziridine diastereoisomer could be produced [Figure 24]. Of course, the extent to which the reaction follows one diastereoisomeric transition state pathway over the other, is dependent solely on the difference in free energies of activation (ΔΔG*) of the competing pathways.
Newly formed chiral centres having opposite configuration

Figure 23

Two heterocycles which appeared to be well suited to test this theory were the N-aminobenzimidazole (38) and the N-aminoquinazolone (53), as both have positions α to the N-amino function to which a chiral substituent could be attached. This was the thinking which led to some preliminary studies being undertaken on the addition of optically active benzimidazolyl and oxoquinazolinyl nitrenes to prochiral alkenes. However, in most of the experiments attempted, very little diastereoselectivity was obtained and the highest asymmetric induction, expressed as a ratio of diastereoisomers, was 2.5:1. The fact that any discrimination was obtained at all was encouraging and as a consequence, more studies in this area were therefore deemed worthwhile.
2.4 Pyramidal Nitrogen Inversion

Inversion at the nitrogen pyramid takes place via a planar T.S. by a change in the hybridisation of the nitrogen from \( sp^3 \) to \( sp^2 \) [Figure 25]. As a consequence, the hybridisation of the nitrogen lone pair orbital changes from \( sp^3 \) to \( p \) in the T.S.

![Diagram](image)

2.4.1 Factors That Effect the Nitrogen Inversion Barrier

a) Ring Strain:

In simple alkyl amines the inversion barrier is low, being less than 5 kcal mol\(^{-1}\). However, incorporation of the nitrogen atom into a small ring system increases the inversion barrier as the ring size becomes smaller. A comparison of the inversion barriers for cyclic amines (71), (73), (75) and (77) in Table 1 shows this barrier to be highest for the 3-membered (aziridine) ring (77). This may be rationalized by the increased ring strain in the T.S. relative to the ground state (G.S.). During inversion it is necessary for the bond angles to increase ideally to 120° and this process is more inhibited in aziridines in which the ring bond angle is smallest.
b) Heteroatoms Bonded to Nitrogen:

With strongly inductively electron withdrawing substituents on N, the inversion barrier is increased. This is apparently due to two effects; firstly, the electron withdrawing inductive effect of the heteroatom demands increased p-character in the N-X bond (X=N, O, Cl) and so reduces the availability of a p-orbital for the nitrogen lone pair, thus making re-hybridisation in the T.S. more difficult. Secondly, heteroatoms usually possess lone pairs of electrons themselves, and unfavourable lone pair–lone pair interactions are increased in the T.S. From Table 1 (e.g. (71)-(76)) it can be seen that N-chloroamines have higher inversion barriers than the corresponding alkyl amines.

The combination of heteroatom substitution and ring strain enabled Brois\textsuperscript{76} to isolate two aziridine invertomers at room temperature: (82) was separated into its two diastereoisomeric forms.

c) Steric Effects:

As the size of the substituents on nitrogen is increased, the greater becomes the steric strain in the G.S. relative to the less hindered T.S. Therefore, more bulky substituents lower the inversion barrier, as seen in aziridines (77)-(79) in Table 1.

d) Electronic Effects:

Conjugation reduces the inversion barrier since delocalization of the nitrogen lone pair occurs better in the planar T.S. This significantly reduces the inversion barrier, as seen in (80), Table 1.

2.4.2 Pyramidal Nitrogen Inversion in 1-Heterocyclic Substituted Aziridines

A characteristic and complicating feature in determining diastereoisomeric aziridine ratios in Figure 24 in the \textsuperscript{1}H n.m.r. spectra at room
TABLE 1

Inversion Barriers in Some Cyclic Amines

<table>
<thead>
<tr>
<th></th>
<th>$\Delta G^\ddagger$ (kcal mol$^{-1}$)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(71) R = Me</td>
<td>6.8</td>
<td>70</td>
</tr>
<tr>
<td>(72) R = Cl</td>
<td>9.2</td>
<td>70</td>
</tr>
<tr>
<td>(73) R = Me</td>
<td>8.3</td>
<td>70</td>
</tr>
<tr>
<td>(74) R = Cl</td>
<td>10.3</td>
<td>70</td>
</tr>
<tr>
<td>(75) R = Me</td>
<td>10.0</td>
<td>70</td>
</tr>
<tr>
<td>(76) R = Cl</td>
<td>13.4</td>
<td>70</td>
</tr>
<tr>
<td>(77) R = Me</td>
<td>~22</td>
<td>71</td>
</tr>
<tr>
<td>(78) R = Et</td>
<td>19.4</td>
<td>72</td>
</tr>
<tr>
<td>(79) R = Bu</td>
<td>17.0</td>
<td>73</td>
</tr>
<tr>
<td>(80) R = COMe</td>
<td>&lt;6</td>
<td>74</td>
</tr>
<tr>
<td>(81) R = Ph</td>
<td>11.2</td>
<td>75</td>
</tr>
<tr>
<td>Me(\text{H})N-R (82) R = Cl</td>
<td>&gt;24</td>
<td>76</td>
</tr>
</tbody>
</table>

temperature of 1-heterocyclic substituted aziridines, is slow$^+$ inversion on the n.m.r. time scale at the aziridine ring nitrogen$^{78}$ [Table 2].

The barrier to inversion in these aziridines (i.e. free energy of activation barrier), $\Delta G^\ddagger$, is of the order of 18-22 kcal mol$^{-1}$. This is in the range of detection by n.m.r. spectroscopy. Below a barrier of ~5 kcal mol$^{-1}$ n.m.r. spectroscopy is unable to resolve signals from the two invertomers. However, with a barrier above ~23 kcal mol$^{-1}$, invertomers may be physically separated at room temperature.$^{76}$

$^+$ "Slow on the n.m.r. time scale" means that the actual inversion rate is $<\sim 100$ cycles s$^{-1}$.
TABLE 2

Rates of Nitrogen Inversion (in solution) in N-(Heterocycle-N-yl) Substituted Aziridines

<table>
<thead>
<tr>
<th>Temperature/°C</th>
<th>N.M.R. time-scale (-100 cycles s(^{-1}))</th>
<th>Real time-scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;-20</td>
<td>Negligible</td>
<td>Negligible</td>
</tr>
<tr>
<td>+20 (Room temperature)</td>
<td>Slow(^{a})</td>
<td>Fast(^{b}) (too fast for isolation of inverterners)</td>
</tr>
<tr>
<td>&gt;+150</td>
<td>Fast</td>
<td>Fast</td>
</tr>
</tbody>
</table>

\(^{a}\) [See footnote on previous page];
\(^{b}\) Inclusion of the aziridine ring into a crystal lattice has been shown to retard the rate of nitrogen inversion [Ref. 77].

The retarded rates of inversion in these aziridines at room temperature often result in the observation of both nitrogen inverterners by n.m.r. spectroscopy;\(^{67}\) the substituent(s) on the aziridine ring being either syn or anti to the heterocyclic ring. The observation of signals from the two nitrogen inverterners in the n.m.r. is due to the magnetic nuclei generally having different chemical shifts in the two species. However, whether signals from the two inverterners are actually seen or not depends on the position of the invertern equilibrium, which in turn is dependent on the ground state interactions of the substituents on the aziridine ring with the heterocycle.\(^{79}\) The ratio of inverterners determined at room temperature is called the thermodynamic ratio.

Formation of the aziridine ring at <-20°C, however, where the rate of nitrogen inversion on the n.m.r. and real time-scales is negligible [Table 2], allows the determination of the kinetic ratio of inverterners.
formed. This kinetically formed ratio invariably favours a syn-relationship of the substituent on the aziridine ring to the heterocycle (syn-selectivity) and is the result of secondary interactions referred to earlier.

2.4.3 The Use of Dynamic N.m.r. Spectroscopy for the Determination of the Energy Barrier for Nitrogen Inversion Processes

When nitrogen inversion is fast (i.e. \( >10^2 \) inversions s\(^{-1}\)) on the n.m.r. time-scale, the respective resonances of the two invertoners are not distinguishable and appear as 'averaged' signals. However, when inversion is slow on the n.m.r. time-scale the groups in the two invertoners become magnetically non-equivalent and are distinguishable. On increasing the temperature of the system, the rate of nitrogen inversion will increase and the two sets of signals will coalesce into one\(^{\dagger}\) [Table 2]. \( \Delta G^\ddagger \) for the nitrogen inversion process can be calculated from data at the coalescence temperature (\( T_c \)) using the expression (a):\(^{134}\)

\[
\Delta G^\ddagger = 19.12 \times T_c (10.32 + \log_{10} \frac{T_c}{K_c}) \quad \ldots \quad (a)
\]

\[
K_c = \frac{\pi \Delta \nu}{\sqrt{2}}
\]

where: \( \Delta G^\ddagger \) = barrier to inversion (in J mol\(^{-1}\))

\( T_c \) = coalescence temperature (in Kelvin)

\( K_c \) = rate of nitrogen inversion at \( T_c \)

\( \Delta \nu \) = frequency separation of coalescing signals in Hz, measured at temperatures lower than \( T_c \).

However, equation (a) is valid only for uncoupled signals and its accuracy has been questioned when unequally populated states in

\(^{\dagger}\) The coalescence point is defined such that a minimum between the 2 coalescing signals has just vanished.
equilibrium are involved.\textsuperscript{80,81,82} Studies by Fraser et al.\textsuperscript{80} have shown the use of the approximate equation (b) to be more reliable for the latter case:

\[
\begin{align*}
\text{e.g.} & \quad A \xrightleftharpoons[\text{major}]{K_B} B \\
& \xrightleftharpoons[\text{minor}]{K_A}
\end{align*}
\]

\[\Delta G^+ = 19.12 \times T_c (10.32 + \log_{10} \frac{T_c}{2} \times K_A \text{ or } K_B) \quad \ldots \quad (b)\]

where: \[K_A = 2 \times K_c \times \rho_B \text{ (i.e. rate constant for } A \rightarrow B)\]

and \[K_B = 2 \times K_c \times \rho_A \text{ (i.e. rate constant for } B \rightarrow A)\]

\(\rho_A\) and \(\rho_B\) represent the relative populations of the two sites as fractions.

Specific examples of calculations used for determining barriers to nitrogen inversion and N-N bond rotation for both equally and non-equally populated equilibria are given in Appendix 3.

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CHAPTER 3
Asymmetric Induction in the Addition of Benzimidazolyl Nitrenes to (Prochiral) Alkenes: Results and Discussion

3.1 Introduction

The following introductory discussion describes or defines certain stereochemical terms which will be routinely used subsequently.

3.1.1 Prochiral Alkene

This is an alkene in which the cis-addition of, for example, the elements H-X results in a chiral molecule. A prochiral alkene may be said to have two faces: attack on one face leading to one enantiomer and attack on the opposite face leading to its mirror image [Scheme 13]. Clearly, the role of H-X could be assumed by O or N to give epoxide or aziridine ring formation respectively.

Addition of one enantiomer of a singlet chiral nitrene, e.g. X(R)N:, however, to both faces of a prochiral alkene will give rise to diastereoisomers (each optically active) [Scheme 14].

Addition of a chiral but racemic nitrene, X(R)N: + X(S)N:, to both faces of a prochiral alkene will give rise to diastereoisomers (each racemic) [Scheme 15]. Aziridines (83) and (85) in Scheme 15 are mirror images, as are (84) and (86).
3.1.2 Asymmetric Induction

For the particular case of addition of a racemic chiral nitrene to a prochiral alkene, as illustrated in Scheme 15, asymmetric induction occurs when an excess of (83) and (85) is produced over (84) and (86) [or vice versa]. In principle this induction should be measurable from the n.m.r. spectrum of the crude nitrene addition product since these (racemic) diastereoisomers may differ in the chemical shifts of some (or all) of their respective resonances.

The 'sense' of asymmetric induction is the configuration of the induced chiral centre relative to the pre-existing nitrene chiral centre in the major diastereoisomer, i.e. 83 (85) or 84 (86). It is
apparent that the sense of asymmetric induction is dependent on the face of the prochiral alkene which is attacked and also on the nitrene enantiomer which is employed. If both of these are changed, the sense of asymmetric induction remains the same, but if either one is changed, the sense of asymmetric induction changes.

3.2 Further to the preliminary studies carried out on the addition of benzimidazolyl and oxoquinazolinyl nitrenes to prochiral alkenes, where a small amount of asymmetric induction was achieved, it was decided to re-examine asymmetric aziridination reactions using substituted benzimidazoles.

In order to bring about maximum discrimination between the two faces of the prochiral alkene, a transition state model was required which would aid in the design and suggest the required placement of the chiral centre on the heterocyclic N-nitrene.

Thus, for the particular case of addition of an optically active benzimidazolyl nitrene to an α,β-unsaturated ester, the two competing diastereoisomeric transition state models proposed are illustrated in Figure 26. Clearly, in this model, which has the secondary interaction between the benzimidazole ring and the s-cis conformation of the ester [see Figure 22], the attachment of the chiral group must be at position 2.

From Figure 26, the sense of asymmetric induction, i.e. which face of the α,β-unsaturated ester is attacked, will depend on the better 'fit' of the chiral substituent with the OR function of the ester. An assumption in this transition state model is that it is the 2-position of the benzimidazole ring which interacts secondarily with the ester and not the alternative position α to the ring nitrogen.
The transition state models illustrated in Figure 26 both lead directly to a single nitrogen pyramid having the ester and benzimidazole syn (the syn-selectivity effect\textsuperscript{67}).

3.3 Preliminary Studies on Asymmetric Aziridination of Prochiral Alkenes using the N-Aminobenzimidazoles (88), (90) and (91) as Nitrene Precursors

3.3.1 Synthesis and Oxidation of 1-Amino-2-(1-hydroxybenzyl)benzimidazole (88)

\[
\begin{align*}
\text{Figure 26} & \\
\text{Figure 27}
\end{align*}
\]

The benzimidazole (87) was prepared using Phillips' method,\textsuperscript{86} from o-phenylenediamine and mandelic acid, and aminated with hydroxylamine-O-sulphonic acid (HOS) to give the N-aminobenzimidazole (88) [Figure 27]. Reactions of the derived nitrene from (88) with methyl acrylate (95) and 2,3-dimethyl-1,3-butadiene (89) at room temperature gave a
ratio of diastereoisomers of 2.0:1 and 1.4:1 respectively [Table 3]. The diastereoisomeric ratios were obtained from the high field (400 MHz) 

$^1$H n.m.r. spectra of the crude oxidation products. These rather low 
levels of asymmetric induction were in agreement with the single 
reaction of (88) with styrene, carried out previously in this 
laboratory,$^{43}$ where a 1.1:1 ratio of diastereoisomers was obtained. 
An alternative chiral group on the 2-position of the benzimidazole ring 
was therefore considered necessary to improve the levels of induction.

3.3.2 Synthesis and Oxidation of 1-Amino-2-(D-gluco-1-acetoxy-(2,3),(4,5)-
diisopropylidene-2,3,4,5-pentanetetraol) benzimidazole (90) and 1-
Amino-2-(D-gluco-(2,3),(4,5)-diisopropylidene-1,2,3,4,5-pentane-
pentaol)benzimidazole (91)

The aim was to synthesize the N-aminobenzimidazoles (90) and (91) to 
see if the chiral acetalized sugar residue would bring about larger 
asymmetric inductions in the formation of aziridines. Protection of 
the free hydroxyl groups in the sugar residue was necessary due to the 
proclivity of lead tetra-acetate (used subsequently for generation of 
the corresponding N-nitrene) to cleave diols.

The N-aminobenzimidazole (90) was prepared by amination of the 
benzimidazole (92) with O-mesitylenesulphonylhydroxylamine. Benzimidazole 
(92) was obtained from D-sodium gluconoate and O-phenylenediamine using 
the Phillips method$^{86}$ for formation of the benzimidazole ring system, 
followed by acetalisation and acetylation [Scheme 16]. Only one isomer, 
(92), was produced in the acetalisation step.

The N-aminobenzimidazole (91) was prepared by base hydrolysis of a 
pure crystalline sample of (92), followed by amination with HOS [Scheme 
16]. This indirect route to (94) was used since the sample obtained 
was purer than that formed directly from acetalisation of (93). The 
use of a different aminating agent for (91) was an attempt to improve
the efficiency of this step which was found to be very low (12% isolated yield) for the amination of (92).

Reaction of the nitrenes derived from (90) and (91) at room temperature with various prochiral alkenes, e.g. 2,3-dimethyl-1,3-butadiene (89), methyl acrylate (95) and styrene, gave good yields of the corresponding aziridines and the addition did, in most cases, proceed with some asymmetric induction. From examination of the crude reaction mixture by high field n.m.r. spectroscopy, the presence of two diastereoisomers was easily distinguishable in every case. However, the degree of asymmetric induction was again low [Table 3] and in no case were the two non-crystalline diastereoisomers separated by chromatography.

Inspection of Table 3 reveals that the two best diastereoselectivities obtained were from addition of the N-nitrenes derived from (91) and (88) to methyl acrylate (95) (i.e. 3.6 : 1 and 2.0 : 1 respectively). What may be significant is that both these N-aminoheterocycles have a free hydroxyl group in the \( \alpha \)-position of their chiral side chains; hydrogen-bonding of this free hydroxyl group either within the benzimidazole-nitrene or with the methyl acrylate, may be a factor that brings about the greater selectivity, though it is difficult to see precisely how this occurs.

According to the proposed model [Figure 26] what ultimately determines which face of the (prochiral) alkene is attacked by the nitrene is whether the three sites for the substituents on the chiral group of the benzimidazole ring are differentiated enough in the T.S. Presumably, the rather flexible portion of the sugar residue (large group), the OH (or OCOCH\(_3\)) (medium group) and H (small group) do not have well-defined site preferences, or the disparity in size (or bulk) between the three
Scheme 16
**TABLE 3**

Asymmetric Induction [expressed as a ratio of aziridine (S) diastereoisomers] in the Addition of Benzimidazolyl Nitrenes to Prochiral Alkenes

<table>
<thead>
<tr>
<th>R*</th>
<th>CH(OH)CH-CH-CH-CH₂</th>
<th>CH(OAc)CH-CH-CH-CH₂</th>
<th>CH(OH)Ph</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO₂Me</td>
<td>3.6 : 1 (96)</td>
<td>1.1 : 1 (97)</td>
<td>2.0 : 1 (98)</td>
</tr>
<tr>
<td></td>
<td>1.4 : 1 (99)</td>
<td>1.2 : 1 (100)</td>
<td>1.4 : 1 (101)</td>
</tr>
<tr>
<td></td>
<td>1.05 : 1 (102)</td>
<td>1.7 : 1 (103)</td>
<td></td>
</tr>
</tbody>
</table>

[R* = Chiral group on 2-position of benzimidazole ring]
groups (particularly with COOCH₃ as a medium sized group) is not sufficient.

It was thought that the level of induction might be enhanced if R* on the 2-position of the benzimidazole ring was selected for the maximum disparity in size between its constituent groups and it was decided to synthesize (104) since, in this case, simple steric interactions would be likely to control which face of the prochiral alkene was preferred in the nitrene attack, without any complications from the hydrogen bonding effects which might be present in the additions of the nitrenes derived from (91) and (88).

\[
\text{Me} \quad \text{NHg} \\
(104)
\]

3.4 Synthesis of 1-Amino-2-(1,2,2-trimethylpropyl)benzimidazole (104)

\[
\text{Me} \quad \text{NHg} \\
(105) \quad (106)
\]

Reagents: i) POCI₃ - pyridine,
ii) NH₂SO₃ mesitylene - CH₂Cl₂

Scheme 17

The starting (racemic) 2,3,3-trimethylbutanoic acid (108) was prepared
by methylation of t-butylacetic acid using lithium diisopropylamide (LDA) and methyl iodide. No attempt was made to resolve the acid (108), although resolution has been previously accomplished by making a salt with a readily available alkaloid base, dehydroabietylamine, followed by separation of the resultant diastereoisomers by fractional recrystallization.  

Construction of the benzimidazole ring system was not straightforward; the usual Phillips' method of heating the carboxylic acid and o-phenylene-diamine in 4N hydrochloric acid proved unsuccessful. This was not too surprising since the hindered acids adamantane 1-carboxylic acid \(^4\) (109) and 2,2-dimethylpropionic acid \(^5,6\) (110) either do not react or give very low yields of the substituted benzimidazole using the Phillips method. This poor reactivity has been rationalized \(^5\) as the effect of steric hindrance and diminished electrophilic reactivity of the carboxyl group.

However, the racemic N-aminobenzimidazole (104) was eventually obtained in good yield by the route shown in Scheme 17. The acid chloride (105), obtained by the reaction of (108) with thionyl chloride, was reacted with o-phenylenediamine to produce the intermediate amide (106). Attempts to cyclise this amide by heating at high temperatures were unsuccessful. However, formation of the benzimidazole ring system was eventually accomplished in good yield using phosphoryl chloride as a cyclising agent. Amination of the benzimidazole (107) with O-mesityl-
enesulphonylhydroxylamine went in moderate yield (~50% by n.m.r.) but the yield of isolated N-aminobenzimidazole (104) was significantly lower (13%) due to the difficulty in its separation from the starting benzimidazole (107). The N-aminobenzimidazole (104) when pure, however, was crystalline and stable. It is possible that the yield in the amination step is reduced by protonation of the benzimidazole nitrogen in (107) by the mesitylenesulphonic acid produced in the reaction, thus rendering the nitrogen unavailable for amination.

3.5 Oxidation of 1-Amino-2-(1,2,2-trimethylpropyl)benzimidazole (104) in the Presence of Various Prochiral Alkenes

Initial studies on the syn-selectivity of the N-aminobenzimidazole (104) were carried out on this occasion in order to confirm that conditions for bringing about asymmetric induction were, in fact, present.

3.5.1 Oxidation of (104) in the Presence of Styrene at -20 to -25°C and at Room Temperature

Oxidation of (104) in the presence of styrene at -20 to -25°C and examination of the solution by n.m.r., without any intermediate warming of the solution, showed clearly that only the syn-invertomer (111a) of the aziridine was present. Allowing the solution to warm to room temperature resulted in complete inversion to the anti-invertomer (111b) [Figure 28].

![Figure 28](image_url)
It was clear, therefore, that the N-aminobenzimidazole (104) showed the same expected syn-specificity as other heterocycles in this family\(^{43}\) and that conditions for bringing about asymmetric induction were indeed present.

Examination of the spectrum of the anti-aziridine (111b) at room temperature and 300 MHz revealed the presence of two diastereoisomers in an 8.0 : 1 ratio. A rationalization for this diastereoselectivity is not easy: inspection of Figure 29, which shows the proposed T.S.G. for the N-nitrene addition to styrene, reveals a lack of a well defined site preference for Me and H and thus from this model the diastereoselectivity would have been anticipated to be low.

![Figure 29]

A repeat of this oxidation at room temperature gave a 5.6 : 1 ratio of diastereoisomers, a difference in selectivity with temperature which is not unexpected. The major diastereoisomer, of unknown configuration, was freed from the minor one by chromatography over alumina and isolated in 45% yield.

A similar oxidation carried out at room temperature, using phenyl iodosodi-acetate as an oxidising agent, produced an identical ratio of diastereoisomers (5.6 : 1) and the major diastereoisomer in this case was isolated by crystallization from acetonitrile in 61% yield. This identity in diastereoisomer ratios is good evidence for the intermediacy of the same species, presumably the N-nitrene, in each room temperature oxidation.
3.5.2 Oxidation of (104) in the Presence of Methyl acrylate (95) at Room Temperature

Examination of the n.m.r. spectrum of the crude reaction mixture obtained from oxidation of N-aminobenzimidazole (104) with methyl acrylate (95) at room temperature, revealed a 2.2:1 ratio of diastereoisomers of aziridine (112) [Figure 30]. Non-identical chemical shifts for all the protons (except aromatic ring protons) in the two diastereoisomers in the crude n.m.r. spectrum, allowed multiple checks on the ratio of diastereoisomers present. Complications from the presence of nitrogen invertdmers was not a problem in this case since the invertdmer equilibrium lay wholly on the side of the anti-isomer and only this invertdmer was observed in the n.m.r. spectrum at room temperature.

```
\[ \text{N} \begin{array}{c}
\text{Me} \\
\text{CHBu}^+ \\
\text{NH}_2 \\
\end{array} + \text{O} \begin{array}{c}
\text{Me} \\
\text{O} \\
\text{Me} \\
\end{array} + \text{Pb}(\text{OAc})_4 \rightarrow \text{N} \begin{array}{c}
\text{Me} \\
\text{CHBu}^+ \\
\text{N} \\
\text{CO}_2\text{Me} \\
\end{array} \]
```

Figure 30

This poor diastereoselectivity may be a consequence of the preferred conformation of the acrylate (95) in which the Me-O bond is cis to the C=O bond. This can be seen more clearly by considering the T.S.G. for the addition of the N-nitrene derived from (104) to methyl acrylate [Figure 31]. In Figure 31 the acrylate lies in a plane below that of

```
\[ \text{N} \begin{array}{c}
\text{Bu}^+ \\
\text{Me} \\
\text{Me(H)} \\
\text{Me} \\
\end{array} \]
```

Figure 31
the benzimidazole, with the substituents H and Me on the chiral group projecting down towards the acrylate and the Bu^ substituent projecting upwards towards the viewer. It is the extent to which the sites for Me and H are differentiated that determines which face of the prochiral alkene that is attacked. According to the model [Figure 31] the Me group of the ester in its preferred conformation is found to be positioned between that of the H and Me substituents on the chiral group. Lack of facial discrimination and hence poor diastereoselectivity is not unexpected, therefore, since well-defined site preferences for the Me and H are absent.

It was decided that with the α-methylene-γ-butyrolactone (65) as a nitrene trap, a more well-defined site preference for H and Me on the chiral group would ensue with a predicted T.S.G. for formation of the major diastereoisomer of the corresponding aziridine as depicted in Figure 32.

\[ \begin{array}{c}
\text{Figure 32}
\end{array} \]

3.5.3 Oxidation of (104) in the Presence of α-Methylene-γ-butyrolactone (65) at Room Temperature

Oxidation of the N-aminobenzimidazole (104) with LTA at room temperature, with α-methylene-γ-butyrolactone (65) as a nitrene trap, gave a 5.5 : 1 ratio of diastereoisomers of aziridine (113) [Figure 33]. This increased diastereoselectivity was in agreement with the predictions made above and, as an X-ray crystal structure on a related compound showed, with the proposed T.S.G. depicted in Figure 32.
Crystallization of the crude product from chloroform-light petroleum gave the pure major diastereoisomer (33%). A repeat of this oxidation using phenyl iodosodi-acetate instead of LTA as the oxidant gave an identical ratio of diastereoisomers (5.5:1) and this once again suggests that the same species, presumably a free nitrene, is involved in both cases.

\[
\text{Me} \quad \text{NH,} \quad (104) \\
\text{O} \quad \text{O} \quad \text{LTA or Phl(OAc)}_2 \\
\text{Bu}^\dagger \quad \text{N} \quad (65) \quad (113)
\]

Figure 33

Significantly, in an oxidation of N-aminophthalimide (50) in the presence of butenolide (66), no aziridine was observed or isolated [Figure 34]. This is evidence for the greater reactivity of the s-cis conformation of lactones and also, presumably, acyclic α,β-unsaturated esters in the T.S.'s for their addition to N-nitrenes.

\[
\text{N} \quad \text{O} \\
\text{O} \quad \text{NH}_2 \\
\text{N} \quad \text{O} \\
\text{O} \quad (50) \quad (66) \quad \text{X}
\]

Figure 34

To exclude the possibility that the species observed in the spectrum of the crude oxidation product of (113) were in fact inverteomers (or other conformational isomers), the crude product was repeatedly crystallized and the major diastereoisomer separated until eventually a ~1.5:1 ratio of diastereoisomers remained; this enrichment of the minor diastereoisomer in the mixture excludes the possibility that
these diastereoisomers are related by inversion at the aziridine ring nitrogen unless the barrier for the latter were abnormally high [see section 2.4.2]. Furthermore, the fact that the major diastereoisomer can be freed from the minor one also excludes the possibility of an invertomer relationship between the 2 species unless, yet again, an abnormally high barrier exists between the latter. However, the possibility that the two diastereoisomers were related by rotation around the N-N bond was not excluded at this point [but see below].

Signals for the aziridine ring protons at δ3.68 (d, J1.7Hz) and 3.35 (d, J1.7Hz) and CHMe(Bu) at δ1.46 (d, J7.2Hz) were clearly identifiable in the minor diastereoisomer, which appeared to exist as a single invertomer.

The major diastereoisomer of (113), in fact, exists as a mixture of 2 nitrogen invertomers (ratio 2.2 : 1), (113a) and (113b). N.m.r. evidence allows assignment of (113a) to the major invertomer, where the lactone carbonyl and heterocycle are syn. This assignment is based on the pronounced shielding of one proton of the methylene group of the lactone ring adjacent to the spiro-centre in the minor invertomer [Figure 35]. Similar shielding effects in analogous N-heterocyclic aziridines have been previously reported.79

The n.m.r. spectrum [Figure 36] of these two nitrogen invertomers is
of interest. Thus, whilst the major invertomer is made up of only sharp signals, most signals from the minor invertomer are broadened significantly in deuterochloroform. This broadening is less in 1,2-dichlorobenzene but is still present, particularly for the aziridine ring protons.

Higher temperature $^1$H n.m.r. studies in 1,2-dichlorobenzene showed the separated Bu$^t$ signals for the two invertomers to coalesce at 75°C, giving an approximate $\Delta G^\#$ of 18 kcal mol$^{-1}$ for the barrier separating the two nitrogen pyramids [see Appendix 3]. This value is in reasonable agreement with the anticipated barrier to inversion in these N-heterocyclic substituted aziridines$^{78}$ (i.e. ca. 21 kcal mol$^{-1}$).

The broadening of the signals in the n.m.r. spectrum of the minor invertomer even at room temperature is believed to be the result of hindered rotation in this invertomer around the N-N bond. Low temperature n.m.r. studies did not reveal signals from the individual rotamers of this minor invertomer as might have been expected. This may possibly be due to complications arising from rotation around the benzimidazole (C-2)-CHMe(Bu$^t$) bond within one rotamer also becoming slow on the n.m.r. time-scale at lower temperatures.

However, inspection of signals from the minor invertomer in the n.m.r. spectrum of an analogous aziridine (114) (minor invertomer: lactone C=O
FIGURE 36

$^1$H n.m.r. spectrum of the major diastereoisomer of aziridine (113):
$\delta$(CDCl$_3$, 300 MHz, room temperature).
anti to het.), which does not have a chiral substituent on the 2-position [and hence lacks the diastereoisomerism present in (113)] revealed the same broadening to be present. On cooling to -90°C in

\[ \text{CD}_2\text{Cl}_2 \], the broadened aziridine ring protons in this minor invertomer do separate into two pairs of doublets (of non-equal intensity): the behaviour of the major invertomer (lactone C=O syn to het.) is the same - the aziridine ring protons separating into two pairs of doublets of non-equal intensity at low temperature. The n.m.r. spectrum of

(114) at -90°C shows a total of seven doublets for the aziridine ring protons, although the signal at 63.71 p.p.m. consists of two overlapping doublets (which are separated in the -75°C spectrum) thus making a total of eight doublets [Figure 37].

Although the major invertomer (113a) does not show any broadening of its proton signals down to -60°C this does not necessarily mean that there is a significantly lower barrier to N-N bond rotation in this invertomer, but could be the result of the rotamer equilibrium lying on one side only [see Chapter 4].

The significantly greater diastereoselectivity in addition of the nitrene derived from (104) to α-methylene-γ-butyrolactone (65) (5.5 : 1) over that from addition to methyl acrylate (95) (2.2 : 1) provided some support for the T.S.G.'s proposed for these additions [Figures 32 and 31, respectively]. It would be reasonable to assume that the minor diastereoisomer obtained in the addition to α-methylene-γ-butyrolactone
$\delta(\text{CD}_2\text{Cl}_2, 400\text{ MHz, } -75^\circ\text{C})$

$\delta(\text{CD}_2\text{Cl}_2, 400\text{ MHz, } -90^\circ\text{C})$

Figure 37
would arise from a T.S.G. as in Figure 32 but with the Me and H on the chiral group interchanged [this would be equivalent to addition of the nitrene, retaining the configuration of the chiral group as in Figure 32, to the opposite face of the lactone (65)].

It was anticipated, therefore, that by using \(\gamma,\gamma\)-dimethyl-\(\alpha\)-methylene-\(\gamma\)-butyrolactone (116), stereospecific addition of the nitrene to the alkene might be the result if this strategically positioned gem-dimethyl group was sufficient to direct the Me and H groups to occupy their respective sites as shown in Figure 38.

![Figure 38](image)

3.5.4 Oxidation of (104) in the Presence of \(\gamma,\gamma\)-dimethyl-\(\alpha\)-methylene-\(\gamma\)-butyrolactone (116) at Room Temperature

The predictions made above were found, seemingly, to be fulfilled as a single diastereoisomer of the product (117) was produced when the benzimidazole (104) was oxidised in the presence of (116) at room temperature [Figure 39]. The n.m.r. spectrum of the crude oxidation product showed no evidence for the presence of the other diastereoisomer: the expectation was that this absent diastereoisomer would

![Figure 39](image)
have aziridine ring protons at similar chemical shift positions as the minor diastereoisomer of the analogous aziridine (113). Chromatography of the crude product over alumina allowed isolation of the single diastereoisomer of (117) as colourless crystals in 69% yield.

The n.m.r. spectrum of this aziridine (117) showed similar features to that of the major diastereoisomer of (113), i.e. in this diastereoisomer both invertomers were present (2.0:1; major invertomer: lactone C=O syn to heterocycle) and peaks of the minor invertomer were broadened at room temperature. Assignments of signals to major and minor invertomers in (117) was, as in the case of (113), based on the pronounced shielding of one of the lactone ring protons adjacent to the spiro centre in the minor invertomer (δH 2.51 and 2.12 p.p.m.) relative to those in the major invertomer (δH 2.84 and 2.42 p.p.m.).

An X-ray crystal structure [Figure 40] of this diastereoisomer (117) was obtained and the relative configuration of the two chiral centres determined and found to be S,S (although the actual compound is, of course, racemic). This relative configuration is that which would be produced directly from the T.S.G. for the reaction shown in Figure 38. The crystal selected was also shown from the X-ray crystal structure to exist as only one invertomer (lactone C=O syn to heterocycle). To establish whether all the aziridine (117) had, in fact, crystallized out as one invertomer (a second order asymmetric transformation), in contrast to the 2.0:1 ratio present in solution at room temperature, the crystalline diastereoisomer (117) was dissolved in deuterochloroform at below -20°C and the n.m.r. spectrum recorded at -40°C without any intermediate warming of the solution. It has been shown that the rate of nitrogen inversion at an aziridine ring nitrogen is grossly retarded in the crystal lattice by comparison with that in solution. This
FIGURE 40
X-ray crystal structure of diastereoisomer (117)
rate of nitrogen inversion is effectively fast on the real time scale at room temperature in solution, but has been found to be negligible below -20°C in solution, hence the invertomer ratio measured from a solution of (117), made up as above by dissolution of the crystals at < -20°C, will be that present (on average) in these crystals. Both invertomers, in a ratio of 3.5:1, were found to be present in the deuterochloroform solution at -40°C but, significantly, on warming the sample to room temperature and re-recording the spectrum at -40°C, the ratio changed to 2.1:1, i.e. close to the thermodynamic equilibrium value (room temperature: 2.0:1). This behaviour is very similar to analogous (simpler) aziridines and is consistent with an invertomer relationship between the two species of (117) which are present in solution, with a barrier to inversion separating them of the expected size.

Disubstituted alkenes, e.g. methyl methacrylate, do not exhibit the same syn-stereospecificity as monosubstituted alkenes, although a high syn-stereoselectivity usually prevails between the ester and heterocycle. This is illustrated for the addition of benzoxazolinone N-nitrene (118) to methyl methacrylate [Figure 41], where a ~6:1 ratio of aziridine invertomers is formed as the kinetic product.

![Figure 41](image)

The above result, coupled with the similarity in structure between N-aminobenzoxazolinone (52) and N-aminobenzimidazole (104) raises the
possibility that addition of benzimidazolyl nitrenes to disubstituted alkenes may not be completely syn-stereospecific. This would be the case if addition of the N-nitrene derived from (104) to α-methylene-γ-butyrolactone (65) and γ,γ-dimethyl-α-methylene-γ-butyrolactone (116) was, to an extent, taking place via a T.S.G. as depicted in Figure 42, in which the secondary interaction was now between the β-methylene group of the lactone ring and the 2-position of the benzimidazole.

![Figure 42](image)

To test this possibility, examination of the kinetically formed products from the low temperature (-20 to -25°C) addition of the N-nitrene derived from benzimidazole (104) to lactones (65) and (116) was carried out; the rate of nitrogen inversion being negligible at this temperature.

3.5.5 Oxidation of (104) in the Presence of γ,γ-Dimethyl-α-methylene-γ-butyrolactone (116) at -20 to -25°C: Observation of Kinetically-Formed Products

Oxidation of (104) in the presence of lactone (116) at -20 to -25°C with examination of the n.m.r. spectrum of the product at low temperature (-40°C) without any intermediate warming of the solution, gave a ~5.3 : 1 ratio of invertomers of aziridine (117): warming the sample to room temperature and re-recording the spectrum at -40°C, brought about a change to the expected thermodynamic ratio of 2.0 : 1. Since in this case only a single diastereoisomer was produced and since both invertomers of this diastereoisomer are present in the kinetically-formed
product, stereospecific addition of the nitrene to the double bond of lactone (116) must be proceeding via T.S.G.'s illustrated in Scheme 18. It should be noted that in these two T.S.G.'s, both the face of the alkene attacked and the configuration of the chiral group have been changed to maintain the same sense of induction.

Scheme 18

3.5.6 Oxidation of (104) in the Presence of α-Methylene-γ-butyrolactone (65) at -20 to -25°C: Observation of Kinetically-Formed Products

A similar oxidation of (104) to that described above in the presence of lactone (65) at -20 to -25°C and examination of the n.m.r. spectrum of the total reaction mixture at -40°C, without any intermediate warming of the solution, revealed the presence of both invertomers of the major diastereoisomer of aziridine (113) in a ratio of ~5:1, with the major invertomer, as expected, having the lactone C=O and heterocycle syn. Warming the sample to room temperature and re-recording the spectrum at -40°C resulted in an increase in the proportion of the minor invertomer of the major diastereoisomer to a thermodynamic equilibrium ratio of 2.2:1. The ratio of diastereoisomers obtained from this low temperature
oxidation was ~8.5 : 1, an expected improvement on the 5.5 : 1 ratio obtained at room temperature. Since both invertomers of the major aziridine diastereoisomer are present in the kinetically-formed product, formation of this major diastereoisomer must therefore be occurring via T.S.G.'s represented by Figures 32 and 43. Note again that in the two T.S.G.'s both the face of the alkene attacked and the configuration at the chiral centre have been changed to maintain the sense of induction in the major diastereoisomer.

The minor diastereoisomer of aziridine (113) was present in such a small amount in the crude spectrum of the kinetically-formed product that measurement of its ratio of invertomers was not possible. As a result of this, the degree of diastereoselectivity involved in each of the two T.S.G.'s [Figures 32 and 43] is unknown.

3.5.7 Oxidations of (50) in the Presence of Equimolar Amounts of α-Methylene-γ-butyrolactone (65) and Methyl methacrylate and in the Presence of 2-Butenolide (66)

Oxidation of N-aminophthalimide (50) in the presence of equimolar amounts of α-methylene-γ-butyrolactone (65) and methyl methacrylate gave a 2.3 : 1 ratio of the corresponding aziridines (120) and (121) in 80% yield. This greater reactivity of the lactone versus the methacrylate, may be rationalized in terms of the greater concentration of the lactone present in the s-cis conformation (100%) compared with the methyl methacrylate (<100%) [see section 2.3.4].
Oxidation of N-aminophthalimide in the presence of 2-butenolide (66) gave none of the corresponding aziridine: (66) has the α,β-unsaturated carbonyl system fixed in the s-trans conformation and so secondary interactions are absent.

3.5.8 Oxidation of (104) in the Presence of 2,3-Dimethyl-1,3-butadiene (89) at Room Temperature

In terms of the asymmetric induction obtained, oxidation of (104) in the presence of the title diene (89) [Figure 44] was less successful: a 1.83 : 1 ratio of diastereoisomers of aziridine (122) was obtained, the major diastereoisomer being isolated in 7% yield after chromatography twice over alumina.

\[
\text{Figure 44}
\]

From examination of the n.m.r. spectra both of the mixture of diastereoisomers of (122) and of the single separated diastereoisomer, only a single inverctor was present in both diastereoisomers in which the isopropenyl group and heterocycle are anti.

The relative configuration of the two chiral centres in the isolated major diastereoisomer remains unknown.

Oxidation of analogous N-aminoheterocycles in the presence of diene (89) at low temperature, showed both nitrogen inverctors of the analogous aziridines to be present in the kinetically-formed product (e.g. addition of phthalimidonitrene to diene (89) at -30°C gave aziridine inverctors, isopropenyl group syn : anti to het., in a ratio
of 63:37). It seems likely, therefore, that the low diastereoselectivity may arise from nitrene addition taking place in this case also, via T.S.'s leading to opposite senses of induction [Figure 45].

![Diagram of molecular structures](image)

\( \equiv \text{Bu}^+ \text{projecting upwards} \)

**Figure 45**

Although it is known that the isopropenyl group has a greater propensity for a *syn*-relationship than methyl,\(^{67}\) what is unknown, however, is the degree of diastereoselectivity involved in each T.S. of Figure 45.

3.5.9 **Oxidation of (104) in the Presence of trans-But-2-ene at 0°C**

![Chemical structures](image)

\((119) + \text{Me} \xrightarrow{0^\circ C} \text{Me} \rightarrow \text{Me} \)

**Oxidation of (104) in the presence of trans-but-2-ene at 0°C** produced a 5.2:1 ratio of diastereoisomers of aziridine (123). Chromatography over alumina allowed isolation of the major diastereoisomer as a colourless oil in 60% yield. The relative configuration of the chiral centres in this major diastereoisomer remains unknown.

This result not only widens the scope of this asymmetric aziridination to include alkyl substituted alkenes, but also suggests that alkyl groups have a useful *syn*-selectivity of their own.
3.6 **N-Nitrene Addition to a Chiral Sulphoxide**

It was of interest at this stage to attempt to bring about asymmetric induction in addition of the N-nitrene (119) derived from (104) to a chiral sulphur atom.

Sulphoxides are known to be good nitrene traps\(^{90,91,92}\) and, furthermore, methyl phenyl sulphoxide (124) appeared to be a suitable candidate to investigate by virtue of its chirality and accessibility. It was anticipated that diastereoselectivity in this case would result from reaction of one enantiomer of the racemic N-aminobenzimidazole (104) preferentially with one particular enantiomer of the racemic sulphoxide (124) to give an excess of RR(SS) over RS(SR) or vice versa.

**3.6.1 Oxidation of (104) in the Presence of (racemic) Methyl Phenyl Sulphoxide (124)**

In the event, oxidation of (104) with LTA at room temperature in the presence of the sulphoxide (124) produced diastereoisomers of the sulphoximine (125) in a 1.2 : 1 ratio [Figure 46]. This lack of diastereoselectivity may be accounted for by the probable absence of secondary interaction in the T.S. between the substituents on the sulphoxide and the benzimidazole ring. Moreover, if the T.S. is as in Figure 47, where the nitrene approaches the lone pair of electrons...
on the sulphur atom at the apex of the tetrahedral sulphoxide, there is no obvious preferred site occupancy for methyl, phenyl or S=O groups of the sulphoxide and the methyl and hydrogen of the chiral group on the 2-position of the benzimidazole ring [Bu^ group on the 2-position of the benzimidazole ring is drawn projecting upwards towards the viewer].

\[
\begin{array}{c}
\text{\text{Bu}^+ \text{projecting upwards}}
\end{array}
\]

Figure 47

3.7 Isolation of a Common By-Product in the Oxidations of the N-Amino- benzimidazole (104) with LTA in the Presence of Various Nitrene Traps

Inspection of the spectra of the crude oxidation products involving LTA and the N-aminobenzimidazole (104), all revealed ~5-10% of a by-product (126), which was absent if phenyl iodosodi-acetate was used in place of LTA as an oxidant. It was decided to carry out experiments to determine whether this by-product was produced \textit{via} an inter- or intramolecular pathway. Conditions favouring an intermolecular route were first investigated, i.e. at high concentration and in the absence of a nitrene trap. Using LTA as an oxidant, a 57% isolated yield (after chromatography) of this by-product (126) was obtained under these conditions.

A complementary experiment was subsequently carried out, in the absence of a nitrene trap, under high dilution conditions [200 ml dichloromethane/50 mg of (104)], i.e. favouring intramolecular reaction.
This resulted in significantly less of the by-product (126) (12% isolated) and the formation of a number of more polar products, which were not identified.

![Chemical structure](image)

(126)

A proposed mechanism for the formation of (126) is given in Scheme 19.

**Assignments of Signals in the $^{13}$C N.m.r. Spectrum of (126)**

![Chemical structure](image)

(126)

$\delta$(CDCl$_3$, 75 MHz):

<table>
<thead>
<tr>
<th>Chemical Shifts (p.p.m.)</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>158.8 (s)</td>
<td>$C_7$ and $C_{20}$</td>
</tr>
<tr>
<td>158.7 (s)</td>
<td></td>
</tr>
<tr>
<td>142.0 (s)</td>
<td>$C_1$, $C_6$, $C_{14}$ and $C_{19}$</td>
</tr>
<tr>
<td>128.0 (s)</td>
<td></td>
</tr>
<tr>
<td>125.0 (d)</td>
<td>$C_5$ and $C_{15}$</td>
</tr>
<tr>
<td>124.4 (d)</td>
<td></td>
</tr>
<tr>
<td>120.4 (d)</td>
<td>$C_2$, $C_3$, $C_4$, $C_{16}$, $C_{17}$ and $C_{18}$</td>
</tr>
<tr>
<td>114.5 (d)</td>
<td></td>
</tr>
<tr>
<td>114.3 (d)</td>
<td></td>
</tr>
<tr>
<td>40.6 (brs)</td>
<td>$C_8$ and $C_{21}$</td>
</tr>
</tbody>
</table>
Scheme 19
## Chemical Shifts (p.p.m.)

<table>
<thead>
<tr>
<th>Chemical Shift</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>35.1 (s)</td>
<td>C₁₀ and C₂₃</td>
</tr>
<tr>
<td>27.8 (q)</td>
<td>C₁₁, C₁₂, C₁₃-equivalent carbons and C₂₄, C₂₅ and C₂₆-equivalent carbons</td>
</tr>
<tr>
<td>15.0 (q)</td>
<td>C₉ and C₂₂</td>
</tr>
</tbody>
</table>

### 3.8 A summary of the reactions and asymmetric inductions obtained for the addition of the N-nitrene derived from (104) to various prochiral alkenes is given in Table 4.

### 3.9 Attempts to Synthesize a more 'Efficient' Chiral Auxiliary

Although the levels of asymmetric induction obtained by oxidation of (104) in the presence of various prochiral alkenes are generally good [Table 4], the system might be improved if one of the substituents on the chiral 2-position was fixed in the plane of the benzimidazole ring. Asymmetric induction (facial selectivity) in nitrene addition to the alkene would then be determined by only two substituents (ideally with the greatest disparity in size).

This was the rationale which led to the synthesis and proposed oxidation of the N-amino-bis-benzimidazole (127). The expectation was that the T.S.G. [Figure 48] (illustrated for the particular case of styrene) would be controlled by two factors: (i) the strong hydrogen-bonding shown in (127) and (ii) the preferred approach of the alkene

![Figure 48](image)
### TABLE 4

Summary of the Results from Oxidations of the N-Aminobenzimidazole (104) at Room Temperature: Asymmetric Inductions Obtained Expressed as Ratios of Diastereoisomers

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkene</th>
<th>Oxidising Agent</th>
<th>Aziridine ( ) diastereoisomer ratios</th>
<th>% Yield</th>
<th>Approx. % of dimer (126) obtained</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{CO}_2\text{Me})</td>
<td>LTA</td>
<td>2.2:1&lt;sup&gt;e&lt;/sup&gt; (112)</td>
<td>71&lt;sup&gt;f&lt;/sup&gt;</td>
<td>5-10</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>LTA</td>
<td>5.5:1&lt;sup&gt;b&lt;/sup&gt; (113)</td>
<td>33</td>
<td>5-10</td>
</tr>
<tr>
<td>3</td>
<td>(\text{Ph(IQAC)}_2)</td>
<td>LTA</td>
<td>5.5:1&lt;sup&gt;b&lt;/sup&gt; (113)</td>
<td>50</td>
<td>Nil</td>
</tr>
<tr>
<td>4</td>
<td>(\text{Ph(OCO)}_2)</td>
<td>LTA</td>
<td>-</td>
<td>Nil</td>
<td>40-50</td>
</tr>
<tr>
<td>5</td>
<td>(\text{Ph(OCO)}_2)</td>
<td>LTA</td>
<td>&gt;50:1&lt;sup&gt;b&lt;/sup&gt; (117)</td>
<td>69</td>
<td>5-10</td>
</tr>
<tr>
<td>6</td>
<td>(\text{Ph(OCO)}_2)</td>
<td>LTA</td>
<td>5.6:1&lt;sup&gt;b&lt;/sup&gt; (111)</td>
<td>45</td>
<td>5-10</td>
</tr>
<tr>
<td>7</td>
<td>(\text{Ph(OCO)}_2)</td>
<td>LTA</td>
<td>5.6:1&lt;sup&gt;b&lt;/sup&gt; (111)</td>
<td>61</td>
<td>Nil</td>
</tr>
<tr>
<td>8</td>
<td>(\text{Ph(OCO)}_2)</td>
<td>LTA</td>
<td>8.0:1&lt;sup&gt;b,d&lt;/sup&gt; (111)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>No alkene present</td>
<td>LTA</td>
<td>-</td>
<td>-</td>
<td>57&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>10</td>
<td>No alkene present</td>
<td>LTA</td>
<td>-</td>
<td>-</td>
<td>12&lt;sup&gt;g,h&lt;/sup&gt;</td>
</tr>
<tr>
<td>11</td>
<td>(\text{Ph(OCO)}_2)</td>
<td>LTA</td>
<td>1.83:1 (122)</td>
<td>7</td>
<td>5-10</td>
</tr>
<tr>
<td>12</td>
<td>(\text{Ph(OCO)}_2)</td>
<td>LTA</td>
<td>5.2:1&lt;sup&gt;e&lt;/sup&gt; (123)</td>
<td>60</td>
<td>5-10</td>
</tr>
</tbody>
</table>
from the less hindered face of the (planar) bis-benzimidazole.

The bis-benzimidazole (128) was prepared in good yield as outlined in Scheme 20, when methyl malondiamide (129) and  o-phenylenediamine were heated together without solvent.

\[
\begin{align*}
\text{Me} & \quad \text{CO}_2\text{H} & \quad \text{CO}_2\text{H} \\
\text{H} & \quad \text{H} & \quad \text{H} \\
\text{EIOH, H}^+ & \quad \Delta & \quad \text{Me} & \quad \text{CO}_2\text{Et} & \quad \text{CO}_2\text{Et} & \quad \text{NH}_3 & \quad \text{Me} & \quad \text{CONH}_2 \\
\text{H} & \quad \text{H} & \quad \text{H} & \quad \text{CONH}_2 \\
\end{align*}
\]

(129)

\[
\begin{align*}
\Delta & \quad \text{O}_2\text{NH}_2 \\
\text{Me} & \quad \text{CONH}_2 \\
\end{align*}
\]

(128)

Attempts to prepare the bis-benzimidazole (128) by Phillips' method\textsuperscript{86} and by the method of Vyas et al.\textsuperscript{93} were unsuccessful. The
Phillips method produced unchanged starting dibasic acid when methyl malonic acid and o-phenylenediamine were heated together in concentrated hydrochloric acid (4N). The method of Vyas et al., which entailed heating methyl malonic acid and o-phenylenediamine together, using polyphosphoric acid as a condensing agent, produced only 2-ethylbenzimidazole (130). This is likely to have occurred by decarboxylation of the intermediate β-ketocarboxylic acid (131) [Figure 49].

\[
\begin{align*}
\text{(131)} & \xrightarrow{\Delta, -\text{CO}_2} \text{(130)}
\end{align*}
\]

**Figure 49**

Amination of the bis-benzimidazole (128) with HOS was not possible due to its insolubility in the aqueous alkaline medium used. Amination of (128) with O-mesitylenesulphonylhydroxylamine in dichloromethane proved more successful and n.m.r. evidence suggested that the amination went in significantly better yield than previous amination attempts, using other benzimidazoles, when this aminating agent was employed.

However, separation of the starting bis-benzimidazole (128) from the aminated material (127) has not yet been achieved: chromatographic separation was not possible due to the very similar Rf values of product and starting material and the insolubility of the crude product. Insolubility of the crude product in a range of solvents also thwarted fractional recrystallization attempts.

Although exploratory oxidations on the crude aminated product, in the presence of styrene and methyl acrylate, revealed evidence of some
aziridine ring formation, the crude oxidation products were too complicated to ascertain the diastereoisomeric ratios. A method to isolate the N-amino-bis-benzimidazole is therefore necessary.

3.10 To capitalize on and extend the results using heterocycle (104) so that the possible synthetic utility of this system might be explored, necessitated either drastic improvement of the amination step of (107) or the examination of another more accessible N-aminoheterocycle. In electing to explore the latter possibility, the corresponding selectivity of the N-nitrene derived from the N-aminouinazolone (132) was examined.

\[
\text{Bu}^+ \quad \text{Me} \quad \text{H} \quad \text{N} \quad \text{NH}_2
\]

(132)
Asymmetric Induction in the Addition of Oxoquinazolinyi Nitrenes to (Prochiral) Alkenes: Oxidation of 3-Amino-2-(1,2,2-trimethylpropyl) quinazolin-(3H)-4-one (132) in the Presence of α-Methylene-γ-butyrolactone (65): Conformational Analysis of the Aziridines Formed: Results and Discussion

4.1 Introduction

In Chapter 3 the asymmetric aziridination of various prochiral alkenes with differently 2-substituted N-aminobenzimidazoles was described. The N-nitrene derived from oxidation of the N-aminobenzimidazole (104) was of particular interest since generally good levels of asymmetric induction were achieved with this heterocycle. However, further studies using (104) were hampered by the difficulty of preparing this in quantity.

The N-aminoquinazolone (132) appeared to be considerably easier to prepare in quantity than (104) and a study of its derived N-nitrene additions to prochiral alkenes was undertaken.

![Structure of 132]

4.2 Synthesis of 3-Amino-2-(1,2,2-trimethylpropyl)quinazolin-(3H)-4-one (132)

The N-aminoquinazolone (132) was prepared via the usual route by reacting the acid chloride of 2,3,3-trimethylbutanoic acid (108) with methyl anthranilate, followed by treating the intermediate N-substituted anthranilate (133), in ethanol, with excess hydrazine hydrate in a sealed tube at 140-150°C overnight [Scheme 21]. Heating the reaction mixture at a lower temperature (~120°C) allowed the isolation of substantial amounts of the intermediate hydrazide (134). This hydrazide
SCHEME 21 - Reagents:
i, SOCl₂; ii, R = H\(\text{NH}_2\text{NH}_2\)-EtOH, 119°C (sealed tube); 
\(\text{R=NO}_2\)\(\text{NH}_2\text{NH}_2\)-EtOH, 6 hr reflux; iv, \(\text{R=H}\)EtOH, 140-150°C (sealed tube); 
\(\text{R=NO}_2\)EtOH, 160-170°C (sealed tube); v, \(\text{R=H}\)\(\text{NH}_2\text{NH}_2\)-EtOH, 140-150°C (sealed tube).

(134) could then be heated at a higher temperature (140-150°C) in the absence of hydrazine to produce (132) in good yield [see Appendix 2].

4.2.1 Assignments of Signals in the \(^{13}\text{C}\) N.M.R. Spectrum of (132)

The following assignments were based on those made by Singh et al. \(^94\)
on similar compounds.
4.3 Oxidation of (132) in the Presence of α-Methylene-γ-butyrolactone (65) and Absence of TFA at Room Temperature

An anticipated drawback to the use of the N-nitrene (138) in bringing about asymmetric induction in addition to the lactone (65) (and other prochiral alkenes) was that the T.S.G. adopted might be (139) rather than (142) [Scheme 22]. It seemed probable that if the reaction proceeded via the T.S.G. (139) very little asymmetric induction would obtain.

This fear was realized when upon oxidation of (132) in the presence of the lactone (65) at room temperature a 1:1.3 ratio of diastereoisomers of aziridines (140a):(140b) (65%) resulted [Scheme 23].

\[
\delta(d_6 \text{ DMSO, 75 MHz}):
\]

<table>
<thead>
<tr>
<th>Chemical Shifts (p.p.m.)</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>165.4 (s)</td>
<td>C_7 \text{ may be interchanged}</td>
</tr>
<tr>
<td>164.9 (s)</td>
<td>C_8</td>
</tr>
<tr>
<td>150.2 (s)</td>
<td>C_6</td>
</tr>
<tr>
<td>138.0 (d)</td>
<td>C_3</td>
</tr>
<tr>
<td>131.2 (d)</td>
<td>C_1</td>
</tr>
<tr>
<td>130.0 (d)</td>
<td>C_2 \text{ may be interchanged}</td>
</tr>
<tr>
<td>129.9 (d)</td>
<td>C_4</td>
</tr>
<tr>
<td>123.8 (s)</td>
<td>C_5</td>
</tr>
<tr>
<td>45.9 (d)</td>
<td>C_9</td>
</tr>
<tr>
<td>38.2 (s)</td>
<td>C_{10}</td>
</tr>
<tr>
<td>31.4 (q)</td>
<td>C_{11}, C_{13}, C_{14}</td>
</tr>
<tr>
<td>18.7 (q)</td>
<td>C_{10}</td>
</tr>
</tbody>
</table>

\[
\begin{align*}
\text{(140a)} & \quad \text{only (R=H)} \\
\text{(132)} & \quad \text{LTA} \\
\text{(137)} & \quad \text{TFA} \\
\end{align*}
\]

All compounds racemic

\[
\begin{align*}
\text{(140a)} & \quad R = H \\
\text{(143a)} & \quad R = \text{NO}_2 \\
\text{(140b)} & \quad R = H \\
\text{(143b)} & \quad R = \text{NO}_2 \\
\end{align*}
\]

Scheme 23
Chromatography over silica gave one of the diastereoisomers (140a) as a crystalline solid, m.p. 174-176°C, and the other (140b) as an oil.

This low diastereoselectivity suggests that, as feared, the reaction proceeds wholly or in large part by the T.S.G. represented by (139) rather than (142). If the T.S.G. (142) had been adopted a diastereoselectivity comparable with that of the analogous reaction of the lactone (65) with the N-aminobenzimidazole (104) [5.5:1 ratio of diastereoisomers; see Chapter 3] would have been anticipated.

The foregoing and the following analysis assumes that only secondary interaction between the lactone carbonyl and the quinazolone is of importance and has neglected possible secondary interactions between the lactone (8) methylene and quinazolone C-2 and C-4 [Figure 50].

In an attempt to establish whether this 1:1.3 ratio was obtained via a combination of T.S.G.'s (139) and (142) or just exclusively via (139), the 7-nitro-substituted N-aminoquinazolone (137) was prepared and oxidized in the presence of the lactone (65) [see Appendix 1].

4.4 Synthesis of 3-Amino-2-(1,2,2-trimethylpropyl)-7-nitroquinazolin-4-(3H)-one (137)

The 7-nitro-substituted N-aminoquinazolone (137) was prepared by a modification of the route [Scheme 21] used to construct the analogous quinazolone ring system (132). Thus when the N-substituted 4-nitro-
anthranilate (135) was heated with excess hydrazine in a sealed tube at 140-150°C, formation of the N-aminoquinazolone ring took place but the nitro group was also reduced to the primary amine. Formation of the intermediate hydrazide (136) by heating under milder conditions and then heating this hydrazide in the absence of hydrazine at 160-170°C obviated this problem [Scheme 21].

4.4.1 Assignments of Signals in the $^{13}$C N.M.R. Spectrum of (137)

The assignment of $^{13}$C n.m.r. signals were based on those made by Singh et al. on similar compounds (as before).

![Structure of 137]

$\delta (d_6$ DMSO, 75 MHz):

<table>
<thead>
<tr>
<th>Chemical Shifts (p.p.m.)</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>168.2 (s)</td>
<td>C$_7$</td>
</tr>
<tr>
<td>164.0 (s)</td>
<td>C$_8$</td>
</tr>
<tr>
<td>155.0 (s)</td>
<td>C$_3$</td>
</tr>
<tr>
<td>150.4 (s)</td>
<td>C$_6$</td>
</tr>
<tr>
<td>132.5 (d)</td>
<td>C$_2$</td>
</tr>
<tr>
<td>127.8 (s)</td>
<td>C$_5$</td>
</tr>
<tr>
<td>126.1 (d)</td>
<td>C$_4$</td>
</tr>
<tr>
<td>123.7 (d)</td>
<td>C$_1$</td>
</tr>
<tr>
<td>46.2 (d)</td>
<td>C$_9$</td>
</tr>
<tr>
<td>38.5 (s)</td>
<td>C$_{11}$</td>
</tr>
<tr>
<td>31.5 (g)</td>
<td>C$<em>{12}$, C$</em>{13}$, C$_{14}$</td>
</tr>
<tr>
<td>18.6 (g)</td>
<td>C$_{16}$</td>
</tr>
</tbody>
</table>

may be interchanged

4.5 Oxidation of (137) in the Presence of $\alpha$-Methylene-\(\gamma\)-butyrolactone (65) and Absence of TFA at Room Temperature

A similar oxidation to that carried out in section 4.3 above, using $N$-aminoquinazolone (137), produced an identical ratio of diastereoisomers
(1:1.3) of aziridine (143). However, it was not possible to separate the (crystalline) diastereoisomers in this case either by chromatography or fractional crystallization.

The identical ratio of diastereoisomers obtained in both these oxidations (measured from the n.m.r. spectra of the crude oxidation products at 90 MHz in both cases) is significant only if it is assumed that the introduction of a nitro group in the 7-position would have a disproportionate effect on the magnitudes of the secondary interactions at the quinazolone C-2 and C-4 [see Appendix 1]. If this assumption holds then the above result suggests that the additions of \(N\)-nitrene (138) and its 7-nitro analogue (141) are both proceeding via the T.S.G. as shown in (139).

Evidently the T.S.G. adopted is not conducive to significant asymmetric induction and in an attempt to bring about a change in the T.S.G. from (139) to (142), the oxidation of the \(N\)-aminoquinazolone (132) was carried out in the presence of trifluoroacetic acid (TFA). It was hoped that protonation of the quinazolone N-1 would bring about a change in the relative magnitudes of the secondary interactions at C-2 and C-4 thus favouring the secondary interaction with the former as in (142).

4.6 Oxidation of (132) in the Presence of Lactone (65) and TFA at Room Temperature

In the event, oxidation of the \(N\)-aminoquinazolone (132) in the presence of lactone (65) and 3.4 mole equivalents of TFA at room temperature, produced only the crystalline diastereoisomer (140a) in 72% yield: none of the signals from the other diastereoisomer (140b) were visible in the \(^1\text{H}\) n.m.r. spectrum of the crude oxidation product [Scheme 23].
An X-ray crystal structure [Figure 51] allowed determination of the relative configuration at the two chiral centres in this single diastereoisomer (140a) and revealed that the sense of induced configuration at the spiro-centre was opposite to that found in the major diastereoisomer of the analogous N-aminobenzimidazole-derived aziridine (113).

To rationalize this stereospecificity and change in induced configuration, using the T.S.G. depicted in (142), a configuration for the chiral 2-substituent which results in attack on the alkene from the required face is that shown in Figure 52. The T.S.G.'s in Figure 52(a) and Figure 32 (benzimidazole) differ (as drawn) in the face of the alkene which is attacked: in a racemic substrate this is equivalent to attack on the same face with different configurations of the chiral group. The change in induced configuration may be the result of protonation on N-1 with some associated solvation preferentially taking place from the underside of the quinazolone ring, i.e. side opposite to the Bu\textsuperscript{t} group. This would have the effect of exchanging the preferred sites for Me and H.

The change in T.S.G. to (142) could have been interpreted as resulting from protonation on the quinazolone carbonyl oxygen, producing the aromatic quinazolinium species [Figure 53] in which C-2 has the superior
FIGURE 51
X-ray crystal structure of aziridine (140a).
secondary interaction. However, the opposite sense of induction in the aziridines (140a) and the major diastereoisomer of (113) would be difficult to explain if this were the case.

![Figure 53]

The difference in the magnitudes of asymmetric induction in the addition of the N-nitrenes (119) and (138) to α-methylene-γ-butyrolactone (65), i.e. 5.5:1 and >50:1 respectively, may simply be the result of a change from a 5- to a 6-membered heterocyclic ring. However, it is possible that TFA augments the lactone carbonyl-quinazolone C-2 interaction to such an extent that the reaction is taking place exclusively via the T.S.G. (142) [Scheme 22] and to the exclusion specifically of the T.S.G. in Figure 50 [section 4.3] having lactone (8) methylene-quinazolone C-2 secondary interaction [c.f. the analogous benzimidazole case, section 3.5.6].

4.7 Rotation About Single Bonds: Introduction

Free rotation around a bond in a molecule may be sterically and electronically hindered. Rotation about a carbon-carbon single bond (the σ-bond is rotationally symmetrical) may be sterically hindered, as in the well-known example of atropisomerism in biphenyl derivatives, but can also be restricted by resonance effects which give a single bond partial double bond character [Figure 54].

Variable temperature n.m.r. spectroscopy can be used to observe the rotational isomers (rotamers) where rotation is effectively fast on the
real time-scale (i.e. $\Delta G^\ddagger < 23$ kcal mol$^{-1}$). Rotation may be fast or slow on the n.m.r. time-scale (ca. $10^2$ rotations per second). In the former case, signals from the individual rotamers may be distinguished by cooling the sample to a low enough temperature before recording the spectrum.

4.8 Rotation About N-N Single Bonds

The hindrance to rotation in nitrosamines [Figure 55] has been known for some time.$^{99}$ The high energy barrier (>20 kcal mol$^{-1}$) separating the preferred planar conformations can be explained by the strong contribution of the polar resonance structure (144). With suitable substitution on the amino nitrogen, the barrier separating the rotamers is so high that they can be isolated as such.$^{100}$ Examples of other classes of compounds with hindered rotation about the N-N bond are shown in Table 5.

4.9 Rotational Barriers in Pyramidal-Planar Hydrazines

The relevant conformational processes in this system are shown in Scheme 24. The enantiomers (145a) and (145b), (146a) and (146b) are interconverted by rotation then inversion (or vice versa). The inversion
### TABLE 5
ΔG⁺ Values for Rotation About Partial N-N Double Bonds

<table>
<thead>
<tr>
<th>Compound</th>
<th>ΔG⁺ (kcal mol⁻¹)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>(CH₃)₂N-N=O</td>
<td>23.3</td>
<td>99</td>
</tr>
<tr>
<td>(CH₃)₂N-N=S</td>
<td>&gt;17.2</td>
<td>101</td>
</tr>
<tr>
<td>(CH₃)₂N=N=N-O(NO₂)</td>
<td>15.7</td>
<td>102</td>
</tr>
</tbody>
</table>

### TABLE 6
Barriers to N-N Bond Rotation in Pyramidal-Planar Hydrazines

<table>
<thead>
<tr>
<th>Compound</th>
<th>Tc/°C</th>
<th>ΔG⁺ (kcal mol⁻¹)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>(147) R = 2,4-dinitrophenyl</td>
<td>59</td>
<td>16.6</td>
<td>107</td>
</tr>
<tr>
<td>(PhCH₂)₂N-NHR (148) R = 2,4,6-trinitrophenyl</td>
<td>50</td>
<td>16.4</td>
<td></td>
</tr>
<tr>
<td>(149) R = 2-pyrimidyl</td>
<td>-34</td>
<td>11.7</td>
<td></td>
</tr>
</tbody>
</table>

where: Tc = coalescence temperature; ΔG⁺ = rotational barrier.
process can occur without eclipsing of the lone-pairs and substituents, with the lone-pairs retaining a 90° angle to each other. This dihedral angle (θ) between the two lone-pairs is 90° in the preferred bisected conformation† and the preference for the bisected conformation is thought to be the result of repulsion between the two pairs of electrons in adjacent orbitals. Rotation, however, must involve eclipsing interactions and it is thought that eclipsing of the lone-pairs of electrons corresponds to the barrier to rotation. Typical values for the barrier to N-N bond rotation are given in Table 6.

† A conformation where the dihedral angle is 0° (i.e. eclipsed lone-pairs) is termed the perpendicular conformation.
4.10 Conformational Analysis of Aziridines (140a) and (140b)

The n.m.r. spectrum of the crystalline diastereoisomer (140a) at 300 MHz and room temperature [Figure 56] is unexceptional and only a single set of well-resolved signals are observed for this compound. However, the n.m.r. spectrum of the other oily diastereoisomer (140b) at 300 MHz and room temperature [Figure 57] consists of a number of broadened signals characteristic of a molecule undergoing a conformational change close to the coalescence temperature. At -40°C, signals from both these conformations are present as sharp peaks and the ratio of the two is ca. 1:1 [Figure 58]. Similar n.m.r. behaviour on lowering the temperature was also observed in the analogous 7-nitroquinazolone case (143b).

Inspection of the X-ray crystal structure of (140a) [Figure 51] reveals a very small dihedral angle\(^+\) (\(\theta = 1^\circ\)) between the electron pair in the p-orbital on the quinazolone N-3 and the lone-pair of electrons on the aziridine ring nitrogen, i.e. a preference for a perpendicular conformation exists in the crystalline state. By viewing the crystal structure from a different perspective, as in Figure 59, this preference may be seen more clearly. In Figure 59 the plane of the quinazolone ring is horizontal and the N-N bond is projecting towards the viewer.

The barrier to rotation in normal hydrazines,\(^{106}\) i.e. the perpendicular conformation in which the two lone-pairs are eclipsed, cannot be assumed to necessarily correspond to the barrier to rotation in these substituted hydrazines (140a) and 140b). A reduction in the eclipsing interaction

\(^+\) The dihedral angles calculated are those between the plane orthogonal to the aziridine ring plane which bisects the C-N-C angle in this ring and the normal to the N-N-C=N (benzimidazole) or N-N-CO (quinazolone) plane.
FIGURE 56

$^1$H N.M.R. spectrum of the crystalline diastereoisomer (140a):

6 (CDCl$_3$, 300 MHz, room temperature).
\textbf{FIGURE 57}

$^1$H n.m.r. spectrum of the 'oily' diastereoisomer (140b): $\delta$(CDCl$_3$, 300 MHz, room temperature). The peaks at $\delta$1.45 (d, J7.0Hz, $-\text{CHMe(Bu}^t\text{)}$) and $\delta$0.98 (s, Bu$^t$) belong to a small amount of the crystalline diastereoisomer (140a) which was not completely separated in the chromatography.
FIGURE 58

$^1$H n.m.r. spectrum of the 'oily' diastereoisomer (140b): $\delta$(CDCl$_3$, 300 MHz, -40°C). The peaks at $\delta$1.50 (d, J7.0Hz, CHMe(Bu$^t$)) and $\delta$0.98 (s, Bu$^t$) belong to a small amount of the 'crystalline' diastereoisomer (140a) which was not completely separated in the chromatography.
FIGURE 59
X-ray crystal structure of aziridine (140a) viewed along the N-N bond. The dotted lines indicate hydrogens lying just outside their Van der Waals radii.
in this perpendicular conformation would be anticipated in any case due to the high $s$-character of the aziridine lone-pair. More significant may be an unfavourable interaction of the quinazolone N-3 lone-pair with the ring bonds of the aziridine in the alternative bisected conformation [Figure 60]. This bisected conformation is the preferred one for the cyclopropylcarbinyl cation, in which delocalization of two of the ring bonds allows maximum stabilization of the cation \(^{108}\) [Figure 61]. Conformational studies on the analogous cyclo-

![Figure 60](image)

![Figure 61](image)

![Figure 63](image)

propylcarbinyl anion (150), however, have not been possible due to its ready ring-opening to an allylcarbinyl anion (151) [Figure 62], although

![Figure 62](image)

it is reasonable to suppose that the filled p-orbital may result in the perpendicular conformation [Figure 63] being preferred \(^{109}\) over the bisected one. It is obvious that the conformation in Figure 63 is that found in (140a) [Figure 59].

To what extent this preference for the perpendicular conformation in (140a) is influenced by interactions between substituents on the two nitrogens is not clear: the bisected conformation would presumably exist as a single rotamer [Figure 64] in which non-bonded interactions
between the bulky chiral group on the quinazolone and the aziridine ring substituents are minimized.

![Figure 64](image)

The ca. 1:1 ratio of conformers of (140b) in solution described earlier can be ascribed to rotamers around the N-N bond, with both having preferred orientations which are close to the perpendicular rather than the bisected. It is difficult to reconcile the rotamer distribution in (140a) (a single rotamer) and (140b) (a ca. 1:1 ratio of rotamers) using the (single) bisected conformation [Figure 64]. Using the perpendicular conformation, however, and with the aid of models, the different rotamer distribution in the two diastereoisomers can be rationalized.

Inspection of the crystal structure of (140a) [Figure 59] reveals the methine hydrogen and the aziridine ring protons lying just outside their combined Van der Waals radii [dotted lines in Figure 59]. Closer examination shows the quinazolone ring at the C-2 substituent bent out of the plane, presumably to facilitate this minimization of Van der Waals interaction. If the methine hydrogen and methyl group on the chiral substituent at C-2 were therefore interchanged [corresponding to a change from (140a) to (140b)], then significantly greater non-bonded interactions with the aziridine ring protons would be anticipated.

Examination of models of the two other perpendicular rotamers (obtained by rotating by 180° around the N-N bond) [Figure 65] suggests greater non-bonded interactions of (140a) with the lactone ring than with
(140b). Consequently, both rotamers of diastereoisomer (140b) are present in a ca. 1:1 ratio in solution due to the presence of non-bonded interactions of comparable size in each of them, whereas in (140a) only one rotamer is observed in the n.m.r. in solution due to the non-bonded interactions being substantially greater in the other rotamer.

The dihedral angle (θ) between the lone-pairs in (140b) would be anticipated to be greater than in (140a), i.e. the N-N bond rotated out of the perpendicular conformation in an attempt to alleviate unfavourable interactions (in both rotamers) of (140b). The preferred conformation, however, would still be perpendicular rather than bisected. Examination of the crystal structure of (117) [Figure 40; see Chapter 3], which is the benzimidazole analogue of one rotamer of (140b), supports this expectation in that a dihedral angle θ of 20° is found [cf. θ = 1° in (140a)].
Evidence for the Conformational Equilibrium Present in (140b) being that between Rotamers rather than Invertomers

The barrier separating the two conformers of (140b) was calculated to be ca. 14 kcal mol\(^{-1}\). This value was obtained using data obtained at the coalescence temperature [see Appendix 3]. The magnitude of this energy barrier is grossly different to the inversion barriers normally associated with these \(N\)-\(N\)-bond containing aziridines.\(^{78}\) Inversion barriers for (152) and (120) (see below) suggest that the inversion barrier in (140b) would be expected to be normal (~21 kcal mol\(^{-1}\)).

Oxidation of the \(N\)-aminoquinazolone (132) in the presence of methyl methacrylate and TFA gave the major diastereoisomer of aziridine (152) as a 1:1.3 ratio of invertomers [see Chapter 5]. Coalescence of the aziridine methyl signals in the n.m.r. spectrum of this diastereoisomer occurred at 115\(^\circ\)C, from which an inversion barrier of 21 kcal mol\(^{-1}\) was calculated [see Appendix 3]. This value is of the order expected in these \(N\)-\(N\) bond-containing aziridines.\(^{78}\) In the major invertomer of (152), where the ester and heterocycle are \textit{syn},\(^{79}\) there is no evidence for the restricted rotation present in (140b) but this is not surprising since free rotation about the C-CO\(_2\)Me bond in (152) will facilitate \(N\)-\(N\) bond rotation.

The aziridine (120), formed by the addition of phthalimidonitrile (62) to \(\alpha\)-methylene-\(\gamma\)-butyrolactone (65), showed the presence of two
nitrogen invertomers in a 12:1 ratio at room temperature (the symmetry of the phthalimido group precludes the possibility of these species being rotamers). N.m.r. studies on this aziridine showed coalescence of the ring proton signals at ~150°C, which corresponds to an approximate inversion barrier of 22 kcal mol⁻¹ [see Appendix 3]. Consequently, it appears that neither the bulky substituent at C-2 of the quinazolone ring, nor the spiro-aziridine-lactone ring fusion significantly lower the aziridine nitrogen inversion barrier and hence the presence of both in (140b) would not be expected to lower the barrier in this compound either. Although the inversion barrier in (140b) is expected to be normal, the equilibrium apparently lies exclusively on one side.

4.12 Effect of TFA on the N.m.r. Spectrum of Diastereoisomer (140b)

An ¹H n.m.r. spectrum at room temperature of a sample of (140b) containing excess TFA, showed a remarkable change and the presence of only one species [Figure 66]. The spectrum of this single species is presumed to be the result of rotation around the N-N bond being fast on the n.m.r. time-scale. This apparent decrease in the rotational barrier can be rationalized by protonation of the quinazolone ring (at N-1 or on the carbonyl oxygen) diminishing the electron density in the p-orbital on the quinazolone N-3 nitrogen through a resonance interaction which consequently reduces the unfavourable interaction between this N-3 lone-pair and the aziridine ring bonds - the barrier to N-N
FIGURE 66
$^1$H n.m.r. spectrum of the 'oily' diastereoisomer (140b) plus TFA:
$\delta$(CDCl$_3$, 300 MHz, room temperature). Peaks at $\delta$1.10 (s, Bu$^t$) and
$\delta$1.55 (d, J7 Hz, CHMe(Bu$^t$)) belong to a small amount of the 'crystalline'
diastereoisomer (140a) which was not completely separated in the
chromatography.
bond rotation.

Support for the postulated protonation of the quinazolone ring in preference to the aziridine ring nitrogen, comes from studies carried out on the aziridine (153). A spectrum of (153) in deuterochloroform containing TFA reveals substantially larger deshielding of the two cis-aziridine ring protons than is normally the case, with little effect on the trans-aziridine ring proton. This is in agreement with the presence of an enhanced ring current in the quinazolone ring which brings about selective deshielding of the two cis-aziridine ring protons: such an enhanced ring current would be in better agreement with protonation on the quinazolone carbonyl oxygen rather than on N-1.

4.13 Examination of Cyclopropyl Analogues of Aziridines (140a) and (140b)

It was anticipated that the cyclopropyl analogues of the aziridines (140a) and (140b) would have a similar propensity for a perpendicular conformation, particularly since a less repulsive C-H, N bonded pair-lone-pair interaction now replaces the N, N lone-pair-lone-pair interaction.

Table 7 contains the six alkanoylated cyclopropylamines retrieved from the Cambridge Data File of Crystallographic Structures and all show a preference for a perpendicular conformation. In each case the angle θ between the normal to the RCN plane and the plane orthogonal to the plane of the cyclopropane ring (i.e. plane bisecting N-A angle)
is tabulated. Although in no case does $\theta$ have the ideal value of 0°, they all, however, show values significantly closer to 0° than 90° which shows the preference for a perpendicular over a bisected conformation. Some of the larger deviations from 0° are presumably to alleviate unfavourable steric interactions.

**TABLE 7**

Alkanoylated Cyclopropylamines Showing a Preference for the Perpendicular (0 ideally 0°) over the Bisected (0 ideally 90°) Conformation

A conformational behaviour in contrast to that illustrated in Table 7 is shown by ring nitro-substituted cyclopropanes [e.g. Figure 67] where a preference for a bisected rather than a perpendicular (i.e. $\theta$ close to 90°) conformation is exhibited. This has been attributed to a favourable overlap of the aziridine ring bonds with the nitro group. ('one of the degenerate pair of HOMO's of the cyclopropane ring with
4.14 Search for an Aziridine Analogous to (140a) and (140b)

The \( \text{N-nitroaziridine (154)} \) was the only aziridine found in the Cambridge Data File containing an (aziridine ring) \( \text{N-N} \) bond.\(^{116}\) This aziridine appears to adopt a conformation closer to the perpendicular (\( \theta = 22^\circ \)) than the bisected conformation.

4.15

The asymmetric induction obtained in the aziridination of \( \alpha \)-methylene-\( \gamma \)-butyrolactone (65) in the presence of TFA should, in principle, be applicable to a range of other prochiral alkenes, but in particular to \( \alpha,\beta \)-unsaturated esters and ketones.
Asymmetric Induction in the Addition of N-Nitrenes to (Electron Deficient) Prochiral Alkenes: Addition of Oxoquinazolinyl Nitrenes to α,β-Unsaturated Esters and Ketones, and 2-Nitropropene: Results and Discussion

5.1 Introduction

As a result of the high levels of asymmetric induction obtained using the readily available nitrene precursor (132), it was decided to study the addition of the derived N-nitrene (138) to a range of α,β-unsaturated esters and ketones in the presence and absence of TFA.

5.2 Aziridination of Various α,β-Unsaturated Esters and Ketones Using (132) as a Nitrene Precursor

Oxidation of the N-aminoquinazolone (132) with LTA at room temperature in the presence of a range of α,β-unsaturated esters and ketones, with the addition of TFA (3.4 mole equivalents) prior to the oxidation, gave the ratios of diastereoisomers of the corresponding aziridines shown in Table 8. Oxidations in the absence of TFA were also carried out and the diastereoisomer ratios obtained are given in Table 8 for comparison.

The low levels of asymmetric induction obtained in the absence of TFA may be attributed to a T.S.G. in every case for reaction of the nitrene with the alkene as shown in Figure 68. This T.S.G., where the chiral substituent of the nitrene is interacting with RCH = terminus of the alkene, is apparently ineffective at bringing about significant facial discrimination. However, the addition of TFA is presumed to
TABLE 8
Ratios of Diastereoisomeric Aziridines † Obtained from Oxidation of N-Aminoquinazolone (132) in the Presence of Various Alkenes (4 mole equivalents) at Room Temperature (except entry 2) as Measured from the N.m.r. Spectra of the Crude Oxidation Products

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkene</th>
<th>Aziridine ( ) diastereoisomer ratio [without TFA]</th>
<th>Aziridine ( ) diastereoisomer ratio [with TFA]</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CO₂Me</td>
<td>(155) 2.4 : 1</td>
<td>(155) 1 : 8.7</td>
<td>(72) 50</td>
</tr>
<tr>
<td>2</td>
<td>CO₂Me</td>
<td>-</td>
<td>(155) 1 : 23</td>
<td>(72) 65B</td>
</tr>
<tr>
<td>3</td>
<td>CO₂Bu</td>
<td>(156) 2.1 : 1</td>
<td>(156) 14 : 1b</td>
<td>(75) 39</td>
</tr>
<tr>
<td>4</td>
<td>CO₂Me</td>
<td>(152) 1.2 : 1</td>
<td>(152) 1 : 5.2b</td>
<td>(72) 46</td>
</tr>
<tr>
<td>5</td>
<td>CO₂Me</td>
<td>(157) -</td>
<td>(157) 7.0 : 1b</td>
<td>(75) 58</td>
</tr>
<tr>
<td>6</td>
<td>COMe</td>
<td>(158) 1.25 : 1</td>
<td>(158) 1 : 6.5</td>
<td>(78) 62</td>
</tr>
<tr>
<td>7</td>
<td>COMe</td>
<td>(159) 1.2 : 1</td>
<td>(159) 8.6 : 1b</td>
<td>(82) 52</td>
</tr>
</tbody>
</table>

† The aziridines given in Table 8 are illustrated in Figure 70.
a 1.1 mole equivalents of alkene; -60°C; isolated yield contains both diastereoisomers;
b Major diastereoisomer crystalline.

Figure 70:
Aziridines given in Table 8
effect a change in the T.S.G. to that depicted in Figure 69 as a result of protonation on N-1 which augments the secondary interaction between the alkene carbonyl and the position C-2 on the quinazolone ring as described earlier.

Implicit in Figures 68 and 69 is the assumption that it is exclusively the carbonyl group of the substituent which is syn to the heterocycle in the T.S. in the presence and absence of TFA. This may not be so for the case of disubstituted alkenes, e.g. methyl methacrylate, methyl crotonate and 3-penten-2-one (entries 4, 5 and 7 respectively in Table 8), in the absence of TFA particularly in view of the results from addition of the benzimidazolyl nitrene (119) to the lactones (65) and (116) [see Chapter 3].

The results in Table 8 in the presence of TFA, however, indicate that the stereoselectivities in aziridinations of the disubstituted alkenes above are not noticeably inferior to those of the monosubstituted alkenes. This suggests that in the presence of TFA, Figure 69 is likely to represent the only T.S.G. through which aziridination occurs, i.e. other possible T.S.G.'s such as those in Figures 71 and 72 are not competitive, at least when R and R² are alkyl groups. This point is of particular importance since exclusive syn-selectivity of one of the substituents on a disubstituted alkene

![Figure 71](image1.png)  ![Figure 72](image2.png)
is mandatory for good asymmetric induction; competitive syn-selectivities would be unlikely to result in the same sense of induction (except fortuitously) and, if generally the case, would limit the scope of these asymmetric aziridination reactions to monosubstituted alkenes.

The isolated yields of products in Table 8 refer to those of the pure major diastereoisomer from oxidations in the presence of TFA. The corresponding yields of the crude oxidation products (containing both diastereoisomers) are indicated in brackets. When the two yields are compared, the losses which have occurred in some cases are either the result of neglect of mixed fractions in the column chromatography (entries 1 and 7) or from direct crystallization of the crude product without any attempt to recover further material from the mother liquor (entries 3 and 4).

The diastereoisomeric ratios shown in Table 8 were obtained by measurements taken from spectra of the crude oxidation products at 300 MHz. Superimposition of some of the respective signals from both diastereoisomers did invariably occur, although fortunately there was also in every case separated respective signals from which a ratio of the diastereoisomers could be obtained.

Although the relative configuration in none of the aziridines shown in Table 8 is known, there are, however, some interesting correlations between diastereoisomer ratios that allow predictions to be made on this point. Inspection of Table 8 shows very similar diastereoisomer ratios in the oxidations without TFA when methyl acrylate and t-butyl acrylate are used as nitrene traps (entries 1 and 3). This close correspondence would be anticipated if both proceed via a T.S.G. as shown in Figure 68 (R=H, R^=OMe, OBu^, R^2=H). However, whereas for methyl acrylate the major diastereoisomer in the absence of TFA becomes
the minor diastereoisomer in the presence of TFA, the opposite obtains for t-butyl acrylate. This strongly implies that the sense of induction from addition of the protonated N-nitrene to the two alkenes is opposite in the two cases; i.e. that the major diastereoisomers produced do not have the same relative configurations at their two chiral centres.

The above deduction, coupled with an examination of models, allow identification of the T.S.G.'s in the addition of the N-nitrene (138) to methyl and t-butyl acrylate, as shown in Figure 73. From Figure 73 it will be noted that the methyl acrylate and t-butyl acrylate are both present in their preferred conformations. In oxidations in the

Figure 73

Ratios of diastereoisomers from T.S.G.'s for addition of the N-nitrene (138) to methyl and t-butyl acrylate in the presence and absence of TFA.

[T.S.G.'s depict formation of the major diastereoisomer in each case.]
presence of TFA, the sites allocated to substituents on the chiral
centre take account of solvation effects which apparently operate in
addition to \(\alpha\)-methylene-\(\gamma\)-butyrolactone (65) [Figure 52, see p.87].

Further evidence which allows tentative assignments of relative
configurations to aziridines (152), (157) and (159) comes from
inspection of the significantly different invertomer ratios for the
two diastereoisomers of each of the latter [Table 9].

**TABLE 9**

Ratios of Aziridine Invertomers as Measured from N.m.r.
Spectra of Separated Diastereoisomers or Mixtures of
Diastereoisomers at 300 MHz

[Syn/anti refers to the ester/ketone-quinazolene relationship.
Assignments (syn/anti) were based on shielding-deshielding
effects. A value of >30:1 indicates that only a single
invertomer was visible. Major/minor diastereoisomers are those
produced in the oxidation with TFA.]

<table>
<thead>
<tr>
<th>Aziridine ( )</th>
<th>Major Diastereoisomer</th>
<th>Minor Diastereoisomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>(152) (\text{Me} \quad \text{CO}_2\text{Me})</td>
<td>1.3 : 1 syn : anti</td>
<td>&gt;30 : 1 syn : anti</td>
</tr>
<tr>
<td>(157) (\text{CO}_2\text{Me})</td>
<td>~16 : 1 syn : anti</td>
<td>5 : 1 syn : anti</td>
</tr>
<tr>
<td>(159) (\text{COMe})</td>
<td>&gt;30 : 1 syn : anti</td>
<td>1.1 : 1 anti : syn</td>
</tr>
</tbody>
</table>

The two preferred rotamers around the N-N bonds in these aziridines
are assumed to be those in which the lone pairs are eclipsed, based on
the evidence derived from conformational analysis of aziridine (140)
[see Chapter 4]. Furthermore, it is assumed that the ester function-
alities of aziridines (152) and (157) have preferred conformations
analogous to those present in the corresponding \(\alpha,\beta\)-unsaturated esters.
although the following analysis would also hold for the conformation in
which the ester was rotated through 180° around the C-CO₂R bond.

Thus, the syn-invertomer of e.g. (157) may be represented as
(157a) \(\rightleftharpoons\) (157b) in one diastereoisomer and (157c) \(\rightleftharpoons\) (157d) in another.

As indicated in (157c) and (157d), non-bonded interactions are expected
to be more severe than in (157a) and (157b) and consequently population
of the anti-invertomer (not shown) will be more likely for the former
than the latter. On this basis, therefore, the major diastereoisomer

\[
\begin{align*}
(157a) & \quad \longrightarrow \\
(157b) & \\
(157c) & \quad \longrightarrow \\
(157d) &
\end{align*}
\]

may be assumed to be that shown in (157a) \(\rightleftharpoons\) (157b) and the same relative
configuration would be expected to obtain for the major diastereoisomer
of aziridine (155) (produced in the oxidation with TFA), which in turn
would be in agreement with that predicted using the T.S.G. for the
nitrene (138) addition to the alkene depicted in Figure 73B. Similar
arguments may be used to predict the relative configuration in the
major diastereoisomer (from the oxidation with TFA) of (152) and (159).
but confirmation must await X-ray structure determinations.

5.3 Effect of the Presence of TFA and Concentration of Methyl Acrylate on the Yield of Aziridine (155) and De-aminated Quinazolone (160) Produced in the Oxidation of (132) with LTA at Room Temperature

A number of small scale experiments at room temperature, involving the oxidation of the N-aminoquinazolone (132) with LTA, were carried out in the presence and absence of TFA and various concentrations of methyl acrylate. The results obtained are summarized in Table 10.

Inspection of Table 10 shows that in oxidations not involving TFA, a reduction in the concentration of alkene from 4 to 1.1 mole equivalents brings about a reduction in yield of aziridine from 75% to ca. 20% (entries 2 and 4). Entries 3 and 4, where only 1.1 mole equivalents of the alkene are employed, suggest that protonation of the quinazolone stabilizes this ring towards intramolecular attack by its attached nitrene. Thus, the yield of aziridine drops from 65% to ca. 20% when TFA is omitted from the oxidation. However, dilution of the reaction mixture by a factor of three, using 1.1 mole equivalents of alkene and no TFA, does not appear to affect the yield of aziridine from that obtained at higher concentration (entries 4 and 5) although there is some evidence of a decrease in the amount of de-aminated quinazolone (160), relative to the aziridine, with increasing dilution. Less de-aminated quinazolone (160) is produced in the presence of TFA than in an analogous reaction without TFA at high concentration with 4 mole equivalents of alkene (entries 1 and 2).

It appears that TFA, presumably via a relayed effect, reduces the nitrenophilicity of the amino group when the quinazolone ring is protonated. The de-amination process has been suggested by Dreiding to occur via intermolecular attack of the N-nitrene on the starting
TABLE 10
Summary of the Oxidations involving N-Aminoquinazoline (132) and Methyl acrylate

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature °C</th>
<th>Scale [a mass of (132)]</th>
<th>ITP dissolved in TPA</th>
<th>Mole equivalents of TPA</th>
<th>ml of dichloromethane /100 mg of (131)</th>
<th>Mole equivalents of CO₂Me</th>
<th>~N.M.R. YIELDS</th>
<th>% Azidine (155) (both diastereoisomers)</th>
<th>% De-aminated Quinazoline (160)</th>
<th>% Other by-products†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+20</td>
<td>Small (~100 mg)</td>
<td>No</td>
<td>3.4</td>
<td>1</td>
<td>4</td>
<td>72</td>
<td>&lt;5</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>2</td>
<td>+20</td>
<td>Small (~100 mg)</td>
<td>-</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>75</td>
<td>10</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>3</td>
<td>+20</td>
<td>Small (~100 mg)</td>
<td>No</td>
<td>3.4</td>
<td>1</td>
<td>1.1</td>
<td>65</td>
<td>35</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>4</td>
<td>+20</td>
<td>Small (~100 mg)</td>
<td>-</td>
<td>0</td>
<td>1</td>
<td>1.1</td>
<td>ca. 20</td>
<td>More (160) than azidine</td>
<td>Large %</td>
<td>Large %</td>
</tr>
<tr>
<td>5</td>
<td>+20</td>
<td>Small (~100 mg)</td>
<td>-</td>
<td>0</td>
<td>3</td>
<td>1.1</td>
<td>ca. 20</td>
<td>Similar % of (160) to azidine</td>
<td>Large %</td>
<td>Large %</td>
</tr>
<tr>
<td>6</td>
<td>-60</td>
<td>Small (~100 mg)</td>
<td>Yes</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>72</td>
<td>&lt;5</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>7</td>
<td>-60</td>
<td>Small (~100 mg)</td>
<td>Yes</td>
<td>6</td>
<td>3</td>
<td>1.1</td>
<td>74</td>
<td>26</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>8</td>
<td>-60</td>
<td>Small (~100 mg)</td>
<td>Yes</td>
<td>6</td>
<td>1</td>
<td>1.1</td>
<td>64</td>
<td>24</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>9</td>
<td>-60</td>
<td>Large (~2 g)</td>
<td>Yes</td>
<td>3.4</td>
<td>1</td>
<td>1.1</td>
<td>&lt;5</td>
<td>90</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>10</td>
<td>-60</td>
<td>Large (~1 g)</td>
<td>Yes</td>
<td>10</td>
<td>1</td>
<td>1.1</td>
<td>&gt;70</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
</tr>
</tbody>
</table>

† The origin of these 'other' by-products is assumed to be via an intramolecular pathway, although this has not, as yet, been proven.
N-aminoheterocycle; his proposed mechanism for the case of N-amino-
phthalimide (150) is shown in Figure 74.

Figure 74

5.4 Studies on the Low Temperature Oxidation of the N-Aminoquinazolone (132) in the Presence of Methyl acrylate

The diastereoselectivities obtained in the oxidations of (132) in the presence of various α,β-unsaturated esters and ketones and TFA, could be expected to be improved upon if the reactions were carried out at lower temperatures. However, lead tetra-acetate is only sparingly soluble in dichloromethane at temperatures below -30°C and the rate of dissolution at this temperature is also very slow (i.e. when the dissolved material is being consumed). As a consequence, larger volumes of dichloromethane are therefore required at these low temperatures which results in less efficient trapping of the nitrene for the same number of mole equivalents of alkene.

It was noticed, however, that LTA is markedly more soluble in dichloromethane solutions containing TFA at room temperature and,
significantly, solutions containing sufficient TFA$^+$ remained homogeneous even at -78°C.

The exact nature of the ligands on the lead in these solutions is unknown. Lead tetra-trifluoroacetate is an isolable$^{117}$ material which, not unsurprisingly, is a more powerful oxidising agent than LTA.$^{118}$ An increase in the oxidising ability of the resultant Pb(IV) species in the CH$_2$Cl$_2$-TFA solution above, therefore, would be anticipated if any exchange of acetate by trifluoroacetate ligands did occur. Even in the absence of ligand exchange, protonation of the acetate ligand before or during the reaction may increase the oxidising potential of the LTA.

Experiments using starch iodide paper suggest that oxidation of the N-aminoquinazolone (132) with LTA, in dichloromethane (~M solutions of LTA and (132)) containing TFA, proceeds slowly at -60°C.

The anticipated increase in diastereoselectivity at lower temperature was examined using methyl acrylate as the trap. Simultaneous but slow addition of solutions of LTA, dissolved in TFA-dichloromethane, and N-aminoquinazolone (132), also dissolved in TFA-dichloromethane (6 mole equivalents of TFA in total), to a solution of methyl acrylate (1.1 mole equivalents) in dichloromethane cooled to -60°C, gave a 64% yield of aziridine (155) with a 23:1 ratio of diastereoisomers (entry 8, Table 10). The solution in this reaction remained homogeneous at all times (no lead di-acetate precipitated out, as was the case in the absence of TFA).

Carrying out a similar oxidation using only 3.4 mole equivalents in total of TFA and 1.1 mole equivalents of methyl acrylate at -60°C, but otherwise under identical conditions, gave a mixture that was hetero-

$^+$ 6 mole equivalents minimum.
geneous at -60°C and only became homogeneous on warming above -30°C; less than 5% aziridine (155) and ~90% of the de-aminated quinazolone (160) was produced. Crystallization of the crude product from ethanol gave the de-aminated quinazolone (160) in 75% isolated yield.

However, when this experiment was repeated at -60°C, using 10 mole equivalents in total of TFA and adding the N-aminoquinazolone (132) (dissolved in dichloromethane) sufficiently slowly to a solution of LTA-TFA and methyl acrylate (1.1 mole equivalents) in dichloromethane at -60°C, a homogeneous solution was observed throughout and the aziridine (155) was, from the crude n.m.r. spectrum, the only product (65% isolated yield; 23:1 ratio of diastereoisomers).

A possible explanation for the production of the de-aminated quinazolone (160) in the presence of only 3.4 mole equivalents of TFA is that the latter is sequestered by LTA (up to a limit of 4 mole equivalents) leaving insufficient for solubilization of (132) at low temperature. Oxidation of the N-aminoquinazolone (132) would only take place on dissolution and if the latter were rapid at -30°C, the nitrene would be generated in the presence of excess of (132) - conditions conducive to the formation of the de-aminated quinazolone (160).

5.5 To obtain a good yield of aziridine from equimolar quantities of nitrene precursor and alkene is without precedent in nitrene chemistry. The importance of this result is two-fold: aziridination of scarce or expensive alkenes may be considered and isolation of the products facilitated.

Likewise, good yields from reactions involving intermolecular trapping of free carbenes invariably use an excess of either the carbene
precursor or trap: dichlorocarbene (161) may be considered analogous to the oxoquinazolinyl nitrene with its suppressed reactivity and preference for addition to \( \pi \)-bonds and absence of insertion into \( \sigma \)-bonds. However, a ~2:1 molar excess of the carbene precursor over

\[
: \text{CCl}_2 \\
(161)
\]

the alkene is used even in the most favourable case of an electron-rich alkene.\(^{121}\)

Benzymercurioiodomethane is an example of a carbenoid that reacts in a 1:1 molar ratio with electron-rich olefins in >70% yield.\(^{120}\)

5.6 The greater diastereoselectivities obtained in these aziridination reactions in the presence of TFA [Table 8] have been rationalized as the result of protonation on N-1 of the N-aminoquinazolone (132) [see Chapter 4]. However, protonation on the carbonyl oxygen of (132) producing (162) and hence the derived nitrene (163) is attractive since the aromatic quinazolinium species (163) is produced [Figure 75]. If this were the case, however, it would be difficult to explain the opposite sense of induction obtained from oxidation of the N-amino-benzimidazole (104) (without TFA present) and N-aminoquinazolone (132) (with TFA present) in the presence of lactone (65) [see Chapter 4].
It has been pointed out [Chapter 4] that an n.m.r. spectrum of the aziridine (153) in deuterochloroform containing TFA shows significant deshielding of the cis-aziridine ring protons. This fact is consistent with the presence of a ring current in the quinazolone ring [cf. (162)] bringing about selective deshielding of the two cis-aziridine ring protons and suggests at least competitive protonation on the amide carbonyl oxygen. Although it is likely that the relative basicities of N-1 and the amide carbonyl oxygen in the aziridine (153) and the N-aminquinazolone (132) will be the same, it is not certain that this relative basicity will be the same for the N-nitrene (138) derived from the latter: a 6-electron nitrene $\mathbb{N}$ claiming some share of the pair of electrons on the amide nitrogen would not necessarily maintain the same relative basicity at the above two sites. Even if exclusive protonation on the oxygen in the N-aminquinazolone (132) occurred, it is possible that deprotonation and reprotonation at N-1 could ensue after formation of the nitrene but before its addition to the alkene.

5.7 The stability to TFA of all the aziridines described in this Chapter is surprising. The ready ring-opening of an analogous aziridine (164) in a deuterochloroform solution containing TFA (3.4 mole equivalents), forming (165) [Figure 76], implies that the stability of the quinazolone-substituted aziridines is not just a consequence of
the poor nucleophilicity of the trifluoroacetate anion but a function of the quinazolone ring itself. Presumably, protonation of the

![Diagram of molecular structures](image)

Figure 76

quinazolone ring reduces the basicity of the aziridine nitrogen's lone-pair via a resonance-relayed effect; protonation of the aziridine ring nitrogen being assumed as the first step in the ring-opening process.

5.8 Oxidation of the N-Aminoquinazolone (132) with LTA at Room Temperature in the Presence and Absence of TFA, using 2-Nitropropene as a Nitrene Trap

Addition of the N-nitrene derived from the oxidation of the N-aminoquinazolone (132) to 2-nitropropene at room temperature in the absence and presence of TFA (3.4 mole equivalents) gave ratios of diastereoisomers of the corresponding aziridine (173) of 3.4 : 1 and 1 : 6.9 respectively. The increase in the diastereoselectivity in the oxidation with TFA is analogous to the effect observed with alkenes bearing substituents containing a carbonyl group.

Although nothing is known about the syn-selectivity preference of nitro groups, it is presumably the nitro group that has the greater propensity for a secondary interaction with the heterocycle and hence the greater susceptibility to the augmented secondary interaction at
C-2 in the presence of TFA, through protonation on N-1.

This result is significant as another step towards widening the scope of this asymmetric aziridination reaction. Table 11 illustrates the importance of TFA in these asymmetric aziridination reactions.

**TABLE 11**

Summary of the Advantages of Using TFA in Asymmetric Aziridination Reactions†

1) Protonates N-1, directs secondary interaction and effects asymmetric aziridination.

2) Solubilizes Pb(OAc)₄ permitting use of concentrated solutions. ⋭ Pb(OAc)₄ ⋭ ? CF₃CO₂H

3) Effects oxidation at lower temperatures. ⋭ Pb(OAc)₄(C₇CO₂)₄₋ₐ

4) Stabilizes the quinazolone ring against intramolecular attack by its own nitrene.

5) Reduces the nitrenophilicity of the unoxidised N-aminquinazolone and hence reduces yields of de-aminated product from this route.

6) Possibly favours C=O (ester or ketone)-C-2 quinazolone secondary interaction over alkyl-C-2 quinazolone interaction and hence broadens scope for asymmetric aziridination.

† These quinazolone-substituted aziridines are not ring-opened by TFA-CH₂Cl₂ (1:1) at room temperature.
Asymmetric Induction in the Addition of N-Nitrenes to (Electron Rich) Prochiral Alkenes: Addition of Oxoquinazolinyl Nitrenes to Various Styrenes and trans-But-2-ene: Results and Discussion

6.1 Introduction

This Chapter describes complementary studies to those described in Chapter 5 using electron-rich alkenes as traps for the oxoquinazolinyl nitrene (138).

Styrenes were obvious candidates for carrying out preliminary investigations, although their use in asymmetric aziridination reactions involving TFA is thwarted by their ready cationic polymerization. Nevertheless, it was hoped that with appropriately substituted styrenes oxidation in the absence of TFA could be carried out with the prospect of obtaining some asymmetric induction.

6.2 Oxidation of the N-Aminoquinazolones (132) and (137) in the Presence of Styrene and Oxidation of (132) in the Presence of cis-6-MethyIstyrene and trans-6-MethyIstyrene at Room Temperature

6.2.1 Oxidation of the N-aminoquinazolone (132) in the presence of styrene at room temperature produced a 1.77:1 ratio of diastereoisomers of aziridine (166). The major and minor diastereoisomers were isolated pure by chromatography in 20% and 18% yields respectively.

When a similar oxidation using the N-amino-7-nitroquinazolone analogue (137) was carried out in the presence of styrene, an identical ratio of diastereoisomers of the corresponding aziridine (167) was obtained. Again the major and minor diastereoisomers were isolated by chromatography in 30% and 20% yield respectively.

In view of the superior 5.6:1 ratio of diastereoisomers obtained in the analogous reaction using N-aminobenzimidazole (104) [see Chapter 3], these results suggest that addition of the nitrene (138) and its 7-nitro derivative (141) to styrene take place wholly or in large part by a
T.S. similar to (168) in Scheme 25. Again this conclusion, however, assumes [as is the case for formation of aziridine (140), see Chapter 4] that the contribution of pathways (168) and (169) to the formation of (166) would be changed by introduction of a 7-nitro substituent, i.e. that this substituent would have a differential effect on the magnitude of the two secondary interactions involved at C-2 and C-4 [see Appendix 1].

6.2.2 Similar oxidations of (132) in the presence of cis and in the presence of trans-β-methylstyrenes produced diastereoisomeric ratios of 1.65 : 1 and 1.7 : 1 respectively of the corresponding aziridines (171) and (172). These ratios were very similar to that obtained in the oxidation with styrene.

The result with cis-β-methylstyrene was surprising, particularly in view of the known greater syn-selectivity of phenyl over methyl. If the N-nitrene addition was predominantly via a T.S.G. as in Figure 77, as would have been predicted, then a greater degree of asymmetric induction might have been anticipated in view of the position of the cis-β-methyl group.

![Figure 77](image)
6.3 Oxidation of (132) in the Presence of trans-But-2-ene, with and without TFA at 0°C

\[
\begin{align*}
\text{Bu}^+ & \quad \text{Me} \\
\text{Me} & \quad \text{H} \\
\text{N} & \quad \text{NH}_2 \\
\end{align*}
\]

(132)

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

(170)

Figure 78

Oxidation of N-aminoquinazolone (132) in the presence of trans-but-2-ene at 0°C gave a 1.22 : 1 ratio of diastereoisomers of aziridine (170). An identical oxidation of (132) in the presence of TFA (3.4 mole equivalents) was possible since no polymerization of the alkene took place as was the case with styrene. The two diastereoisomers of the aziridine (170) were produced in a ratio of 1 : 3.9 and the major diastereoisomer of (170) was isolated by chromatography in 45% yield: both aziridines were unaffected by the TFA present.

This result suggests that TFA also brings about a change in T.S.G. for addition of the nitrene to alkyl-substituted alkenes analogous to that believed to obtain for π-electron-containing substituents [Figures 68 and 69].

The scope of these asymmetric aziridinations is increased by this observation.

6.4 A summary of the diastereoselectivities obtained in this Chapter using the N-aminoquinazolone (132) and various electron-rich alkenes is given in Table 12.
### TABLE 12
Summary of the Results from Oxidations of the N-Amino-quinazolone (132) with LTA in the Presence of Various Electron-Rich Alkenes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkene</th>
<th>Temp./°C</th>
<th>Aziridine ( ) Diastereoisomer Ratios</th>
<th>% Yield^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>+20</td>
<td>1.77:1 (166)</td>
<td>18^b</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>+20</td>
<td>1.78:1^d (167)</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>Me Ph</td>
<td>+20</td>
<td>1.65:1 (171)</td>
<td>35^c</td>
</tr>
<tr>
<td>4</td>
<td>Ph Me</td>
<td>+20</td>
<td>1.7:1 (172)</td>
<td>24^b</td>
</tr>
<tr>
<td>5</td>
<td>Me Me</td>
<td>0</td>
<td>3.9:1^e (170)</td>
<td>45</td>
</tr>
<tr>
<td>6</td>
<td>Me Me</td>
<td>0</td>
<td>1:1.22 (170)</td>
<td>-</td>
</tr>
</tbody>
</table>

^a Isolated yield of major diastereoisomer;  
^b Isolated yield of minor diastereoisomer;  
^c Mixture of diastereoisomers;  
^d Oxidation of 7-nitroquinazolone analogue (137);  
^e Oxidation in the presence of TFA (3.4 mole equivalents).
EXPERIMENTAL
INSTRUMENTATION

All 90 MHz $^1$H n.m.r. spectra were recorded on a Varian EM 390 spectrometer. High field $^1$H n.m.r. (300 MHz) and $^{13}$C n.m.r. (75 MHz) spectra were recorded on a Bruker AM 300 spectrometer. High field $^1$H n.m.r. (400 MHz) spectra were recorded by courtesy of the high field n.m.r. service at Warwick University. All n.m.r. spectra were recorded at room temperature, unless stated otherwise. Infra-red spectra of crystalline compounds were determined using Nujol mulls and liquid compounds as thin films, using a Perkin-Elmer 298 spectrometer. Mass spectra were determined on a Micromass 16B spectrometer. High resolution mass spectral measurements were made at P.C.M.U. Harwell, Oxford, and elemental analyses were carried out by CHN Analysis, Wigston, Leicester. Melting-points were determined on a Kofler hot-stage and are uncorrected.

General Experimental

Unless synthesized, the alkenes used as nitrene traps were used as supplied.

Flash column chromatography was carried out according to the method of Still,$^{22}$ using either MN-Kieselgel 60 (230-400 mesh) or basic (pH 9) activated alumina UG1 (100s mesh). Solvents used for flash column chromatography were distilled prior to use.

Light petroleum refers to the fraction of petroleum ether boiling in the range 60-80°C.

"Dry solvents" were distilled prior to use under nitrogen from the drying agents below. Tetrahydrofuran (THF) was distilled from sodium metal in the presence of benzophenone and used immediately. Ether was initially sodium dried and then distilled from lithium aluminium...
hydride. Dichloromethane, pyridine, triethylamine and diisopropylamine were distilled from powdered calcium hydride. Methanol and ethanol were distilled from magnesium methoxide. All other reactants and solvents were reagent grade unless stated otherwise.

Saturated sodium bicarbonate solution was used in basic work-ups.

**Physical Data**

Infra-red (i.r.) spectra are measured in units of cm$^{-1}$. The abbreviations used in determining i.r. data are:

- br: broad
- s: strong
- m: medium
- w: weak

Nuclear magnetic resonance (n.m.r.) spectra chemical shifts are expressed in p.p.m. on the $\delta$ scale relative to internal tetramethylsilane (TMS). The following abbreviations are used in recording n.m.r. data:

- J: coupling constant (in Hz)
- s: singlet
- d: doublet
- t: triplet
- q: quartet
- m: multiplet
- dd: double doublet
- ddd: double doublet of doublets
- dq: doublet of quartets
- Ar: aromatic signals
- het.: heterocycle

Mass spectra were determined in units of mass relative to charge (M/Z).
EXPERIMENTAL
CHAPTER 3
Preparation of 2-(1-hydroxybenzyl)benzimidazole (87)

This was prepared by Woodthorpe\textsuperscript{43} using Phillips' method,\textsuperscript{86} from \(\gamma\)-phenylenediamine and mandelic acid (absolute configuration not specified).

Preparation of Hydroxylamine-O-sulphonic acid (HQS)

This was prepared\textsuperscript{123} from hydroxylamine sulphate and oleum, as colourless crystals, in 82% yield. The crude product after washing with ether, without purification, was used within 4 weeks and stored at 0°C in the meantime.

Preparation of 1-Amino-2-(1-hydroxybenzyl)benzimidazole (88)

\[
\text{N} \quad \text{CH(OH)} \text{Ph} \quad \text{(88)}
\]

The title compound (88) was prepared by the method of Woodthorpe,\textsuperscript{43} from (87) and hydroxylamine-O-sulphonic acid, as a colourless solid (32%), m.p. 158-161°C (from acetonitrile) (Found: C, 70.24; H, 5.58; N, 17.46. \(\text{C}_{14}\text{H}_{13}\text{N}_{2}\text{O}\) requires C, 70.27; H, 5.48; N, 17.56%);

\(\nu_{\text{max}}\) (Nujol): 3420 (m), 3265 (m), 3195 (w), 1630 (m), 1610 (m) cm\(^{-1}\);

\(\delta_{\text{H}}\) (CDCl\(_3\), 90 MHz): 7.25 (m, 9 \times \text{ArH, OH}), 6.16 (s, CH\text{OH(Ph)}), 4.49 (brs, exch. \text{D}_2\text{O, NH}_2).

General Procedure (A) for the Oxidation of N-Aminobenzimidazoles at Room Temperature with Lead tetra-acetate in the Presence of Alkenes

Powdered N-aminobenzimidazole (1 mole equivalent) was intimately mixed with acetic acid free lead tetra-acetate (LTA) (1.1 mole equivalents). The mixture was then added in small amounts over fifteen minutes to a vigorously stirred solution of the nitrene trap (2 to 10
mole equivalents, depending on the ease of removal from the product) in dry dichloromethane (1 ml/100 mg of N-aminobenzimidazole). The mixture was then stirred for a further 30 minutes at room temperature, the insoluble lead di-acetate separated and washed with dichloromethane, and the total filtrate washed successively with sodium bicarbonate solution and then with water. The solution was finally dried with magnesium sulphate and the solvent removed under reduced pressure.

General Procedure (B) for the Oxidation of N-Aminobenzimidazoles with Phenyl Iodosodi-acetate at Room Temperature in the Presence of Alkenes

Powdered N-aminobenzimidazole (1 mole equivalent) was intimately mixed with phenyl iodosodi-acetate (1.1 mole equivalents) and suspended in dry dichloromethane (1 ml/100 mg of N-aminobenzimidazole) containing the nitrene trap (2 to 10 mole equivalents) and allowed to stir at room temperature overnight. The resulting mixture was washed with sodium bicarbonate solution and then with water, dried with magnesium sulphate and the solvent removed under reduced pressure.

General Procedure (C) for the Oxidation of N-Aminobenzimidazoles with Lead tetra-acetate at -20 to -25°C in the Presence of Alkenes

Powdered N-aminobenzimidazole (1 mole equivalent) was intimately mixed with acetic acid free lead tetra-acetate (LTA) (1.1 mole equivalents) and the mixture added in small amounts over 15 minutes to a solution of the nitrene trap (~2.5 mole equivalents) in deuteriochloroform (1 ml/100 mg of N-aminobenzimidazole) at -20 to -25°C. The mixture was then stirred for a further 30 minutes at this temperature and then filtered at low temperature (<-30°C). Routinely a high field $^1$H n.m.r. spectrum was recorded at -40°C, without any intermediate warming of the sample, thus allowing the kinetically-formed product to
be observed. A spectrum at -40°C was re-recorded after allowing the sample to stand in warm water (-40°C) for ~10 minutes, and finally a room temperature spectrum was also recorded. The crude reaction product was successively washed with sodium bicarbonate solution, then water, dried with magnesium sulphate and the solvent removed by rotary evaporation under reduced pressure.

**Preparation of 2,3-Dimethyl-1,3-butadiene (89)**

This was prepared by treatment of pinacol with hydrobromic acid. Fractional distillation and collection of the fraction with b.p. 68-68.5°C (lit. 69-70.5°C) gave the product (89) in 27% yield.

**Oxidation of 1-Amino-2-(1-hydroxybenzyl)benzimidazole (88) with LTA at Room Temperature in the Presence of**

a) 2,3-Dimethyl-1,3-butadiene (89)

![Chemical Structure](image)

The general oxidation procedure (A) was followed using N-amino-benzimidazole (88) (0.206g, 8.619 x 10^-4 moles), LTA (0.386g, 8.964 x 10^-4 moles) and 2,3-dimethyl-1,3-butadiene (89) (1.02g, 8.619 x 10^-3 moles) in dry dichloromethane (2 ml). Chromatography of the crude oxidation product [which comprised a 1.4 : 1 (±0.2) ratio of diastereoisomers of aziridine (101)] over activated basic alumina, with ethyl acetate-light petroleum (1:2) as eluant, gave the pure 1-[(2-(1-hydroxybenzyl)-benzimidazol-1-yl)-2-methyl-2-isopropenylaziridine (101) as a colourless oil (0.140g, 51%), as a mixture of diastereoisomers;

\n\[ \nu_{\text{max}}(\text{film}): 3150(\text{br,m}), 1640(\text{w}), 1610(\text{w}), 1450(\text{s}), 1380(\text{m}), 1315(\text{m}), \]
1275(m), 1230(m), 1185(m), 1050(m), 910(m), 740(s) cm⁻¹;

δ_H (CDCl₃, 90 MHz):

<table>
<thead>
<tr>
<th>Major Diastereoisomer</th>
<th>Minor Diastereoisomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.80-7.00 (m, 9 × ArH, OH)</td>
<td></td>
</tr>
<tr>
<td>6.10 (s, CHO(H(Ph))</td>
<td>6.18 (s, CHO(Ph))</td>
</tr>
<tr>
<td>5.30-5.00 (m, MeC=CH₂)</td>
<td></td>
</tr>
<tr>
<td>3.15 (d, J2 Hz, aziridine ring proton cis to het.)</td>
<td>3.00 (d, J2 Hz, aziridine ring proton cis to het.)</td>
</tr>
<tr>
<td>2.50 (d, J2 Hz, aziridine ring proton trans to het.)</td>
<td>2.62 (d, J2 Hz, aziridine ring proton trans to het.)</td>
</tr>
<tr>
<td>1.65 (s, H = C H₂)</td>
<td>1.70 (s, MeC=CH₂)</td>
</tr>
<tr>
<td>1.13 (s, aziridine ring Me)</td>
<td>0.95 (s, aziridine ring Me)</td>
</tr>
</tbody>
</table>

In both diastereoisomers only one invertomer is evident in the ¹H n.m.r. spectrum at room temperature (major invertomer: aziridine ring Me and het. syn);

M/Z (%): 319(M⁺, 24), 301(14), 207(44), 206(81), 194(37), 105(76), 96(41), 85(70), 83(100), 77(93).

b) Methyl acrylate (95)

\[
\begin{align*}
\text{CH(OH) Ph} \\
\text{N} \\
\text{N} \\
\text{CO₂Me}
\end{align*}
\]

(98)

The general oxidation procedure (A) was followed using N-aminobenzimidazole (88) (0.200g, 8.368 × 10⁻⁴ moles), LTA (0.389g, 8.786 × 10⁻⁴ moles) and methyl acrylate (95) (0.720g, 8.368 × 10⁻³ moles) in dry dichloromethane (2 ml). Chromatography of the crude oxidation product [which comprised a 2.0 : 1 ratio of diastereoisomers of aziridine (98)] over activated basic alumina, with ethyl acetate-light petroleum (1:2)
as eluant, gave the pure methyl 1-(2-(1-hydroxybenzyl)benzimidazol-1-yl)aziridine-2-carboxylate (98) as a colourless oil (0.124g, 46%), as a mixture of diastereoisomers;

\[ \text{\textit{V} \text{m} \text{x} \text{(film): } 3150 (\text{br}, \text{s}), 1745 (\text{s}), 1610 (\text{w}), 1440 (\text{s}), 1390 (\text{m}), 1225 (\text{m}), 1040 (\text{s}), 895 (\text{m}), 750 (\text{s}) \text{ cm}^{-1};} \]

\[ \delta_H (\text{CDCl}_3, 90 \text{ MHz}): \]

<table>
<thead>
<tr>
<th>Major Diastereoisomer</th>
<th>Minor Diastereoisomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.80-6.85 (m, 9 \times \text{ArH, OH})</td>
<td></td>
</tr>
<tr>
<td>6.16 (s, \text{CHOH(Ph)})</td>
<td></td>
</tr>
<tr>
<td>3.53 (s, \text{CO}_2\text{Me})</td>
<td>3.60 (s, \text{CO}_2\text{Me})</td>
</tr>
<tr>
<td>2.96 (dd, J 8 and 2Hz, \text{gem. aziridine ring proton cis to het.})</td>
<td></td>
</tr>
<tr>
<td>2.65 (dd, J 6 and 2Hz, \text{gem. aziridine ring proton trans to het.})</td>
<td>2.55 (dd, J 6 and 2Hz, \text{gem. aziridine ring proton trans to het.})</td>
</tr>
</tbody>
</table>

The aziridine ring proton \text{cis} to het. and \text{gem.} to \text{CO}_2\text{Me}, in both diastereoisomers, is not distinguishable. In both diastereoisomers only one invertomer is evident in the \textsuperscript{1}H n.m.r. spectrum at room temperature (major invertomer: \text{CO}_2\text{Me} and het. \text{anti});

\[ M/2 (\%) : 323 (M^+, 29), 237 (13), 236 (14), 107 (51), 105 (50), 103 (100), 79 (35), 77 (51). \]

Preparation of 2-(D-gluc0-1,2,3,4,5-pentanepentaol)benzimidazole (93)

\[
\begin{align*}
\text{N} &
\text{O} \\
\text{N} &
\text{CH(CHOH)}_3\text{CH}_2\text{OH}
\end{align*}
\]

(93)

This was prepared\textsuperscript{125} using Phillips' method\textsuperscript{86} from \text{9-phenylenediamine} and sodium gluconoate (D-(+)-enantiomer) in 62\% yield, m.p. 211-215°C (from water) (lit.\textsuperscript{125} 215°C).
Preparation of 2-(D-glucol-1-acetoxy-(2,3), (4,5)-diisopropylidene-2,3,4,5-pentanetetraol) benzimidazole (92)

\[
\text{OAc} \quad \begin{array}{c}
\text{N} \\
\text{H}
\end{array}
\]

\[
\begin{array}{c}
\text{C} = \text{C} \\
\text{CH} - \text{CH} - \text{CH} - \text{CH}_2
\end{array}
\]

(92)

The benzimidazole (93) (6.00g, 0.022 moles) was dissolved in dry acetone (~120g) containing ~1% hydrogen chloride. The homogeneous mixture was allowed to stand for 36 hours at room temperature, then poured into sodium carbonate solution (30 ml). Extraction with ether (2 x 50 ml), drying of the ether solution with magnesium sulphate, and evaporation under reduced pressure gave a syrup to which pyridine (66 ml) and acetic anhydride (22 ml) were added. The mixture was set aside at room temperature for 2 hours. After pouring into water and setting aside for a further 10 minutes, the solution was extracted with ether (70 ml), the ether freed from acetic acid by washing cautiously with sodium carbonate solution, then dried with magnesium sulphate and the solvent removed under reduced pressure. The residual oil solidified on addition to ice-water. Recrystallization from ethanol-water gave the benzimidazole (92) (4.80g, 55%) as colourless crystals, m.p. 181-182°C (from ethanol-water) (Found: C, 61.28; H, 6.67; N, 7.12. C_{20}H_{26}N_{2}O_{6} requires C, 61.53; H, 6.71; N, 7.18%); \nu_{\text{max}} (Nujol): 2750(br,m), 2620(br,m), 2520(br,m), 1750(s), 1595(w), 1535(w), 1225(s), 1075(s), 840(s), 745(s) cm\(^{-1}\); \delta_{H} (CDCl_{3}, 90 MHz): 9.70(brs, NH), 7.73 (m, 1 x ArH), 7.26 (m, 3 x ArH), 6.30 (d, J=\text{Hz}, 1'-H), 4.49 (dd, J=7 and 3Hz, 2'-H), 3.96 (m, 3', 4' and 2 x 5'-H), 2.10 (s, CH_{3}CO), 1.36 (4 x s, 4 x CH_{3}); M/Z (%): 390 (M^+, 4), 375 (28), 273 (36), 190 (84), 150 (100), 147 (44), 85 (24).
Preparation of 0-mesitylenesulphonylhydroxylamine

This was prepared by treatment of ethyl O-(mesitylenesulphonyl)-acetohydroximate with 70% perchloric acid, at 0°C, in 80% yield. The product was recrystallized from ether - light petroleum to give colourless crystals, m.p. 80-82°C (lit. 93-94°C).

Preparation of 1-Amino-2-(D-gluco-1-acetoxy-(2,3), (4,5)-diisopropylidene-2,3,4,5-pentanetetraol)benzimidazole (90)

\[
\begin{align*}
\text{NH}_2 & \quad \text{OAc} \\
\text{CH} & \quad \text{CH} \\
\text{CH} & \quad \text{CH} \\
\end{align*}
\]

A solution of 0-mesitylenesulphonylhydroxylamine (0.382g, 1.777 x 10^{-3} moles) in dichloromethane (10 ml) was washed once with ice-cold water and then added dropwise with stirring to an ice-cooled solution of (92) (0.66g, 1.692 x 10^{-3} moles) in dichloromethane (40 ml), in which solid sodium bicarbonate (~1g) was suspended. After addition, the mixture was stirred at room temperature for a further 1½ hours and then extracted with sodium hydroxide (3M, 20 ml). The organic layer was separated and extracted with more sodium hydroxide (3M, 3 x 20 ml), then washed with water (2 x 20 ml), dried with magnesium sulphate and the solvent removed by rotary evaporation under reduced pressure to yield the aminated product (90) (0.08lg, 12%), m.p. 130-131°C (from ether);

\[
\begin{align*}
\nu_{\text{max}} \text{ (Nujol)} & : 3310(\text{m}), 3180(\text{m}), 1735(\text{s}), 1615(\text{w}), 1510(\text{w}), 855(\text{s}), 745(\text{s}) \ \text{cm}^{-1}; \\
\delta_{\text{H}} \text{ (CDCl}_3, 90 \text{ MHz)} & : 7.65 (\text{m, 1 x ArH}), 7.25 (\text{m, 3 x ArH}), 6.35 (\text{d, J6Hz, 1'-H}), 4.80 (\text{s, exch. } \text{D}_2\text{O, NH}_2), 4.65 (\text{m, 2'-H}), 3.90 (\text{m, 3', 4' and 2 x 5'-H}), 2.10 (\text{s, CH}_3\text{CO}), 1.35 (\text{s, 2 x CH}_3), 1.00 (2 x s, 2 x CH}_3);
\end{align*}
\]
M/Z (%): 405(M⁺, 3), 391(19), 273(30), 205(45), 190(82), 162(56), 147(100), 143(74), 101(48).

Oxidation of 1-Amino-2-(D-gluco-1-acetoxy-(2,3),(4,5)-diisopropylidene-2,3,4,5-pentanetetraol)benzimidazole (90) with LTA at Room Temperature in the Presence of
a) 2,3-Dimethyl-1,3-butadiene (89)

The general oxidation procedure (A) was followed using the N-amino-benzimidazole (90) (0.067g, 1.654 x 10⁻⁴ moles), LTA (0.078g, 1.761 x 10⁻⁴ moles) and 2,3-dimethyl-1,3-butadiene (89) (0.195g, 1.654 x 10⁻³ moles) in dry dichloromethane (1 ml). Chromatography of the crude oxidation product [which comprised a 1.20 : 1 (±0.09) ratio of diastereoisomers of aziridine (100)] over activated basic alumina, with ethyl acetate-light petroleum (1:2) as eluant, gave the pure 1-(2-(D-gluco-1-acetoxy-(2,3),(4,5)-diisopropylidene-2,3,4,5-pentanetetraol)benzimidazol-1-yl)-2-methyl-2-isopropenylaziridine (100) as a light brown oil (0.04g, 50%), as a mixture of diastereoisomers;

νmax (film): 2990(m), 1750(s), 1450(m), 1370(s), 1230(s), 1070(s), 845(m), 750(m) cm⁻¹;
δH (CDCl₃, 400 MHz):

<table>
<thead>
<tr>
<th>Major Diastereoisomer</th>
<th>Minor Diastereoisomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.81-7.17 (m, 4 × ArH)</td>
<td></td>
</tr>
<tr>
<td>6.23 (d, J7.0Hz, 1′-H)</td>
<td>6.39 (d, J7.2Hz, 1′-H)</td>
</tr>
<tr>
<td>5.17 (m, MeC=CH₂)</td>
<td>5.35 (brs, MeC=CH₂)</td>
</tr>
</tbody>
</table>
4.64 (dd, J13.2 and 7.2Hz, 2'-H)

4.18-3.72 (m, 3', 4' and 2 × 5'-H)

3.46 (d, J1.2Hz, gem. aziridine ring proton cis to het.)  3.02 (d, J1.2Hz, gem. aziridine ring proton trans to het.)

3.02 (d, J1.2Hz, gem. aziridine ring proton trans to het.)  2.88 (brs, gem. aziridine ring proton trans to het.)

2.24 (s, CH₃CO)  2.22 (s, CH₃CO)

1.86 (s, MeC=CH₂)  1.90 (s, MeC=CH₂)

1.50-0.84 (4 × s and 1 × s, 4 × CH₃ and aziridine ring Me cis to het.)

In both diastereoisomers only one invertomer is evident in the ¹H n.m.r. spectrum at room temperature (major invertomer: isopropenyl group and het. anti);

M/Z (%): 485(M⁺, 6), 470(22), 368(23), 285(24), 242(28), 190(28), 147(71), 143(33), 101(24), 96(100).

b) Methyl acrylate (95)

The general oxidation procedure (A) was followed using the N-amino-benzimidazole (90) (0.060g, 1.482 × 10⁻⁴ moles), LTA (0.069g, 1.556 × 10⁻⁴ moles) and methyl acrylate (95) (0.128g, 1.482 × 10⁻³ moles) in dry dichloromethane (0.75 ml). Chromatography of the crude oxidation
product [which comprised a 1.1:1 (±0.1) ratio of diastereoisomers of aziridine (97)] over activated basic alumina, with ethyl acetate-light petroleum (1:2) as eluant, gave the pure methyl 1-(2-(D-glucopyranosyl- (2,3),(4,5)-diisopropylidene-2,3,4,5-pentanetetraol) benzimidazol-1-yl)aziridine-2-carboxylate (97) as a pale yellow oil (0.032g, 44%), as a mixture of diastereoisomers;

$\nu_{\text{max}}$ (film): 2990(m), 1745(s), 1450(m), 1370(s), 1230(s), 1070(s), 845(m), 745(m) cm$^{-1}$;

$\delta_H$ (CDCl$_3$, 90 MHz):

<table>
<thead>
<tr>
<th>Major Diastereoisomer</th>
<th>Minor Diastereoisomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.80-7.00 (m, 4 xArH)</td>
<td></td>
</tr>
<tr>
<td>6.20 (d, J9Hz, 1'-H)</td>
<td>6.30 (d, J9Hz, 1'-H)</td>
</tr>
<tr>
<td>4.60 (dd, J9 and 3Hz, 2'-H)</td>
<td>4.65 (dd, J9 and 3Hz, 2'-H)</td>
</tr>
<tr>
<td>4.20-3.60 (m, 3', 4', 2 x 5'-H and aziridine ring proton cis to het. and gem. to CO$_2$Me)</td>
<td></td>
</tr>
<tr>
<td>3.40 (dd, J8 and 2Hz, gem. aziridine ring proton cis to het.)</td>
<td>3.25 (dd, J8 and 2Hz, gem. aziridine ring proton cis to het.)</td>
</tr>
<tr>
<td>3.00 (dd, J6 and 2Hz, gem. aziridine ring proton trans to het.)</td>
<td></td>
</tr>
<tr>
<td>2.13 (s, CH$_3$CO)</td>
<td>2.10 (s, CH$_3$CO)</td>
</tr>
<tr>
<td>1.35 (s, 2 x CH$_3$)</td>
<td></td>
</tr>
<tr>
<td>0.90 (2 x s, 2 x CH$_3$)</td>
<td></td>
</tr>
</tbody>
</table>

In both diastereoisomers only one invertoemer is evident in the $^1$H n.m.r. spectrum at room temperature (major invertoemer: CO$_2$Me and het. anti);

M/Z (%): 489(M$^+$, 6), 474(40), 372(46), 289(100), 246(56), 202(23), 190(36), 147(99), 143(53), 101(35), 85(33).

-140-
c) **Styrene**

![Chemical Structure](image)

The general oxidation procedure (A) was followed using the N-amino-benzimidazole (90) (0.101g, 2.494 x 10^-4 moles), LTA (0.115g, 2.594 x 10^-4 moles) and styrene (0.260g, 2.494 x 10^-3 moles) in dry dichloromethane (1 ml). Chromatography of the crude oxidation product [which comprised a 1.74:1 (±0.01) ratio of diastereoisomers of aziridine (103)] over activated basic alumina, with ethyl acetate–light petroleum (1:2) as eluant, gave the pure l-(2-(D-gluco-1-acetoxy-(2,3),(4,5)-diisopropylidene-2,3,4,5-pentanetetraol)benzimidazol-1-yl)-2-phenylaziridine (103) as a pale yellow oil (0.024g, 19%), as a mixture of diastereoisomers; 

\[ \nu_{\text{max}} \text{ (film): } 2990 \text{ (s)}, 2930 \text{ (s)}, 1740 \text{ (s)}, 1605 \text{ (w)}, 1500 \text{ (w)}, 1450 \text{ (m)}, 1370 \text{ (s)}, 1230 \text{ (s)}, 1070 \text{ (s)}, 845 \text{ (m)}, 740 \text{ (m) cm}^{-1}; \]

\[ \delta_{\text{H}} \text{ (CDCl}_3\text{, } 400 \text{ MHz):} \]

<table>
<thead>
<tr>
<th>Major Diastereoisomer</th>
<th>Minor Diastereoisomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.77-7.14 (m, 9 x ArH)</td>
<td>6.41 (d, J8.3Hz, 1'-H)</td>
</tr>
<tr>
<td>6.01 (d, J8.3Hz, 1'-H)</td>
<td>4.50 (dd, J8.3 and 6.0Hz, 2'-H)</td>
</tr>
<tr>
<td>4.15-3.47 (m, 3', 4' and 2 x 5'-H)</td>
<td>4.39 (dd, J8.3 and 5.6Hz, 2'-H)</td>
</tr>
<tr>
<td>3.86 (dd, J8.2 and 6.2Hz, aziridine ring proton gem. to Ph and cis to het.)</td>
<td>4.01 (dd, J8.3 and 6.1Hz, aziridine ring proton gem. to Ph and cis to het.)</td>
</tr>
</tbody>
</table>
3.44 (dd, J8.2 and 1.6Hz, 
gem. aziridine ring proton 
cis to het.)
2.92 (dd, J6.2 and 1.6Hz, 
gem. aziridine ring proton 
trans to het.)
2.19 (s, CH₃CO)
3.62 (dd, J8.3 and 1.8Hz, 
gem. aziridine ring proton 
cis to het.)
2.79 (dd, J6.1 and 1.8Hz, 
gem. aziridine ring proton 
trans to het.)
2.22 (s, CH₃CO)
1.46-0.7 (4 × s, 4 × CH₃)

In both diastereoisomers only one invertomer is evident in the ¹H n.m.r.
spectrum at room temperature (major invertomer: Ph and het. anti);
M/Z (%) : 507 (M⁺, 23), 492 (28), 390 (34), 307 (49), 264 (38), 248 (25),
234 (14), 147 (45), 143 (27), 118 (75), 104 (36), 91 (100).

Preparation of 1-Amino-2-[(D-gluco-(2,3),(4,5)-diisopropylidene-
1,2,3,4,5-pentanepentaol)benzimidazole (91)]

\[
\begin{array}{c}
\text{OH} \\
\text{CHCH-CHCH-CH}_2 \\
\text{NH}_2 \\
\end{array}
\]
\[(91)\]

The acetylated benzimidazole (92) (3.01g, 7.718 × 10⁻³ moles) was
heated under reflux for 2 hours with sodium hydroxide (5M, 50 ml).
After cooling, the solution was extracted with ether, the ether dried
with magnesium sulphate and the solvent removed under reduced pressure
to yield a white foam (2.19g). This foam was dissolved in water (10 ml)
and ethanol (10 ml) at 60°C and solid potassium hydroxide (2.03g, 0.0362
moles) was added in portions at this temperature, followed by hydroxyl-
amine-O-sulphonic acid (1.70g, 0.0151 moles) at such a rate so as to
keep the temperature at 55-65°C. The mixture was stirred for a further
20 minutes at 60°C, then cooled and the solid separated. This solid was
heated in boiling acetonitrile and the insoluble potassium sulphate
separated. Ice-cooling of the solution gave the N-aminobenzimidazole (91) (0.04g, 19%) as colourless crystals, m.p. 213-214°C (from acetonitrile) (Found: C, 59.56; H, 6.89; N, 11.42. C₁₈H₂₅N₃O₅ requires C, 59.49; H, 6.93; N, 11.56%);

νₓmax (Nujol): 3360 (s), 3340 (w), 3280 (w), 1635 (w), 1515 (w), 1255 (s), 1215 (m), 1170 (s), 1145 (m), 1070 (s), 840 (s), 750 (s) cm⁻¹;

δH (d₆ DMSO, 90 MHz): 7.45 (m, 2 x ArH), 7.13 (m, 2 x ArH), 5.93 (s, NH₂), 5.73 (d, J6Hz, OH), 5.10 (dd, J6 and 3Hz, 1'-H), 4.36 (m, 2'-H), 4.15-3.53 (m, 3', 4' and 2 x 5'-H), 1.30 (s, 2 × CH₃), 1.13 (s, 2 × CH₃);

M/Z (%): 363 (M⁺, 5), 349 (22), 163 (100), 147 (88), 143 (77), 59 (50).

Oxidation of 1-Amino-2-(D-gluco-(2,3), (4,5)-diisopropylidene-1,2,3,4,5-pentanepentaol)benzimidazole (91) with LTA at Room Temperature in the Presence of

a) 2,3-Dimethyl-1,3-butadiene (89)

The general oxidation procedure (A) was followed using the N-aminobenzimidazole (91) (0.100g, 2.755 x 10⁻⁴ moles), LTA (0.127g, 2.867 x 10⁻⁴ moles) and 2,3-dimethyl-1,3-butadiene (89) (0.226g, 2.755 x 10⁻³ moles) in dry dichloromethane (1 ml). Chromatography of the crude oxidation product [which comprised a 1.4 : 1 (±0.2) ratio of diastereoisomers of aziridine (99)] over silica, with ethyl acetate-light petroleum (1:1) as eluant, gave the pure 1-(2-(D-gluco-(2,3), (4,5)-diisopropylidene-1,2,3,4,5-pentanepentaol)benzimidazol-1-yl)-2-methyl-2-isopropenylaziridine (99) as a colourless oil (0.072g, 59%), as a
mixture of diastereoisomers;

$\nu_{\text{max}}$ (film): 3300 (br, m), 2990 (s), 1640 (w), 1610 (w), 1500 (w), 1450 (s),
1380 (s), 1370 (s), 1215 (s), 1070 (s), 845 (s), 750 (s) cm$^{-1}$;

$\delta_{\text{H}}$ (CDCl$_3$, 90 MHz):

<table>
<thead>
<tr>
<th>Major Diastereoisomer</th>
<th>Minor Diastereoisomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.80-7.00 (m, 4 x ArH)</td>
<td></td>
</tr>
<tr>
<td>5.32-4.85 (m, OH, 1'-H and MeC=CH$_2$)</td>
<td></td>
</tr>
<tr>
<td>4.55 (m, 2'-H)</td>
<td></td>
</tr>
<tr>
<td>4.25-3.66 (m, 3', 4' and 2 x 5'-H)</td>
<td></td>
</tr>
<tr>
<td>3.20 (d, J2Hz, gem. aziridine ring proton cis to het.)</td>
<td>3.10 (d, J2Hz, gem. aziridine ring proton cis to het.)</td>
</tr>
<tr>
<td>2.90 (d, J2Hz, gem. aziridine ring proton trans to het.)</td>
<td>2.80 (d, J2Hz, gem. aziridine ring proton trans to het.)</td>
</tr>
<tr>
<td>1.88 (s, MeC=CH$_2$)</td>
<td>1.80 (s, MeC=CH$_2$)</td>
</tr>
<tr>
<td>1.50-1.00 (m, 4 x CH$_3$ and aziridine ring Me cis to het.)</td>
<td></td>
</tr>
</tbody>
</table>

In both diastereoisomers only one inveromer is evident in the $^1$H n.m.r. spectrum at room temperature (major inveromer: isopropenyl group and het. anti);

M/Z (%): 443(M$^+$, 6), 428(21), 242(22), 214(23), 161(21), 148(98),
147(55), 143(75), 101(34), 96(100).
b) Methyl acrylate (95)

![Chemical structure](image)

The general oxidation procedure (A) was followed using the N-amino­benzimidazole (91) (0.100g, \(2.755 \times 10^{-4}\) moles), LTA (0.127g, \(2.867 \times 10^{-4}\) moles) and methyl acrylate (0.237g, \(2.755 \times 10^{-3}\) moles) in dry dichloro­methane (1 ml). Chromatography of the crude oxidation product [which comprised a 3.60:1 (±0.03) ratio of diastereoisomers of aziridine (96)] over silica, with ethyl acetate-light petroleum (2:1) as eluant, gave the pure methyl 1-[(2-(D-gluc­o-(2,3),(4,5)-diisopropylidene-1,2,3,4,5-pentanepentaol)benzimidazol-1-yl)aziridine-2-carboxylate (96) as a colourless oil (0.106g, 86%), as a mixture of diastereoisomers; 

\[ \Delta_{\text{max}}\text{(film): 3400 (br,m), 2990 (s), 1745 (s), 1610 (w), 1510 (w), 1450 (s), 1380 (s), 1370 (s), 1220 (s), 1070 (s), 845 (m), 750 (s) cm}^{-1}; \]

\[ \delta_{H}\text{ (CDCl}_{3}\text{, 400 MHz):} \]

<table>
<thead>
<tr>
<th>Major Diastereoisomer</th>
<th>Minor Diastereoisomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.70-7.14 (m, 4 x ArH)</td>
<td></td>
</tr>
<tr>
<td>5.25 (brs, 1'-H)</td>
<td></td>
</tr>
<tr>
<td>4.52 (dd, J7.5 and 2.6Hz, 2'-H)</td>
<td></td>
</tr>
<tr>
<td>4.16-3.88 (m, 3', 4' and 2 x 5'-H)</td>
<td></td>
</tr>
<tr>
<td>3.83 (s, -CO₂Me)</td>
<td>3.79 (s, -CO₂Me)</td>
</tr>
<tr>
<td>3.67 (dd, J7.9 and 5.2Hz, aziridine ring proton <em>gem</em> to CO₂Me and <em>cis</em> to het.)</td>
<td>3.73 (dd, J7.9 and 5.1Hz, aziridine ring proton <em>gem</em> to CO₂Me and <em>cis</em> to het.)</td>
</tr>
</tbody>
</table>
3.13 (dd, J7.9 and 1.5 Hz, gem, aziridine ring proton cis to het.)
3.27 (dd, J7.9 and 1.5 Hz, gem, aziridine ring proton cis to het.)
2.93 (dd, J5.2 and 1.5 Hz, gem, aziridine ring proton trans to het.)
1.38-1.18 (4 x s, 4 x CH₃)

In both diastereoisomers only one invertingomer is evident in the ^1H n.m.r.
spectrum at room temperature (major invertingomer: CO₂Me and het. anti);
M/Z (%): 447(M⁺, 5), 432(16), 247(33), 218(23), 161(58), 147(82),
143(100), 118(18), 101(53), 59(60).

c) Styrene

\[ \text{OH} \]
\[ \begin{array}{c}
\text{O} \\
\text{L} \\
\text{N} \\
\text{N}
\end{array} \]
\[ \text{CH₃-CH₃-CH₂} \]
\[ \text{0} \]
\[ \text{0} \]
\[ \text{0} \]
\[ \text{0} \]
\[ \text{Ph} \]

The general oxidation procedure (A) was followed using the N-amino-
benzimidazole (91) (0.100g, 2.755 x 10⁻⁴ moles), LTA (0.128g, 2.893 x 10⁻⁴ moles) and styrene (0.287g, 2.755 x 10⁻³ moles) in dry dichloromethane
(1 ml). Chromatography of the crude oxidation product [which comprised
a 1.05 : 1 (±0.05) ratio of diastereoisomers of aziridine (102)] over silica, with ethyl acetate-light petroleum (2:1) as eluant, gave the
pure 1-(2-(D-gluco-(2,3),(4,5)-diisopropylidene-1,2,3,4,5-pentane-
pentaol)benzimidazol-1-yl)-2-phenylaziridine (102) as a colourless oil
(0.096g, 75%), as a mixture of diastereoisomers;
\( v_{\text{max}} \) (film): 3300 (br,m), 2990 (s), 1610 (w), 1500 (m), 1450 (s), 1380 (s),
1370 (s), 1215 (s), 1070 (s), 845 (s), 750 (s) cm⁻¹;
\( \delta_H \) (CDCl₃, 400 MHz):
Major Diastereoisomer | Minor Diastereoisomer

7.72-7.12 (m, 9 × ArH) | 
5.53 (brd, J7Hz, CH) | 
5.16 (brs, 1'-H) | 
4.52 (dd, J7.8 and 2.3Hz, 2'-H) | 4.46 (dd, J7.4 and 3.5Hz, 2'-H) 
4.17-3.80 (m, 3', 4', 2 × 5'-H and aziridine ring proton gem. to Ph and cis to het.) | 
3.24 (dd, J8.1 and 1.8Hz, gem. aziridine ring proton cis to het.) | 3.36 (dd, J8.1 and 1.8Hz, gem. aziridine ring proton cis to het.) 
2.74 (dd, J5.4 and 1.8Hz, gem. aziridine ring proton trans to het.) | 
1.37-1.02 (4 × s, 4 × CH₃) | 

In both diastereoisomers only one invertomer is evident in the ¹H n.m.r. spectrum at room temperature (major invertomer: Ph and het. anti).

Preparation of 2,3,3-trimethylbutanoic acid (108)

This was prepared from t-butylacetic acid by a modification of the literature method.¹²⁷ Thus, dry THF (68 ml) and re-distilled diisopropylamine (12.66 ml, 0.0903 moles) were added to a flame-dried and dry nitrogen-flushed 3-necked flask under a nitrogen atmosphere. The flask was cooled to -78°C and a solution of n-butyl lithium (36.71 ml, 0.0903 moles) was added, with stirring, over 20 minutes from a dropping funnel and then the mixture stirred at -78°C for a further 30 minutes. t-Butylacetic acid (5.00g, 0.0430 moles) was then added to the solution at -78°C over ~5 minutes via a syringe through a septum cap and the
mixture stirred for 3 hours at room temperature. After re-cooling the solution to -78°C, methyl iodide (2.68 ml, 0.0430 moles) was added briskly at this temperature and then the solution allowed to warm to room temperature at which point a white precipitate was formed. The mixture was stirred for a further 1½ hours at room temperature, then neutralized with ice-cold hydrochloric acid solution (10%) and extracted with light petroleum (2 x 100 ml). The combined organic layers were washed successively with hydrochloric acid solution (10%, 3 x 100 ml), water (3 x 100 ml) and brine (3 x 100 ml), dried with magnesium sulphate and the solvent removed under reduced pressure.

The crude product (108) from this procedure was contaminated only with t-butylacetic acid (~5%) and was used directly for the procedure below;

$\delta_H$ (CDCl$_3$, 90 MHz): 11.30 (brs, exch. D$_2$O, CO$_2$H), 2.27 (q, J7Hz, CHMe(Bu$^t$)), 1.12 (d, J7Hz, CHMe(Bu$^t$)), 1.03 (s, Bu$^t$).

**Preparation of the Monoamide (106)**

```
Me
\[ \text{NHCOCHBu}^t \]
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2,3,3-Trimethylbutanoic acid (108) (17.55g, 0.135 moles) and an excess of thionyl chloride (~5 mole equivalents) were heated to 40-50°C for 1½ hours, by which time evolution of bubbles had ceased to be observable. Excess thionyl chloride was removed by evaporation under reduced pressure and the residual acid chloride diluted with dry dichloromethane (~200 ml) and added dropwise over ca. 45 minutes, via a dropping funnel equipped with a drying tube, to a briskly stirred solution of O-phenylenediamine (32.08g, 0.297 moles) in dry dichlоро-
methane (500 ml). After addition was complete, the mixture was set aside overnight, after which time the insoluble hydrochloride was separated off and the dichloromethane solution washed successively with sodium bicarbonate solution (2 x 100 ml) and water (1 x 100 ml), dried with magnesium sulphate and the solvent evaporated under reduced pressure. Crystallization of the solid obtained from ethyl acetate gave the monoamide (106) (12.1g, 41%) as colourless crystals, m.p. 173-178°C (with sublimation);

$\nu_{\text{max}}$ (Nujol): 3390(m), 3310(s), 3250(s), 1630(s), 1490(s), 1315(m), 1285(m), 1220(s), 1170(m), 1085(m), 1040(m), 985(m), 920(m) cm$^{-1}$;

$\delta_{\text{H}}$ (CDCl$_3$, 90 MHz): 7.40-6.50 (m, 4 x ArH), 7.20 (brs, exch. D$_2$O, -NH), 3.55 (s, exch. D$_2$O, NH$_2$), 2.13 (q, J=6Hz, CHMe(Bu$^t$)), 1.16 (d, J=6Hz, CHMe(Bu$^t$)), 1.00 (s, Bu$^t$).

Preparation of 2-(1,2,2-trimethylpropyl)benzimidazole (107)

The monoamide (106) (9.04g, 0.0411 moles) was dissolved in dry pyridine (30 ml) and phosphoryl chloride (7.6g, 0.0493 moles) was added. The resulting mixture was heated under a nitrogen atmosphere for 20 minutes at 80°C, poured into ice-water, made acidic with concentrated hydrochloric acid, and upon making alkaline with concentrated ammonium hydroxide an off-white solid was precipitated out, which was collected and washed several times with cold water. Crystallization from ethanol-water gave the benzimidazole (107) (4.65g, 56%) as colourless crystals, m.p. 209-211°C (Found: C, 77.06; H, 8.93; N, 13.75. C$_{13}$H$_{18}$N$_2$ requires C, 77.18; H, 8.97; N, 13.85%);
$\nu_{\text{max}}$ (Nujol): 2740 (br, s), 2630 (br, m), 1620 (w), 1585 (w), 1325 (m),
1275 (s), 1215 (m), 1095 (m), 1020 (m), 990 (m), 770 (m), 745 (m), 735 (s) cm$^{-1}$;
$\delta_{H}$ (CDCl$_3$, 90 MHz): 7.80 (brs, exch. D$_2$O, NH), 7.60-7.00 (m, 4 x ArH),
2.88 (q, J7Hz, $\text{CHMe(Bu^t)}$), 1.38 (d, J7Hz, $\text{CHMe(Bu^t)}$), 1.00 (s, Bu$^t$);
M/Z (%): 202(M$^+$, 14), 187(11), 147(14), 146(100), 145(78), 132(12),
92(15), 65(11).

Preparation of 1-Amino-2-(1,2,2-trimethylpropyl)benzimidazole (104)

The benzimidazole (107) (1.81g, 8.960 x 10$^{-3}$ moles) was suspended in
dichloromethane (100 ml) and cooled to 0°C. O-Mesitylenesulphonyl-
hydroxylamine (2.31g, 0.020 moles) in dry dichloromethane (20 ml) was
added dropwise with stirring over 5 minutes and the resulting solution
stirred for 2 hours. The dichloromethane solution was washed with
saturated sodium carbonate solution (50 ml), dried with magnesium
sulphate and evaporated under reduced pressure. The residual solid
(1.77g) was found by n.m.r. to be a ca. 1:1 mixture of the required
N-aminobenzimidazole (104) and the starting benzimidazole (107), and
the bulk of the latter was separated by triturating the solid with
ethyl acetate–light petroleum (1:2) and filtering. The filtrate,
which contained the bulk of the aminated material, was evaporated and
the residue chromatographed over silica using light petroleum–ethyl
acetate (1:3). The N-aminobenzimidazole (104) was obtained as colour-
less crystals (0.243g, 13%), m.p. 173-174°C (from acetonitrile) (Found:
C, 71.74; H, 8.78; N, 19.32. C$_{13}$H$_{19}$N$_3$ requires C, 71.85; H, 8.81;
N, 19.34%);

\( \nu_{\text{max}} (\text{Nujol}): 3310 (\text{s}), 3120 (\text{m}), 1595 (\text{w}), 1490 (\text{m}), 1270 (\text{m}), 1215 (\text{m}), 1080 (\text{w}), 765 (\text{m}), 745 (\text{m}), 735 (\text{s}) \text{ cm}^{-1}; \)

\( \delta_H (\text{CDCl}_3, 90 \text{ MHz}): 7.65 (\text{m}, 1 \times \text{ArH}), 7.38-7.05 (\text{m}, 3 \times \text{ArH}), 4.52 (\text{s}, \text{exch. D}_2\text{O, NH}_2), 3.42 (\text{q}, J=7\text{Hz}, \text{CHMe(Bu}^\dagger\text{)}), 1.35 (\text{d}, J=7\text{Hz}, \text{CHMe(Bu}^\dagger\text{)}), 1.00 (\text{s, Bu}^\dagger); \)

\( \text{M/Z} \quad (\%): 217 (\text{M}^+, 23), 202 (15), 161 (100), 160 (34), 147 (28), 146 (24), 145 (99), 143 (29), 119 (15), 77 (17). \)

Oxidation of 1-Amino-2-(1,2,2-trimethylpropyl)benzimidazole (104) with LTA at -20 to -25°C in the Presence of Styrene: Formation of syn Aziridine (111a)

\[
\text{N}
\]

The general oxidation procedure (C) was followed using the N-amino-benzimidazole (104) (0.051g, 2.350 \times 10^{-3} \text{ moles}), LTA (0.115g, 2.585 \times 10^{-4} \text{ moles}) and styrene (0.061g, 5.875 \times 10^{-4} \text{ moles}) in deuterochloroform (0.5 ml). An n.m.r. spectrum recorded at -40°C, without any intermediate warming of the solution, showed the presence of only the \text{syn}-invertedmer of aziridine (111a) which has \( \delta (\text{CDCl}_3, 300 \text{ MHz}, -40^\circ\text{C}) \) (major diastereoisomer): 7.95-7.10 (m, 9 \times \text{ArH}), 3.83 (dd, J=7.0 and 6.6Hz, aziridine ring proton \text{trans} to het. and \text{gem.} to Ph), 3.52 (dd, J=6.6 and 2.4Hz, \text{gem.} aziridine ring proton \text{cis} to het.), 3.34 (dd, J=7.0 and 2.4Hz, \text{gem.} aziridine ring proton \text{trans} to het.), 2.57 (q, J=7.1Hz, \text{CHMe(Bu}^\dagger\text{)}), 0.86 (s, \text{Bu}^\dagger), 0.22 (d, J=7.1Hz, \text{CHMe(Bu}^\dagger\text{)}).

The minor diastereoisomer (presumably present as its \text{syn} invertedmer) of aziridine (111a) was not distinguishable at -40°C, and only became
evident as the anti-invertomer in the room temperature spectrum. After allowing the solution to warm to room temperature and then re-recording at -40°C, the spectrum was found to contain all the signals from that of the pure anti-invertomer of the major diastereoisomer of aziridine (111b) (see below). The ratio of diastereoisomers of aziridine (111b) from the crude oxidation product was found to be 8.0:1. 1H n.m.r. data for the anti-invertomer of the major diastereoisomer (and minor diastereoisomer) of aziridine (111b) at room temperature will be found in the following section.

Oxidation of 1-Amino-2-(1,2,2-trimethylpropyl)benzimidazole (104) with LTA at Room Temperature in the Presence of Styrene

The general oxidation procedure (A) was followed using the N-amino-benzimidazole (104) (0.053 g, 2.442 × 10^-4 moles), LTA (0.119 g, 2.686 × 10^-4 moles) and styrene (0.102 g, 9.768 × 10^-4 moles) in dry dichloromethane (0.6 ml). Chromatography of the crude oxidation product [which comprised a 5.6:1 (±0.3) ratio of diastereoisomers of aziridine (111b)] over activated basic alumina, with dichloromethane as eluant, separated the aziridines from a less polar impurity (126) and crystallization from ethanol gave the major diastereoisomer of the 1-(2-(1,2,2-trimethylpropyl)benzimidazol-1-yl)-2-phenylaziridine (111b) as a colourless solid (0.035 g, 45%), m.p. 152-154°C (from acetonitrile) (Found: C, 78.90; H, 7.89; N, 13.16. C_{21}H_{25}N_{3} requires C, 78.96; H, 7.89; N, 13.15%); \nu_{max} (Nujol): 1605 (w), 1585 (w), 1500 (m), 1410 (m), 1300 (m), 1275 (m), 1225 (m), 1095 (m), 990 (w), 880 (w), 765 (m), 735 (s), 705 (s) cm^{-1};
\( \delta_H (\text{CDCl}_3, 300 \text{ MHz}) \) (major diastereoisomer): 7.80-7.10 (m, 9 × ArH), 3.95 (dd, J8.1 and 5.3Hz, aziridine ring proton cis to het. and gem. to Ph), 3.34 (q, J7.2Hz, CHMe(Bu^t)), 3.06 (dd, J8.1 and 1.4Hz, gem. aziridine ring proton cis to het.), 2.81 (dd, J5.3 and 1.4Hz, gem. aziridine ring proton trans to het.), 1.43 (d, J7.2Hz, CHMe(Bu^t)), 1.02 (s, Bu^t). Only one invertomer (Ph and het. anti) is evident in the n.m.r. spectrum of the major diastereoisomer;

M/Z (%): 319(M^+, 5), 145(55), 144(90), 130(45), 117(100), 91(25), 77(20).

The following peaks in the n.m.r. spectrum of the crude reaction product were assignable to the minor diastereoisomer:

\( \delta_H (\text{CDCl}_3, 300 \text{ MHz}) \): 7.80-7.10 (m, 9 × ArH), 3.55 (dd, J8.0 and 5.4Hz, aziridine ring proton cis to het. and gem. to Ph), 3.22 (q, J7.2Hz, CHMe(Bu^t)), 2.85 (dd, J5.4 and 1.6Hz, gem. aziridine ring proton trans to het.), 1.39 (d, J7.2Hz, CHMe(Bu^t)), 0.88 (s, Bu^t). Only one invertomer (Ph and het. anti) is evident in the n.m.r. spectrum of this minor diastereoisomer.

Oxidation of 1-Amino-2-(1,2,2-trimethylpropyl)benzimidazole (104) with Phenyl iodosodi-acetate at Room Temperature in the Presence of Styrene

The general oxidation procedure (B) was followed using the N-amino-benzimidazole (104) (0.100g, 4.608 × 10^{-4} moles), phenyl iodosodi-acetate (0.156g, 4.838 × 10^{-4} moles) and styrene (0.479g, 4.608 × 10^{-3} moles) in dry dichloromethane (1 ml). The 300 MHz spectrum of the crude reaction product showed that the ratio of diastereoisomers of aziridine (111b) present was 5.6 : 1 and the major diastereoisomer was isolated by crystallization from acetonitrile (0.089g, 61%) as a colourless solid, m.p. 152-154°C, identical in all respects with the major diastereoisomer isolated from the previous experiment.
Oxidation of 1-Amino-2-(1,2,2-trimethylpropyl)benzimidazole (104) with LTA at Room Temperature in the Presence of Methyl acrylate (95)

The general oxidation procedure (A) was followed using the N-amino-benzimidazole (104) (0.076 g, 3.502 x 10⁻⁴ moles), LTA (0.171 g, 3.852 x 10⁻⁴ moles) and methyl acrylate (0.302 g, 3.502 x 10⁻³ moles) in dry dichloromethane (0.8 ml). The methyl 1-(2-(1,2,2-trimethylpropyl)benzimidazol-1-y1)aziridine-2-carboxylate (112) was obtained as a light yellow oil (0.075 g, 71%). Chromatography over silica, with ethyl acetate-light petroleum (1:1.5) as eluant, failed to separate the two diastereoisomers of aziridine (112), which n.m.r. showed were present in a 2.15:1 (±0.05) ratio;

\[ \nu_{\text{max}}^\text{film}: 2950 \text{(s)}, 1745 \text{(s)}, 1610 \text{w), 1505 (s)}, 1450 \text{(s)}, 1390 \text{(s), 1365 (m), 1270 (s), 1220 (s), 1070 (m), 1040 (m), 765 (m), 740 (s) cm}^{-1}; \]

\( \delta_H \) (CDCl₃, 400 MHz):

<table>
<thead>
<tr>
<th>Major Diastereoisomer</th>
<th>Minor Diastereoisomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.85-7.19 (m, 4 x ArH)</td>
<td></td>
</tr>
<tr>
<td>3.88 (s, CO₂Me)</td>
<td>3.38 (dd, J7.8 and 5.0Hz, aziridine ring proton cis to het. and gem. to CO₂Me)</td>
</tr>
<tr>
<td>3.70 (dd, J7.6 and 5.0Hz, aziridine ring proton cis to het. and gem. to CO₂Me)</td>
<td>3.33 (q, J7.2Hz, -CHMe(Bu⁰))</td>
</tr>
<tr>
<td>3.08 (dd, J7.6 and 1.2Hz, gem. aziridine ring proton cis to het.)</td>
<td>3.25 (q, J7.2Hz, -CHMe(Bu⁰))</td>
</tr>
<tr>
<td>2.99 (dd, J5.0 and 1.2Hz,</td>
<td>3.23 (dd, J7.8 and 1.2Hz,</td>
</tr>
</tbody>
</table>
gem. aziridine ring proton
trans to het.)

1.40 (d, J7.2Hz, CHMe(Bu))
1.00 (s, Bu)

gem. aziridine ring proton
trans to het.)

1.41 (d, J7.2Hz, CHMe(Bu))
0.99 (s, Bu)

In both diastereoisomers only one inveromer is evident in the n.m.r.
spectrum at room temperature (major inveromer: CO2Me and het. anti);
M/Z (%): 301(M+17), 286(15), 245(15), 145(28), 130(73), 129(22),
117(100), 103(14).

Oxidation of 1-Amino-2-(1,2,2-trimethylpropyl)benzimidazole (104)
with LTA at Room Temperature in the Presence of α-Methylene-γ-
butyrolactone (65)

The general oxidation procedure (A) was followed using the N-amino-
benzimidazole (104) (0.074g, 3.410 x 10^{-4} moles), LTA (0.166g, 3.751 x
10^{-4} moles) and α-methylene-γ-butyrolactone (65) (0.100g, 1.023 x 10^{-3}
moles) in dry dichloromethane (0.8 ml). Chromatography of the crude
oxidation product [which comprised a 5.5:1 (±0.5) ratio of diastereo-
ismers of aziridine (113)] over activated basic alumina, with light
petroleum-ethyl acetate (1.5:1) as eluant, separated the two
diastereoisomeric aziridines from a less polar by-product and
 crystallization from chloroform-light petroleum gave the major
diastereoisomer of 7-(2-(1,2,2-trimethylpropyl)benzimidazol-1-yl)-2-
ocxa-7-aza-spiro[4,2]-heptane-1-one (113) as a colourless solid (0.035g,
33%), m.p. 189-191°C (Found: C, 68.45; H, 7.25; N, 13.20. C_{18}H_{23}N_{3}O_{2}
requires C, 68.98; H, 7.40; N, 13.41%);
$\nu_{\text{max}}$ (Nujol): 1775(s), 1605(w), 1505(m), 1305(m), 1275(s), 1225(s), 1130(s), 1100(s), 1030(s), 1005(w), 970(w), 770(s), 750(s), 740(m), 710(m) cm$^{-1}$;

$\delta_{\text{H}}$ (CDCl$_3$, 300 MHz) (major diastereoisomer):

<table>
<thead>
<tr>
<th>Major Invertomer</th>
<th>Minor Invertomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>(lactone C=O syn to het.)</td>
<td>(lactone C=O anti to het.)</td>
</tr>
<tr>
<td>$7.73$-$7.08$ (m, $4 \times$ ArH)</td>
<td>$4.66$-$4.56$ (m, $-\text{CH}_2-\text{CH}_2\text{O}_2\text{C}$)</td>
</tr>
<tr>
<td>$3.71$ (d, J1.2Hz, aziridine ring proton cis to het.)</td>
<td>$4.29$ (ddd, J9.4, 9.2 and 6.4Hz, $-\text{CH}_2-\text{CHH-CH}_2\text{O}_2\text{C}$)</td>
</tr>
<tr>
<td>$3.19$ (d, J1.2Hz, aziridine ring proton trans to het.)</td>
<td>$3.87$ (brs, aziridine ring proton cis to het.)</td>
</tr>
<tr>
<td>$2.78$ (ddd, J15, 9 and 6Hz, $-\text{CHCH}_2\text{O}_2\text{C}$)</td>
<td>$3.40$ (brs, $\text{CHMe(But)}$)</td>
</tr>
<tr>
<td>$2.69$ (ddd, J15, 9 and 5Hz, $-\text{CHCH}_2\text{O}_2\text{C}$)</td>
<td>$3.02$ (brs, aziridine ring proton trans to het.)</td>
</tr>
<tr>
<td>$2.48$ (q, J7.1Hz, $-\text{CHMe(But)}$)</td>
<td>$2.73$ (m, $-\text{CHCH}_2\text{O}_2\text{C}$)</td>
</tr>
<tr>
<td>$1.32$ (d, J7.1Hz, $-\text{CHMe(But)}$)</td>
<td>$2.21$ (brs, $-\text{CHCH}_2\text{O}_2\text{C}$)</td>
</tr>
<tr>
<td>$0.95$ (s, $\text{Bu}^+$)</td>
<td>$1.34$ (d, J7.1Hz, $-\text{CHMe(But)}$)</td>
</tr>
<tr>
<td></td>
<td>$0.92$ (s, $\text{Bu}^+$)</td>
</tr>
</tbody>
</table>

Ratio of inverteromers in major diastereoisomer at room temperature in CDCl$_3$, lactone C=O syn : anti to het., : 2.2 : 1 (±0.3);

M/Z (%): 313(M$^+$, 6), 257(1), 202(3), 187(5), 145(39), 132(57), 117(100), 98(9), 76(14).

A sample containing a 1.5 : 1 ratio of the major:minor diastereoisomers was obtained by repeated crystallization from chloroform - light petroleum and removal of the major diastereoisomer, followed by evaporation of the solvent under reduced pressure. From the n.m.r.
spectrum of this sample, the following assignments of signals from the minor diastereoisomer can be made:

\[ \delta_H (\text{CDCl}_3, 300 \text{ MHz}): 3.68 (d, J1.7\text{Hz}, \text{aziridine ring proton cis to het.}), 3.35 (d, J1.7\text{Hz}, \text{aziridine ring proton trans to het.}), 1.46 (d, J7.2\text{Hz}, \text{CHMe(Bu}^t)) , 0.97 (s, \text{Bu}^t); \text{other signals from this minor diastereoisomer were obscured by those from the major diastereoisomer.} \]

Only one invertomer is evident in the n.m.r. spectrum of the minor diastereoisomer at room temperature: this is presumed to be that with lactone C=O and het. \textit{syn}.

**Oxidation of 1-Amino-2-(1,2,2-trimethylpropyl)benzimidazole (104) with Phenyl iodosodi-acetate at Room Temperature in the Presence of α-Methylene-γ-butyrolactone (65)**

The general oxidation procedure (B) was followed using the N-amino­benzimidazole (104) (0.170g, 7.834 \times 10^{-4} \text{ moles}), phenyl iodosodi-acetate (0.278g, 8.617 \times 10^{-4} \text{ moles}) and α-methylene-γ-butyrolactone (65) (0.154g, 1.567 \times 10^{-3} \text{ moles}) in dry dichloromethane (1.5 ml). The ratio of aziridine diastereoisomers (113) (5.5:1) in the crude product was identical to that obtained in the analogous oxidation using LTA above and the major diastereoisomer was obtained as a colourless solid (0.122g, 50%), m.p. 189-191°C, by crystallization from chloroform - light petroleum.

**Preparation of 2-Butenolide (66)**

This was prepared\textsuperscript{129} by the treatment of furan with anhydrous sodium acetate, acetic acid, acetic anhydride and bromine. Final distillation of the product, b.p. 88-90°C/13 mmHg (lit.\textsuperscript{129} 96-98°C/20 mmHg), gave a 10% yield of the pure butenolide (66).
Preparation of N-Aminophthalimide (50)

This was prepared\textsuperscript{128} in 47% yield from phthalimide and hydrazine hydrate. Crystallization of the crude product from acetonitrile gave (50) as colourless crystals, m.p. 197-201°C (lit.\textsuperscript{128} 200-205°C).

Oxidation of N-Aminophthalimide (50) with LTA at Room Temperature in the Presence of 2-Butenolide (66)

The general oxidation procedure (A) was followed using N-aminophthalimide (50) (0.102g, \(6.296 \times 10^{-4}\) moles), LTA (0.290g, \(6.548 \times 10^{-4}\) moles) and 2-butenolide (66) (0.212g, \(2.524 \times 10^{-3}\) moles) in dry dichloromethane (1 ml). No aziridine was evident in the 90 MHz \(^1\text{H}\) n.m.r. spectrum of the crude oxidation product. The compound (126) was estimated to be present in ~40-50% (from n.m.r.). No purification of the crude oxidation product was attempted.

Preparation of 2-Methylbenzimidazole

This was prepared\textsuperscript{36} from glacial acetic acid and \(\alpha\)-phenylenediamine in concentrated hydrochloric acid (40% yield). Crystallization of the crude product from water gave light brown crystals of the benzimidazole, m.p. 178-180°C (lit.\textsuperscript{36} 176-177°C).

Preparation of 1-Amino-2-methylbenzimidazole (115)

This was prepared\textsuperscript{130} in 22% yield by the amination of 2-methylbenzimidazole with HOS. Crystallization of the crude product from acetonitrile gave off-white crystals of the N-aminobenzimidazole (115), m.p. 154-155°C.
Oxidation of 1-Amino-2-methylbenzimidazole (115) with LTA at Room Temperature in the Presence of α-Methylene-γ-butyrolactone (65)

The general oxidation procedure (A) was followed, with the exception that the N-aminobenzimidazole (115) (0.114g, 7.755 x 10⁻⁴ moles) and LTA (0.378g, 8.531 x 10⁻⁴ moles) were added separately over the fifteen minute period to α-methylene-γ-butyrolactone (65) (0.228g, 2.327 x 10⁻³ moles) in dry dichloromethane (1 ml) [N.B. LTA and (115) react in the solid state]. Chromatography over activated basic alumina, with ethyl acetate as eluant, gave the pure 7-(2-methylbenzimidazol-1-yl)-2-oxa-7-aza-spiro[4,2]-heptane-1-one (114) as a pale yellow oil (0.03g, 16%)

(Found: M/Z, 243.1010. C₁₃H₁₃N₃O₂ requires M, 243.1008);
νmax(film): 2925(w), 1770(s), 1525(w), 1460(m), 1390(s), 1285(s), 1235(m), 1025(m), 745(s) cm⁻¹;
δH (CD₂Cl₂, 400 MHz):

<table>
<thead>
<tr>
<th>Major Invertomer</th>
<th>Minor Invertomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>(lactone C=O syn to het.)</td>
<td>(lactone C=O anti to het.)</td>
</tr>
<tr>
<td>7.68-7.20 (m, 4 × ArH)</td>
<td></td>
</tr>
<tr>
<td>4.81-4.50 (m, -CH₂CH₂O₂C)</td>
<td></td>
</tr>
<tr>
<td>3.34-3.28 (2 × d, 2 × aziridine ring protons; cis and trans not distinguishable because of rotamer complication)</td>
<td>3.72-3.64 (2 × brs, 2 × aziridine ring protons; cis and trans not distinguishable because of rotamer complication)</td>
</tr>
<tr>
<td>2.88 (ddd, J15, 9 and 6Hz, CH₃CH₂O₂C)</td>
<td>2.56 (brs, -CH₃)</td>
</tr>
</tbody>
</table>
The sample temperature was then lowered and n.m.r. spectra recorded at: 0°C, -15°C, -30°C, -45°C, -60°C, -75°C and -90°C. As the temperature was lowered, the two invertomers of aziridine (114), which were present as a ~1.2:1 ratio in CD$_2$Cl$_2$ at room temperature (major invertomer: lactone C=O and het. syn), were each found to separate into two rotational isomers. Separation was complete by ~90°C and it was observed that the rotamers were unequally populated in both the major and minor invertomers.

**Preparation of γ,γ-Dimethyl-α-methylene-γ-butyrolactone (116)**

This was prepared by a two-step synthesis:

(i) γ,γ-Dimethylbutyrolactone was prepared$^{131}$ by the Grignard reaction of methyl magnesium iodide on ethyl levulinate, lactone ring formation occurring via an acid-catalyzed reaction of the corresponding γ-hydroxy acid. The product was distilled, b.p. 90-93°C/20 mmHg (lit.$^{131}$ 201-206°C/760 mmHg), and isolated in 24% yield.

(ii) The required lactone (116) was formed$^{132}$ by methylenation of the γ,γ-dimethylbutyrolactone, using Eschenmoser's salt (dimethyl-(methylene) ammonium iodide). Chromatography over silica, with dichloromethane–acetone (9:1) as eluant, gave the pure lactone (116) in 20% yield.
Oxidation of l-Amino-2-(l,2,2-trimethylpropyl)benzimidazole (104) with LTA at Room Temperature in the Presence of γ,γ-Dimethyl-α-methylene-γ-butyrolactone (116)

The general oxidation procedure (A) was followed using the N-amino-benzimidazole (104) (0.065g, 2.995 x 10^-4 moles), LTA (0.146g, 3.295 x 10^-4 moles) and γ,γ-dimethyl-α-methylene-γ-butyrolactone (116) (0.065g, 5.159 x 10^-4 moles) in dry dichloromethane (0.5 ml). Chromatography of the crude oxidation product [in which only a single diastereoisomer of aziridine (117) was evident (i.e. >50:1 ratio of diastereoisomers)] over activated basic alumina, with dichloromethane as eluant, gave the single diastereoisomer of 7-(2-(1,2,2-trimethylpropyl)benzimidazol-1-yl)-2-oxa-7-aza-3,3-dimethyl-spiro[4,2]-heptane-1-one (117) as colourless crystals (0.070g, 69%), m.p. 136-137°C (from ethanol) (Found: M/Z, 341.2107. C_{20}H_{27}N_{3}O_{2} requires M, 341.2103);

\[ v_{\text{max}} \text{(Nujol): 1765(s), 1610(w), 1295(m), 1270(m), 1220(w), 1185(w), 1140(w), 1130(m), 1085(m), 925(m), 740(s) cm}^{-1}; \]

\[ \delta_{\text{H}} \text{(CDCl}_3, 300 \text{ MHz):} \]

<table>
<thead>
<tr>
<th>Major Invertomer</th>
<th>Minor Invertomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>(lactone C=O and het. syn)</td>
<td>(lactone C=O and het. anti)</td>
</tr>
<tr>
<td>7.81-7.14 (m, 4 × ArH)</td>
<td></td>
</tr>
<tr>
<td>3.74 (d, J0.9Hz, aziridine ring proton cis to het.)</td>
<td>4.01 (brs, aziridine ring proton cis to het.)</td>
</tr>
<tr>
<td>3.27 (d, J0.9Hz, aziridine ring proton trans to het.)</td>
<td>3.62 (brq, J7.0Hz, CHMe(Bu^t))</td>
</tr>
<tr>
<td>2.84 (d, J14Hz,</td>
<td>3.05 (brs, aziridine ring</td>
</tr>
</tbody>
</table>
CHH-C(CH₃)₂O₂C) proton trans to het.
2.64 (q, J7.0Hz, CHMe(Bu⁺)) 2.51 (d, J14Hz, CHH-C(CH₃)₂O₂C)
2.42 (d, J14Hz, CHH-C(CH₃)₂O₂C) 2.12 (d, J14Hz, CHH-C(CH₃)₂O₂C)
1.70 (s, CH₂C(CH₃)O₂C)
1.55 (s, CH₂C(CH₃)CH₃O₂C) 1.57 (s, CH₂C(CH₃)CH₃O₂C)
1.38 (d, J7.0Hz, CHMe(Bu⁺))
1.02 (s, Bu⁺) 1.00 (s, Bu⁺)

The ratio of invertoners in this diastereoisomer in CDCl₃ at room temperature (lactone C=O syn : anti to het.) = 2.0:1 (±0.4);
M/Z (%): 342(M⁺+1,8), 187(14), 146(80), 145(93), 131(95), 117(100), 111(49), 68(76).

Oxidation of 1-Amino-2-(1,2,2-trimethylpropyl)benzimidazole (104)
with LTA at -20 to -25°C in the Presence of α-Methylene-γ-butyrolactone (65): Kinetic Ratio of Aziridines (113)

The general oxidation procedure (C) was followed using the N-amino-
benzimidazole (104) (0.065g, 2.995 x 10⁻⁴ moles), LTA (0.146g, 3.295 x 10⁻⁴ moles) and α-methylene-γ-butyrolactone (65) (0.059g, 5.990 x 10⁻⁴ moles) in deuterocloroform (0.7 ml). From comparison of the spectra
obtained on the filtered (<-30°C) deuterocloroform solution at -40°C before and after warming to room temperature and, in particular, from
integration of the signals at 63.40 (aziridine ring proton trans to het.
in major invertomer) and 3.27 (CHMe(Bu⁺) in minor invertomer) in the
spectrum obtained before warming, the kinetic ratio of syn : anti
invertoners in the major diastereoisomer of aziridine (113) was found
to be ~5:1 (syn and anti invertoners refers to the relationship between
lactone C=O and het.). The ratio of diastereoisomers formed in this
low temperature oxidation, determined from the spectrum of the crude
oxidation product, was found to be 8.5:1.

Oxidation of 1-Amino-2-(1,2,2-trimethylpropyl)benzimidazole (104) with LTA at -20 to -25°C in the Presence of γ,γ-Dimethyl-α-methylene-γ-butyrolactone (116): Kinetic Ratio of Aziridines (117)

The general oxidation procedure (C) was followed using the N-amino-benzimidazole (104) (0.081g, \(3.733 \times 10^{-4}\) moles), LTA (0.182g, \(4.106 \times 10^{-4}\) moles) and γ,γ-dimethyl-α-methylene-γ-butyrolactone (116) (0.271g, \(2.151 \times 10^{-3}\) moles) in deuterochloroform (0.8 ml). From comparison of the spectra obtained on the filtered (<30°C) deuterochloroform solution at -40°C before and after warming to room temperature and, in particular, from integration of signals at δ3.48 (aziridine ring proton trans to het. in major invertdomer) and 4.28 (aziridine ring proton cis to het. in minor invertdomer) in the spectrum obtained before warming, the kinetic ratio of syn:anti invertdomers in the single diastereoisomer of aziridine (117) was found to be ~5.3:1 (syn and anti invertdomers refers to the relationship between lactone C=O and het.).

Oxidation of N-Aminophthalimide (50) with LTA at Room Temperature in the Presence of α-Methylene-γ-butyrolactone (65)

\[
\begin{align*}
\text{N} & \quad \text{O} \\
\text{O} & \quad \text{N} \\
\text{N} & \quad \text{O} \\
\end{align*}
\]

(120) (syn)

The general oxidation procedure (A) was followed using N-aminophthalimide (50) (0.124g, \(7.654 \times 10^{-4}\) moles), LTA (0.373g, \(8.419 \times 10^{-4}\) moles) and α-methylene-γ-butyrolactone (65) (0.300g, \(3.062 \times 10^{-3}\) moles) in dry dichloromethane (1.2 ml). Crystallization of the crude reaction mixture from ethanol, gave pale yellow crystals of the 7-phthalimido-2-
oxa-7-aza-spiro[4,2]-heptane-1-one (120) (0.091g, 46%), m.p. 149-150°C

(Found: C, 60.44; H, 3.98; N, 10.80. C₁₃H₁₀N₂O₄ requires C, 60.46; H, 3.90; N, 10.85%);

νₘₐₓ (Nujol): 1765(s), 1710(s), 1280(s), 1210(m), 1185(m), 1165(m), 1105(m), 1065(m), 1015(m), 990(m), 885(m), 795(m), 715(s) cm⁻¹;

δ_H (CDCl₃, 300 MHz):

<table>
<thead>
<tr>
<th>Major Invertomer</th>
<th>Minor Invertomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>(lactone C=O and het. syn)</td>
<td>(lactone C=O and het. anti)</td>
</tr>
<tr>
<td>8.03-7.66 (m, 4 × ArH)</td>
<td></td>
</tr>
<tr>
<td>4.90 (ddd, J 8.7, 8.5 and 8.3Hz, -CH₂CHHO₂C)</td>
<td>4.69 (ddd, J 8.7, 8.2 and 8.2Hz, CH₂CHHO₂C)</td>
</tr>
<tr>
<td>3.36 (d, J 2.4Hz, aziridine ring proton cis to het.)</td>
<td>3.23 (d, J 2.6Hz, aziridine ring proton cis to het.)</td>
</tr>
<tr>
<td>2.99 (d, J 2.4Hz, aziridine ring proton trans to het.)</td>
<td>3.18 (d, J 2.6Hz, aziridine ring proton trans to het.)</td>
</tr>
<tr>
<td>2.65 (dd, J 8.3 and 6.2Hz, CH₂CH₂O₂C)</td>
<td>2.45 (dd, J 8.2 and 6.9Hz, CH₂CH₂O₂C)</td>
</tr>
</tbody>
</table>

Ratio of invertomers in CDCl₃ at room temperature: lactone C=O syn : anti to het. = 12:1;

M/Z (%): 258(M⁺, 26), 147(9), 132(16), 105(17), 104(100), 76(41).

**Oxidation of N-Aminophthalimide (50) with LTA at Room Temperature in the Presence of Equimolar Proportions of α-Methylene-γ-butyrolactone (65) and Methyl methacrylate**

The general oxidation procedure (A) was followed using N-amino-
phthalimide (50) (0.106g, 6.543 × 10⁻⁴ moles), LTA (0.302g, 6.805 × 10⁻³ moles), α-methylene-γ-butyrolactone (65) (0.265g, 2.704 × 10⁻³ moles) and methyl methacrylate (0.270g, 2.704 × 10⁻³ moles) in dry dichloro-
methane (1 ml). Inspection of the $^1$H n.m.r. spectrum of the crude oxidation product showed the aziridine (120) and aziridine$^{55}$ (121) to be present in a ratio of 2.3 : 1 respectively. No attempt at isolation of the aziridines was made: both have been previously characterized.

Oxidation of 1-Amino-2-(1,2,2-trimethylpropyl)benzimidazole (104) with LTA at Room Temperature in the Presence of 2,3-Dimethyl-1,3-butadiene (89)

The general oxidation procedure (A) was followed using the N-amino-benzimidazole (104) (0.106g, 4.885 x $10^{-4}$ moles), LTA (0.238g, 5.374 x $10^{-4}$ moles) and 2,3-dimethyl-1,3-butadiene (89) (0.401g, 4.885 x $10^{-3}$ moles) in dry dichloromethane (1 ml). Chromatography of the crude oxidation product [which comprised a 1.83 : 1 (±0.21) ratio of diastereoisomers of aziridine (122)] twice over activated basic alumina, with light petroleum - ethyl acetate (6:1) as eluant, gave the major diastereoisomer of 1-(2-(1,2,2-trimethylpropyl)benzimidazol-1-yl)-2-ethyl-2-isopropenylaziridine (122) as a colourless oil (0.010g, 7%) (Found: M/Z, 297.2209. C$_{19}$H$_{27}$N$_3$ requires M, 297.2205);

$\nu_{\text{max}}$(film): 2970(s), 1640(w), 1610(w), 1505(m), 1450(s), 1365(m), 1275(s), 1225(s), 1055(m), 900(m), 770(m), 735(s)$ cm$^{-1}$;

$\delta_{\text{H}}$(CDCl$_3$, 400 MHz) (major diastereoisomer): 7.79-7.06 (m, 4 x ArH), 5.22 (d, J1.0Hz, MeC=CHH), 5.08 (d, J1.0Hz, MeC=CHH), 3.06 (d, J1.6Hz, gem. aziridine ring proton cis to het.), 2.94 (q, J7.1Hz, CHMe(Bu$^+$)), 2.89 (d, J1.6Hz, gem. aziridine ring proton trans to het.), 1.79 (dd, J1.4 and 0.7Hz, MeC=CH$_2$), 1.37 (d, J7.1Hz, CHMe(Bu$^+$)), 1.23 (d, J0.6Hz,
aziridine ring Me), 0.89 (s, But).

In the major diastereoisomer of aziridine (122) only one invertomer (isopropanyl group and het. anti) is evident in the \( ^1H \) n.m.r. spectrum at room temperature.

From the n.m.r. spectrum of the crude oxidation product, the following assignments of signals from the minor diastereoisomer of aziridine (122) can be made:

\[ \delta_H (CDCl_3, 400 MHz): 3.02 \text{ (q, } J=7.2 \text{Hz, CHMe(Bu^t))}, 2.85 \text{ (d, } J=1.4 \text{Hz, gem, aziridine ring proton cis to het.}), 2.76 \text{ (d, } J=1.4 \text{Hz, gem, aziridine ring proton trans to het.}), 1.82 \text{ (dd, } J=1.4 \text{ and } 0.8 \text{Hz, Me=CH}_2), 1.34 \text{ (d, } J=7.2 \text{Hz, CHMe(Bu^t))}, 1.11 \text{ (d, } J=0.6 \text{Hz, aziridine ring Me}); \]

other signals from the minor diastereoisomer are not distinguishable. In the minor diastereoisomer of aziridine (122) only one invertomer (isopropanyl group and het. anti) is evident in the \( ^1H \) n.m.r. spectrum at room temperature.

Oxidation of 1-Amino-2-(1,2,2-trimethylpropyl)benzimidazole (104) with LTA at 0°C in the Presence of trans-But-2-ene

\[ (123) \]

The general oxidation procedure (A) was followed, with the exception that the oxidation was carried out at 0°C (trans-but-2-ene is a gas at room temperature). The N-aminobenzimidazole (104) (0.088g, \( 4.055 \times 10^{-4} \) moles), LTA (0.189g, \( 4.258 \times 10^{-4} \) moles) and trans-but-2-ene (0.200g, \( 3.571 \times 10^{-3} \) moles) in dry dichloromethane (1 ml) were used in the oxidation. Chromatography of the crude oxidation product (which comprised
a 5.2:1 (±0.2) ratio of diastereoisomers of aziridine (123) over activated basic alumina, with light petroleum-ethyl acetate (5:1) as eluant, gave the major diastereoisomer of 1-(2-(1,2,2-trimethylpropyl)-benzimidazol-1-yl)-trans-2,3-dimethylaziridine (123) as a colourless oil (0.066g, 60%) (Found: M/Z, 271.2064. C₁₇H₂₅N₃ requires M, 271.2048);

νₘₐₓ (film): 2960 (s), 1500 (m), 1365 (m), 1275 (s), 1225 (m), 1085 (m), 765 (m), 735 (s) cm⁻¹;

δₜₗ (CDCl₃, 300 MHz) (major diastereoisomer): 7.80-7.10 (m, 4 x ArH), 3.08 (q, J 7.2 Hz, CHMe(Bu⁵)), 2.99 (dq, J 5.7 and 5.3 Hz, aziridine ring proton cis to het.), 2.51 (dq, J 5.8 and 5.3 Hz, aziridine ring proton trans to het.), 1.56 (d, J 5.7 Hz, aziridine ring Me trans to het.), 1.46 (d, J 7.2 Hz, CHMe(Bu⁵)), 1.06 (d, J 5.8 Hz, aziridine ring Me cis to het.), 0.99 (s, Bu⁵).

From the n.m.r. spectrum of the crude oxidation product, the following assignments of signals from the minor diastereoisomer of aziridine (123) can be made:

δₜₗ (CDCl₃, 300 MHz): 2.64 (dq, J 5.8 and 5.3 Hz, aziridine ring proton trans to het.), 1.57 (d, J 5.6 Hz, aziridine ring Me trans to het.), 1.43 (d, J 7.1 Hz, CHMe(Bu⁵)), 1.17 (d, J 5.8 Hz, aziridine ring Me cis to het.), 1.03 (s, Bu⁵); other signals from the minor diastereoisomer were not distinguishable.

Preparation of Methyl phenyl sulfoxide (racemic) (124)

This was prepared by the oxidation of thioanisole with sodium metaperiodate. The sulfoxide was distilled, b.p. 99-100°C/0.4 mmHg (lit. 78-79°C/0.1 mmHg), and isolated in 50% yield.
Oxidation of 1-Amino-2-(1,2,2-trimethylpropyl)benzimidazole (104) with LTA at Room Temperature in the Presence of Methyl phenyl sulfoxide (124)

The general oxidation procedure (A) was followed (substituting a sulfoxide for an alkene) using the N-aminobenzimidazole (104) (0.080g, \(3.687 \times 10^{-4}\) moles), LTA (0.170g, \(3.835 \times 10^{-4}\) moles), and methyl phenyl sulfoxide (124) (0.053g, \(3.761 \times 10^{-4}\) moles) in dry dichloromethane (0.5 ml). Chromatography of the crude oxidation product [which comprised a 1:2 : 1 ratio of diastereoisomers of the sulphoximine (125)] over silica, with light petroleum-ethyl acetate (1:1) as eluant, gave the N-(2-(1,2,2-trimethylpropyl)benzimidazol-1-yl)-S-methyl-S-phenylsulphoximine (125) as an opaque oil (0.04g, 31%), as a mixture of diastereoisomers;

\[\nu_{\text{max}}\text{(film)}: 2925\text{(s)}, 1610\text{(w)}, 1500\text{(w)}, 1450\text{(s)}, 1390\text{(w)}, 1360\text{(s)}, 1265\text{(m)}, 1215\text{(s)}, 1085\text{(m)}, 975\text{(m)}, 765\text{(m)}, 740\text{(s)} \text{ cm}^{-1}\];

\[\delta_H\text{ (CDCl}_3, \text{ 90 MHz)}:\]

<table>
<thead>
<tr>
<th>Major Diastereoisomer</th>
<th>Minor Diastereoisomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.20-6.85 (m, 9 \times \text{ArH})</td>
<td></td>
</tr>
<tr>
<td>3.27  (q, \text{J}7\text{Hz}, \text{CHMe(Bu}^\text{t}))</td>
<td></td>
</tr>
<tr>
<td>3.18 (s, -\text{SMe})</td>
<td>3.15 (s, -\text{SMe})</td>
</tr>
<tr>
<td>1.00 (s, \text{Bu}^\text{t})</td>
<td>0.93 (s, \text{Bu}^\text{t})</td>
</tr>
</tbody>
</table>

Other signals from the two diastereoisomers were not distinguishable; M/Z (%): 355(M^+, 5), 161(60), 145(100), 131(88), 125(94), 117(95), 97(61).
Oxidation of 1-Amino-2-(1,2,2-trimethylpropyl)benzimidazole (104) with LTA at Room Temperature in the Absence of a Nitrene Trap

The general oxidation procedure (A) was followed in the absence of a nitrene trap. The oxidation was carried out using the N-aminobenzimidazole (104) (0.112g, 5.161 x 10^-4 moles) and LTA (0.240g, 5.419 x 10^-4 moles) in dry dichloromethane (1 ml). Chromatography over silica, with ethyl acetate-light petroleum (1:1) as eluant, gave the dimer (126) \((R_f = 0.67)\) (0.063g, 57%) as a colourless solid, m.p. 252-254°C (from chloroform/ethanol) (Found: C, 72.21; H, 7.92; N, 19.45. \(C_{26}H_{34}N_6\) requires C, 72.52; H, 7.96; N, 19.52%);

\[ \nu_{max} \text{ (Nujol): 2130(w), 1720(w), 1605(w), 1535(m), 1295(s), 1260(s), 1215(s), 1180(s), 1155(s), 1085(m), 1020(w), 930(m), 850(w), 765(m), 745(s) cm}^{-1}; \]

\[ \delta_H \text{ (CDCl}_3, 300 \text{ MHz): 8.28 (m, 2 x ArH), 7.85 (m, 2 x ArH), 7.44 (m, 4 x ArH), 3.64 (2 x q, J7.1Hz, 2 x CHMe(Bu^t)), 1.58 and 1.57 (2 x d, J7.1Hz, 2 x CHMe(Bu^t)), 1.11 and 1.09 (2 x s, 2 x Bu^t);} \]

\[ \delta_C \text{ (CDCl}_3, 75 \text{ MHz): 158.8(s), 158.7(s), 142.0(s), 128.0(s), 125.0(d), 124.4(d), 120.4(d), 114.5(d), 114.3(d), 50.6(brs), 35.1(s), 27.8(q), 15.0(q);}\]

\[ \text{M/Z (%): 430(M^+, 31), 415(1), 229(49), 201(100), 145(94), 91(84).}\]

Oxidation of 1-Amino-2-(1,2,2-trimethylpropyl)benzimidazole (104) with LTA at Room Temperature in the Absence of a Nitrene Trap and Under High Dilution Conditions

The N-aminobenzimidazole (104) (0.044g, 2.028 x 10^-4 moles) was
dissolved in dry dichloromethane (50 ml) and LTA (0.103g, 2.332 \times 10^{-4} moles) was dissolved in an equal volume of dry dichloromethane (50 ml). The two solutions were then added simultaneously dropwise, over 15 minutes at room temperature (LTA solution slightly ahead of the \(N\)-amino-benzimidazole solution), via separate dropping funnels to a flame-dried 3-necked flask containing a dichloromethane solution (100 ml) without a nitrene trap. After addition was complete, the reaction mixture was stirred at room temperature for 20 minutes, the lead di-acetate separated and the solution washed successively with sodium bicarbonate solution, then water, dried with magnesium sulphate and the solvent removed by evaporation under reduced pressure. Chromatography of the crude oxidation product over silica, with ethyl acetate–light petroleum (1:1) as eluant, isolated the dimer (126) \((R_f = 0.67)\) as a colourless solid (0.010g, 12%), m.p. 252-254°C (from chloroform/ethanol). I.r., n.m.r. and mass spectral data were also identical with the compound produced in the previous experiment. A number of more polar products were also separated (as mixtures) but not identified.

**Preparation of 2,2'-(1,1-ethanediyl)-1H-benzimidazole (128)**

\[ \text{Me} \]
\[ \text{H} \]
\[ \text{N} \]
\[ \text{N} \]
\[ \text{H} \]
\[ \text{H} \]

(128)

This was prepared by an adaptation of the method of Lane,\(^{13}\) by heating methyl malondiamide (1.34g, 0.012 moles) and \(o\)-phenylenediamine (5.01g, 0.0464 moles) in the absence of solvent at 200°C for 4 hours. After this period, the reaction mixture was poured into hot water and the insoluble material separated and washed several times with hot water. Crystallization of the crude product from ethylene glycol gave
the bis-benzimidazole (128) (1.29g, 42%) as pale pink crystals, m.p. 350°C (decomp.) (Found: C, 72.75; H, 5.48; N, 21.14. \( \text{C}_{16}\text{H}_{14}\text{N}_4 \) requires C, 73.26; H, 5.38; N, 21.36%);

\( \nu_{\text{max}} \) (Nujol): 2720 (brs), 2590 (brs), 1625 (w), 1590 (w), 1530 (w), 1315 (m), 1305 (m), 1275 (s), 1225 (m), 1080 (m), 1020 (m), 995 (m), 750 (s), 740 (s) cm\(^{-1}\);

\( \delta_H \) (d<sub>6</sub> DMSO, 90 MHz): 12.00 (brs, 2 × NH), 7.63-7.28 (m, 4 × ArH), 7.28-6.90 (m, 4 × ArH), 4.73 (q, \( J = 7 \) Hz, CHMe), 1.85 (d, \( J = 7 \) Hz, CHMe);

M/Z (%): 262(\( M^+ \), 100), 261(63), 260(83), 259(62), 247(55), 145(25), 143(29), 131(28), 119(29), 92(26).

**Preparation of 1-Amino-2,2'- (1,1-ethanediyl)-1H-benzimidazole (127)**

\( \text{Me} \)

\( \text{NH}_2 \)

This was aminated using the same procedure as for the preparation of the benzimidazole (104), using the bis-benzimidazole (128) (1.19g, 4.542 \( \times 10^{-3} \) moles) and O-mesitylenesulphonylhydroxylamine (1.17g, 5.450 \( \times 10^{-3} \) moles) in dry dichloromethane (120 ml). A \( ^1 \)H n.m.r. spectrum of the crude product revealed a >50% yield of the monoaminated product (127). However, due to the insolubility of the crude product in a large range of solvents, purification by both column chromatography and recrystallization was thwarted and a pure sample was not obtained.
EXPERIMENTAL
CHAPTER 4
Preparation of 2,3,3-Trimethylbutanoic acid (108)

This was prepared by a modified literature method,\textsuperscript{127} outlined in the experimental relating to Chapter 3.

Preparation of Methyl-N-(2,3,3-trimethylbutanoyl)anthranilate (133)

This was prepared by a general procedure\textsuperscript{14} for the synthesis of methyl N-substituted anthranilates. Thus, 2,3,3-trimethylbutanoic acid (108) (4.42g, 0.034 moles) and an excess of thionyl chloride (~10 mole equivalents) were heated to 40-50°C for 1-3 hr., by which time evolution of bubbles had ceased to be observable. Excess thionyl chloride was removed by evaporation under reduced pressure (an i.r. spectrum on the residue showed $\nu_{\text{max}}$ CO at 1795 cm$^{-1}$ only) and the residual acid chloride diluted with dry ether (50 ml) and added dropwise but briskly with stirring to methyl anthranilate (20.56g, 0.136 moles) in dry ether (200 ml). The mixture was set aside overnight, after which the insoluble hydrochloride was separated and the ether solution washed several times (~10) with dilute hydrochloric acid (2M) and then once with water, dried with magnesium sulphate and evaporated under reduced pressure. After evaporation of the ether solution, the product (133) was obtained as a light yellow oil (5.63g, 63%) and was found to be sufficiently pure to be used directly in the next step;

$\nu_{\text{max}}$ (film): 3320 (s), 2950 (s), 1685 (s), 1585 (s), 1515 (s), 1440 (s), 1365 (s), 1155 (s), 1095 (s), 1045 (m), 755 (s) cm$^{-1}$;

$\delta_{\text{H}}$ (CDCl$_3$, 90 MHz): 11.00 (brs, exch. D$_2$O, -NH), 8.73 (dd, J8 and 1 Hz),
ArH), 7.98 (dd, J7 and 2Hz, ArH), 7.46 (ddd, J8, 8 and 2Hz, ArH), 7.02 (ddd, J8, 7 and 1Hz, ArH), 3.87 (s, CO2), 2.23 (q, J7Hz, CHMe(Bu)), 1.24 (d, J7Hz, CHMe(Bu)), 1.03 (s, Bu).

Preparation of 3-Amino-2-(1,2,2-trimethylpropyl)quinazolin-4(3H)-one (132)

This was prepared by a modified general procedure, using the anthranilate (133) (5.36g, 0.0204 moles) and hydrazine hydrate (95%, 5.12g, 0.102 moles), with ethanol (30 ml) as solvent. After 2-3 freeze-thaw cycles to eliminate oxygen, the mixture was sealed in vacuo in a Carius tube and heated overnight at 140-150°C. On cooling, the N-aminquinazolone (132) was obtained as colourless crystals (3.68g, 74%), m.p. 118-120°C (from ethanol) (Found: C, 68.59; H, 7.82; N, 17.19. C14H13N3O requires C, 68.54; H, 7.81; N, 17.13%);

νmax (Nujol): 3315(s), 3210(m), 1660(s), 1590(s), 1250(m), 1225(m), 1180(m), 955(m), 915(m), 765(s), 690(s) cm⁻¹;

δH (CDCl3, 90 MHz): 8.17 (dd, J8 and 1Hz, ArH), 7.74-7.17 (m, ArH, -H7 and -H8), 4.78 (brs, exch. D2O, -NH2), 3.85 (q, J7Hz, CHMe(Bu)), 1.30 (d, J7Hz, CHMe(Bu)), 1.02 (s, Bu);

δC (d6 DMSO, 75 MHz): 165.4(s), 164.9(s), 150.2(s), 138.0(d), 131.2(d), 130.0(d), 129.9(d), 123.8(s), 45.9(d), 38.2(s), 31.4(q), 18.7(q);

M/Z (%): 245(M⁺, 9), 230(18), 190(15), 189(100), 188(9), 175(29), 173(24), 130(8), 120(35), 119(36).

In an experiment in which the oven temperature above was maintained
at 119°C overnight, the yield of (132) was 24%. After removal of the bulk of the ethanol filtrate under reduced pressure, the residue was dissolved in ether, the ether washed once with water, dried with magnesium sulphate and evaporated to give the hydrazide (134) (55%) as colourless crystals, m.p. 125-127°C (from dichloromethane - light petroleum) (Found: C, 63.91; H, 7.96; N, 15.95. C_{14}H_{21}N_{3}O_{2} requires C, 63.85; H, 8.04; N, 15.96%);

ν_{max} (Nujol): 3305 (s), 1665 (s), 1630 (s), 1585 (s), 1515 (s), 1290 (s), 1165 (m), 1085 (w), 945 (m), 755 (s), 745 (s) cm^{-1};

δ_{H} (CDCl_{3}, 90 MHz):

\[
\begin{align*}
\text{HN} & \quad \text{CO} \quad \text{HN} \\
\text{Bu}^+ & \quad \text{CONHNH}_2
\end{align*}
\]

10.63 (brs, exch. D_{2}O, -NH), 8.54 (dd, J=8 and 1Hz, ArH_3), 7.56-6.78 (m, ArH_4, -H_5 and -H_6), 4.67 (brs, exch. D_{2}O, N\_NHNH_2), 2.17 (q, J=7Hz, CHMe(Bu^+)), 1.20 (d, J=7Hz, CHMe(Bu^+)), 1.00 (s, Bu^+);

M/Z (%): 263(M^+, 6), 233(100), 189(15), 176(71), 175(43), 158(20), 146(18), 120(73), 92(21), 85(67).

Further heating of the above hydrazide (134) in a degassed Carius tube in ethanol at 140-150°C overnight, resulted in quantitative conversion to the N-aminoquinazolone (132).

**General Procedure (D) for the Oxidation of N-Aminoquinazolones with Lead Tetra-acetate at Room Temperature in the Presence of Alkenes and Absence of Trifluoroacetic Acid**

Powdered N-aminoquinazolone (1 mole equivalent) and acetic acid free lead tetra-acetate (LTA) (1.05-1.10 mole equivalents) were added alternately and continuously in very small portions over 15 minutes to
a vigorously stirred solution of dry dichloromethane (1 ml/100 mg of N-aminoquinazolone) and the alkene (4-10 mole equivalents) at room temperature. The mixture was then stirred for a further 30 minutes at room temperature, the insoluble lead di-acetate separated and washed with dichloromethane and the total filtrate washed successively with sodium bicarbonate solution and water, dried with magnesium sulphate and the solvent removed under reduced pressure.

**General Procedure (E) for the Oxidation of N-Aminoquinazolones with Lead Tetra-acetate at Room Temperature in the Presence of Alkenes and Trifluoroacetic Acid**

Powdered N-aminoquinazolone (1 mole equivalent) and acetic acid free lead tetra-acetate (LTA) (1.1 mole equivalents) were added alternately and continuously in very small portions over 15 minutes to a vigorously stirred solution of dry dichloromethane (1 ml/100 mg of N-aminoquinazolone), the alkene (4 mole equivalents) and trifluoroacetic acid (TFA) (3.4 mole equivalents) at room temperature. The mixture was then stirred for 30 minutes at room temperature (lead di-acetate remaining in solution) and then washed successively with sodium bicarbonate solution and water, dried with magnesium sulphate and the solvent removed under reduced pressure.

**Oxidation of 3-Amino-2-(1,2,2-trimethylpropyl)quinazolin-4(3H)-one (132) with Lead Tetra-acetate at Room Temperature in the Presence of α-Methylene-γ-butyrolactone (65) and Absence of Trifluoroacetic Acid**

The general oxidation procedure (D) was followed using N-aminoquin-
azolone (132) (0.100g, 4.082 x 10^{-4} moles), LTA (0.190g, 4.286 x 10^{-4} moles) and \( \alpha \)-methylene-\( \gamma \)-butyrolactone (65) (0.160g, 1.633 x 10^{-3} moles) in dry dichloromethane (1 ml). An n.m.r. spectrum of the crude oxidation product showed the presence of two diastereoisomers of aziridine (140), (140a) and (140b), in a ratio of 1:1.3 respectively. Chromatography over activated alumina, with ethyl acetate-light petroleum (1:1) as eluant, gave (140a) as colourless crystals (0.005g, 4%), m.p. 174-176°C (from ethanol) (Found: C, 67.00; H, 6.83; N, 12.35. \( \text{C}_{19}\text{H}_{23}\text{N}_{3}\text{O}_{3} \) requires C, 66.84; H, 6.79; N, 12.31%);

\[ \nu_{\text{max}} (\text{Nujol}): \ 1755(\text{s}), 1655(\text{s}), 1575(\text{s}), 1280(\text{s}), 1250(\text{s}), 1210(\text{m}) \] 1015(\text{s}), 790(\text{s}) \text{ cm}^{-1};

\[ \delta_{\text{H}} (\text{CDCl}_3, 300 \text{ MHz}): \ 8.15 (\text{ddd}, J8.0, 1.5 \text{ and } 0.6 \text{Hz}, \text{ArH}_5), \ 7.68 (\text{ddd}, J8.2, 6.5 \text{ and } 1.5 \text{Hz}, \text{ArH}_7), \ 7.64 (\text{ddd}, J8.2, 1.6 \text{ and } 0.6 \text{Hz}, \text{ArH}_5), \ 7.39 (\text{ddd}, J8.0, 6.5 \text{ and } 1.6 \text{Hz}, \text{ArH}_7), \ 5.00 (\text{ddd}, J8.4, 8.4 \text{ and } 8.4 \text{Hz}, \text{CH}_2\text{CH}_2\text{O}_2\text{C}), \ 4.56 (\text{ddd}, J8.9, 8.4 \text{ and } 3.6 \text{Hz}, \text{CH}_2\text{CH}_2\text{O}_2\text{C}), \ 3.30 (q, J7.0Hz, \text{CHMe(Bu}^t)) , \ 3.11 (d, J1.1Hz, \text{aziridine ring proton cis to het.}), \ 2.92 (m, \text{CHHCH}_2\text{O}_2\text{C}), \ 2.88 (d, J1.1Hz, \text{aziridine ring proton trans to het.}), \ 2.65 (\text{ddd}, J15.1, 8.9 \text{ and } 8.1 \text{Hz}, \text{CHHCH}_2\text{O}_2\text{C}), \ 1.45 (d, J7.0Hz, \text{CHMe(Bu}^t)), \ 0.98 (s, \text{Bu}^t); \]

In the crystalline diastereoisomer (140a) only a single invertomer (lactone C=O syn to het.) is evident in the \(^1\text{H} \) n.m.r. spectrum at room temperature;

\[ \text{M/Z} \ (%): \ 341(M^+, 3), \ 286(41), \ 215(15), \ 189(29), \ 174(100), \ 173(61), \ 159(38), \ 131(28), \ 117(38), \ 98(41). \]

Further elution with ethyl acetate-light petroleum (1:1) gave (140b) as an oil (0.021g, 15%), whose low temperature (-40°C) n.m.r. spectrum showed the presence of 2 rotamers in ca. 1:1 ratio. Only a single invertomer of this diastereoisomer (140b) (lactone C=O syn to
het.) was evident in the $^1$H n.m.r. spectrum at low temperature;
$\delta_H$ (CDCl$_3$, 300 MHz, -40°C) (140b): 8.25-7.38 (m, ArH$_s$, -H$_s$, -H, and
-H$_s$, both rotamers), 5.05 (ddd, J8, 8 and 8Hz, CH$_2$CH$_2$O$_2$C, in both
rotamers), 4.66 (m, CH$_2$CH$_2$O$_2$C, in both rotamers), 3.49 (d, J1Hz,
2× aziridine ring proton in one rotamer), 3.30 (q, J7Hz, CHMe(Bu$^t$),
in both rotamers), 3.23 (d, J1Hz, aziridine ring proton cis to het. in
one rotamer), 3.04 (d, J1Hz, aziridine ring proton trans to het. in
one rotamer), 3.00-2.63 (m, CH$_2$CH$_2$O$_2$C, in both rotamers), 1.37 (d,
J7Hz, CHMe(Bu$^t$), in one rotamer), 1.28 (d, J7Hz, CHMe(Bu$^t$), in one
rotamer), 1.25 (s, Bu$^t$, in one rotamer), 1.00 (s, Bu$^t$, in one rotamer).

Preparation of Methyl-N-(2,3,3-trimethylbutanoyl)-4-nitroanthranilate (135)

![Structure of 135](image)

The 4-nitroanthranilate (135) was obtained from 2,3,3-trimethyl-
butanoic acid (108) (4.00g, 0.0307 moles) by conversion to the acid
chloride and then adding the latter dropwise with stirring to a
solution of methyl 4-nitroanthranilate (6.63g, 0.0338 moles) and dry
pyridine (2.73 ml, 0.0338 moles) dissolved in dichloromethane (150 ml).
After setting aside overnight, the insoluble material was separated
and the solution washed with dilute hydrochloric acid and then water
before drying and evaporating. The crude product obtained contained
c. 50% of the required amide which was separated from the more
insoluble unchanged methyl 4-nitroanthranilate by trituration with
ether. Evaporation of the ether and crystallization from chloroform-
light petroleum gave the 4-nitroanthranilate (135) (4.57g, 58%) as
orange crystals, m.p. 82-85°C;
δ_H (CDCl_3, 90 MHz): 11.04 (brs, exch. D_2O, -NH), 9.64 (d, J2Hz, ArH₃),
8.27-7.27 (m, ArH₅ and H₆), 3.98 (s, CO₂Me), 2.26 (q, J7Hz, CHMe(Bu^t)),
1.25 (d, J7Hz, CHMe(Bu^t)), 1.03 (s, Bu^t).

Preparation of (N-(2,3,3-trimethylbutanoyl)) -4-nitroanthranilhydrazide
(136)

The amide (135) (2.92g, 9.460 x10^-3 moles) was heated under reflux
with hydrazine hydrate (2.37g, 0.0473 moles) in ethanol (50 ml) under
a nitrogen atmosphere. After cooling, the ethanol was removed under
reduced pressure, the residue dissolved in dichloromethane (100 ml)
and the organic layer washed once with water, dried with magnesium
sulphate and then evaporated under reduced pressure. Crystallization
of the residue from dichloromethane - light petroleum gave the hydrazide
(136) (0.78g, 27%) as pale orange crystals, m.p. 170-175°C;
ν_max (Nujol): 3340(s), 3130(s), 1685(s), 1660(s), 1600(s), 1530(s),
1350(s), 1295(s), 1260(s), 1160(s), 1095(s), 1065(m), 940(s), 905(s),
820(s), 745(s) cm^-1;
δ_H (CDCl_3, 90 MHz): 10.82 (brs, exch. D_2O, -NH), 9.43 (d, J2Hz, ArH₃),
7.87-7.20 (m, ArH₅ and H₆), 4.44 (brs, exch. D_2O, NHNH₂), 2.21 (q,
J7Hz, CHMe(Bu^t)), 1.24 (d, J7Hz, CHMe(Bu^t)), 1.01 (s, Bu^t);
M/Z (%): 308(M^+,1), 277(11), 234(8), 221(25), 190(21), 165(14), 113(26),
85(100).
Preparation of 3-Amino-2-(1,2,2-trimethylpropyl)-7-nitroquijiazolin-4(3H)-one (137)

The hydrazide (136) (2.00g, 6.487 x 10^-3 moles) was heated in oxygen free ethanol (30 ml) in a Carius tube at 160-170°C overnight. Evaporation of the ethanol and crystallization of the N-aminoquinazolone (137) gave pale yellow needles (0.96g, 51%), m.p. 187-189°C (from ethanol) (Found: C, 58.09; H, 6.47; N, 19.03. C_{14}H_{18}N_{4}O_{3} requires C, 57.92; H, 6.25; N, 19.30%);

ν_{max} (Nujol): 3330(s), 3270(s), 1675(s), 1595(s), 1530(s), 1345(s), 1265(m), 1170(m), 1070(m), 905(s), 830(s), 790(m), 740(s), 730(s) cm^{-1};

δ_{H} (CDCl_{3}, 90 MHz): 8.54-8.00 (m, ArH_{5}, -H_{6} and H_{9}), 4.80 (brs, exch. D_{2}O, NH_{2}), 3.85 (q, J_{7Hz}, CHMe(Bu^{t})), 1.30 (d, J_{7Hz}, CHMe(Bu^{t})), 1.00 (s, Bu^{t});

δ_{C} (d^{6} DMSO, 75 MHz): 168.2(s), 164.0(s), 155.0(s), 150.4(s), 132.5(d), 127.8(s), 126.1(d), 123.7(d), 46.2(d), 38.5(s), 31.5(q), 18.6(q);

M/Z (%): 290(M^{+},<1), 275(6), 234(100), 218(24), 164(33), 75(10).

Oxidation of 3-Amino-2-(1,2,2-trimethylpropyl)-7-nitroquiazolin-4(3H)-one (137) with Lead Tetra-acetate at Room Temperature in the Presence of α-Methylene-γ-butyrolactone (65) and Absence of Trifluoroacetic Acid
The general oxidation procedure (D) was followed using N-aminoquinazolone (137) (0.100g, 3.448 x 10^-4 moles), LTA (0.160g, 3.618 x 10^-4 moles) and α-methylene-γ-butyrolactone (65) in dry dichloromethane (1 ml). Chromatography of the crude oxidation product [which comprised a 1:1.3 ratio of diastereoisomers, (143a) and (143b) respectively, of aziridine (143)] over silica, with ethyl acetate - light petroleum (1:1) as eluant, gave the 7-(3,4-dihydro-2-(1,2,2-trimethylpropyl)-4-oxo-7-nitroquinazolin-3-yl)-2-oxa-7-aza-spiro[4,2]-heptane-1-one (143) (Rf = 0.61) as a pale yellow solid (0.049g, 37%), as a mixture of diastereoisomers. Crystallization of this solid from dichloromethane - ethyl acetate was successful but did not separate the two diastereoisomers; 

νmax (Nujol): 1765(s), 1675(s), 1590(s), 1535(s), 1345(s), 1345(s), 1295(s), 1215(m), 1160(s), 1115(s), 1020(s), 900(m), 830(m), 740(m) cm⁻¹;

δH (CDCl₃, 300 MHz) (143a): 8.55-8.10 (m, ArH₅, -H₆ and -H₇), 4.98 (ddd, J8.5, 8.5 and 8.2Hz, CH₂CHHO₂C), 4.60 (m, CH₂CHHO₂C), 3.32 (q, J7.0Hz, CHMe(Buᵗ)), 3.17 (d, J1.3Hz, aziridine ring proton cis to het.), 2.94 (m, CH₂CH₂O₂C), 2.89 (d, J1.3Hz, aziridine ring proton trans to het.), 2.67 (m, CH₂CH₂O₂C), 1.48 (d, J7.0Hz, CHMe(Buᵗ)), 1.00 (s, Buᵗ).

For (143b), at 300 MHz all signals were broadened at room temperature [rotamers: see (140b)]; at 90 MHz δH (CDCl₃, 143b): 8.55-8.10 (m, ArH₅, -H₆ and H₇), 4.98 (brs, CH₂CHHO₂C), 4.60 (brs, CH₂CHHO₂C), 3.30 (brs, CHMe(Buᵗ) and aziridine ring proton cis to het.), 2.90 (brs, aziridine ring proton trans to het. and CH₂CH₂O₂C), 2.68 (brs, CH₂CH₂O₂C), 1.32 (d, J6.8Hz, CHMe(Buᵗ)), 1.15 (brs, Buᵗ).

In both diastereoisomers only one inverter (lactone C=O syn to het.) is evident in the n.m.r. spectrum in CDCl₃ at room temperature;

M/Z (%): 386(M⁺,<1), 371(13), 330(100), 231(26), 219(36), 204(40), 176(87), 162(90), 75(37).
The general oxidation procedure (E) was followed using the N-amino quinazolone (132) (0.100g, 4.082 x 10^-4 moles), LTA (0.190g, 4.286 x 10^-4 moles) α-methylene-γ-butyrolactone (65) (0.080g, 8.164 x 10^-4 moles) and TFA (0.158g, 1.388 x 10^-3 moles) in dry dichloromethane (1 ml). An n.m.r. spectrum of the crude oxidation product showed the presence of only the crystalline diastereoisomer (140a) of aziridine (140) and crystallization of this material from ethanol gave (140a) (0.100g, 72%), m.p. 174-176°C. This diastereoisomer (140a) was identical in all respects with that isolated previously.

Oxidation of (132) at Room Temperature with Lead Tetra-acetate in the Presence of Methyl Methacrylate and TFA

See experimental relating to Chapter 5.

Oxidation of N-Aminophthalimide (50) at Room Temperature with Lead Tetra-acetate in the Presence of α-Methylene-γ-butyrolactone (65) and Absence of TFA

See experimental relating to Chapter 3.

Effect of TFA on the N.m.r. Spectrum of Diastereoisomer (140b)

Addition of excess TFA at room temperature to the diastereoisomer (140b) in CDCl₃, transforms the broad featureless n.m.r. spectrum into a mainly resolved spectrum, showing the presence of predominantly one species thus:
\( \delta_H (\text{CDCl}_3, 300 \text{ MHz}) \): 8.32 (dd, J8 and 1.5Hz, ArH_5), 8.01 (ddd, J8, 7 and 1.5Hz, ArH_7), 7.93 (dd, J8 and 1.5Hz, ArH_8), 7.79 (ddd, J8, 7 and 1.5Hz, ArH_6), 4.73 (m, CH_2CH_2O_2C), 3.65 (brs, aziridine ring proton cis to het.), 3.49 (d, J3.8Hz, aziridine ring proton trans to het.), 3.27 (brs, -\text{CHMe} (\text{Bu}^t)), 2.93 (m, CH\text{HCH}_2O_2C), 2.83 (m, CH\text{HCH}_2O_2C), 1.54 (d, J7.4Hz, \text{CHMe}(\text{Bu}^t)), 1.13 (s, \text{Bu}^t).

Preparation of Methyl 1-(3,4-dihydro-2-ethyl-4-oxo-quinazolin-3-yl)-aziridine-2-carboxylate (153)

This was prepared\(^\text{119}\) from 3-amino-2-ethylquinazolin-4(3H)-one and methyl acrylate;

\( \delta_H (\text{CDCl}_3, 300 \text{ MHz}) \): 8.17 (ddd, J8.0, 1.5 and 0.6Hz, ArH_5), 8.12 (ddd, J8.2, 7.4 and 1.5Hz, ArH_7), 7.62 (ddd, J8.2, 1.3 and 0.6Hz, ArH_8), 7.42 (ddd, J8.0, 7.4 and 1.3Hz, ArH_6), 3.86 (s, CO_2Me), 3.67 (dd, J7.5 and 5.4Hz, aziridine ring proton gem. to CO_2Me and cis to het.), 3.18 (dd, J7.5 and 1.5Hz, gem. aziridine ring proton cis to het.), 3.08 (dq, J7.5 and 6.6Hz, CH_3CH_2), 2.92 (dd, J5.4 and 1.5Hz, gem. aziridine ring proton trans to het.), 1.42 (t, J7.5Hz, CH_3CH_2).

In aziridine (153) only one inverctor (CO_2Me and het. anti) is evident in the n.m.r. spectrum at room temperature.

Effect of Adding TFA (3.4 mole equivalents) on the N.m.r. Spectrum of Aziridine (153)

TFA (3.4 mole equivalents) was added to a sample of aziridine (153) in CDCl_3 at room temperature, and the following n.m.r. spectrum
recorded:

$\delta$H (CDCl$_3$, 300 MHz): 8.28 (ddd, J8.1, 1.4 and 0.9Hz, ArH$_5$), 7.99 (ddd, J8.2, 6.9 and 1.4Hz, ArH$_7$), 7.77 (dd, J8.2 and 0.9Hz, ArH$_8$), 7.71 (dd, J8.1 and 6.9Hz, ArH$_6$), 4.23 (dd, J8.0 and 5.0Hz, aziridine ring proton gem. to CO$_2$Me and cis to het.), 3.94 (s, CO$_2$Me), 3.65 (dd, J8.0 and 1.4Hz, gem. aziridine ring proton cis to het.), 3.38 (m, CH$_2$CH$_3$), 3.02 (dd, J5.0 and 1.4Hz, gem. aziridine ring proton trans to het.), 1.54 (t, J7.5Hz, CH$_2$CH$_3$).
EXPERIMENTAL

CHAPTER 5
Oxidation of 3-Amino-2-(1,2,2-trimethylpropyl)quinazolin-4 (3H) -one (132) in the Presence of Alkenes

This oxidation was carried out at room temperature both in the absence of TFA (procedure D) and in the presence of TFA (procedure E).

(i) Using methyl acrylate (95):

\[ \text{Bu}^+ \]

\[ \text{Me} \]

\[ \text{CO}_2\text{Me} \]

The general oxidation procedure (E) was followed using N-amino-quinazolone (132) (0.114g, 4.653 \times 10^{-4} \text{ moles}), LTA (0.227g, 5.118 \times 10^{-4} \text{ moles}), methyl acrylate (0.160g, 1.861 \times 10^{-3} \text{ moles}) and TFA (0.180g, 1.582 \times 10^{-3} \text{ moles}) in dry dichloromethane (1 ml). Chromatography of the crude oxidation product over silica, with ethyl acetate-light petroleum (1:2) as eluant, isolated the major diastereoisomer of 1-(3,4-dihydro-2-(1,2,2-trimethylpropyl)-4-oxoquinazolin-3-yl)aziridine-2-carboxylate (155) (R_f = 0.43) as a colourless oil (0.077g, 50%) (Found: M/Z 329.1743. C_{18}H_{23}N_{3}O_{3} requires M, 329.1739);

\[ \nu_{\text{max}} (\text{film}) : 2960 (\text{m}), 1745 (\text{s}), 1675 (\text{s}), 1590 (\text{s}), 1475 (\text{m}), 1375 (\text{m}), 1280 (\text{m}), 1220 (\text{s}), 775 (\text{m}), 695 (\text{m}) \text{ cm}^{-1} ; \]

\[ \delta_{\text{H}} (\text{CDCl}_3, 300 \text{ MHz}) \] (major diastereoisomer): 8.15 (ddd, J8.0, 1.5 and 0.6Hz, ArH_5), 7.68 (ddd, J8.2, 6.9 and 1.5Hz, ArH_7), 7.62 (ddd, J8.2, 1.5 and 0.6Hz, ArH_9), 7.41 (ddd, J8.0, 6.9 and 1.5Hz, ArH_6), 3.84 (s, CO_2Me), 3.55 (q, J7.0Hz, CHMe(Bu^t)), 3.40 (dd, J7.7 and 4.8Hz, aziridine ring proton gem. to CO_2Me and cis to het.), 3.33 (dd, J7.7 and 1.4Hz, gem. aziridine ring proton cis to het.), 3.03 (dd, J4.8 and 1.4Hz, gem. aziridine ring proton trans to het.), 1.37 (d, J7.0Hz, CHMe(Bu^t)), 1.02
In this diastereoisomer only one invertoomer (CO$_2$Me and het. anti) is evident in the n.m.r. spectrum at room temperature;

M/Z (%): 329(M$^+$,1), 314(6), 274(18), 273(100), 214(11), 187(19), 174(44), 159(40), 131(31), 117(36), 77(15).

The ratio of major : minor diastereoisomers in the above experiment from non-superimposed signals in the n.m.r. spectrum of the crude reaction product was 8.7 : 1.

An identical oxidation carried out in the absence of TFA (procedure D), gave a 1 : 2.4 ratio of the respective diastereoisomers. The major diastereoisomer produced in this experiment (which corresponds to the minor diastereoisomer in the oxidation with TFA above) has chemical shifts at:

$\delta_H$ (CDCl$_3$, 300 MHz): 8.30-7.36 (m, ArH$_5$, -H$_6$, -H$_7$ and -H$_8$), 3.87 (s, CO$_2$Me), 3.76 (dd, J8 and 5Hz, aziridine ring proton gem. to CO$_2$Me and cis to het.), 3.72 (q, J7Hz, CHMe(Bu$^t$)), 3.04 (dd, J8 and 1.5Hz, gem. aziridine ring proton cis to het.), 2.86 (dd, J5 and 1.5Hz, gem. aziridine ring proton trans to het.), 1.39 (d, J7Hz, CHMe(Bu$^t$)), 1.01 (s, Bu$^t$).

In this diastereoisomer only one invertoomer (CO$_2$Me and het. anti) is evident in the n.m.r. spectrum at room temperature.

(ii) **Using t-butyl acrylate:**
The general oxidation procedure (E) was followed using N-amino-quinazolone (132) (0.171g, 6.980 \times 10^{-4} moles), LTA (0.340g, 7.678 \times 10^{-4} moles), t-butyl acrylate (0.357g, 2.792 \times 10^{-3} moles) and TFA (0.271g, 2.373 \times 10^{-3} moles) in dry dichloromethane (1.7 ml). Crystallization of the crude product from ethanol gave the major diastereoisomer of t-butyl 1-(3,4-dihydro-2-(1,2,2-trimethylpropyl)-4-oxoquinazolin-3-yl)-aziridine-2-carboxylate (156) as colourless crystals (0.10g, 39%), m.p. 124-125°C (Found: C, 67.77; H, 7.85; N, 11.14. C_{21}H_{29}N_{3}O_{3}
requires C, 67.90; H, 7.87; N, 11.31%);

$\nu_{\text{max}}$ (Nujol): 1725(s), 1670(s), 1590(s), 1345(m), 1280(s), 1235(s), 1150(s), 1085(m), 1000(m), 900(m), 840(m), 775(s), 695(s) cm$^{-1}$;

$\delta_{H}$ (CDCl$_3$, 300 MHz) (major diastereoisomer):

<table>
<thead>
<tr>
<th>Major Invertomer</th>
<th>Minor Invertomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>(CO$_2$Bu$^t$ anti to het.)</td>
<td>(CO$_2$Bu$^t$ syn to het.)</td>
</tr>
<tr>
<td>8.17 (ddd, J8.0, 1.5 and 0.6Hz, ArH$_3$)</td>
<td></td>
</tr>
<tr>
<td>7.68 (ddd, J8.3, 6.8 and 1.5Hz, ArH$_7$)</td>
<td></td>
</tr>
<tr>
<td>7.63 (ddd, J8.3, 1.5 and 0.6Hz, ArH$_7$)</td>
<td></td>
</tr>
<tr>
<td>7.39 (ddd, J8.0, 6.8 and 1.5Hz, ArH$_7$)</td>
<td></td>
</tr>
<tr>
<td>3.55 (q, J7.0Hz, CHMe(Bu$^t$))</td>
<td>3.36 (q, J7.0Hz, CHMe(Bu$^t$))</td>
</tr>
<tr>
<td>3.23-3.00 (m, 3 x aziridine ring protons)</td>
<td></td>
</tr>
<tr>
<td>1.54 (s, CO$_2$Bu$^t$)</td>
<td>1.32 (s, CO$_2$Bu$^t$)</td>
</tr>
<tr>
<td>1.41 (d, J7.0Hz, CHMe(Bu$^t$))</td>
<td></td>
</tr>
<tr>
<td>1.01 (s, Bu$^t$)</td>
<td>0.99 (s, Bu$^t$)</td>
</tr>
</tbody>
</table>
In this diastereoisomer the ratio of invertomers, CO$_2$Bu$^t$ anti : syn to het., was ca. 16:1; 

M/Z (%): 371(M$^+$, 5), 315(88), 298(15), 259(26), 214(15), 187(21), 174(100), 173(53), 159(48), 131(30), 117(40).

The ratio of major : minor diastereoisomers in the n.m.r. spectrum of the crude oxidation product was 14:1.

An identical oxidation carried out in the absence of TFA (procedure D), gave a 2.1 : 1 ratio of the respective diastereoisomers, with unobscured signals from the minor diastereoisomer at $\delta_H$ (CDCl$_3$, 300 MHz): 3.83 (q, J7.0Hz, CHMe(Bu$^t$)), 3.78 (dd, J7.4 and 4.7Hz, aziridine ring proton gem. to CO$_2$Bu$^t$ and cis to het.), 3.27 (d, J7.4Hz, gem. aziridine ring proton cis to het.), 2.71 (d, J4.7Hz, gem. aziridine ring proton trans to het.), 1.53 (s, CO$_2$Bu$^t$), 1.37 (d, J7.0Hz, CHMe(Bu$^t$)), 1.04 (s, Bu$^t$).

In this minor diastereoisomer only one invertomer (CO$_2$Bu$^t$ and het. anti) is evident in the n.m.r. spectrum at room temperature.

(iii) Using methyl methacrylate:

![Chemical Structure](image)

The general oxidation procedure (E) was followed using N-aminooquinazolone (132) (0.308g, 1.257 x 10$^{-3}$ moles), LTA (0.613g, 1.383 x 10$^{-3}$ moles), methyl methacrylate (0.503g, 5.028 x 10$^{-3}$ moles) and TFA (0.487g, 4.274 x 10$^{-3}$ moles) in dry dichloromethane (3 ml). Crystallization of the crude product from ethanol gave the major diastereoisomer of methyl 1-(3,4-dihydro-2-(1,2,2-trimethylpropyl)-4-oxoquinazolin-3-yl)-
2-methylaziridine-2-carboxylate (152) as colourless crystals (0.20g, 46%), m.p. 123-125°C (Found: C, 66.52; H, 7.28; N, 12.24. C\textsubscript{19}H\textsubscript{25}N\textsubscript{3}O\textsubscript{3} requires C, 66.45; H, 7.34; N, 12.24%);

\(\nu_{\text{max}}\) (Nujol): 1730 (s), 1660 (s), 1610 (m), 1585 (s), 1305 (s), 1165 (s), 1070 (m), 980 (m), 955 (m), 930 (w), 840 (w), 775 (s), 745 (m), 695 (s) cm\(^{-1}\);

\(\delta_{\text{H}}\) (CDCl\(_3\), 300 MHz) (Major diastereoisomer):

<table>
<thead>
<tr>
<th>Major Invertomer</th>
<th>Minor Invertomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>(CO\textsubscript{2}Me and het. syn)</td>
<td>(CO\textsubscript{2}Me and het. anti)</td>
</tr>
<tr>
<td>8.25-7.34 (m, ArH(_5), -H(_6), -H(_7), and -H(_8))</td>
<td></td>
</tr>
<tr>
<td>3.52 (s, CO\textsubscript{2}Me)</td>
<td>3.84 (s, CO\textsubscript{2}Me)</td>
</tr>
<tr>
<td>3.47 (d, J2.3Hz, aziridine ring proton cis to het.)</td>
<td>3.17 (q, J6.9Hz, CHMe(But))</td>
</tr>
<tr>
<td>3.32 (q, J7.0Hz, CHMe(But))</td>
<td>2.96 (d, J0.6Hz, aziridine ring proton cis to het.)</td>
</tr>
<tr>
<td>3.20 (d, J2.3Hz, aziridine ring proton trans to het.)</td>
<td>2.84 (d, J0.6Hz, aziridine ring proton trans to het.)</td>
</tr>
<tr>
<td>1.82 (s, aziridine ring Me trans to het.)</td>
<td>1.42 (d, J6.9Hz, CHMe(But))</td>
</tr>
<tr>
<td>1.45 (d, J7.0Hz, CHMe(But))</td>
<td>1.36 (s, aziridine ring Me cis to het.)</td>
</tr>
<tr>
<td>1.01 (s, But)</td>
<td>0.95 (s, But)</td>
</tr>
</tbody>
</table>

In the major diastereoisomer the ratio of major : minor invertomers was 1.3 : 1;

M/Z (%): 343(M\(^+\), 4), 328(12), 287(100), 228(16), 200(19), 174(54), 159(94), 131(70), 130(41), 117(79), 103(16), 77(22).

The ratio of major:minor diastereoisomers in the n.m.r. spectrum of the crude oxidation product was 5.2 : 1 (±0.3).

An identical oxidation carried out in the absence of TFA (procedure
D) gave a 1:1.2 (±0.2) ratio of the respective diastereoisomers. The major diastereoisomer obtained in this experiment (corresponding to the minor diastereoisomer in the oxidation with TFA) has chemical shifts at $\delta_H$ (CDCl$_3$, 300 MHz): 8.25-7.34 (m, ArH$_5$, -H$_6$, -H$_7$ and H$_8$), 3.56 (d, J2.6Hz, aziridine ring proton cis to het.), 3.55 (s, CO$_2$Me), 3.18 (q, J7.0Hz, CHMe(Bu$^t$)), 3.03 (d, J2.6Hz, aziridine ring proton trans to het.), 1.75 (s, aziridine ring Me trans to het.), 1.24 (d, J7.0Hz, CHMe(Bu$^t$)), 1.02 (s, Bu$^t$).

In this diastereoisomer only a single inveromer (CO$_2$Me and het. syn) was evident in the n.m.r. spectrum at room temperature.

(iv) Using methyl crotonate:

The general oxidation procedure (E) was followed using N-aminooquinazolone (132) (0.320g, 1.306 x 10$^{-3}$ moles), LTA (0.636g, 1.437 x 10$^{-3}$ moles), methyl crotonate (0.523g, 5.224 x 10$^{-3}$ moles) and TFA (0.506g, 4.440 x 10$^{-3}$ moles) in dry dichloromethane (3 ml). Chromatography of the crude product over silica, with ethyl acetate-light petroleum (1:1.5) as eluant, gave the minor diastereoisomer of aziridine (157) as a colourless oil ($R_f$ = 0.53) (0.015g, 3%);

$\delta_H$ (CDCl$_3$, 300 MHz) (minor diastereoisomer):

<table>
<thead>
<tr>
<th>Major Inveromer</th>
<th>Minor Inveromer</th>
</tr>
</thead>
<tbody>
<tr>
<td>(CO$_2$Me and het. syn)</td>
<td>(CO$_2$Me and het. anti)</td>
</tr>
<tr>
<td>8.26-7.36 (m, ArH$_5$,</td>
<td></td>
</tr>
</tbody>
</table>

| -H₆, -H₇ and -H₈ | 
|-----------------|-----------------|
| 3.64 (s, CO₂Me) | 3.88 (s, CO₂Me) |
| 3.61 (dq, J5.7 and 5.0Hz, aziridine ring proton gem. to aziridine ring Me) |  
| 3.26 (q, J7.0Hz, CHMe(Buᵗ)) | 3.48 (d, J5.0Hz, aziridine ring proton cis to het. and gem. to CO₂Me) |
| 3.11 (d, J5.0Hz, aziridine ring proton trans to het. and gem. to CO₂Me) | 3.40 (q, J7.0Hz, CHMe(Buᵗ)) |
| 1.65 (d, J5.7Hz, aziridine ring Me trans to het.) | 1.45 (d, J7.0Hz, CHMe(Buᵗ)) |
| 1.23 (d, J7.0Hz, CHMe(Buᵗ)) | 1.32 (d, J5.7Hz, aziridine ring Me cis to het.) |
| 0.99 (s, Buᵗ) | 1.04 (s, Buᵗ) |

In the minor diastereoisomer the ratio of major : minor invertomers was 5:1. Further elution with ethyl acetate - light petroleum (1 : 1.5) gave the major diastereoisomer of trans-methyl 1-(3,4-dihydro-2-(1,2,2-trimethylpropyl)-4-oxoquinazolin-3-yl)-2-methylaziridine-3-carboxylate (157) (Rᶠ = 0.42) as colourless crystals (0.26g, 58%), m.p. 117-119°C (from ethanol) (Found: C, 66.44; H, 7.38; N, 12.20. C₁₉H₂₅N₃O₃ requires C, 66.45; H, 7.34; N, 12.24%);

ν_max (Nujol): 1735(s), 1665(s), 1585(s), 1330(s), 1280(m), 1200(s), 1160(s), 1065(s), 775(s), 695(s) cm⁻¹;

δ_H (CDCl₃, 300 MHz) (major diastereoisomer):

<table>
<thead>
<tr>
<th>Major Invertomer</th>
<th>Minor Invertomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>(CO₂Me and het. syn)</td>
<td>(CO₂Me and het. anti)</td>
</tr>
<tr>
<td>8.12 (ddd, J8.0, 1.5 and 0.7Hz, ArH₅)</td>
<td></td>
</tr>
</tbody>
</table>

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7.68 (ddd, J8.2, 6.3 and 1.5Hz, ArHt)
7.63 (ddd, J8.2, 2.0 and 0.7Hz, ArHt)
7.38 (ddd, J8.0, 6.3 and 2.0Hz, ArHt)

3.59 (s, CO$_2$Me) 3.86 (s, CO$_2$Me)

3.39 (d, J4.7Hz, aziridine ring proton gem. to CO$_2$Me)
3.22 (q, J7.0Hz, $\text{CH}_2$(Bu))
2.99 (dq, J5.7 and 4.7Hz, aziridine ring proton gem. to aziridine ring Me)

1.62 (d, J5.7Hz, aziridine ring Me trans to het.)
1.34 (d, J5.7Hz, aziridine ring Me cis to het.)

1.44 (d, J7.0Hz, CH$_2$(Bu))
1.40 (d, J7.0Hz, CH$_2$(Bu))

1.01 (s, Bu) 1.04 (s, Bu)

The ratio of major:minor invertomers in the major diastereoisomer was ~16:1;
M/Z (%): 343(M$^+$,<1), 287(52), 228(17), 215(8), 174(100), 173(34), 159(34), 131(27), 117(33), 77(9).

The ratio of major:minor diastereoisomers in the n.m.r. spectrum of the crude reaction product was 7.0:1.

(v) *Using methyl vinyl ketone:*

![Diagram](158)
The general oxidation procedure (E) was followed using N-aminoquinazolone (132) (0.102g, 4.163×10⁻⁴ moles), LTA (0.203g, 4.579×10⁻⁴ moles) and TFA (0.161g, 1.415×10⁻³ moles) in dry dichloromethane (1 ml). Chromatography of the crude product over silica, with ethyl acetate-light petroleum (1:1.5) as eluant, gave the major diastereoisomer of methyl 1-(3,4-dihydro-2-(1,2,2-trimethylpropyl)-4-oxoquinazolin-3-yl)aziridine-2-yl-ketone (158) (RF = 0.46) as a colourless oil (0.081g, 62%) (Found: M/Z 313.1787. C₁₈H₂₃N₃O₂ requires M, 313.1790); νmax (film): 2950 (s), 1705 (s), 1670 (s), 1590 (s), 1470 (s), 1360 (s), 1220 (m), 775 (s) cm⁻¹; δH (CDCl₃, 300 MHz) (major diastereoisomer): 8.17 (ddd, J₈.0, 1.5 and 0.6Hz, ArH₅), 7.70 (ddd, J₈.2, 6.9 and 1.5Hz, ArH₇), 7.63 (ddd, J₈.2, 1.4 and 0.6Hz, ArH₆), 7.42 (ddd, J₈.0, 6.9 and 1.4Hz, ArH₆), 3.31 (q, J₇.0Hz, CHMe(Bu⁴)), 3.26 (m, 2×aziridine ring protons cis to het.), 3.08 (dd, J₃.6 and 0.8Hz, gem. aziridine ring proton trans to het.), 2.27 (s, COMe), 1.36 (d, J₇.0Hz, CHMe(Bu⁴)), 1.02 (s, Bu⁴).

In the major diastereoisomer of this aziridine (158) only a single inveromer (COMe and het. anti) is evident in the n.m.r. spectrum at room temperature.

The ratio of major:minor diastereoisomers in the n.m.r. spectrum of the crude reaction product was 6.5:1 (±0.5).

An identical oxidation carried out in the absence of TFA (procedure D) gave a 1:1.25 ratio of the respective diastereoisomers. The major diastereoisomer obtained in this oxidation (corresponding to the minor diastereoisomer in the oxidation with TFA above) has δ(CDCl₃, 300 MHz): 8.30-7.38 (m, ArH₅, -H₆, -H₇, -H₈), 3.56 (dd, J₈.0 and 5.4Hz, aziridine ring proton gem. to COCH₃ and cis to het.), 3.54 (q,
J7.0Hz, CHMe(Bu^t)), 2.93 (dd, J5.4 and 1.0Hz, gem. aziridine ring proton trans to het.), 2.71 (dd, J8.0 and 1.0Hz, gem. aziridine ring proton cis to het.), 2.46 (s, COMe), 1.41 (d, J7.0Hz, CHMe(Bu^t)), 1.01 (s, Bu^t).

In this diastereoisomer only a single inveromer (COMe and het. anti) is evident in the n.m.r. spectrum at room temperature.

(vi) Using 3-penten-2-one:

\[ \text{(159)} \]

The general procedure (E) was followed using N-aminoquinazolone (132) (0.103g, 4.204 x 10^{-4} moles), LTA (0.205g, 4.624 x 10^{-4} moles), 3-penten-2-one (0.141g, 1.682 x 10^{-3} moles) and TFA (0.163g, 1.429 x 10^{-3} moles) in dry dichloromethane (1 ml). Chromatography of the crude oxidation product over silica, with ethyl acetate-light petroleum (1:1) as eluant, gave the major diastereoisomer of methyl-trans-1-(3,4-dihydro-2-(1,2,2-trimethylpropyl)-4-oxoquinazolin-3-yl)-2-methylaziridine-3-yl-ketone (159) (R_f = 0.48) as colourless crystals (0.071g, 52%), m.p. 147-149°C (from ethanol) (Found: C, 69.58; H, 7.70; N, 12.80. C_{19}H_{25}N_{3}O_{2} requires C, 69.70; H, 7.70; N, 12.83%);

\[ \nu_{\text{max}} (\text{Nujol}): \quad 1705(s), 1665(s), 1610(s), 1585(s), 1280(s), 1185(s), 1160(s), 1085(m), 945(m), 775(s), 675(s) \text{ cm}^{-1}; \]

\[ \delta_{H} (\text{CDCl}_3, 300 \text{ MHz} \text{ (major diastereoisomer):} \quad 8.08 \text{ (ddd, J8.0, 1.4 and 0.7Hz, ArH}_5), 7.80-7.58 \text{ (m, ArH}_7, \text{ and } -\text{H}_8), 7.36 \text{ (ddd, J8.0, 5.6 and 1.4Hz, ArH}_6), 3.57 \text{ (d, J4.7Hz, aziridine ring proton trans to het.)}, \]

\[ -193- \]
3.23 (q, J7.0Hz, CHMe(Bu\textsuperscript{t})), 2.92 (dq, J5.7 and 4.7Hz, aziridine ring proton cis to het.), 2.48 (s, COMe), 1.60 (d, J5.7Hz, aziridine ring Me), 1.46 (d, J7.0Hz, CHMe(Bu\textsuperscript{t})), 1.00 (s, Bu\textsuperscript{t}). In this major diastereoisomer only a single inverter (COMe and het. syn) is evident in the n.m.r. spectrum at room temperature;

M/Z (%): 327(M\textsuperscript{+},1), 284(15), 271(56), 228(22), 174(100), 159(43), 131(37), 117(42), 77(16).

The ratio of major : minor diastereoisomers in the n.m.r. spectrum of the crude reaction product was 8.6 : 1.

An identical oxidation was carried out in the absence of TFA (procedure D), using N-aminoquinazolone (132) (0.205g, 8.367 x 10\textsuperscript{-4} moles), LTA (0.408g, 9.204 x 10\textsuperscript{-4} moles) and 3-penten-2-one (0.282g, 3.347 x 10\textsuperscript{-3} moles) in dry dichloromethane (2 ml). The crude oxidation product revealed a 1.2 : 1 ratio of the respective diastereoisomers of aziridine (159) and chromatography of this mixture over silica, with ethyl acetate - light petroleum (1:1) as eluant, isolated the minor diastereoisomer of aziridine (159) (R\textsubscript{f} = 0.57) as a colourless oil (0.04g, 15%);

δ\textsubscript{H} (CDCl\textsubscript{3}, 300 MHz) (minor diastereoisomer):

<table>
<thead>
<tr>
<th>Major Inverter (COMe and het. anti)</th>
<th>Minor Inverter (COMe and het. syn)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.25-7.32 (m, ArH\textsubscript{5}, -H\textsubscript{6}, -H\textsubscript{7}, -H\textsubscript{8})</td>
<td>3.47-3.33 (m, aziridine ring proton gem. to COMe)</td>
</tr>
<tr>
<td>3.47-3.33 (m, CHMe(Bu\textsuperscript{t}))</td>
<td>3.47-3.33 (m, aziridine ring proton gem. to Me and cis to het.)</td>
</tr>
<tr>
<td>3.05 (dq, J5.3 and 4.7Hz, CHMe(Bu\textsuperscript{t}))</td>
<td>3.14 (q, J7.0Hz, CHMe(Bu\textsuperscript{t}))</td>
</tr>
</tbody>
</table>
The ratio of major : minor invertners in this minor diastereoismomer was 1.1 : 1. Further elution with ethyl acetate - light petroleum (1:1) gave the major diastereoismomer of aziridine (159) (Rf = 0.48) as colourless crystals (0.04g, 15%), m.p. 147-149°C (from ethanol), which was identical in all respects with the major diastereoismomer isolated previously from the oxidation in the presence of TFA.

Oxidation of 3-Amino-2-(1,2,2-trimethylpropyl)quinazolin-4(3H)-one (132) with LTA at Room Temperature in the Presence and Absence of TFA and Various Concentrations of Methyl acrylate (95)

A number of small-scale experiments at room temperature, involving the oxidation of the N-aminoquinazolone (132) with LTA, were carried out in the presence and absence of TFA and various concentrations of methyl acrylate (95). The yields of products were estimated from the ¹H n.m.r. spectra of the crude oxidation products. No attempt at isolation of the products was made but the major diastereoismomer of aziridine (155) and deaminated quinazolone (160) were recognised by the presence of their characteristic n.m.r. signals; a number of other minor products remained unidentified.
Procedure for the Determination of the Minimum Temperature at which Oxidation takes place when the N-Aminoquinazolone (132) is Oxidised in the Presence of TFA, using Methyl acrylate (95) as a Nitrene Trap

LTA (0.128g, $2.906 \times 10^{-4}$ moles, 0.8 mole equivalents) was dissolved in TFA (0.249g, $2.180 \times 10^{-3}$ moles) and added to a solution of methyl acrylate (95) (0.094g, $1.090 \times 10^{-3}$ moles) in dry dichloromethane (3 ml). The solution was cooled to $-78^\circ$C and the N-aminoquinazolone (132) (0.089g, $3.633 \times 10^{-4}$ moles, 1.0 mole equivalents) added in small portions, as the solid, at this temperature over 15 minutes. The mixture was stirred for a further 30 minutes at $-78^\circ$C and tested for unreacted oxidising agent at this temperature by immersing a piece of starch iodide paper into the solution and comparing its colour with a control (control: a duplicate experiment in which the N-aminoquinazolone had been omitted). This procedure was then repeated at 5°C intervals up to $-20^\circ$C to determine the temperature at which oxidation took place. It was discovered that no oxidising agent remained at $-60^\circ$C, thus indicating that oxidation was complete at this temperature.

Oxidation of 3-Amino-2-(1,2,2-trimethylpropyl)quinazolin-4(3H)-one (132) in the Presence of Methyl acrylate (95) and TFA at $-60^\circ$C

(i) LTA (2.287g, 5.163 $\times 10^{-3}$ moles) was dissolved in dichloromethane (10 ml) containing TFA (5.35g, $4.694 \times 10^{-2}$ moles, 10 mole equivalents) and methyl acrylate (0.44g, 5.163 $\times 10^{-3}$ moles, 1.1 mole equivalents) and this solution was cooled to $-60^\circ$C. A solution of the N-aminoquinazolone (132) (1.15g, $4.694 \times 10^{-3}$ moles, 1.0 mole equivalents) in dry dichloromethane (8 ml) was then added over 30 minutes by continuous dropwise addition to the solution above, keeping the temperature at $-60^\circ$C. After stirring for a further 30 minutes at this temperature and working-up as usual, an n.m.r. spectrum of the crude product showed signals from aziridine (155) only. Chromatography over silica, with
ethyl acetate–light petroleum (1:2) as eluant, isolated the aziridine (155) (1.01g, 65%) as a mixture (23:1) of diastereoisomers. The major diastereoisomer of aziridine (155) had been previously characterized.

(ii) LTA (4.25g, $9.594 \times 10^{-3}$ moles) was dissolved in dichloromethane (5 ml) containing TFA (1.69g, 0.0148 moles, 1.7 mole equivalents) and the N-aminooquinazolone (132) (2.14g, $8.735 \times 10^{-3}$ moles) was dissolved in dichloromethane (5 ml) containing TFA (1.69g, 0.0148 moles, 1.7 mole equivalents). Both these solutions were added slowly but continuously dropwise via different dropping funnels over 30 minutes to methyl acrylate (95) (0.82g, $9.535 \times 10^{-3}$ moles, 1.1 mole equivalents) in dichloromethane (10 ml), but ensuring that at all times addition of the LTA solution was ahead of that of the N-aminooquinazolone solution. A solid was observable during the addition and the solution only became homogeneous on warming above -30°C. After the usual work-up, the only product isolated was the de-aminated quinazolone (160) (1.5g, 75%), m.p. 147-150°C (from ethanol) (Found: C, 72.98; H, 8.17; N, 11.94. C$_{14}$H$_{14}$N$_{2}$O requires C, 73.01; H, 7.88; N, 12.16%);

$\nu_{\text{max}}$ (Nujol): 3180(m), 3120(m), 1675(s), 1605(s), 1250(m), 970(m), 780(s), 630(s) cm$^{-1}$;

$\delta_{H}$ (CDCl$_3$, 90 MHz): 10.48 (brs, exch. D$_2$O, NH), 8.35-7.15 (m, ArH$_5$, -H$_6$, -H$_7$, -H$_8$), 2.69 (q, J$_7$Hz, CH$_3$(Bu$^t$)), 1.40 (d, J$_7$Hz, CH$_3$(Bu$^t$)), 1.03 (s, Bu$^t$).

(iii) LTA (0.203g, $4.580 \times 10^{-4}$ moles) was dissolved in dry dichloromethane (0.25 ml) containing TFA (0.143g, $1.254 \times 10^{-3}$ moles, 3.0 mole equivalents) and the N-aminooquinazolone (132) (0.102g, $4.163 \times 10^{-4}$ moles, 1.0 mole equivalents) was dissolved in dry dichloromethane (0.25 ml) containing TFA (0.143g, $1.254 \times 10^{-3}$ moles, 3.0 mole equivalents)

-197-
(6.0 mole equivalents of TFA in total). Both these solutions were
added dropwise and continuously over 15 minutes to a stirred solution
of methyl acrylate (0.039g, 4.580 x 10^-10 moles, 1.1 mole equivalents)
in dichloromethane (0.5 ml) at -60°C, ensuring that at all times
addition of the LTA solution was slightly ahead of that of the N-amino-
quinazolone solution. The mixture was stirred for a further 15 minutes
at -60°C, the solution remaining homogeneous throughout, and then
allowed to warm to room temperature and worked-up in the usual way.
A ^1H n.m.r. spectrum showed the aziridine (155) (mixture of diastereo-
mers) and de-aminated quinazolone (160) to be present in 64% and
24% yields respectively.

(iv) Two further experiments, using the N-aminoquinazolone (132) (which
was added as the solid), 6 mole equivalents of TFA and equal volumes
of dichloromethane [3 ml/100 mg of (132)] at -60°C were found to yield
(by ^1H n.m.r.) 72% and 74% of the aziridine (155) when 3 and 1.1 mole
equivalents respectively of methyl acrylate were used as a nitrone
trap. The respective yields of the de-aminated quinazolone (160) were
<5% and 26% (by ^1H n.m.r.).

Preparation of Methyl 1-phthalimidoaziridine-2-carboxylate (164)

This was prepared^55 from N-aminophthalimide (50) and methyl acrylate
in 50% yield.
Ring-opening of the Aziridine (164) with TFA

The aziridine (164) (0.05g, 2.02 × 10⁻²⁵ moles) was dissolved in deuterochloroform (~0.3 ml) in an n.m.r. tube and TFA (0.078g, 6.850 × 10⁻²⁵ moles) was added at room temperature. An n.m.r. spectrum was then recorded immediately and only ring-opened material was found to be present. Washing of the deuterochloroform solution with sodium bicarbonate solution, drying with magnesium sulphate and solvent removal by rotary evaporation under reduced pressure, gave the ring-opened material as a colourless oil in quantitative yield. Inspection of the n.m.r. spectrum of the crude ring-opened product revealed the presence of only one regioisomer (165);

δ_H (d₆ DMSO, 300 MHz): 7.98-7.60 (m, 4 × ArH), 6.32 (d, J3.6Hz, NH), 4.64 (dd, J11.4 and 5.1Hz, CF₃COCHH), 4.57 (dd, J11.4 and 5.1Hz, CO₂Me), 4.28 (d dd, J5.1, 5.1 and 3.6Hz, CH₂CO₂Me), 3.73 (s, CO₂Me).

Preparation of 2-Nitropropene

This was prepared¹⁶ by the dehydration of 2-nitropropan-1-ol¹⁵ with phthalic anhydride. The product was distilled, b.p. 53°C/75 mmHg (lit.¹⁶ 56-57°C/86 mmHg), and isolated in 70% yield.
Oxidation of 3-Amino-2-(1,2,2-trimethylpropyl)quinazolin-4(3H)-one (132) in the Presence of 2-Nitropropene

This oxidation was carried out at room temperature both in the absence of TFA (procedure D) and in the presence of TFA (procedure E).

The general oxidation procedure (E) was followed using the N-aminoquinazolone (132) (0.154g, 6.286 x 10^-4 moles), LTA (0.306g, 6.915 x 10^-4 moles), 2-nitropropene (0.219g, 2.514 x 10^-3 moles) and TFA (0.244g, 2.137 x 10^-3 moles) in dry dichloromethane (1.5 ml). Chromatography of the crude oxidation product over silica, with ethyl acetate-light petroleum (1:2) as eluant, gave the major diastereoisomer of 1-(3,4-dihydro-2-(1,2,2-trimethylpropyl)-4-oxoquinazolin-3-yl)-2-methyl-2-nitroaziridine (173) (Rf = 0.55) as an unstable† pale yellow oil (0.091g, 44%);

υ max (film): 2960 (m), 1675 (s), 1595 (s), 1555 (s), 1470 (m), 1365 (m), 1335 (m), 1225 (m), 775 (m) cm⁻¹;

δ H (CDCl₃, 300 MHz) (major diastereoisomer): 8.15 (dd, J8.0 and 1.1Hz, ArH₃), 7.74 (ddd, J8.2, 6.9 and 1.1Hz, ArH₇), 7.66 (ddd, J8.2, 1.4 and 0.6Hz, ArH₈), 7.44 (ddd, J8.0, 6.9 and 1.4Hz, ArH₆), 4.00 (d, J3.5Hz, aziridine ring proton cis to het.), 3.84 (d, J3.5Hz, aziridine ring proton trans to het.), 3.13 (q, J7.0Hz, CHMe(Buᵗ)), 1.84 (s, aziridine ring Me trans to het.), 1.38 (d, J7.0Hz, CHMe(Buᵗ)), 0.96 (s, Buᵗ).

† Due to decomposition, no molecular ion peak was observed in the high resolution mass spectrum.
In this major diastereoisomer only one invertoomer (assumed to be NO₂ syn to het.) is evident in the n.m.r. spectrum at room temperature. The ratio of major : minor diastereoisomers from the crude reaction product was 6.9 : 1 (±0.2).

An identical oxidation carried out in the absence of TFA (procedure D), gave a 1 : 3.4 (±0.4) ratio of the respective diastereoisomers. The major diastereoisomer in this experiment (corresponding to the minor diastereoisomer in the oxidation in the presence of TFA above) has chemical shifts at δH (CDCl₃, 300 MHz):

<table>
<thead>
<tr>
<th>Major Invertoomer</th>
<th>Minor Invertoomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>(NO₂ and het. syn)</td>
<td>(NO₂ and het. anti)</td>
</tr>
<tr>
<td>8.23-7.40 (m, ArH₅, -H₆, -H₇, -H₈)</td>
<td></td>
</tr>
<tr>
<td>4.45 (brs, aziridine ring proton cis to het.)</td>
<td>4.25 (brs, aziridine ring proton cis to het.)</td>
</tr>
<tr>
<td>3.53 (brs, aziridine ring proton trans to het.)</td>
<td></td>
</tr>
<tr>
<td>3.33 (q, J6.9Hz, CHMe(Buᵗ))</td>
<td>2.95 (brs, CHMe(Buᵗ))</td>
</tr>
<tr>
<td>2.18 (s, aziridine ring Me trans to het.)</td>
<td>2.03 (s, aziridine ring Me cis to het.)</td>
</tr>
<tr>
<td>1.33 (d, J6.9Hz, CHMe(Buᵗ))</td>
<td></td>
</tr>
<tr>
<td>1.04 (s, Buᵗ)</td>
<td></td>
</tr>
</tbody>
</table>
EXPERIMENTAL
CHAPTER 6
Oxidation of 3-Amino-2-(1,2,2-trimethylpropyl)quinazolin-4(3H)-one (132) in the Presence of Styrene at Room Temperature

The general procedure (D) [see p.174] was followed using N-aminquinazolone (132) (0.100g, $4.082 \times 10^{-4}$ moles), LTA (0.199g, $4.490 \times 10^{-4}$ moles) and styrene (0.425g, $4.082 \times 10^{-3}$ moles) in dry dichloromethane (1 ml). Chromatography of the crude oxidation product [which comprised a 1.77 : 1 ($\pm 0.09$) ratio of diastereoisomers of aziridine (166)] over activated basic alumina, with ethyl acetate-light petroleum (1:5) as eluant, gave the minor diastereoisomer of 1-(3,4-dihydro-2-(1,2,2-trimethylpropyl)-4-oxoquinazolin-3-yl)-2-phenylaziridine (166) ($R_f = 0.70$) as colourless crystals (0.025g, 18%), m.p. 113-116°C (from ethanol) (Found: C, 76.09; H, 7.21; N, 12.05. C$_{22}$H$_{25}$N$_3$O requires C, 76.05; H, 7.25; N, 12.09%);

$\nu_{\text{max}}$ (Nujol): 1670(s), 1580(s), 1560(s), 1280(m), 1220(m), 1190(m), 930(m), 780(s), 745(m), 700(m) cm$^{-1}$;

$\delta$$_H$ (CDCl$_3$, 300 MHz) (minor diastereoisomer): 8.25-7.20 (m, 9 × ArH), 3.86 (dd, J7.9 and 5.7Hz, aziridine ring proton gem. to Ph and cis to het.), 3.63 (q, J7.0Hz, CHMe(Bu$^t$)), 2.88 (dd, J7.9 and 1.6Hz, gem. aziridine ring proton cis to het.), 2.83 (dd, J5.7 and 1.6Hz, gem. aziridine ring proton trans to het.), 1.39 (d, J7.0Hz, CHMe(Bu$^t$)), 1.00 (s, Bu$^t$).

In this minor diastereoisomer only a single inver'tomer (Ph and het. anti) is evident in the n.m.r. spectrum at room temperature;

-202-
Further elution with ethyl acetate-light petroleum (1:5) gave the major diastereoisomer of aziridine (166) ($R_f = 0.59$) as a colourless oil (0.028g, 20%);

$\delta_H$ (CDCl$_3$, 300 MHz) (major diastereoisomer): 8.22 (d, J7.7Hz, ArH$_5$), 7.67 (ddd, J8.2, 6.8 and 1.4Hz, ArH$_7$), 7.63 (m, ArH$_8$), 7.45-7.30 (m, ArH$_6$ and 5 x PhH), 3.37 (q, J7.0Hz, CHMeO$_2^-$), 3.24 (dd, J7.9 and 5.5Hz, aziridine ring proton gem. to Ph and cis to het.), 3.15 (dd, J7.9 and 2.9Hz, gem. aziridine ring proton cis to het.), 3.07 (dd, J5.5 and 2.9Hz, gem. aziridine ring proton trans to het.), 1.29 (d, J7.0Hz, CHMeO$_2^-$), 0.80 (s, Bu$^t$).

In this major diastereoisomer only a single inveromer (Ph and het. anti) is evident in the n.m.r. spectrum at room temperature.

Oxidation of 3-Amino-2-(1,2,2-trimethylpropyl)-7-nitroquinazolin-4(3H)-one (137) in the Presence of Styrene at Room Temperature

The general oxidation procedure (D) was followed using the N-aminoquinazolone (137) (0.084g, $2.897 \times 10^{-4}$ moles), LTA (0.135g, $3.042 \times 10^{-4}$ moles) and styrene (0.302g, $2.897 \times 10^{-3}$ moles) in dry dichloromethane (1 ml). Chromatography of the crude oxidation product [which comprised a 1.78 : 1 ($\pm 0.04$) ratio of diastereoisomers of aziridine (167)] over activated basic alumina, with ethyl acetate-light petroleum (1:5) as eluant, gave the minor diastereoisomer of aziridine (167) ($R_f = 0.67$) as
pale yellow crystals (0.023g, 20%);

δ<sub>H</sub> (CDCl<sub>3</sub>, 300 MHz) (minor diastereoisomer): 8.49 (dd, J2.2 and 0.5Hz, ArH<sub>4</sub>), 8.34 (dd, J8.8 and 0.5Hz, ArH<sub>5</sub>), 8.16 (dd, J8.8 and 2.2Hz, ArH<sub>6</sub>), 7.50-7.32 (m, 5×PhH), 3.86 (dd, J7.6 and 6.1Hz, aziridine ring proton <i>gem</i>. to Ph and <i>cis</i> to het.), 3.64 (q, J7.0Hz, CHMe(Bu<sup>t</sup>)), 2.93-2.87 (m, 2×<i>gem.</i> aziridine ring protons <i>cis</i> and <i>trans</i> to het.), 1.40 (d, J7.0Hz, CHMe(Bu<sup>t</sup>)), 1.01 (s, Bu<sup>t</sup>).

In this minor diastereoisomer only a single inverctor (Ph and het. <i>anti</i>) is evident in the n.m.r. spectrum at room temperature.

Further elution with ethyl acetate-light petroleum (1:5) gave the major diastereoisomer of 1-(3,4-dihydro-2-(1,2,2-trimethylpropyl)-4-oxo-7-nitroquinazolin-3-yl)-2-phenylaziridine (167) (R<sub>f</sub> = 0.54) as pale yellow crystals (0.034g, 30%), m.p. 151-153°C (from ethanol) (Found: C, 67.32; H, 6.27; N, 14.28. C<sub>22</sub>H<sub>24</sub>N<sub>4</sub>O<sub>3</sub> requires C, 67.33; H, 6.16; N, 14.28%);

ν<sub>max</sub> (Nujol): 1675 (s), 1585 (s), 1520 (s), 1345 (s), 1285 (m), 1215 (m), 910 (m), 825 (m), 740 (s), 700 (s) cm<sup>-1</sup>;

δ<sub>H</sub> (CDCl<sub>3</sub>, 300 MHz) (major diastereoisomer): 8.49 (dd, J2.2 and 0.5Hz, ArH<sub>4</sub>), 8.37 (dd, J8.8 and 0.5Hz, ArH<sub>5</sub>), 8.17 (dd, J8.8 and 2.2Hz, ArH<sub>6</sub>), 7.47-7.32 (m, 5×PhH), 3.40 (q, J7.0Hz, CHMe(Bu<sup>t</sup>)), 3.29 (dd, J7.9 and 5.7Hz, aziridine ring proton <i>gem</i>. to Ph and <i>cis</i> to het.), 3.16 (dd, J7.9 and 3.2Hz, <i>gem</i>. aziridine ring proton <i>cis</i> to het.), 3.12 (dd, J5.7 and 3.2Hz, <i>gem</i>. aziridine ring proton <i>trans</i> to het.), 1.30 (d, J7.0Hz, CHMe(Bu<sup>t</sup>)), 0.81 (s, Bu<sup>t</sup>).

In this major diastereoisomer only a single inverctor (Ph and het. <i>anti</i>) is evident in the n.m.r. spectrum at room temperature;

M/Z (%): 392(M<sup>+</sup>, 11), 336 (12), 301 (100), 245 (38), 219 (51), 172 (13), 118 (45), 117 (39), 91 (41).
Oxidation of 3-Amino-2-(1,2,2-trimethylpropyl)quinazolin-4(3H)-one (132) in the Presence of cis-β-Methylstyrene at Room Temperature

The general oxidation procedure (D) was followed using the N-aminoquinazolone (132) (0.200 g, 8.163 × 10⁻⁴ moles), LTA (0.376 g, 8.490 × 10⁻⁴ moles) and cis-β-methylstyrene (0.193 g, 1.633 × 10⁻³ moles) in dry dichloromethane (2 ml). Chromatography of the crude oxidation product [which comprised a 1.65:1 (±0.03) ratio of diastereoisomers of aziridine (171)] over activated basic alumina, with ethyl acetate-light petroleum (1:7) as eluant, gave the 1-(3,4-dihydro-2-(1,2,2-trimethylpropyl)-4-oxoquinazolin-3-yl)-cis-2-methyl-3-phenylaziridine (171) (R_f = 0.40) as a colourless oil (0.103 g, 35%) and as a mixture of diastereoisomers;

ν_max (film): 2940 (s), 1660 (s), 1570 (s), 1455 (m), 1350 (m), 1200 (m), 760 (m), 690 (m) cm⁻¹;

δ_H (CDCl₃, 400 MHz) (major diastereoisomer): 8.28-7.17 (m, 9 × ArH), 3.42 (d, J 8.2 Hz, aziridine ring proton gem to Ph and cis to het.), 3.35 (q, J 7.0 Hz, CHMe(Bu⁺)), 3.10 (dq, J 8.2 and 6.0 Hz, aziridine ring proton gem to Me and cis to het.), 1.41 (d, J 6.0 Hz, aziridine ring Me), 1.37 (d, J 7.0 Hz, CHMe(Bu⁺)), 1.04 (s, Bu⁺);

δ_H (CDCl₃, 400 MHz) (minor diastereoisomer): 8.28-7.17 (m, 9 × ArH), 3.79 (d, J 8.2 Hz, aziridine ring proton gem to Ph and cis to het.), 3.48 (q, J 7.0 Hz, CHMe(Bu⁺)), 2.87 (dq, J 8.2 and 5.9 Hz, aziridine ring proton
gem. to Me and cis to het.), 1.29 (d, J5.9Hz, aziridine ring Me), 1.18 (d, J7.0Hz, CHMe(Bu^)), 1.00 (s, Bu^).

In both diastereoisomers only a single inveromer (aziridine ring Me and Ph both anti to het.) is evident in the n.m.r. spectrum at room temperature.

**Oxidation of 3-Amino-2-(1,2,2-trimethylpropyl)quinazolin-4(3H)-one (132) in the Presence of trans-β-Methylstylene at Room Temperature**

![Chemical Structure](image)

The general oxidation procedure (D) was followed using the N-amino-quinazolone (132) (0.200g, 8.163 x 10^-4 moles), LTA (0.376g, 8.490 x 10^-4 moles) and trans-β-methylstylene (0.193g, 1.633 x 10^-3 moles) in dry dichloromethane (2 ml). Chromatography of the crude oxidation product [which comprised a 1.7 : 1 ratio of diastereoisomers of aziridine (172)] over activated basic alumina, with ethyl acetate-light petroleum (1:6) as eluant, gave the minor diastereoisomer of 1-(3,4-dihydro-2-(1,2,2-trimethylpropyl)-4-oxoquinazolin-3-yl)-trans-2-methyl-3-phenyl-aziridine (172) (Rf = 0.47) as a colourless oil (0.070g, 24%) (Found: M/Z 361.2153. C_{23}H_{27}N_{3}O requires M, 361.2154); ν\text{max} (film): 2970 (s), 1675 (s), 1585 (s), 1470 (s), 1375 (m), 1275 (m), 1220 (m), 1100 (m), 775 (s), 695 (s) cm\(^{-1}\); δ\text{H} (CDCl\(_3\), 300 MHz) (minor diastereoisomer):
<table>
<thead>
<tr>
<th>Major Invertomer</th>
<th>Minor Invertomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>(aziridine ring Me syn to het.)</td>
<td>(aziridine ring Me anti to het.)</td>
</tr>
<tr>
<td>8.35-6.80 (m, 9 × ArH)</td>
<td></td>
</tr>
<tr>
<td>3.89 (d, J6.0Hz, aziridine ring proton gem. to Ph and cis to het.)</td>
<td>3.55 (q, J7.0Hz, CHMe(Bu^))</td>
</tr>
<tr>
<td>3.10 (q, J7.0Hz, CHMe(Bu^))</td>
<td>3.53 (dq, J6.0 and 5.0Hz, aziridine ring proton gem. to Me and cis to het.)</td>
</tr>
<tr>
<td>2.87 (dq, J6.0 and 6.0Hz, aziridine ring proton gem. to Me and trans to het.)</td>
<td>3.47 (d, J6.0Hz, aziridine ring proton gem. to Ph and trans to het.)</td>
</tr>
<tr>
<td>1.48 (d, J7.0Hz, CHMe(Bu^))</td>
<td>1.44 (d, J5.0Hz, aziridine ring Me trans to het.)</td>
</tr>
<tr>
<td>1.28 (d, J6.0Hz, aziridine ring Me cis to het.)</td>
<td></td>
</tr>
<tr>
<td>1.02 and 0.89 (2 × s, 2 × Bu^)</td>
<td>0.35 (d, J7.0Hz, CHMe(Bu^))</td>
</tr>
</tbody>
</table>

The ratio of major : minor invertomers in the minor diastereoisomer was 1.6 : 1.

**Oxidation of 3-Amino-2-(1,2,2-trimethylpropyl)quinazolin-4(3H)-one (132) in the Presence of trans-But-2-ene**
This oxidation was carried out at 0°C both in the absence of TFA (procedure D) and in the presence of TFA (procedure E).

The general oxidation procedure (E) was followed at 0°C using N-aminooquinazolone (132) (0.102g, 4.163 × 10^{-4} moles), LTA (0.203g, 4.579 × 10^{-4} moles), trans-but-2-ene (0.117g, 2.082 × 10^{-3} moles) and TFA (0.161g, 1.415 × 10^{-3} moles) in dry dichloromethane (1 ml) at 0°C. Chromatography of the crude oxidation product [which comprised a 3.9:1 (±0.1) ratio of diastereoisomers of the aziridine (170)] over silica, with ethyl acetate-light petroleum (1:3) as eluant, gave the major diastereoisomer of 1-(3,4-dihydro-2-(1,2,2-trimethylpropyl)-4-oxoquinazolin-3-yl)-trans-2,3-dimethylaziridine (170) (R_f = 0.56) as colourless crystals (0.056g, 45%), m.p. 128-130°C (from ethanol) (Found: C, 72.14; H, 8.42; N, 13.95. C_{18}H_{25}N_{3}O requires C, 72.21; H, 8.42; N, 14.04%); \( \nu_\text{max} (\text{Nujol}) \): 1680(s), 1590(s), 1520(s), 1280(w), 1215(m), 1140(w), 1045(w), 1035(w), 775(m) cm^{-1};
\( \delta_\text{H} (\text{CDCl}_3, 300 \text{ MHz}) \) (major diastereoisomer): 8.18 (ddd, J8.0, 1.5 and 0.6Hz, ArH_5), 7.72 (ddd, J8.2, 6.6 and 1.5Hz, ArH_7), 7.65 (ddd, J8.2, 1.5 and 0.6Hz, ArH_8), 7.46 (ddd, J8.0, 6.6 and 1.5Hz, ArH_6), 3.46 (q, J6.9Hz, CHMe(Bu^t)), 2.73 (dq, J5.7 and 5.0Hz, aziridine ring proton cis to het.), 2.49 (dq, J5.7 and 5.0Hz, aziridine ring proton trans to het.), 1.54 (d, J5.7Hz, aziridine Me trans to het.), 1.45 (d, J6.9Hz, CHMe(Bu^t)), 1.11 (d, J5.7Hz, aziridine Me cis to het.), 0.96 (s, Bu^t);
\( M/\text{Z} (%) \): 299(M^+, 25), 284(16), 243(73), 229(15), 228(45), 174(30), 159(59), 131(33), 117(42), 70(100).

An identical oxidation carried out in the absence of TFA (procedure D) gave a 1:1.22 (±0.08) ratio of the respective diastereoisomers. The major diastereoisomer produced in this experiment [which corresponds to the minor diastereoisomer in the oxidation in the presence of TFA]
above \( \delta_H(\text{CDCl}_3, 300 \text{ MHz}) \): 8.26-7.35 (m, ArH\(_5\), -H\(_6\), -H\(_7\), -H\(_8\)),
3.23 (q, J7.0Hz, CHMe(Bu\(^t\))), 2.73 (dq, J5.7 and 5.0Hz, aziridine ring proton \textit{cis} to het.), 2.49 (dq, J5.7 and 5.0Hz, aziridine ring proton \textit{trans} to het.), 1.53 (d, J5.7Hz, aziridine ring Me \textit{trans} to het.),
1.40 (d, J7.0Hz, CHMe(Bu\(^t\))), 1.17 (d, J5.7Hz, aziridine ring Me \textit{cis} to het.), 1.04 (s, Bu\(^t\)).
APPENDICES
Synthesis of the title N-aminoquinazolone (137) was attempted in an effort to determine whether the N-nitrene (138) was adding to the lactone (65) and styrene exclusively via the T.S.G.'s shown in (139) and (168) or whether there was competitive addition via a secondary interaction at C-2 and C-4.

It was conceivable that if addition was taking place via the latter, then a 7-nitro group could have a differential effect on the size of the two secondary interactions which would be involved.

In the event, oxidation of the 7-nitroaminoquinazolone (137) and trapping the resulting N-nitrene with both α-methylene-γ-butyrolactone (65) and styrene, was found in each case to give the same ratios of diastereoisomers to those obtained using the N-aminoquinazolone (132).

Synthesis of the 6-nitro-N-aminoquinazolone (174) was also considered worthwhile in an attempt to mimic the effect of TFA. Inspection of Figure 79 shows that whereas a resonance structure can be drawn with a positive charge on C-2, no equivalent resonance structure can be drawn with a positive charge on C-4. A 6-nitro substituent, therefore, might be expected to have a significantly greater effect on the diastereoselectivity than a 7-nitro substituent.
Attempted Synthesis of (174)

The route attempted was via nitration of the methyl N-substituted anthranilate (133) since it was anticipated that methyl anthranilate (175) would not have nitrated predominantly in the 5-position. The former, however, would be expected to nitrate predominantly in the 5-position since the NHCOR group (unlike NH₂) is not completely protonated in acid solution.

In practice, however, on nitration of (133) via the method of Adams et al.³ using fuming nitric acid at 0°C as a nitrating agent, followed by addition to ice-water, the amide was hydrolyzed to the 2,3,3-trimethylbutanoic acid (108) [Figure 80].
[Equation or reaction diagram]

Figure 80
APPENDIX 2

Experimental Evidence for the Mechanism of Formation of the N-Aminoquinazolone (132)

When methyl-N-(2,3,3-trimethylbutanoyl)anthranilate (133) was heated with excess hydrazine hydrate (ethanol as solvent) at ~140-150°C overnight in a sealed tube, the N-aminoquinazolone (132) was obtained in good yield (74%) [Figure 81].

\[ \text{Figure 81} \]

A repeat of this experiment at a lower temperature (119°C) allowed the isolation of a substantial amount (55%) of an intermediate which was shown to have the structure (134). The isolation of this intermediate hydrazide (134) is consistent with nucleophilic attack of the hydrazine taking place initially on the carbonyl of the ester moiety.

Heating the hydrazide (134) on its own, with ethanol as solvent, in a sealed tube at 140-150°C overnight completed the cyclisation producing the N-aminoquinazolone (132) in good yield.
APPENDIX 3

Calculation of Conformational Barriers in ~ Equally and Non-Equally Populated Equilibria [see Chapter 2]

Barriers for ~ equally populated equilibria were estimated using equation (a):\textsuperscript{134}

\[
\Delta G^\ddagger = 19.12 \times T_c (10.32 + \log_{10} \frac{T_c}{K_c}) \quad \text{.... (a)}
\]

The coalescence temperature (in Kelvin).

\[
\left( K_c = \frac{\pi \Delta \nu}{\sqrt{2}} \right)
\]

where: \( \Delta G^\ddagger \) = barrier to inversion or rotation (in J mol\(^{-1}\))

\( T_c \) = coalescence temperature (in Kelvin)

\( K_c \) = rate of nitrogen inversion or rotation at \( T_c \)

\( \Delta \nu \) = frequency separation of coalescing signals (in Hz, measured at a temperature lower than \( T_c \)).

Barriers for non-equally populated equilibria were estimated using equation (b):\textsuperscript{80}

\[
A \xrightarrow{\text{(minor)}} B \quad \xrightarrow{\text{K_A}} \quad \xrightarrow{\text{K_B}} \quad \text{(major)}
\]

\[
\Delta G^\ddagger = 19.12 \times T_c (10.32 + \log_{10} \frac{T_c}{2 \times K_A \text{ or } K_B}) \quad \text{.... (b)}
\]

where: \( K_A = 2 \times K_c \times \rho_B \) (i.e. rate constant for A \( \rightarrow \) B)

\( K_B = 2 \times K_c \times \rho_A \) (i.e. rate constant for B \( \rightarrow \) A)

\( \rho_B \) and \( \rho_A \) represent the fractional populations of the two sites.

Substitution of the data given in Table 13 into the relevant equation [(a) or (b)] will give an estimate of the conformational barrier.
TABLE 13
Data Used for Calculation of the Conformational Barriers in Aziridine (120) and One Diastereoisomer of Aziridines (140a), (152) and (113)

<table>
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<tr>
<th>Aziridine</th>
<th>N.M.R. Solvent</th>
<th>Tc/K</th>
<th>Δν/Hz</th>
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<th>Conformer Ratio/Room Temp.</th>
<th>Ke</th>
<th>KA</th>
<th>KB</th>
<th>ρA</th>
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<th>ΔG°(kcal mol⁻¹)</th>
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<td>293</td>
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<td>1 : 1</td>
<td>166.74</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>59.2₉</td>
<td>14.2₉</td>
</tr>
<tr>
<td>(152)</td>
<td>d₃ pyridine</td>
<td>388</td>
<td>6.00</td>
<td>Bu⁺</td>
<td>1.3 : 1</td>
<td>13.34</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>87.4₉</td>
<td>20.9₉</td>
</tr>
<tr>
<td>(113)</td>
<td>1,2-dichlorobenzene</td>
<td>348</td>
<td>37.93</td>
<td>Bu²</td>
<td>2.9 : 1</td>
<td>84.29</td>
<td>124.75</td>
<td>43.83</td>
<td>0.26</td>
<td>0.74</td>
<td>74.7₉ (±3.0)</td>
<td>17.9₉ (±0.8)</td>
</tr>
<tr>
<td>(120)</td>
<td>1,2-dichlorobenzene</td>
<td>&gt;423 ⁶</td>
<td>100.00</td>
<td>Aziridine ring H cis to het.</td>
<td>12 : 1</td>
<td>222.21</td>
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<td>0.08</td>
<td>0.92</td>
<td>&gt;92.2₉</td>
<td>&gt;22.0₉</td>
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₉ barrier to N⁻N bond rotation;
₉ barrier to N⁻inversion;
⁶ temperature at which the aziridine ring protons in the 2 diastereomers start to broaden.
APPENDIX 4

X-Ray Crystal Structure Data

(i) Aziridine (117):

Fractional Atomic Co-ordinates

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-217-
Aziridine (140a):

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Current research in these laboratories\textsuperscript{135} has revealed that the N-acetoxyaminoquinazolone (178), obtained from the low temperature oxidation of the N-aminoquinazolone (177) with LTA, is apparently playing the rôle previously assigned to the N-nitrene in the aziridination of alkenes.

\[
\begin{align*}
\text{NH}_2 & \quad \text{NHOCOCH}_3 \\
(177) & \quad (178)
\end{align*}
\]

It is conceivable, therefore, that the intermediate involved in the asymmetric aziridination reactions contained in this thesis may not be an N-nitrene.
REFERENCES


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29. R. S. Atkinson in ref. 28, p.247 et seq.


130. K. L. Woodthorpe, unpublished work, Leicester University.


135. R. S. Atkinson and B. J. Kelly, work to be published, Leicester University.
PUBLICATIONS
Chiral Aziridination of Alkenes

Robert S. Atkinson,* John Fawcett, David R. Russell, and Gary Tughan
Department of Chemistry, Leicester University, Leicester LEI 7RH, U.K.

Oxidation of the 2-substituted N-aminobenzimidazole (5) in the presence of prochiral alkenes gives aziridines stereoselectively: addition, to \(\gamma,\gamma\)′-dimethyl-\(\alpha\)-methylenebutyrolactone is stereospecific and the relative configuration of the two chiral centres in the product has been confirmed by a single crystal X-ray diffraction study and is in agreement with a transition state geometry resembling (11).

Reprinted from the Journal of The Chemical Society
Chemical Communications 1986
Chiral Aziridination of Alkenes

Robert S. Atkinson, John Fawcett, David R. Russell, and Gary Tughan
Department of Chemistry, Leicester University, Leicester LE1 7RH, U.K.

Oxidation of the 2-substituted N-aminobenzimidazole (5) in the presence of prochiral alkenes gives aziridines stereoselectively: addition, to y,y-dimethyl-α-methylenebutyrolactone is stereospecific and the relative configuration of the two chiral centres in the product has been confirmed by a single crystal X-ray diffraction study and is in agreement with a transition state geometry resembling (11).

Epoxidation of alkenes followed by regio- and stereo-specific ring-opening of the epoxides is an invaluable routine in synthesis. The recent finding of Sharpless et al.1 that epoxides can be obtained in high enantiomeric excess by epoxidation of prochiral allylic alcohols has broadened the scope of this routine to include synthesis of chiral products. By contrast, aziridination is still an unfamiliar term in the organic chemist's vocabulary in spite of the fact that, like epoxides, aziridines can easily be ring-opened in a controlled way.2 Although some nitrenes R-N: add to alkenes directly,3 the reactions are blighted by low yields and/or lack of stereospecificity, particularly at low concentrations of alkenes, and do not enjoy widespread use in synthesis of aziridines and their transformation products.

There is, however, a family of N-aminoheterocyclic compounds (1) whose oxidation generates the corresponding N-nitrenes (2) which are trapped by alkenes to give aziridines (3), often in good yields.4 The singlet ground states of these nitrenes mean that their additions to alkenes are stereospecific and, unlike most other nitrenes which can be trapped intermolecularly, there is no competition from insertion of (2) into C-H bonds.5 A further advantage in the use of (2) is their ambiphilic character: they react to give good yields of aziridines with e.g. styrene or methyl acrylate.6

To make use of aziridines (3) produced as in equation (1) would, in general, require that the heterocyclic ring be jettisoned by cleavage of the N-N bond7 either in the aziridines (3) or, more expediently, in their ring-opened products.8

In this communication we show that the heterocycle in (1) can serve as more than just an appendage on the nitrene and can in practice be used to bring about efficient induction of chirality in aziridination of prochiral alkenes.9

N-Aminobenzimidazole is one member of the family (1) referred to above. Attempts to prepare benzimidazole (4) by the Phillips method10 for construction of this ring system were...
unsuccesful but (4) was obtained and aminated to (5) by the procedure outlined in Scheme 1.

Oxidation of N-aminobenzimidazole (5) with lead tetraacetate (LTA) in dichloromethane in the presence of methyl acrylate gave a 2.1:1 ratio of stereoisomers (6) (71%). However, a similar oxidation of (5) with phenyl iodosodiacetate in the presence of α-methylene-γ-butyrolactone (7) at room temperature gave a 5.3:1 ratio of stereoisomers (8) (from the 300 MHz spectrum of the crude product) from which the major product, m.p. 189—191 °C, was isolated (50%) by crystallisation. An identical ratio of stereoisomers of (8) was produced when LTA was substituted for phenyl iodosodiacetate suggesting that the free nitrene was involved in both cases.

Introduction of a gem-dimethyl group into the butyrolactone as in (9) and reaction of 2 mol equiv. of the latter with the N-nitrene derived from (5) results in formation of (10) (69% isolated) as a single stereoisomer: the other stereoisomer was not evident in the n.m.r. spectrum of the crude product.

Our rationale for the chiral induction in formation of these aziridines uses the 'syn-selectivity' which is also a feature of these N-nitrene additions to alkenes. Attack of the N-nitrene derived from (5) with butyrolactone (9) is believed to occur via a transition state geometry as shown in (11) in which the benzimidazole and butyrolactone are contained in parallel planes, the N-N(nitrene) bond is orthogonal to the plane containing the alkene π-electrons, and there is an attractive secondary interaction between the C=O of the butyrolactone and the 2-position of the heterocycle.

The configuration of the newly-created chiral centre in (10) was established by X-ray crystallography (Figure 1) and is in agreement with that predicted from the transition state model (11). Although both invertomers at the aziridine nitrogen of

Crystal data for (10): C₉H₈N₂O₂, M = 341.40, monoclinic space group P2₁/a, a = 14.367(13), b = 18.574(16), c = 7.327(30) Å, β = 96.71(10), U = 1941.9 Å³, Z = 4, D, = 1.17 g cm⁻³, µ(Mo-Kα) = 0.7107 Å, D, = 0.43 cm⁻¹. The crystals were colourless prisms. The intensities of 1488 unique reflections (2θ < 50°, ±h, ±k, ±l) were measured on a Stoe STADI-2 Weissenberg diffractometer using an o-scan technique. The data were corrected for Lorentz and polarisation effects, to yield 618 reflections with I > 3σ(I). The structure was solved using the TREOR direct methods option of SHELXS 84 (G. M. Sheldrick, SHELXS 84, personal communication). All subsequent calculations were carried out using the computer program SHELX (G. M. Sheldrick, SHELXS 76, Program for Crystal Structure determination. University of Cambridge, 1976). The hydrogen atom of positional interest (H15) was located and refined as a normal atom, all other hydrogen atoms were included in calculated positions for structure factor calculations. Final cycles employed a weighting parameter g(0.00336) [w = (1/σ²(F) + g(F)²)²] and gave the final residual indices R = Σ(|Fo| - |Fc|)/Σ|Fo| = 0.098 and R indexes [Σ(|Fo| - |Fc|)²/Σ|Fo|²]¹/² = 0.0944. The final difference Fourier map was featureless, and an analysis of the weighting scheme over |Fo| and σ(Fo) was satisfactory. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors. Issue No. 1, 1986.

Figure 1. Molecular structure of (10).
(10) [and (8)] are present in solution (from n.m.r. spectroscopy) only the more abundant invertomer, which is apparently configurationally stable at nitrogen in the crystalline form, was present in the crystal used in the X-ray study. We suspect that the improved stereoselectivity in formation of aziridines (8) and (10) by comparison with (6) may be the consequence of the preference of methyl acrylate for the conformation shown [(5) \( \rightarrow \) (6)].

The stereoselectivity of reaction of the nitrene derived from (5) with styrene and (E)-butene was also encouraging: a 5:1 ratio of stereoisomers was obtained in both cases. The major stereoisomer from addition to styrene was separated by crystallisation, m.p. 152—154 °C (61%), and that from addition to (E)-butene by chromatography (oil) (60%).

If (5) can be prepared as a single enantiomer then synthesis of chiral aziridines and their ring-opened products is in prospect.

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4 R. S. Atkinson in ref. 3b pp. 258—291.


9 Earlier attempts to accomplish this (R. S. Atkinson, J. R. Malpass, and K. L. Woodthorpe) are given in the thesis of K. L. Woodthorpe, Leicester University, 1983.


Chiral Aziridination of Alkenes: Oxidation of 3-Amino-2-(1,2,2-trimethyl)propylquinazolin-4(3H)-one in the Presence of Alkenes

Robert S. Atkinson and Gary Tughan
Department of Chemistry, Leicester University, Leicester LE1 7RH, U.K.

Oxidation of the title N-aminoquinazolone (2) in dichloromethane in the presence of α-methylene-γ-butyrolactone gave a 1:1:3 ratio of stereoisomers (3): if the oxidation is carried out in the presence of a small quantity of trifluoroacetic acid (TFA), only one of these stereoisomers is produced in 72% yield.

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In the previous communication, the N-nitrene derived by oxidation of the N-aminobenzimidazole (1) was shown to add to prochiral alkenes [styrene, (E)-butene, and α-methylene-γ-butyrolactones] with high stereoselectivity. We have also examined the corresponding selectivity of the N-nitrene derived from oxidation of the N-aminoquinazolone (2). An advantage in using (2) over (1) was the availability of the former in quantity by the usual route from 2′-butyl-2-methylacetic acid.2

Oxidation of (2) with lead tetra-acetate (LTA) in dichloromethane in the presence of α-methylene-γ-butyrolactone (2 mol equiv.) gave a 1:1:3 ratio of stereoisomers of (3) (65%), a selectivity which compares unfavourably with the 5:3:1 ratio obtained in the analogous reaction using N-aminobenzimidazole (1) and the same trap. Separation of these two stereoisomers of (3) was accomplished by chromatography (silica) to give one of these stereoisomers (3a) as a crystalline solid. m.p. 174—176 °C and the other as an oil.†

This loss of stereoselectivity in the addition of the N-nitrene derived from (2) can be rationalised by assuming that the reaction proceeds, wholly or in large part, by the transition state geometry represented in (I): only if the transition state geometry as in (II) is obtained would the resulting stereoselectivity be expected to resemble that found from the analogous oxidation of (1). Oxidation of the 7-nitro-substituted N-aminoquinazolone (4) in the presence of α-methylene-γ-butyrolactone gives an identical ratio of stereoisomers of (5) as in the case of (3).

Oxidation of (2) using α-methylene-γ-butyrolactone as the trap but in dichloromethane containing trifluoroacetic acid (TFA) (3.4 mol equiv.) gave only the crystalline stereoisomer (3a) (72%). Thus inclusion of this small amount of acid is sufficient to bring about stereospecificity in addition of the nitrene which can most economically be rationalised by

† The n.m.r. spectra of these aziridines are remarkably different: the crystalline one exists as a single invertoomer whereas the other is an interconverting mixture (~1:1) of invertoomers at room temperature.
assuming a change in transition state geometry from that represented by (I) to (II).†

Although the relative configuration at the two chiral centres in (3a) is as yet unproven, it is reasonable to assume that shown by analogy with the known relative configuration at the corresponding centres in the aziridine obtained from oxidation of (1) in the presence of γ,γ-dimethyl-α-methylene-γ-

butyrolactone.†

The ratio of stereoisomeric aziridines (6) obtained by addition of the nitrene derived from (2) to (E)-butene is also changed from 1.2:1 in dichloromethane to ~1:4 in dichloromethane containing TFA. The major stereoisomer of (6) was isolated from the latter reaction as a crystalline solid, m.p. 128—130 °C (45%) after chromatography over silica.

It appears from these results that some control can be exercised over the site of secondary interaction between the heterocycle and the alkene substituent. Clearly this is of importance for achieving high levels of asymmetric induction in these N-nitrene additions.

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References
Chiral Aziridination of α,β-Unsaturated Esters and Ketones using N-Nitrenes in the Presence of Trifluoroacetic Acid

Robert S. Atkinson* and Gary Tughan
Department of Chemistry, Leicester University, Leicester LE1 7RH, U.K.

Room temperature oxidations of the N-aminoquinazolone (1) in dichloromethane containing trifluoroacetic acid (TFA) in the presence of α,β-unsaturated esters or ketones gave aziridines with modest to high stereoselectivities; the presence of TFA allows these oxidations to be carried out at −60 °C with the expected improvement in selectivity and in the presence of ca. 1 mol. equiv. of alkene.

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Oxidation of the N-aminoquinazolone (1) in the presence of small amounts of trifluoroacetic acid (TFA) was reported to give a mixture of crystalline and oily stereoisomeric aziridines (2) with very little asymmetric induction (ratio crystalline : oily 1:1.3). In the presence of small amounts of trifluoroacetic acid (TFA) (3.4 mol. equiv.), however, the reaction was stereospecific and only the crystalline stereoisomer was formed. This effect of TFA was ascribed to a change in transition state geometry and the presence of 1.1 mol. equiv. of alkene and 10 mol. equiv. of TFA without separation of stereoisomers. * Major stereoisomer crystalline. * Major stereoisomer in TFA oxidation separated by crystallisation but yield is not optimised.

Table 1. Ratios of aziridinie stereoisomers from oxidation of N-aminoquinazolone (1) by LTA in the presence of various α,β-unsaturated esters and ketones (4 mol. equiv.) at room temperature with and without TFA (3.4 mol. equiv.).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkene</th>
<th>Stereoisomer ratio without TFA</th>
<th>Stereoisomer ratio with TFA</th>
<th>Yield/%*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂C-CHCO₂Me</td>
<td>2.4:1</td>
<td>1:8.7</td>
<td>50(77)</td>
</tr>
<tr>
<td>2</td>
<td>H₂C-CHCO₂Me</td>
<td>--</td>
<td>1:23⁠</td>
<td>65(72)</td>
</tr>
<tr>
<td>3</td>
<td>H₂C-CHCO₂Bu⁠</td>
<td>2.1:1</td>
<td>14:1⁠</td>
<td>39(75)⁠</td>
</tr>
<tr>
<td>4</td>
<td>H₂C-(Me)CO₂Me</td>
<td>1.2:1</td>
<td>1:5.2⁠</td>
<td>46(72)⁠</td>
</tr>
<tr>
<td>5</td>
<td>trans-MeCH=CHCO₂Me</td>
<td>--</td>
<td>7:1⁠</td>
<td>58(78)</td>
</tr>
<tr>
<td>6</td>
<td>H₂C-CHC(O)Me</td>
<td>1.25:1</td>
<td>1:6.5</td>
<td>62(78)</td>
</tr>
<tr>
<td>7</td>
<td>trans-(Me)C=CHC(O)Me</td>
<td>1.2:1</td>
<td>8.6:1⁠</td>
<td>52(82)⁠</td>
</tr>
</tbody>
</table>

* Isolated yield of the major stereoisomer in the TFA oxidation after separation by chromatography (*H n.m.r. yield of major stereoisomer in brackets). The major difference in n.m.r. and isolated yields is the result of neglecting mixed fractions in the chromatography. † Oxidation carried out at −60 °C in the presence of 1.1 mol. equiv. of alkene and 10 mol. equiv. of TFA without separation of stereoisomers. ‡ Major stereoisomer crystalline. †† Major stereoisomer in TFA oxidation separated by crystallisation but yield is not optimised.
All compounds are racemic.

(1) from (3) to (4) brought about by protonation at N-1 of the N-aminoquinazolone and hence the derived N-nitrene.

Oxidation of the N-aminoquinazolone (1) in the presence of a number of a,b-unsaturated esters and ketones with lead tetra-acetate (LTA) in the presence of TFA has been found to lead to reasonable yields of aziridines and significant asymmetric induction (Table 1). We find that the use of TFA in these oxidations has two advantages: (i) the reaction can be carried out at -60 °C with the expected improvement in the degree of induction; and (b) the alkene may be employed in approximately equimolar quantities with only small losses in yield. The results in Table 1 (except entry 2) were obtained at room temperature in the presence of 4 mol. equiv. of the alkene. Entry 2 is the reaction at -60 °C using only 1.1 mol. equiv. of methyl acrylate. From a comparison of entries 1 and 2 it is clear that an increase in selectivity occurs at -60 °C with little loss in yield. From a number of experiments carried out using 1.1 mol. equiv. of the alkene, it appears that TFA stabilises the protonated N-1 nitrene against intramolecular decay and also that the N-1 protonated aminooquinazolone (1) is less reactive at its free amino group towards the N-1 protonated nitrene.

Entries 1 and 3 in Table 1 strongly suggest that the derived aziridines from methyl and t-butyl acrylate have the opposite induced configuration at the newly-created chiral centre. This conclusion follows from a comparison of the stereoisomer ratios in the absence and presence of TFA. In the absence of TFA, the transition state in both cases will resemble (3) and low but similar degrees of induction are anticipated which is found to be the case. In the presence of TFA, the predominant stereoisomer resulting from addition to methyl acrylate is the minor one produced in the absence of TFA whereas the reverse is obtained in addition to t-butyl acrylate.

The relative configuration of the two chiral centres in the crystalline stereoisomer of (2) was predicted to be (2b) by analogy with that of the single stereoisomer (5) obtained from oxidation of the corresponding N-aminobenzimidazole (6) in the presence of a-methylene-γ,γ-dimethyl-γ-butyrolactone (in the absence of TFA) whose structure was confirmed by X-ray crystallography. An X-ray crystal structure determination of this stereoisomer, however, shows it to have the structure (2a). We suggest that this unexpected change in the induced configuration at the spiro-centre is evidence for protonation of the N-nitrene at the N-1 position. The transition state for the addition, therefore, must resemble (7) in which methyl and hydrogen have exchanged their site occupancy (by comparison with the corresponding transition state leading to (5)) possibly because of preferential solvation of N-1 on the side of the quinazolone ring opposite to the t-butyl group.

Additions of the N-nitrene derived from (1) to the a,b-unsaturated esters in Table 1 are accommodated by a transition state (8) resembling (7) but with the esters present in their preferred conformations. For a given configuration of (R*), the face of the alkene preferentially attacked will depend on the nature of both R1 and R2 in a predictable way.

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References

† The change in the transition state geometry from (3) to (4) in the presence of TFA could be interpreted as resulting from protonation at the quinazolone carbonyl oxygen but it is difficult to account for the difference in induced configuration in (2a) by comparison with (5) if this were the case.
Conformational Analysis of \( N-[3,4\text{-Dihydro-4-oxoquinazolin-3-yl}]\)aziridines

Robert S. Atkinson*, John Fawcett, David R. Russell, and Gary Tughan

Department of Chemistry, Leicester University, Leicester LE1 7RH, U.K.

The X-ray crystal structure of the aziridine (7a) shows that the preferred orientation around the N–N bond has the lone pairs of electrons on adjacent nitrogens eclipsed; the rotamer equilibria around the N–N bonds in the two stereoisomers (7a) and (7b) suggest that this is also the preferred conformation for these substituted hydrazines in solution.

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The cyclopropylcarbinyl cation is at its most stable in the bisected conformation (1) in which stabilisation of the cation by delocalisation of the cyclopropyl ring bonds is at a maximum.1 Experimental evidence for the preferred conformation of the cyclopropylcarbinyl anion is lacking4 but calculations suggest that there is a slight preference for the perpendicular conformation (2) (sp2-hybridisation of the carbanion assumed).3

Our interest has been in the related problem of the preferred conformation of aziridines of the general formula (3) which are obtained by addition of the heterocyclic N-nitrenes (4) to alkenes.4 Invariably in these aziridines, (3), the nitrogen of the heterocycle is sp2-hybridised. Consideration of (3) as a substituted hydrazine would suggest that the most stable conformation would be the bisected one (5) since it is in this conformation that repulsion between electron pairs is at a minimum. The perpendicular conformation (6), however, is that which would minimise possible unfavourable interactions between the aziridine ring bonds and the sp2-hybridised heterocyclic ring nitrogen lone pair.

In this communication we report that aziridine stereoisomer (7a) shows a preference for the perpendicular arrangement (6) in the crystalline state and present evidence that this is the preferred conformation in solution also.

The spiro-fused aziridines (7a) and (7b) are obtained by oxidation of the corresponding N- aminoquinazolone in the presence of a-methylene-y-butyrolactone.5 An X-ray crystal structure determination of the stereoisomer (7a) is shown in Figure 1 and a view which shows the eclipsing of the lone pairs on adjacent nitrogens is shown in Figure 2, which has the plane of the quinazoline ring horizontal and the N–N bond projecting towards the viewer.†

† Simple cyclopropylcarbinyl carbanions are prone to ring open to the corresponding allylcarbinyl anions, see ref. 2.

‡ Crystal data: C19H21N3O3, M = 339.39, monoclinic, space group P21/n (Alt. P21/c, No. 14), a = 10.503(2), b = 27.399(6), c = 6.401(12) Å, β = 103.9(1)°, U = 1788.33 Å, Z = 4, D = 1.23 g cm−3, λ(Mo-Kα) = 0.7107 Å. The intensities of 3051 reflections with 7 < 2θ < 54 and ±κ, ±ι were measured on a Stoe STADI-2 Weissenberg diffractometer with graphite monochromated Mo-Kα radiation using an ω-scan technique. The data were corrected for Lorentz and polarisation effects to yield 1809 reflections with I > 3σ(I). The structure was solved using the TREF direct methods option of SHELXS 84. All subsequent calculations were carried out using the computer program SHELX.1 All hydrogen atoms were located from a difference Fourier map and the positional and isotropic thermal parameters were refined independently. All other atoms were refined anisotropically. The final cycles of refinement employed a weighting scheme w = 1/[σ(Fo)]^2 + 0.0003(Fo)^2 and gave the final residual indices R = [Σ(|Fo|−|Fp|)]/Σ|Fo| 0.0400 and wR2 = [Σw(|Fo|−|Fp|)^2] / [Σw|Fo|^2] 0.0426. The remaining difference Fourier map was featureless and an analysis of the weighting scheme over |Fo| and sinθ/λ was satisfactory.

Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

The other (oily) stereoisomer (7b) shows an n.m.r. spectrum at 300 MHz and room temperature in which there are broadened signals typical of a system undergoing a conformational change close to the coalescence temperature. At −40 °C, well-resolved spectra of both these conformers were obtained and the ratio of the two was ca. 1:1.

A number of factors suggest that these conformers of (7b) are rotamers around the N–N bond and not invertomers.6 Thus the barrier which separates these two conformations is calculated from data at the coalescence temperature to be ca. 14 kcal mol−1 (1 kcal = 4.142 kJ) which is 7 kcal mol−1 lower than that expected for inversion in aziridines of this type. Neither the bulky substituent at C-2 of the quinazolone nor the spiro-ring fusion to the aziridine ring in (7b) would be expected to bring about a reduction in the inversion barrier in (7b) of this magnitude. Thus the aziridines (8) (one stereoisomer) and (9) have inversion barriers of 21 kcal mol−1 and >21 kcal mol−1, respectively [(9) exists as a 5:1 ratio of invertomers and the symmetry of the phthalimido ring means that no rotamers around the N–N bond will be visible].
The existence of a 1:1 rotamer ratio for (7b) and a single rotamer for (7a) would be difficult to reconcile with bisected conformations, e.g. (10) for these rotamers; the more stable conformation of (3) is, therefore, the perpendicular arrangement both in the crystalline state and also in solution.

The X-ray structure of (11) shows that the preferred conformation around the N-N bond does not have the electron pairs as nicely eclipsed as in (7a) (the angle between the two planes containing these lone pairs is ca. 20° in (11) compared with 1° for (7a)). It appears that there is some rotation away from the eclipsed conformation in (11) to relieve steric interactions between the lactone ring and the chiral substituent at position 2 which would otherwise result.

We thank the S.E.R.C. for support.

References
6 G. M. Sheldrick, SHELXS 84, personal communication.
8 See footnote in ref. 5.

§ The quinazolone C-2 atom is tilted slightly out of the plane of the remainder of this ring presumably to accommodate the methine C-H-aziridine ring proton interaction.

¶ Alkanoylated aminocyclopropanes (having sp²-hybridised N) retrieved from the Cambridge Crystallographic Data Centre show a similar preference for the perpendicular conformation.