THE STEREOCHEMICAL CONSEQUENCES OF N-N CHIRAL AXES

IN 3-ACYLAMINOQUINAZOLINONES

A thesis submitted for the degree of
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TO MUM AND DAD
STATEMENT OF ORIGINALITY

The accompanying thesis submitted for the degree of Doctor of Philosophy entitled "The Stereochemical Consequences of N-N Chiral Axes in 3-Acylaminoquinazoliones" is based on work conducted by the author in the Department of Chemistry at the University of Leicester mainly during the period between October 1992 and August 1995.

All the work recorded in this thesis is original unless otherwise acknowledged in the text or by references.

None of the work has been submitted for another degree in this or any other University.

Signed: .............................................................. Date: ..............................
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It now remains for me to thank my Mum and Dad for everything they have done for me. Their love and support has made this task possible, so I therefore dedicate this thesis to them. I would also like to thank Paul for without his love and support throughout my studies at Leicester it would have been a difficult task and also for proof reading this thesis.
ABBREVIATIONS

Ac - acetyl
approx. - approximately
Ar - aryl
azir. - aziridine
t-Bu - tert-butyl
Decomp. - decomposed
DABCO - diazabicyclo[2.2.2]octane
DMAP - 4-dimethylaminopyridine
DMF - N,N-dimethylformamide
DMSO - dimethylsulfoxide
Et - ethyl
Ether - diethyl ether
Equiv. - equivalent
Het - heterocycle
HMDS - hexamethyldisilazane
h. - hour
LTA - lead tetra-acetate
mCPBA - meta-chloroperbenzoic acid
m.p. - melting point
Me - methyl
min. - minute
Ph - phenyl
Phthal - phthalimide
Pyrid = Py - pyridine
THF - tetrahydrofuran
TFA - trifluoroacetic acid
Throughout this thesis
THE STEROEOCHEMICAL CONSEQUENCES OF N,N CHIRAL AXES IN 3-ACYLAMINOQUINAZOLINONES

Emma Barker

Abstract

The N,N-diacylation of 3-aminoquinazolinones results in the formation of imides. X-ray crystal structures of some of these compounds confirm the presence of N-N chiral axes. Both enantiopure diastereoisomers of one imide have been separated and each behaves as a chiral acylating agent. The faster eluted diastereoisomer reacts with \( \alpha \)-methylbenzylamine with partial kinetic resolution to give a 3.6 : 1 ratio of diastereoisomers of the amide. The ability of 3-diacetylaminoquinazolinones to selectively acetylate one amine in the presence of another amine is also illustrated.

Attempted aziridination of cyclic \( \beta \)-ketoesters, \( \beta \)-diketones and enol silyl ethers with 3-acetoxyamino-2-isopropyl-quinazolinone proceed in good yield with C-N bond cleavage of the intermediate aziridine. The products from treatment of these \( \alpha \)-(quinazolin-3-yl)amino cyclic ketone derivatives with LTA are dependent on the solvent used. In methanol, ring-cleavage occurs for 5- and 6-membered rings to give imine-esters. In dichloromethane, 5-membered ring ketones undergo a ring-expansion reaction whereas when 6-membered ring analogues are used, no expansion occurs and the only product isolated is the benzoazinone. A mechanism which accounts for this dependence on solvent is presented; radicals do not appear to be involved.

The reaction of 3-aminoquinazolinones with ketones results in disparate ratios of C=N isomers of imines. The barriers to N-N bond rotation in some of these compounds have been calculated. The potential use of these imines for the preparation of enantiopure amines is examined.

Addition of triethylamine (or other tertiary amines) to a solution of 3-acetoxyaminoquinazolinone, results in the formation of triethylammonium imide. Solutions of this compound react with alkenes at -30 °C to give aziridines; the reactivity of the aziridinating intermediate is consistent with its formulation as an azaimide (N-nitrene).

Aziridination by the addition of 3-acetoxyaminoquinazolinones to alkenes in the presence of HMDS results in increased yields of aziridine products compared to those obtained in the absence of HMDS. The role of HMDS in these reactions is not clearly understood, although it seems likely that it is behaving in a similar way to trifluoroacetic acid which also brings about an enhancement of yields in these aziridinations.
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INTRODUCTION - CHAPTER ONE
1.1 Introduction

The most common cause of chirality in organic molecules is the presence of a tetrahedral sp^3 hybridised carbon atom bonded to four different atoms or groups. Less well known are molecules which contain a chiral axis, for example substituted allenes.¹ In allenes, prohibited rotation gives rise to two perpendicular planes (Figure 1).

![Figure 1](image)

The central carbon has two p-orbitals that are perpendicular to one another, and each overlaps with a p-orbital of each terminal carbon atom. This forces the two remaining bonds of each carbon into perpendicular planes and thus, for example, (1) is a chiral molecule.

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{C} = \text{C} = \text{C} \\
\text{H} & \quad \text{CH}_3
\end{align*}
\]

(1)

When four, six, or any even number of cumulative double bonds are present, the terminal groups are in two perpendicular planes, so optical activity is possible.

The 2,2'-disubstituted derivatives of 1,1'-binaphthyl also contain chiral axes. The chirality arises due to the steric hindrance which is present between the two peri hydrogens in the 8,8'-positions.
Preparation of derivative (3)\(^2\) was achieved by the self coupling of 2-naphthol (2), using an \textit{in situ} generated complex of CuCl\(_2\) and (-)-sparteine in methanol (Scheme 1). The overall enantioselection (up to 100\%) is mainly controlled via a second-order asymmetric transformation of the product (3) as a complex with sparteine i.e. the two diastereoisomers are in mobile equilibrium but crystallisation of the mixture followed by acid cleavage of the complex leads to a single enantiomer of the product.

Another class of compounds that can contain chiral axes are \(N\)-phenyl imides (4) and amides (5).\(^3\)

\(\text{O} \quad \text{N} \quad \text{O} \quad \text{R}^1 \quad \text{R}^2\)

\(\text{O} \quad \text{N} \quad \text{R}^1 \quad \text{R}^2\)

\((\text{R}^1, \text{R}^2 = \text{H})\) low barrier to rotation \\
\((\text{R}^1, \text{R}^2 = \text{n-alkyl}, \text{OR}, \text{NR}_2)\) high barrier to rotation \\
\((\text{R}^1 = \text{H}, \text{R}^2 = 3^\circ\text{-alkyl})\) high barrier to rotation
These compounds are not planar in the ground state and twist to relieve unfavourable steric interactions between the ortho substituents on the phenyl ring and the imide or amide substituents. The barriers to rotation in these compounds are dependent on the types of ortho substituent present. When the substituents are large enough to prevent rotation around the Ph-N bond, then atropisomers can be separated as for example, in (6).

![Diagram](image_url)

(6)

This type of chirality can also be present in substituted hydrazine systems. In this case, it is the restricted rotation around the N-N bond which gives rise to the chiral axis.

![Diagram](image_url)

N-N Bond Rotation

This axis may be referred to as stereolabile when rotation around it takes place on the real time-scale. When rotation is prevented or greatly slowed on the real time-scale, it may be called a stereostable chiral axis.
1.2 Factors that affect the barrier to N-N bond rotation

Substituted hydrazine compounds have N-N bond rotational barriers which are strongly influenced by the type of substituent present on both nitrogens. Fletcher and Sutherland\(^5\) have studied the conformational behaviour of several tetra-alkyl hydrazine systems which are bipyramidal in shape. They showed that the magnitude of the N-N bond rotational barriers present are in the order of 45 kJ / mol.

Other compounds of this type, where torsional barriers have been measured by NMR spectroscopic methods, include the N-S bond in sulfenamides\(^6\) and sulfinamides\(^7\), the N-O bond in hydroxylamines\(^8\) and the N-P bond in aminophosphines.\(^9\)

Barriers to N-N bond rotation in substituted hydrazine compounds are increased significantly when both nitrogens are sp\(^2\) hybridised.\(^10\) This planarisation can be achieved by incorporating them into amides. In this case, barriers are of the order 84 kJ / mol or more.
The enhanced rotational barriers observed in these latter cases can be explained by considering the lone pairs on both nitrogens. These lone pairs are contained in p-orbitals which must become eclipsed for rotation to occur. The electrostatic and quantum mechanical repulsions between these two parallel filled p-orbitals in the transition state are therefore the main contribution to N-N bond torsional barriers; the non-bonding repulsions between the substituents usually have a smaller effect.

This explanation was supported by the similarly high barriers to rotation around the N-C bond in several N-malonyl-imide sodium salts.\textsuperscript{11}

The reasons why N-N rotational barriers in acylated hydrazines are larger than in alkyl hydrazines can now be explained. The flattening at nitrogen that accompanies acylation increases the p-character of the nitrogen lone pair. This increases the lone pair-lone pair interaction at the N-N rotation transition state relative to that for the s-richer lone pairs of alkylated nitrogens. The preferred configuration with the lone pairs orthogonal to one another for some substituted hydrazines containing two sp\textsuperscript{2}-hybridised nitrogens has been proved by microwave spectroscopy and electron diffraction.

A number of tri- and tetra-acyl substituted hydrazine derivatives have been prepared by Verma.\textsuperscript{12-15} In many of these compounds, the effects of restricted rotation around the N-N' bond have been observed by NMR spectroscopy. For example, N'-sulfonyl derivatives of N-amino camphorimide (7) have been investigated and $\Delta G^\neq$ values for N-N' bond rotations calculated from variable-temperature spectra using Eyring's rate equation.\textsuperscript{15} (Table 1)
Table 1: Bond rotations in derivatives of N-amino camphorimide (7).

<table>
<thead>
<tr>
<th>Substituent $R^1$</th>
<th>Substituent $R^2$</th>
<th>Spectral change studied</th>
<th>$\Delta G^* \text{kJ / mol}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{SO}_2\text{CH}_3$</td>
<td>$\text{SO}_2\text{CH}_3$</td>
<td>Decrease in $\Delta\nu$ of the $\text{SO}_2\text{CH}_3$ signals</td>
<td>99.5</td>
</tr>
<tr>
<td>$\text{SO}_2\text{CH}_3$</td>
<td>$\text{COCH}_3$</td>
<td>Decrease in $\Delta\nu$ of the acetyl signals</td>
<td>85.3</td>
</tr>
<tr>
<td>$\text{SO}_2\text{C}_6\text{H}_4$-CH$_3$-$p$</td>
<td>$\text{COC}_6\text{H}_5$</td>
<td>Decrease in $\Delta\nu$ of the $\beta$-methyl signals</td>
<td>82.7</td>
</tr>
<tr>
<td>$\text{SO}_2\text{CH}_3$</td>
<td>$\text{COC}_6\text{H}_5$</td>
<td>Decrease in $\Delta\nu$ of the $\beta$-methyl signals</td>
<td>83.6</td>
</tr>
<tr>
<td>$\text{COCH}_3$</td>
<td>$\text{COC}_6\text{H}_5$</td>
<td>Decrease in $\Delta\nu$ of the $\beta$-methyl signals</td>
<td>83.2</td>
</tr>
</tbody>
</table>

The $N,N'$-disulfonyl and the $N'$-sulfonyl-$N$'-acyl derivatives prefer non-eclipsed conformations about the $N,N'$ bond as expected and the high torsional barriers in $N'$-
sulfonyl-N'-acyl derivatives are of the same order of magnitude of those in the N,N'-diacyl compounds (see Table 1).\textsuperscript{14}

Research in this Department has been carried out by P. J. Edwards on various substituted 3-aminoquinazolinones.\textsuperscript{16} Mono-N-acylation of the 3-aminoquinazolinone (8) was achieved using acetic anhydride (Scheme 2). The NMR spectrum of this compound (9) shows the methyl groups of the isopropyl group to be non-equivalent. This is due to either hindered rotation around the N-N bond or possibly hindered rotation around the N-CO bond (with fast N-N bond rotation on the NMR time-scale).

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\textsuperscript{1}O\textsubscript{N}H\textsubscript{2}};
\node (b) at (2,2) {\textsuperscript{1}O\textsubscript{N}H\textsubscript{2}};
\node (c) at (4,4) {\textsuperscript{1}O\textsubscript{N}H\textsubscript{2}};
\node (d) at (6,6) {\textsuperscript{1}O\textsubscript{N}H\textsubscript{2}};
\draw (a) -- (b);
\draw (b) -- (c);
\draw (c) -- (d);
\end{tikzpicture}
\end{center}

\textit{Scheme 2}

Variable temperature NMR studies were carried out to determine a minimum energy barrier for rotation and this was calculated to be at least 85 kJ / mol. This value is
larger than those found for amide rotational barriers in $\text{N}_2\text{N}$-dialkylacetamides (10)\textsuperscript{17} and on this basis, the measured barrier was assigned to that for $\text{N}_2\text{N}$ bond rotation.

\[ (10) \]

\[
\begin{align*}
R = \text{Me} & \quad 76.0 \text{ kJ/mol} \\
R = \text{Et} & \quad 71.0 \text{ kJ/mol} \\
R = \text{Pr} & \quad 71.4 \text{ kJ/mol} \\
R = \text{i-Pr} & \quad 65.9 \text{ kJ/mol}
\end{align*}
\]

1.3 The stereostructure of imides

Di-acetylated 3-aminoquinazolinone (11) has been prepared by reaction of acetic anhydride with (8) in pyridine.\textsuperscript{16}

\[ (11) \]

This compound does not contain an $\text{N}_2\text{N}$ chiral axis due to the plane of symmetry present. One singlet is observed for both acetyl methyl groups in its proton NMR spectrum.

Imide functional groups (12) ($R^3 = \text{alkyl}$) are, however capable of existing as (non-isolable) stereoisomers\textsuperscript{18} which can be shown to be present from the NMR spectra of these compounds at low temperature.
These configurations (E,E, E,Z, Z,Z) are possible for acyclic, symmetrical imides (R^1 = R^2). In unsymmetrical imides, where R^1 and R^2 are different, four configurations are possible since there are two different E.Z-stereoisomers.

Dipole-dipole interactions and steric interactions appear to be important factors in determining the conformational preferences of these imides. The Z,Z-conformation is the least favoured due to the large adverse dipole-dipole interactions present between the two carbonyl oxygens. The E,E-conformation is more favourable when R is small since the carbonyl groups are far apart and electrostatic repulsions are less. However, when R^1 / R^2 interaction is significant, the E.Z-conformation reduces the interference between these groups and so becomes more favourable.

Cyclic imides, in which two R substituents are joined in a part of the ring, will be constrained to adopt the E,E-configuration (unless the ring is large enough to contain a trans double bond). Similarly, N-acyl lactams are restricted to the E.Z and Z.Z-configurations unless the lactam ring is large.
A wide variety of experimental tools, including studies of dipole moments, infrared, ultraviolet and microwave spectroscopy have been used to determine the configurational preferences in these compounds. NMR spectroscopy is also a powerful tool both for determining the configurations of imides in solution and for studying their barriers to topomerisation / stereoisomerism.

1.4 Topomerisation of imides

Raban has assigned the configuration and measured the free energy of activation for topomerisation of several imides from a study of their NMR spectra at various temperatures. He concluded that the most likely pathway involves interconversion via sequential rotation about carbon-nitrogen bonds as shown in Scheme 3.
A less probable alternative involves the intermediate formation of an enol tautomer which suffers rapid rotation about the carbonyl to nitrogen bond (Scheme 4).

![Scheme 4](image)

1.5 Alkali metal chelation by diacetamide

Raban\textsuperscript{24} has also shown that alkali metal chelation by diacetamide is possible using LiI, NaI or KI (Scheme 5).

![Scheme 5](image)

$M^+ = \text{Li}^+, \text{Na}^+ \text{ or } \text{K}^+$.
Proton NMR spectroscopy indicates that diacetamide exists as an equilibrium mixture of Z,Z and E,Z diastereoisomers in methanol solution. Addition of LiI, NaI or KI shifts the equilibrium towards the Z,Z-isomer because of bidentate complexation (chelation) by the imide carbonyl oxygens. The relative effectiveness of the alkali metal ions in shifting the configurational equilibrium towards the Z,Z-isomer of diacetamide is $\text{Na}^+ < \text{K}^+ < \text{Li}^+$.  

1.6 $\text{N=N}$ rotational barriers in imines

As well as $\text{N-(Q)}$imides, the preferred conformations of other types of quinazolinones bearing other substituted 3-amino substituents are of interest. Imines, for example, would be expected to have lower barriers to $\text{N=N}$ bond rotation since some stabilisation of the planar transition state would be anticipated (Scheme 6).

![Scheme 6](image)

The pyranone-imine (13)$^{16}$ was prepared by the reaction of the 3-acetoxyaminoquinazolinone (14) with 1-(2-furyl)ethanol (Scheme 7).
The proton NMR spectrum of this compound at room temperature showed broadened signals for the quinazolinone isopropyl groups and for the protons on the pyranone ring. The broadening of these signals is due to N-N bond rotation which is becoming fast on the NMR time-scale (Scheme 8).

At -40 °C, a 2:1 ratio of the rotamers was seen and from the coalescence of the pyranone imine ring protons (CH$_3$CHO) at 273K, a barrier to rotation of $\Delta G^\neq = 55$ kJ / mol was calculated.
1.7 Asymmetric induction in a Diels-Alder cycloaddition reaction mediated by a chiral axis

Asymmetric induction is mediated by the Ar-N chiral axis in (15) and reaction with 2,3 dimethylbutadiene occurs to give a single diastereoisomer of (16) (Scheme 9).3 X-ray structures of both (15) and (16) highlight the features that control the shape of these molecules and the stereoselectivity of their reactions. In (15) the two planes containing the imide and aryl ring are twisted by 90° and the ortho t-butyl group significantly shields the approach of the diene to one face; the face containing the meta t-butyl group is reasonably open to attack. This Diels-Alder reaction exhibits especially high selectivity because of the endo approach of the dienophile, so as a result only one stereoisomer of (16) is formed.

1.8 Asymmetric induction mediated by an N-N chiral axis

When 3-aminoquinazolinone (17) is oxidised with LTA in the presence of 3-methylpentane-2,4-dione, the enol (18) is isolated. This compound is chiral by virtue of the high barrier to rotation around its N-N bond. Asymmetric induction is mediated by
this chiral axis in protonation of the double bond with glacial acetic acid to give a single diastereoisomer of keto-amide (19) (Scheme 10).  

Clearly if this aziridination could be carried out to yield an imide resembling (19) in enantiopure form, cleavage of the N-N bond should deliver the amino-ketone in enantiopure form.

1.9 N-N bond cleavage in substituted hydrazines

There are several methods available for the reductive cleavage of N-N bonds. These include aluminium amalgam, Raney nickel, sodium in liquid ammonia, sodium in ethanol or zinc in acetic acid. The conditions required to cleave this bond can depend markedly on the substituents attached to the nitrogens. Work by Mellor and Smith has
shown that the presence of carbonyl or sulphonyl substituents on both nitrogens facilitates reductive cleavage of this bond.

When only one of the nitrogens in the hydrazine system is acylated, samarium diiodide can be used to bring about N-N bond cleavage. In the example shown below, the amine is produced in 80% yield (Scheme 11).

\[
\text{Scheme 11}
\]

1.10 Methods for the preparation of epoxides

There are a wide variety of synthetic methods for the preparation of epoxides. These include epoxidation of alkenes, Darzens condensation, the Payne rearrangement, cyclisation of halohydrins and many more. One of the most common reactions involves treatment of an alkene with a peroxyacid. Many different peroxyacids can be used in this reaction, but m-chloroperoxybenzoic acid (21) is most widely used (Scheme 12).
The transition state for epoxidation using a peroxyacid is illustrated by the Bartlett mechanism (Figure 2).

Enantiopurified epoxides can also be prepared by the epoxidation of allylic alcohols. This method has been developed by Sharpless \(^{32}\) and the reactions routinely give enantiomeric excesses of greater than 90\% (Scheme 13).
1.11 Kinetic resolution of alcohols using the Sharpless epoxidation

Since enantiomers react with chiral compounds at different rates it is sometimes possible to effect a partial or even complete separation of racemates using chiral (enantiopure) reagents. An important application of this method is the resolution of racemic allylic alcohols using the Sharpless' epoxidation method.
1.12 Aziridination Of Alkenes

There are fewer synthetic methods available for the aziridination of alkenes. Direct conversion of electron-rich alkenes into aziridines may be achieved using e.g. Ω-toluene-p-sulfonylhydroxylamine (22) but the yields are not high (Scheme 14).

Another method involves a Michael type addition of free sulfimides to electron-deficient alkenes (Scheme 15) but this aziridination is not stereospecific since the same trans-substituted aziridine is formed using the cis-alkene.

Reactions mediated by nitrenes / nitrenoids can also be used to achieve this conversion. An example involves the copper catalysed aziridination of alkenes using the nitrenoid precursor shown (Scheme 16).
Alkoxy-nitrenes, sulfenyl-nitrenes and amino-nitrenes also have been shown to bring about aziridination of alkenes. In the latter (R₁R₂N₁-N₂) the electron-deficient nitrogen (N₂) is bonded to another nitrogen (N₁) and the substituents (R₁ and R₂) on this nitrogen may be acyl groups, or most often, form part of a heterocyclic ring.

1.13 The nature of the aziridinating species in the LTA-mediated oxidation of N-aminophthalimide

One of the best known examples of aziridination mediated, it was believed, by an amino-nitrene, is the oxidative addition of N-aminophthalimide (23) to alkenes.

Evidence for the phthalimido-nitrene intermediate (24) was its apparent generation by three different routes and its efficient reaction with styrene and with methyl acrylate (two alkenes of very different electron availability). These routes involved the thermolysis of aziridinobenzofurans (25), of benzo-7-azanorbornadiene (26) and of sulfimide (27) in boiling benzene. It was subsequently shown that all three routes gave the same ratio of aziridines (28) and (29) (1 : 1.8) in competitive aziridination of a 1 : 1 mixture of styrene and methyl acrylate confirming the intermediacy of phthalimido-nitrene (24) (Scheme 17).
However, when N-aminophthalimide was oxidised with LTA at 80°C in the presence of a 1:1 mixture of styrene and methyl acrylate a different ratio of aziridines (28) and (29) was obtained (1:1.3) (Scheme 18); this indicates that in this case the same phthalimido-nitrene intermediate is not involved. The identity of the intermediate in these aziridinations brought about by LTA oxidations of N-aminophthalimide (23) will be revealed later.
An aziridinating species, thought to be phthalimido-nitrene (24) has also been generated photochemically.\textsuperscript{41} Oxidation of \textit{N}-aminophthalimide (23) with LTA in the presence of nitrosoamine (30) gives (31); photolysis in the presence of cyclohexene gives the aziridine (32) (Scheme 19).
1.14 Stereospecificity in aziridination reactions mediated by phthalimido-nitrene

Reaction of phthalimido-nitrene (24) with cis- and trans-alkenes is stereospecific. Skell's hypothesis\(^{42}\) states that the addition of singlet carbenes to alkenes is stereospecific, whereas with triplet carbenes it is not. Adapting this hypothesis to nitrenes indicates that phthalimido-nitrene has a singlet ground state.

1.15 Aziridination of alkenes using LTA-mediated oxidative addition of other N-aminoheterocyclic compounds to alkenes

A method for the preparation of aziridines by the oxidative addition of various N-aminoheterocycles was discovered by Rees and co-workers.\(^{43-44}\) These compounds included N-aminophthalimide (23) (as mentioned previously), N-aminobenzoxazolinone (33), N-aminouinazolinone (34), N-aminquinolinone (35), N-aminopyrrole (36), N-aminotriazole (37), N-aminotriazolinone (38) and N-aminobenzimidazole (39).
These heterocycles all contain features that reduce the availability of the lone pair on the trivalent nitrogen (N-1) for donation to and stabilisation of, the univalent nitrene nitrogen. Thus, either one or both of the N-1 substituents is a carbonyl or imino function or the N-1 lone pair is part of an aromatic ring. If these features are absent in the heterocycle, the double bond character of the N-N bond in the N-nitrene is increased which appears to facilitate intramolecular elimination of nitrogen.

1.16 The identity of the aziridinating agent in LTA-mediated oxidative addition of 3-aminoquinazolinones to alkenes

The mechanism of aziridination using LTA-mediated oxidative addition of 3-aminoquinazolinones to alkenes was examined by B. J. Kelly. He oxidised 3-amino-2-ethylquinazolin-4(3H)-one (17) in CDCl₃ with LTA at -20°C, separated the lead diacetate and base-washed the solution at this temperature. A 300MHz proton NMR
spectrum of the resulting solution at -20°C, without it being allowed any intermediate warming showed the formation of a product which contained only an NH singlet, four quinazolinone ring protons, a methyl singlet, diastereotopic methylene protons and a methyl triplet. A $^{13}$C spectrum was also obtained and both this and the $^1$H spectrum showed that this intermediate was the 3-acetoxyaminoquinazolinone (20): it was shown that this 3-acetoxyaminoquinazolinone was also the species which brought about aziridination of alkenes.

It was assumed by analogy that oxidative addition of analogous N-aminoheterocycles (see above) with LTA or benzene iodosodiacetate [PhI(OAc)$_2$] to alkenes is mediated by the corresponding N-acetoxyaminoheterocyclic intermediates, but work done by the author and described later in this thesis suggests that whilst this is probably the case for N-aminophthalimide (23) it may not be so for other N-aminoheterocyclic compounds.

Reaction of (20) with alkenes gives the corresponding aziridines. For example, reaction with styrene or diethyl fumarate gives the corresponding aziridines in approx. 80% yields (Scheme 20).
The proposed transition state for aziridination using (20) resembles that for epoxidation, i.e. the Bartlett mechanism.

\[ X = N\cdot O^2 \quad : \text{aziridination} \]
\[ X = O \quad : \text{epoxidation} \]
1.17 The properties of the intermediates derived from LTA-mediated oxidative addition of (23) and (33) - (39) to alkenes

The intermediates generated from the oxidation of N-aminoheterocycles (23) and (33) - (39) display a number of characteristic properties.

1) They have an ambiphilic nature and react with both electron-rich and with electron-deficient double bonds. For example, reactions with both diethyl fumarate and with styrene give excellent yields with modest excesses of the respective alkene.

2) They show considerable selectivity in competitive reactions with two different alkenes; in the presence of a 1:1 mixture of styrene and diethyl fumarate, (34) reacts with styrene only.

3) Their reactions with alkenes are stereospecific, even at low concentrations of alkene. This is illustrated by their reactions with both cis- and trans- but-2-ene to give products in which the configuration of the respective alkene is retained.
They give no products from insertion into sigma (σ)-bonds of alkenes (cf. nitrenes).

5) Their reactions with substituted alkenes result in the formation of a single aziridine N-invertomer which is often not the thermodynamically preferred one (see below).

1.18 Syn-selectivity in aziridination of alkenes

The rate of inversion of the aziridine ring nitrogen bearing e.g. the phthalamido group is, fortuitously, very slow on the real time-scale at -20 °C. When an alkene bearing e.g. a phenyl or ester group on the double bond is aziridinated using N-acetoxyaminophthalimide (Scheme 21), the first formed product is the cis-aziridine. This invertomer is clearly formed under kinetic control since on warming to room temperature, the cis-aziridine is converted to the trans-aziridine by nitrogen inversion.
This syn-selectivity in aziridinations of alkenes was first reported using oxidative addition of N-aminophthalimide (23) to methyl acrylate at temperatures of less than -10°C. Examination of the solution by proton NMR spectroscopy at temperatures less than -30°C showed the cis-aziridine (29a) to be the only invertomer present.

When the solution was allowed to warm up, signals from the two aziridines (29a) : (29b) were present (ratio 1 : 5) and this ratio, which reflects the thermodynamic stability of the two invertomers, remained unchanged on re-cooling to -35°C.

The exclusive formation of the kinetically favoured cis-aziridine (29a) was attributed to an attractive donor-acceptor interaction between the ester carbonyl oxygen and the phthalimide carbonyl carbon in the transition state of the reaction (Figure 3).
The large preference in these aziridinations for the s-cis conformations of the α,β-
unsaturated alkenes is revealed in the selectivity of these reactions with α,β-unsaturated
esters and 1,3-dienes. Aziridination of α-methylene-γ-butyrolactone (40) by oxidative
addition of N-aminophthalimide (23) occurs efficiently, whereas with butenolide (41) no
aziridine product is obtained. This therefore indicates that the α,β-unsaturated
system is required to react via its s-cis conformation. Likewise, whereas isoprene (42) is
aziridinated efficiently by oxidative addition of N-aminophthalimide, Z-penta-1,3-diene
(43), a diene having little of the s-cis conformation populated, yields no aziridination
product. This syn-selectivity resembles the secondary orbital endo-overlap present in the
Diels-Alder reaction. However, whereas in the Diels-Alder reaction, cycloaddition still
occurs in the absence of the secondary orbital interaction, no aziridination occurs in the
absence of the secondary interaction in Figure 3, at least for the case of α,β-unsaturated
esters.

(40)  (41)  (42)  (43)
CHAPTER TWO
2.1 Introduction

The barriers to rotation around \( \text{N-N} \) bonds in di-, tri-, and tetra-acyl-substituted hydrazines are large by comparison with those around most other single bonds. Verma et al\(^{14}\) have shown that the barrier to rotation around the \( \text{N-N} \) bond in \( \text{N,N}-\text{diacetylaminocamphorimide} \) (44) is in excess of 97 kJ / mol since no coalescence of the signals from the acetyl methyl groups were observed in its NMR spectrum at 150 °C.

\[
\text{(44)}
\]

This chapter examines the stereostructure and preferred conformations of some acyl-substituted hydrazine systems and their selectivity in acylating reactions with primary and secondary amines.

2.2 \( \text{N-N} \) Rotational Barriers in 3-Acylaminoquinazolinones

The preparation of amide (9) has been carried out by Edwards\(^{16}\).

\[
\text{(9)}
\]
The NMR spectrum of this compound shows the isopropyl methyl groups to be non-equivalent. Just conceivably the apparent non-equivalence of the methyl groups in the isopropyl could actually be two non-equivalent isopropyl groups as a result of hindered rotation around the N-CO bond. To eliminate this possibility the mono-acylated compound (45) was prepared. Acylation of (8) using pivaloyl chloride gave (45) as colourless crystals in 55% yield (Scheme 22).

![Scheme 22](image)

The NMR spectrum of amide (45) showed two signals for the isopropyl methyl groups of equal intensity (analogous to (9)). If hindered N-CO bond rotation was giving rise to the observed spectra (with N-N bond rotation assumed to be rapid) it is very unlikely that both amides (9) and (45) would both exist in 1:1 rotamer ratios. On these grounds, the stereoisomerism observed in the NMR spectra for all mono-acyl compounds of this type is presumed to be due to hindered N-N bond rotation. (In this interpretation, the two methyl groups of the isopropyl are diastereotopic by virtue of the N-N chiral axis present).

It was therefore of interest to synthesise 3-aminoquinazolinones N,N-substituted with different acyl groups for which significantly increased rotational barriers would be
anticipated. The objective is the production of a stereostable N-N chiral axis so that a study of the stereochemistry of these (N-quinazolinonyl)-imides could be undertaken.

Mono-acylation of 3-aminoquinazolinone (8) using 2-phenylpropionyl chloride gave 3-acylaminoquinazolinone (46) in 57% yield whose NMR spectrum showed the presence of a 2 : 1 ratio of diastereoisomers at room temperature (Scheme 23). The isopropyl methyl groups within each diastereoisomer are diastereotopic as a result of the N-N chiral axis / chiral centre.

\[
\begin{align*}
&\text{O}^1 \\
&\text{Ph} \\
&\text{O} \\
&\text{Cl}
\end{align*}
\]

(8)

\[
\begin{align*}
&\text{O}^1 \\
&\text{HN} \\
&\text{Ph}
\end{align*}
\]

(46)

Scheme 23

A crystalline sample of amide (46) was dissolved in CD$_3$OD at -50 °C and a series of NMR spectra at different temperatures were obtained. The ratios of diastereoisomers obtained at -50, -40, +25 then -40 °C are 7 : 1, 5 : 1, 2 : 1, and 2 : 1 respectively. The fact that the ratio of 2 : 1 at +25 °C does not change on re-cooling to -40 °C suggests that this is an equilibrium value and that on crystallisation, a second order asymmetric transformation is taking place in formation of the crystalline sample of amide (46). The two diastereoisomers are in mobile equilibrium, but crystallisation of one diastereoisomer occurs preferentially; the perturbed equilibrium is then re-established, and further crystallisation occurs until the majority of the product has crystallized. The diastereoisomer
composition of the product in the crystal thus differs appreciably from that present at equilibrium (Scheme 24).

![Chemical structure for Scheme 24](image)

**Scheme 24**

3-Amino-2-t-butylquinazolinone (47) was N-acylated using 2-phenylpropionyl chloride to give amide (48) in 68% yield (Scheme 25). It was thought that the N-N rotational barrier in this mono-acylaminoquinazolinone might be sufficient to allow separation of diastereoisomers at room temperature. In the event, this barrier did appear to be enhanced.

![Chemical structure for Scheme 25](image)

**Scheme 25**

At room temperature in solution, amide (48) exists as a 2.4 : 1 ratio of diastereoisomers. Fractional crystallisation of one diastereoisomer was attempted from
ethanol / water and the highest ratio obtained was 3 : 1. NMR studies in CD$_3$OD show that thermodynamic equilibration occurs at a temperature between 35 and 55 °C.

These N-mono-acylation products (46) and (48) are isolated in good yields because N,N-diacylation is a much slower reaction under the same conditions: this allows reaction to be carried out with a second acyl group that is different from the first. Using this method, further acetylation of amide (46) was achieved using acetyl chloride-pyridine to give a 1.8 : 1 mixture of diastereoisomers (49a) and (49b) in 61% yield (Scheme 26). These were subsequently separated by careful column chromatography or by the use of a chromatotron.

A comparison of the NMR spectra of (49a) and (49b) showed a difference of 0.8 p.p.m. for the chemical shift of the proton next to the phenyl group (CH$_3$CH Ph). At this point the possibility of O-acetylation to give (50) in preference to N-acetylation could not be excluded. To eliminate the possibility that O-acetylation to give (50) has occurred, synthesis of the di-acetylated aminoquinazolinone (51) was then carried out.
The proton NMR spectrum of this imide (51) showed both COCH$_3$ signals were equivalent as were the methylene protons of the Q$^2$ ethyl group due to the absence of the 
N-N chiral axis so giving supportive evidence for N,N-diacylation.

To determine the relative configurations of both imide diastereoisomers (49a) and (49b), X-ray crystal structures were obtained (Figures 4 and 5). As anticipated, both molecules comprise two orthogonal planes containing the quinazolinone and diacylimide units, respectively, with the N-N bond as a chiral axis. The exo-endo arrangement of the acyl carbonyl groups with one cis (endo) to the quinazolinone and one trans (exo), is known to be the preferred conformation for simple imides.$^{18}$
N-(Quinazolinonyl)-Imide (49a) – X-Ray Crystal Structure Determination

Figure 4
N-(Quinazolinonyl)-Imide (49b) – X-Ray Crystal Structure Determination

Figure 5
The second diastereoisomer eluted from the column (49b) was heated in d₉-toluene and thermal equilibration with the first diastereoisomer (49a) was carried out at three different temperatures. Measurement of the rate constants for its interconversion with (49a) at each temperature were undertaken and gave the following values: ΔG° = 121 kJ / mol; ΔH° = 77 kJ / mol; ΔS° = -118 J / K mol (Appendix 2). In the NMR spectra of imides (49a) and (49b) there is broadening of the quartet and doublet signals from the CH₂CHPh groups relative to the rest of the signals in these compounds, which is presumed to be due to the onset of slow rotation around imide N-CO bonds on the NMR time-scale.

The identity in chemical shift of the two acetyl methyl groups in (N-quinazolinonyl)-imide (51) above requires that if the exo-endo conformation of the imide is the preferred one, then interconversion of the exo-endo ⇌ endo-exo is fast on the NMR time-scale ((51a) ⇌ (51b)) (Scheme 27). Analysis of the NMR spectrum of imide (51) at -83 °C in d₉-acetone shows the methylene protons of the ethyl side chain to be diastereotopic. Two broadened singlets at δ 2.60 and 2.20 of equal intensity are observed for the COCH₃ groups at this temperature also. This indicates that the two imide conformations that are in equilibrium are the two (identical) exo-endo and endo-exo ones; at -83 °C the N-N bond becomes a chiral axis on the NMR time-scale. It is likely that an analogous process is responsible for the broadening of the signals in the NMR spectra of imides (49a) and (49b) as suggested above.
2.3 Selectivities in Acetylation of Primary and Secondary Amines with N-(Quinazolinon-3-yl)-Imides

Several reagents are available for the chemoselective acylation of primary amines in the presence of secondary amines. These include acyl cyanides,\textsuperscript{50} poly(3-acyl-2-oxazolones),\textsuperscript{51} N-methoxydiacetamide,\textsuperscript{52} acylimidazoles\textsuperscript{53} and also ethyl trifluoroacetate.\textsuperscript{54}

3-Diacylaminoquinazolinones such as (52) can also function as selective acylating agents. Reaction of imide (52) with spermidine (0.5 mol equiv.) at room temperature gives acetylation exclusively at the primary positions, along with the acetylaminoquinazolinone (53) (Scheme 28); no secondary amine acetylation is observed. The product (54) is separated from the amide by-product (53) by extraction with 0.1M hydrochloric acid and is obtained in 90% yield after freeze drying (as the HCl salt). This chemoselectivity is also matched using imide (11).
Scheme 28

The 3-diacylaminoquinazolone (11) also selectively acylates one amine in the presence of another similar amine (Table 2). Only in the competitive reaction of dimethylamine and N-ethylmethylamine were both amide derivatives present (9 : 1 respectively) from examination of the crude reaction mixture by NMR spectroscopy. These experiments were carried out in dichloromethane using 1 mol equiv. of each of the amines and 1 mol equiv. of imide (11). Comparison by NMR with authentic samples of both amide products were made in each case. Control experiments in each case using acetic anhydride showed some selectivity but nothing like comparable with that using imide (11). This acetylating agent is less selective in its reactions with primary amines but does react preferentially with sec-butylamine in the presence of t-butylamine (Table 2).
<table>
<thead>
<tr>
<th>Imide</th>
<th>Amine(s)</th>
<th>Product(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(52)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(11)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(11)</td>
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<td>(11)</td>
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<td>(11)</td>
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<td>(55)</td>
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<td>(55)</td>
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</tr>
</tbody>
</table>

Table 2: Illustrates the selectivity of imides (52) and (11) in acetylation of amines
The selectivity of these reactions can be interpreted in terms of reaction with the less sterically hindered amine. For the N,N-diacetyl-3-aminoquinazolinone (11) the absence of N-N bond rotation and the endo-exo arrangement of carbonyl groups means that each carbonyl group has two faces.

![Figure 6](image)

Molecular modelling reveals that, using a secondary amine, attack on one face of the endo carbonyl group is preferred. In Figure 6, it is apparent that in attack from this preferred face and with hydrogen bonding of the amino group hydrogen to the quinazolinone oxygen, there are two sites for the two alkyl groups, one of which is more hindered than the other.

Other reagents have been reported to accomplish the selective acylation of spermidine on its terminal amino groups including N-methoxydiacetamide (55). Selectivity of reaction between pairs of amines using imide (55) have also been determined and the results are shown in Table 2. In the competitive reaction of this imide with sec-butylamine and t-butylamine, imide (55) would appear to be more selective than N-(quinazolinon-3-yl)-imide (11).
2.4 Studies Directed Towards the Kinetic Resolution of Amines using N-(Quinazolinon-3-yl)-Imides

N-(Quinazolinon-3-yl)-imides were found to act as acylating agents for amines (see above) and the use of enantiopure N-(quinazolinon-3-yl)-imides for kinetic resolution of racemic amines was examined. Several of these imides were prepared in addition to those prepared previously which also have sufficiently high barriers to rotation around their N-N bond for this to constitute a chiral element on the real time-scale in each case. When another chiral centre is present in the molecule, diastereoisomers can be separated which will both be enantiopure if the chiral centre has a defined absolute configuration (cf. Scheme 26).

\[
\begin{align*}
\text{Single enantiopure diastereoisomer} \\
R_2^* = \text{CH(Me)OCOMe} \\
R_3^* = \text{CH(Me)Ph}
\end{align*}
\]

Scheme 29

Attempted kinetic resolution (Scheme 29) using these reactions were carried out using 1 mol equivalent of the imide (56) to 2 mol equiv. of the racemic amine (57) in
various solvents and also at different temperatures. The results obtained will be discussed later.

The extent of resolution is obtained by measuring the ratio of diastereoisomers present in the proton NMR spectrum of the amide (58) and the signal in each diastereoisomer chosen for the best comparison is the CH$_3$CO singlet. Comparison with authentic samples of the amide diastereoisomers (58a) and (58b), prepared from commercially available enantiomers of the amine (57), shows which enantiomer of the amine (if any) reacts preferentially.

\[
\begin{align*}
(58a) & \quad (58b) \\
\text{Me} & \quad \text{Me} \\
\text{O} & \quad \text{O} \\
\text{COMe} & \quad \text{COMe}
\end{align*}
\]

(58a) Has a singlet for the CH$_3$CO group at $\delta$ 2.10, whereas in (58b) it is present at $\delta$ 2.11. A mixture of (58a) and (58b) shows two singlets which at 300 MHz are sufficiently well resolved for integration to be practicable.

Several enantiopure N-(quinazolinonyl)-imides have been prepared and their ability to resolve $\alpha$-methylbenzylamine has been investigated. The preparation and characteristics of these imides will now be discussed. Di-acylation of 3-aminoquinazolinone (8) using (S)-2-acetoxypropionyl chloride gave imide (59) in 77% yield after chromatography (Scheme 30). The NMR spectrum of this compound shows the isopropyl methyl groups to be non-equivalent. It is noteworthy that although this compound has no plane of symmetry the N-N bond cannot be described as a chiral axis on this real time-scale because rapid exo-endo $\rightleftharpoons$ endo-exo interconversion is occurring.
This compound (59) is a chiral acylating agent; it reacts with racemic α-methylbenzylamine exclusively at the 2-acetoxypropanoyl amide carbonyl group with no competitive attack on the ester group. Acylations using (59) were carried out in ethanol at various temperatures and the ratios of diastereoisomers measured (see Table 3) but were never better than 1.3 : 1.

Mono-acylation of 3-aminoquinazolinone (8) using (S)-2-acetoxypropionyl chloride gave amide (60) in 75% yield as a 1.55 : 1 ratio of diastereoisomers on the NMR time-scale. Further acylation using isobutyryl chloride-pyridine gave imide (61) as a 1.8 : 1 mixture of diastereoisomers. Separation of these diastereoisomers by column chromatography gave (61a) in 33% yield followed by (61b) in 31% yield (Scheme 31).
In the kinetic resolution experiments using imide (61) the steric bulk of the amide isopropyl group presumably inhibits attack by the amine at the adjacent carbonyl; attack at the α-acetoxypropionyl carbonyl group is also assisted by the activating α-OAc group. Unfortunately it cannot be assumed that (61) is undergoing attack only via the E,Z stereoisomer illustrated in Figure 7.

![Figure 7](image)

It was hoped that the steric bulk of the isopropyl group on the 2-position of the quinazolinone ring would disfavour attack from the front face in Figure 7 with an exo-disposed α-acetoxyethyl group, allowing attack from the back face to occur more readily.

Kinetic resolution experiments were carried out in ethanol, ether, THF and toluene. The ratios obtained were slightly higher than for the imide (59), the best result (1:2 ratio of diastereoisomers) being obtained in toluene (see Table 3). Experiments using this imide were also undertaken in THF containing anhydrous MgBr₂ with the expectation that coordination of the two imide carbonyls in the Z,Z conformation would occur as in Figure 8 (similar to the chelation deduced by Raban).
Figure 8

The ratios observed surprisingly were worse than those obtained in the absence of MgBr$_2$. Possibly the MgBr$_2$ coordinated preferentially with the (more Lewis basic) carbonyl group present on the quinazolinone ring.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Solvent</th>
<th>Temp / °C</th>
<th>Ratio (58b) : (58a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(59)</td>
<td>Ethanol</td>
<td>-40</td>
<td>1 : 1.1</td>
</tr>
<tr>
<td>(59)</td>
<td>Ethanol</td>
<td>0</td>
<td>1.3 : 1</td>
</tr>
<tr>
<td>(59)</td>
<td>Ethanol</td>
<td>+25</td>
<td>1.3 : 1</td>
</tr>
<tr>
<td>(61a)</td>
<td>Ethanol</td>
<td>+25</td>
<td>1 : 1.5</td>
</tr>
<tr>
<td>(61a)</td>
<td>Ether</td>
<td>+25</td>
<td>1 : 1.8</td>
</tr>
<tr>
<td>(61a)</td>
<td>THF</td>
<td>+25</td>
<td>1 : 1.8</td>
</tr>
<tr>
<td>(61a)</td>
<td>THF + MgBr$_2$</td>
<td>+25</td>
<td>1 : 1</td>
</tr>
<tr>
<td>(61a)</td>
<td>Toluene</td>
<td>+25</td>
<td>1 : 1.9</td>
</tr>
<tr>
<td>(61a)</td>
<td>Toluene</td>
<td>0</td>
<td>1 : 2.0</td>
</tr>
<tr>
<td>(61b)</td>
<td>Toluene</td>
<td>0</td>
<td>1.6 : 1</td>
</tr>
<tr>
<td>(75a)</td>
<td>Toluene</td>
<td>0</td>
<td>1 : 2.1</td>
</tr>
<tr>
<td>(75a)</td>
<td>Toluene</td>
<td>-20</td>
<td>1 : 3.6</td>
</tr>
<tr>
<td>(75b)</td>
<td>Toluene</td>
<td>-20</td>
<td>2.3 : 1</td>
</tr>
</tbody>
</table>

*Table 3*: Results obtained from kinetic resolution experiments using imides.
Ideally the best chance of kinetic resolution will arise when attack of the amine takes place on one face of one imide acyl group in one *exo-endo* conformation of the imide. If this *endo-exo* conformation could also be the major or exclusive one present for the imide, this would be advantageous. One possibility would be to synthesise an imide substituted by one bulky R₂ group and one small R₁ group so that one *exo-endo* conformation is much preferred to the other (Scheme 32).

![Scheme 32](image)

There is, of course the possibility that a given acyl group may show different reactivity when it is in the *exo* or in the *endo* position. In an attempt to bias the conformational equilibrium between the two *exo-endo* stereoisomers to one side, preparation of (62) was attempted. It was anticipated that the bulky sulfonyl group in 3-(*N*-acyl, *N*-sulfonyl)quinazolinone (62) may favour one amide rotamer over the other.

Mono-sulfonylation of 3-aminoquinazolinone (8) using benzenesulfonyl chloride in pyridine was attempted. The only product obtained however was the di-substituted compound (63), implying that the mono-substituted compound was more reactive towards benzenesulfonyl chloride than the starting material. The reaction was repeated without pyridine, but only unreacted starting material was isolated.
The proton NMR spectrum of this compound (63) shows one doublet for the methyls of the isopropyl group which is not unexpected since the N-N bond is not a chiral axis due to the plane of symmetry present. A further attempt to prepare imide (62) involved the reaction of benzenesulfonyl chloride with the mono-acylaminoquinazolinone (9) but only unreacted starting material was recovered from this reaction.

In a further attempt to bias the endo-exo equilibrium using two disparate acyl substituents, the preparation of imide (64) was attempted using amide (61) and pivaloyl chloride. No acylation occurred presumably due to steric effects.

To test the possible effect of an increase in size of the 2-substituent on the quinazolinone ring on the endo-exo equilibrium and hence in the kinetic resolution experiments, mono-acylation of 3-aminoquinazolinone (47) with acetic anhydride was carried out to give amide (65) in 71% yield. Further acylation was attempted using enantiopure (S)-2-acetoxypropionyl chloride. The only homogeneous products isolated were (66), (67) and the N-diacetylated aminoquinazolinone (68) in 8, 3 and 9% isolated yields respectively (Scheme 33).
A possible mechanism for the formation of compounds (66) and (67) whose assigned structures are based on spectroscopic data is shown in Scheme 34.
In the formation of compounds (66) and (67), competitive O-acetylation of the amide (65) is postulated to be taking place as a result of the steric bulk of the 2-t-butyl group.

In a further attempt to assess the effect in these kinetic resolution experiments of an increase in size of the quinazolinone 2-substituent, 3-aminoquinazolinone (69) was prepared using the method outlined in Scheme 35.
Cyclisation of the hydrazide (72) to give (69) was accomplished in ethanol at 185°C in a sealed tube. It was anticipated that the diphenylmethyl group present on the 2-position of the quinazolinone would not only help to screen one side of the carbonyl group undergoing attack in the derived imides, but might also increase the disparity in the E,Z (endo-exo) stereoisomer ratios referred to previously.
The 3-aminoquinazolinone (69) was acylated using (S)-2-acetoxypropionyl chloride to give (73) in 78% yield (Scheme 36). The amide (73) exists as a 1.8 : 1 ratio of presumably interconverting diastereoisomers at room temperature from examination of its NMR spectrum. Subsequent reaction with isobutyryl chloride-pyridine followed by flash chromatography allowed the separation of two diastereoisomers of imide (75a) and (75b) (the slower eluted imide (75b) was not completely freed from amide (76) which was identified in the mixture by NMR comparison with an authentic sample). Also isolated from chromatography were imide (74) and further amide (76). Formation of imide (74) is believed to arise by selective nucleophilic attack by chloride anion on the 2-acetoxypropanoyl group of one or both diastereoisomers of (75), followed by re-acylation of (76) with isobutanoyl chloride and is an indication of the susceptibility towards nucleophilic attack of these N-(quinazolin-3-yl)-imides (see later).
An X-ray crystal structure determination has been carried out on the faster-eluted diastereoisomer (75a) (Figure 9). As in the previous crystal structures of imides of this type (Figures 4 and 5), the quinazolinone and imide planes are orthogonal and linked by the chiral N-N axis: the \textit{exo-endo} arrangement of the imide carbonyl groups is also present. The NMR spectrum of imide (75a) showed three doublets for the CH$_3$CH$_2$H and CH$_3$CHCO methyl groups. To identify which signal belonged to the CH$_3$CHCO group, a double irradiation experiment was carried out. Irradiation of the CH$_3$CHCO signal at $\delta$ 6.07 caused the collapse of the doublet at $\delta$ 1.64 (CH$_3$CHCO). The remaining doublets at $\delta$ 0.19 and 0.94 are now assigned as the isopropyl methyls. The high $\delta$ values for these isopropyl methyl groups can be correlated with its location in the shielding region of one of the phenyl rings present (see crystal structure). This implies that the \textit{exo-endo} conformation with the isopropyl methyls occupying predominantly the \textit{endo} position in the crystal structure is probably present in solution also.

Both diastereoisomers (75a) and (75b) react with racemic $\alpha$-methylbenzylamine exclusively at the 2-acetoxypropanoyl imide carbonyl group like the other imides examined containing this acyl group. When the faster eluted diastereoisomer (75a) is treated with $\alpha$-methylbenzylamine in toluene at -20 °C, the reaction is accompanied by kinetic resolution giving a 3.6 : 1 ratio of diastereoisomers of amides (58a) and (58b). From comparison with authentic samples of both diastereoisomers, it is the R enantiomer of the amine which reacts preferentially. Using the slower eluted diastereoisomer (75b) (containing a little amide (76) see above), a 2.3 : 1 ratio of amides is obtained in which the S enantiomer of the amine reacts preferentially (Scheme 37).55
Clearly the kinetic resolution obtained in these acylations is dominated by the chiral axis since both diastereoisomers of the imide have the S configuration at the 2-acetoxypropanoyl chiral centre. In contrast, (S)-2-acetoxypropanoyl chloride reacts with α-methylbenzylamine with little, if any, kinetic resolution.

\[
\begin{align*}
\text{(57)} & \quad \text{(58a)} : \quad \text{(58b)} & \quad \text{(76)} \\
(75a) & \quad 3.6 : 1 \\
(75b) & \quad 1 : 2.3
\end{align*}
\]

Scheme 37

Kinetic resolution of other racemic amines have been attempted with imide (75a) including sec-butylamine, 1,2-dimethylpropylamine, 2-amino-1-methoxypropane, exo-2-aminonorbornane, 2-ethylhexylamine: in no case was the ratio of diastereoisomers better than 1.4 : 1 from examination of respective peaks in the NMR spectra of the crude acetylated amines in the reaction products.

**Conclusion:** Enantiopure imides (61a), (61b), (75a) and (75b) effect the partial kinetic resolution of α-methylbenzylamine with the extent of resolution greatest with imide (75) having the largest 2-substituent. If the face of the carbonyl group undergoing attack is that illustrated in (A) the CHPh₂ group may both discourage attack from the bottom face relative to CHMe₂ and also disfavour the population of, and hence reaction from, the alternative exo-endo (E,Z) imide conformer (B) (Figure 10).
In view of the superior chemoselectivity in the reactions of diacetylaminoquinazolinone (11) with pairs of closely related secondary amines (Table 2) it seems worthwhile in future work to examine the kinetic resolution of racemic secondary amines using enantiopure N-(quinazolinonyl)-imides.

Figure 10

\[ R^1 = \text{iPr} \]
\[ R = \text{CH(Me)OCOMe} \]
3.1 Introduction

The reaction of 3-acetoxyaminoquinazolinone (20) with acyclic β-diketones as a route to e.g N-acyl-N(Q²)-α-amino ketones (77) has been examined by Edwards\textsuperscript{56} (Scheme 38). This conversion, which is analogous to that first discovered by Foucaud et al\textsuperscript{57} using oxidative addition of N-aminophthalimide to β-diketones, involves the enolic form of the β-diketone and ring-opening of the intermediate aziridine (78) by C-C bond cleavage. Simple acyclic β-ketoesters are unreactive in this reaction, presumably because of their low enol content.

\begin{align*}
\text{(17)} & \xrightarrow{\text{LTA, -20 °C}} \text{(20)} \\
\text{(77)} & \xrightarrow{\text{C-C bond cleavage}} \text{(78)}
\end{align*}

Scheme 38

Compounds of type (77) are of interest because there is no rotation around the Q²-N bond at room temperature and this bond, therefore, constitutes a chiral axis.\textsuperscript{58} Previous
work was concerned with the synthesis of the cyclic N-(Q\textsuperscript{1})-tetrahydro-\textalpha-pyrone (79) in order to study the diastereoselectivity of its alkylation \textalpha to the ester under the influence of the chiral N-N axis. Since cyclic \(\beta\)-ketoesters contain substantial amounts of enol tautomer, it was thought that the (ring-expanded) product (79) could be obtained in one step from the reaction of ethyl 2-oxocyclopentane carboxylate (80) with Q\textsuperscript{1}NHOAc (14) via Foucaud type C-C bond cleavage of the intermediate aziridine (81) (Scheme 39).

However, as shown in Scheme 39, the product from this reaction was shown by Edwards to be the \(\alpha\)-Q\textsuperscript{1}NH-\(\beta\)-ketoester (82) isolated in 77% yield. This product presumably arises from the more usual C-N bond cleavage of the intermediate aziridine (81), catalysed by acetic acid. The absence of C-C bond cleavage (the Foucaud reaction) in this reaction is presumed to be the result of strain which is expected in the first formed
conformation of the product (79) from the opening of the aziridine ring when n is 3 or 4 (Scheme 40).

When the $\alpha$-$Q^1$NH-$\beta$-ketoester (82) was dissolved in dichloromethane and stirred with LTA overnight, the major product was the $\alpha$-acetoxyester (83). A large barrier to $Q^1$N bond rotation would be expected and this, together with the chiral centre, means that this compound can exist in diastereoisomeric forms. However, from its NMR spectrum, (83) appeared to be a single diastereoisomer. Thermal elimination of acetic acid by heating (83) at 250 °C (Kugelrohr distillation) gave the enamide (84) in 98% yield. Reduction with Adams catalyst gave the tetrahydro-$\alpha$-pyridone (79) that was originally expected (Scheme 41) as a separable mixture of diastereoisomers (2 : 1 ratio).
3.2 Dependence of Ring-Expansion on Ring Size

This work was continued by the present author to determine if these reactions were generally applicable to a range of cyclic β-ketoesters and other enol derivatives. Investigations into the dependence of the ring expansion on changes in ring size and also substitution were carried out.

Oxidation of 3-aminoquinazolinone (8) with LTA and subsequent reaction with ethyl-2-oxocyclohexane carboxylate gave the α-Q^1NH-β-ketoester (85) in 66% yield after column chromatography and crystallisation from ethanol (Scheme 42). The diastereotopic methyls of the isopropyl group in the NMR spectrum of compound (85) suggest that the N-N bond is a chiral axis as would be expected, at least on the NMR time-scale.
From treatment of \( \alpha\)-Q\(^1\)NH-\( \beta\)-ketoester (85) with LTA in dichloromethane no ring expanded product (86) was isolated. In this case, the oxidation was slower as judged by the rate of disappearance of starting material (t.i.c.) and the only homogeneous product isolated was identified as 2-isopropylbenzoxazinone (87) by comparison with an authentic sample (Scheme 43).
To determine whether the ester group was playing a role in this reaction, 3-aminoquinazolinone (8) was acetylated with LTA and reacted with 1-methyl-2-trimethylsilyloxyhexene to give the α-(Q^1NH)-substituted ketone (88) in 62% yield. Further oxidation of (88) with LTA in dichloromethane also gave the benzoxoxazinone (87) in 79% yield (based on recovered starting material) as the only isolated product (Scheme 44). The absence of 6→7 ring expansion therefore is not a consequence of the electron-withdrawing effect of the α-ester group in α-Q^1NH-β-ketoester (85).

Scheme 44

Finally, oxidative substitution of the Q^1NH group into the α-position of the β-ketoester was carried out in 69% yield (Scheme 45).

Scheme 45
Further treatment of compound (89) with LTA in dichloromethane also gave the benzoxazinone (87) only, indicating that the ring-expansion only occurs from the 5- to the 6-membered ring.

The formation of benzoxazinone in these oxidations could arise by the route shown in Scheme 46. There appear to be factors which retard attack by the Q1-NH nitrogen on the presumably reversibly formed carbocation (90) in the 6-membered ring case. It is possible that, whatever these factors are, they allow a slower attack of the quinazolinone carbonyl oxygen to supervene.

Benzoxazinones have been isolated previously from attempted reactions of 3-acetoxyaminoquinazolinones with other substrates.60
Proposed Mechanism for Conversion of (85) → (87) by LTA / CH₂Cl₂

Scheme 46
3.3 Investigation into the Dependence of the Previously Described Ring Expansion of α-Q^1NH-Cyclopentanones on Substitution

Reaction of Q^1NHOAc (14) with methyl indan-1-one-2-carboxylate gave the α-Q^1NH-β-ketoester (91) in 64% yield. The proton NMR spectrum of this compound shows the two methyl groups of the isopropyl to be non-equivalent, indicating the presence of the N-N chiral axis. Further oxidation of (91) with LTA in dichloromethane gave the ring-expanded product (92) in 60% yield (Scheme 47).

![Scheme 47]

$$
\begin{align*}
\text{Q}^1
\text{NHOAc} & \quad \text{CO}_2\text{Me} \\
\text{CO}_2\text{Me} & \quad \text{NHO}_1^1 \\
\text{CO}_2\text{Me} & \quad \text{CO}_2\text{Me}
\end{align*}
$$
Reaction of the Silyl Enol Ether with 3-Acetoxyaminooquinazoline (14)

Oxidative substitution of the $Q^1$NH group into the $\alpha$-position of the silyl enol ether of 2-methylcyclopentanone also took place in its reaction with $Q^1$NHOAc (14) with the formation of $\alpha$-$Q^1$NH-cyclopentanone (93) in 59% yield (Scheme 48). Further oxidation of (93) with LTA in dichloromethane gave the enamide (94) as a colourless oil (60%). This indicates that the ester group is not required in the expansion reaction.

The oxidation was then carried out using the $\alpha$-$Q^1$NH-$\beta$-diketone (95). This compound was prepared in the usual way from (14), LTA and 2-acetylcyclopentanone in 66% isolated yield. Its oxidation with LTA in dichloromethane resulted in a mixture of a
number of products as judged by t.l.c. examination, but no homogeneous product was isolated by column chromatography (Scheme 49).

This indicates that the acetyl group is interfering with the expansion reaction, possibly by competing with the cyclic ketone for coordination by LTA.

To obtain some evidence for the mechanism of the ring-expansion reaction, the synthesis of α-Q'NH-ester (96) lacking the ring carbonyl group was attempted in order to examine the products of its reaction with LTA (Scheme 50).
The proposed route for the synthesis of amino-ester (96) is illustrated in Scheme 51.

Reduction of (82) with sodium borohydride gave a single diastereoisomer of alcohol (97) in 58% yield. The NMR spectrum of this compound shows the methyl groups of the isopropyl and also the methylene protons within the ester group to be non-equivalent (diastereotopic). Acetylation of alcohol (97) proceeded smoothly to give a single diastereoisomer of acetate (98). Elimination of acetic acid was attempted at 250 °C (Kugelrohr) and 0.2 mmHg pressure but was unsuccessful and resulted in partial decomposition of (98) to give products which did not appear to include the required alkene product (99).

The synthesis of α-chloro analogue (100) was then carried out in order to examine its reaction with LTA.
Aziridination of ethyl cyclopentene 1-carboxylate with 3-acetoxyaminoquinazolinone (14) was carried out and gave the aziridine (101) as colourless crystals in 63% yield. Ring-opening of the aziridine with HCl afforded a separable mixture of α-chloroester (102) and β-chloroester (100) (ratio 1 : 2.6). Although the proton NMR spectra of these two ring-opened products were consistent with their assigned structures, with the NH proton in (102) appearing as a doublet, but as a singlet in (100), the carbon spectrum of (102) showed some apparent overlapping of three carbon resonances (CH₂, CH, 2 x CH₃) to form a single broad resonance at δ 21.05. This overlapping is probably due to the onset of slow rotation around the N-N bond on the NMR time-scale. (The barrier to rotation around this N-N bond is much lower when the exocyclic nitrogen is sp³-hybridised, than when it is sp²-hybridised -see Chapter 1). To confirm the structure of α-chloroester (102), it was reconverted back to aziridine (101) by treatment with sodium hydride in DMF in good yield (Scheme 52).
Treatment of (100) with LTA in dichloromethane (under the same conditions which brought about complete reaction of (93)) resulted in no reaction (Scheme 53). This result supports a mechanism for the ring expansion reaction in which the presence of a carbonyl group is required (see later).

\[
\begin{align*}
\text{Cl} & \quad \text{LTA} \quad \text{CH}_2\text{Cl}_2 \\
\text{N} & \quad \text{CO} & \quad \text{Et} \\
\text{NHQ}^1 & \quad \text{CO}_2\text{Et} \\
\end{align*}
\]

(100)

Scheme 53

**Reductive Cleavage of the N-N Bond in N-Quinazolinon-3-yl-dihydro-α-pyridones**

For the ring-expansion reaction products in this chapter to be synthetically useful, methods for removing the quinazolinone must be considered.

\[
\begin{align*}
\text{O} & \quad \text{O}^1 & \quad \text{CO}_2\text{Et} \\
\text{N} & \quad \text{CO}_2\text{Et} \\
\text{H} \\
\end{align*}
\]

(84)

\[
\begin{align*}
\text{O} & \quad \text{O}^1 & \quad \text{CO}_2\text{Et} \\
\text{N} & \quad \text{CO}_2\text{Et} \\
\text{H} \\
\end{align*}
\]

(103) + (104)

Scheme 54
Reductive cleavage of the N-N bond has been previously achieved using samarium diiodide. Applying the method in this case, gave the dihydro-α-pyridone derivative (103) which was isolated in 70% yield (Scheme 54).

**Reaction of α-O²¹NH-Substituted Cyclic Ketones with LTA in Methanol**

Previous work carried out by Edwards also involved the oxidation of α-O²¹NH-ester (82) with LTA in methanol. He suggested that the product had structure (105) and had arisen from a ring expansion reaction which involved quenching of the carbocation by methanol; this product (105) was present supposedly as a 1.8 : 1 ratio of diastereoisomers (Scheme 55).

![Scheme 55](image)

However, work by the present author suggests that the structure of this product is the imine-diester (106) from a ring-cleavage reaction with C=N double bond isomers present in a 1.8 : 1 ratio.
One indication in the NMR spectrum of (106) that loss of chirality had occurred was the equivalence of the two methyls of the isopropyl group, and of the methylene protons of the ethyl ester. In the NMR spectrum of the ring-expanded pyridone (83), these methyl groups are non-equivalent (diastereotopic) as are the two methylene protons. Another indication that ring opening to give N(Q\textsuperscript{1}Q)-imine (106) had occurred was the changed appearance of the signals in the NMR spectrum for the aliphatic protons (CH\textsubscript{2})\textsubscript{3} by comparison with those expected for the ring-containing product (105) i.e. similar in appearance to those in \(\alpha\)-acetoxypyridone (83).

### 3.4 LTA-Methanol Mediated Ring Cleavage in 6-Membered Ring \(\alpha-(Q\textsuperscript{1}NH)\)-Substituted Ketones

The oxidation of \(\alpha\)-Q\textsuperscript{1}NH-\(\beta\)-ketoester (85) with LTA in methanol gave a mixture of ring-opened imine-diesters (107) and (108) as a result of some ester exchange having occurred. These two imine-diesters were separated by flash chromatography; from measurement of respective peaks in their NMR spectra their C=N double bond isomer ratios were 2.4 : 1 and 4.1 : 1 respectively (Scheme 56). In the NMR spectra of both
compounds (107) and (108) the methyl groups of the isopropyls are equivalent indicating that rotation around their N-N bonds are fast on the NMR time-scale.

A similar ring cleavage reaction occurred in the reaction of (88) with LTA in methanol. In this case the imine-ester product (109) was present in a 5 : 1 ratio of C=N isomers and chromatography afforded the major isomer in pure form. In the NMR spectrum of (109) the methyl groups of the isopropyl are non-equivalent, indicating that in this particular compound, rotation around the N-N bond is slow on the NMR time-scale, so rendering the groups diastereotopic (Scheme 57). The greater barrier to N-N bond rotation in this compound (compared with imine-ester (107)) is a result of the increased steric hindrance around this bond from the methyl group in (109).
Oxidation of the 5-membered ring $\alpha$-$\text{Q}^1\text{NH}$-substituted ketone (93) with LTA in methanol gave the imine-ester (110) as a 5.2 : 1 ratio of C=N isomers (Scheme 58). The minor component of this mixture was shown to be identical with the major C=N double bond isomer in an authentic sample prepared by heating the keto-ester (111) with 3-aminoquinazolinone (8) at 130 °C: in this case the C=N isomer ratio was -1 : 7. A crystalline sample of the pure major C=N isomer of (110) in this latter case was obtained from ethanol. On heating at 250 °C for 30 min. it was converted by thermodynamic equilibration into a 1 : 6 ratio of double bond isomers in which the major component is believed to have the Q and methyl groups cis. The quinazolinone ring has apparently a shielding effect on the imine methyl group which is cis to it in the NMR spectrum of this isomer ($\delta$ 1.85) compared with $\delta$ 2.35 for the compound having the Q and methyl groups trans (see Chapter 4).
A mechanism for the LTA oxidations reported in this chapter which accounts for the different course taken in dichloromethane and in methanol is shown in Scheme 59. Since neither chloroesters (100) nor (102) are affected, the keto group is required for both the ring-cleavage and the ring-expansion reactions. Coordination of the LTA to the carbonyl oxygen is presumably the first step in the oxidations of ketones with this reagent.\(^6\)

In methanol, the carbocation (112) is trapped by the solvent and fragmentation with elimination of lead di-acetate occurs. Intermediates analogous to the fragmentation...
product (110) have previously been proposed in LTA oxidations of α-amino ketones but initial attack of lead IV on nitrogen was proposed in this case.

Ring expansions of cyclic α-amino ketones are known, with incorporation of the nitrogen into the ring, by way of nitrogen centred radical intermediates (Scheme 60). However, in the present work there was no evidence for the intermediacy of radicals even though the QNR radical might be expected to be relatively stabilised.
Conclusion: Cyclic β-keto esters and enol silyl ethers are converted into the corresponding α-(Q\(1\)NH)-cyclic ketone derivatives by reaction with Q\(1\)NHOAc (14). Further oxidation of these products with LTA gives products whose nature depends on the solvent used.

In dichloromethane, 5-membered ring ketones give ring-expanded products. These are chiral molecules as a result of the N-N chiral axes they contain. If prepared in enantiopure form they could prove useful for the synthesis of enantiopure substituted tetrahydro-α-pyridones by diastereoselective addition to the enamide double bond followed by N-Q bond cleavage.

In methanol, ring-cleavage occurs to give e.g. imine-esters containing three differentiated electrophilic carbon atoms in the chain which are potential amino acid precursors. Therefore both the ring-cleavage reactions in methanol and ring-expansion reactions in dichloromethane could prove useful in synthesis.
CHAPTER FOUR
4.1 Introduction

The previous chapter dealt with the formation of N-(quinazolin-3-yl)-imines from LTA mediated ring-cleavage reactions using methanol as solvent. This chapter is concerned with their synthesis by condensation of 3-aminoquinazolinones and ketones and investigates the potential use of these imines in the formation of enantiopure amines or amino acids.

Imines of enantiopure L-amino-2-methoxymethylpyrrolidine (SAMP or RAMP) have for some time been used by Enders et al\textsuperscript{5} to bring about overall enantioselective synthesis of \( \alpha \)-substituted aldehydes or ketones as in Scheme 61.

This synthesis is based on the diastereoselective \( \alpha \)-alkylation of sulfenylated acetaldehyde SAMP hydrazones, followed by a chemoselective oxidative cleavage with...
ozone. Very similar reactions have been carried out using N-aminoaziridinyl hydrazones (113).66

For N-(quinazolinon-3-yl)-imines (hydrazones) there are some stereostructural features of interest, some of which have been touched upon in Chapter 3.

Scheme 62

Firstly there is the very high barrier to inversion at the sp2-hybridised exocyclic nitrogen which allows the separation of double bond isomers of the imine.

Secondly, with the 2-substituent on the Q as a chiral centre, a high enough barrier to rotation around the N-N bond would result in isolable diastereoisomers (Scheme 62). Previous experimental results suggest that this barrier is not sufficient to allow this isolation but the possibility that one rotamer might be favoured over another or might react faster than the other still exists.
The good leaving group ability of the quinazolinone ring was revealed by Edwards\(^1\) when he attempted alkylation reactions under basic conditions \(\alpha\) to the exocyclic nitrogen in compounds of the type (114).

\[
\text{base} \quad \text{Q}^- \quad + \quad \begin{pmatrix} \text{R}^1 \quad \text{N} \quad \text{R}^2 \\ \text{H} \quad \text{O} \end{pmatrix}
\]

(114)

It was therefore also of interest to determine if this loss of Q would occur from N-(quinazolinon-3-yl)-imines.

4.2 Investigations into the Leaving Group Ability of the Quinazolinone Ring in N-(Quinazolinon-3-yl)-Imines

The Beckmann rearrangement\(^6\) is a well known method for the conversion of oximes into amides using \(\text{PCl}_5\), although reagents such as \(\text{SOCl}_2\)\(^6\) and polyphosphoric acid\(^9\) can be used (Scheme 63).

By analogy, the rearrangement of N(Q)-imines could also give amides if the elimination of Q was possible.
The hydrazone (115) used in these reactions was prepared from 3-aminoquinazolinone (17) and 2-heptanone by heating at 130 °C (Scheme 64).

\[
\begin{align*}
\text{NH}_2 & \quad \text{Q}^2 \\
\text{O} & \quad 130 \degree C \\
(17) & \quad (115)
\end{align*}
\]

Scheme 64

The NMR spectrum of this compound shows the two methylene protons of the ethyl side chain to be diastereotopic, due to the N-N chiral axis present. This product was obtained as a 7.7 : 1 ratio of C=N double bond isomers, the major component having the Q and methyl groups cis (see Chapter 3). This is deduced from the observed shielding effect of the quinazolinone ring on the imine methyl group in the NMR spectrum of this isomer (δ 1.83) compared with δ 2.29 for the compound having the Q and methyl groups trans. The carbon NMR spectrum of the major component shows clearly the presence of the C=N group at δ 181.85.

The Beckmann rearrangement was attempted on the major isomer of (115) using either TMS triflate or polyphosphoric acid. No reaction occurred with either reagent, indicating a poor leaving group ability of the Q group under the conditions used (Scheme 65).
TMS triflate or polyphosphoric acid $\rightleftharpoons X \rightleftharpoons \text{R}^-$

Scheme 65

Oxime tosylates are converted by base into $\alpha$-amino-ketones (the Neber rearrangement) $^7$ (Scheme 66).

R $\rightleftharpoons$ H$_2$O

Scheme 66

Hydrazone (115) was treated with LDA in the hope that an analogous elimination of Q would occur to give the azirine (116) or ring-opened products derived from it. However, the only material isolated from this reaction was unreacted starting material (Scheme 67).

Scheme 67
4.3 Preparation of \( N\)-(Quinazolinon-3-yl)-Imines and Examination of their Reduction with Sodium Borohydride

The title \( N\)-imines (hydrazones) are prepared in high yield from the reaction of 3-aminoquinazolinone (117) with an aldehyde or ketone (as described previously). Reaction with a ketone gives a mixture of \( C=N \) double bond isomers, generally in a disparate ratio (\( > 5:1 \)) which can be separated by chromatography. In Scheme 68, a chiral group is placed at the 2-position of the \( Q \) ring. Reduction of a single \( C=N \) isomer of this compound with sodium borohydride might give \( N(Q) \)-amine (118) highly diastereoselectively. Reductive cleavage of the \( N-N \) bond in a single diastereoisomer would then deliver the amine (119) in enantiopure form if the 3-aminoquinazolinone used initially was enantiopure.

This synthesis was investigated using achiral \( N(Q) \)-imines initially. Hydrazone (120) was produced from (8) and 2-heptanone as a 9.6 : 1 ratio of \( C=N \) double bond isomers.
Chromatography afforded the major trans-isomer and a proton NMR spectrum indicates the isopropyl methyl groups are non-equivalent as expected. Reduction of (120) with an excess of sodium borohydride gave not only N(Q)amine (121) but also (122) and (123) which arise from competitive reduction at the imine group of the quinazolinone (Scheme 69).
The expected product (121) from this reaction shows very broad peaks in its proton NMR spectrum at 298 K. The maximally broadened signal at δ 3.83 indicates that the coalescence temperature for N-N bond rotation has been reached; when a proton NMR spectrum is run at 235 K, this signal separates into two heptets at δ 3.93 and 3.82. The process which is becoming fast on the NMR time-scale here is believed to be rotation around the N-N bond (Scheme 70) and from these data, the barrier for this rotation was calculated as ΔG* = 60 kJ / mol (see Appendix 2).
Compound (122) has had both of its imine groups reduced, so as a consequence two chiral centres have been created. Two diastereoisomers were obtained but only one was obtained pure. The proton NMR spectrum of the pure diastereoisomer contains sharp signals indicating either that \( \text{N-N} \) bond rotation is fast on the NMR time-scale or that the equilibrium favours one rotamer over the other.

The final product (123) from this reaction has had only the imine group of the quinazolinone ring reduced. The proton NMR spectrum of this compound also shows only sharp signals. The isopropyl methyl groups are non-equivalent due to the adjacent chiral centre present.

This compound was reduced further with sodium borohydride and gave (122) as a mixture of diastereoisomers, thereby confirming its structure and suggesting that formation of the tetrahydro-derivative (122) proceeds via the dihydro-derivative.

To help reduce the likelihood of competitive attack at the imine group of the quinazolinone ring, an imine (124) was produced from a quinazolinone containing a more bulky 2-substituent.
Reduction of hydrazone (124) with sodium borohydride occurred at the ester and exocyclic imine groups only, with no competitive attack at the quinazolinone imine (Scheme 71). The two bulky phenyl groups apparently shield the imine of the quinazolinone ring and so prevent reaction with sodium borohydride as expected. The hydrazone alcohol (125) was further reduced to give more of amine (126). This compound shows very broad signals in its NMR spectrum at room temperature (cf. (121)). When a spectrum was run at 378 K, the signals sharpened up considerably since N-N bond rotation now becomes fast on the NMR time-scale at this temperature.

These reactions were then carried out using chiral quinazolinones. The production of a chiral N(Q^2)-imine was attempted by heating 3-aminoquinazolinone (127) \(^27\) with butyraldehyde (Scheme 72).
The cyclised product (128) was in fact produced as a 1.8 : 1 ratio of diastereoisomers. Fractional crystallisation using ethanol / water gave the pure major diastereoisomer (128a): in a double irradiation NMR experiment the NH signal at δ 6.05 was irradiated and this caused the adjacent CH signal to collapse to a triplet.

In order to prevent this cyclisation occurring, the OH must be protected and its methylation was carried out by the method of Coogan.71

Reaction of (129) with 2-heptanone gave a 4.8 : 1 ratio of NQ^-imine double bond isomers (130a) and (130b). Separation was achieved by column chromatography (Scheme 73). The major trans-isomer (130a) is present as a 1 : 1 ratio of N-N bond rotamers at room temperature. This is apparent from the two signals for the CHOCH₃ proton at δ 4.48 and 4.63 in the NMR spectrum at 298 K. At 343 K these two signals are replaced by a sharp quartet at δ 4.58 indicating at this temperature N-N bond rotation is fast on the NMR time-scale. From these values a barrier to N-N bond rotation ΔG° = 65 kJ / mol was calculated.
The NMR spectrum of the minor cis-diastereoisomer (130b) showed a 1.3 : 1 ratio of rotamers present at room temperature. Reduction of the major diastereoisomer (130a) with sodium borohydride gave dihydroquinazolinonylimine (131) in 29% yield apparently as a single diastereoisomer and a mixture of inseparable products (Scheme 74).

The structure of this dihydro-Q⁶-imine (131) was confirmed by proton NMR including double irradiation experiments: irradiation of the CH signal at δ 4.55-4.59 caused the collapse of the CHOCH₃ signal to a quartet, thereby confirming the coupling. Clearly, the chiral 2-substituent on the quinazolinone wasn't effective in shielding the quinazolinonyl imine group from reduction. From the results of experiments reported previously, a more
bulky substituent on the chiral centre is required to inhibit this unwanted reduction. The hydrazone (132) was therefore prepared in 84% yield from racemic 3-aminoquinazolinone (133)\(^4\) and heptanone (Scheme 75).

\[
\begin{array}{c}
\text{Q}^7 \\
\text{NH}_2
\end{array}
\xrightarrow{130 \, ^\circ \text{C}}
\text{Q}^7
\begin{array}{c}
\text{N}
\end{array}
\text{CH}_2\text{CH}_3
\]

(133) \quad (132)

Scheme 75

Chromatography gave a single C=N double bond isomer of hydrazone (132) whose proton NMR spectrum indicated that again a 1:1 ratio of rotamers was present at room temperature. Reduction of this hydrazone (132) gave the amine (134) in 74% yield with no competitive attack at the imine group of the quinazolinone ring (Scheme 76). At room temperature most of the signals in the proton NMR spectrum of this amine are very broad. At 373 K, these signals sharpen and a 1.2:1 ratio of diastereoisomers is seen to be present which were not separated by column chromatography.

\[
\begin{array}{c}
\text{Q}^7 \\
\text{N}
\end{array}
\xrightarrow{\text{NaBH}_4}
\text{Q}^7
\begin{array}{c}
\text{N}
\end{array}
\begin{array}{c}
\text{H}
\end{array}
\begin{array}{c}
\text{H}
\end{array}
\text{CH}_2\text{CH}_3
\]

(132) \quad (134)

Scheme 76
The reduction of 3-acylaminoquinazolinone (9) with sodium borohydride results in the formation of amine (135) in 76% yield (Scheme 77).

![Scheme 77](image)

On heating at 250 °C and 0.2 mmHg pressure elimination occurred to give 2-isopropylquinazolinone (104) presumably via the syn-elimination illustrated in Scheme 78.

![Scheme 78](image)

**Conclusion:** The reaction of 3-aminoquinazolinones with ketones results in disparate ratios of C=N isomers of hydrazones. The barriers to N-N bond rotation in N-(quinazolinonyl)-amine (121) and N-(quinazolinonyl)-imine (130a) have been calculated. Using a bulky 2-substituent on the Q ring, reduction of the chiral hydrazone (132) occurs at the exocyclic imine group only. To bring about completely stereoselective reduction of the hydrazone
C=N double bond in compounds like (132) bearing a chiral 2-substituent on the quinazolinone ring, it is likely that a disparate ratio of rotamers will be required (see earlier). For the eventual preparation of Q-free enantiopure amines by cleavage of the N-N bond, it is clear that the chiral 3-aminoquinazolinone must be used in enantiopure form.
CHAPTER FIVE
5.1 Introduction

A large number of pyridinium imides are known, the majority having the additional substituent on the divalent nitrogen as CO$_2$R, COR, SO$_2$Ar or Ar.$^{72}$ There are several methods available for the generation of these compounds.

One route involves the condensation of acyl hydrazines with pyrylium salts (Scheme 79).

\[
\text{RCONHNH}_2 + \begin{array}{c}
\text{Ph} \\
\text{Ph}
\end{array} \rightarrow \begin{array}{c}
\text{Ph} \\
\text{N} \\
\text{COR} \\
\text{Ph}
\end{array}
\]

\[
\text{R} = \text{Ph, } p-\text{MeC}_6\text{H}_4, p-\text{MeOC}_6\text{H}_4, \text{Me}
\]

Scheme 79

A second route involves acylation of N-aminopyridinium salts (Scheme 80).

\[
\text{RCOCI} + \begin{array}{c}
\text{Ph} \\
\text{Ph} \\
\text{N} \\
\text{NH}_2 \\
\text{Ph}
\end{array} \rightarrow \begin{array}{c}
\text{Ph} \\
\text{N} \\
\text{COR} \\
\text{Ph}
\end{array}
\]

\[
\text{R} = p-\text{ClC}_6\text{H}_4, \text{PhCH:CH, PhCH}_2, n-\text{C}_9\text{H}_7
\]

Scheme 80

On pyrolysis these N-imides (136) produce isocyanates (137)$^{73}$ in a reaction which resembles the Curtius rearrangement (Scheme 81).$^{74}$
Pyridinium imides may also be prepared from the reaction of pyridines with nitrenes, e.g. thermolysis of sulfonyl azides in pyridines as illustrated in Scheme 82.

\[
\text{MeSO}_2\text{N}_3 + \text{C}_5\text{H}_5\text{N} \xrightarrow{\Delta} \text{MeSO}_2\text{NH}_2 + \text{C}_5\text{H}_5\text{N}^+\text{NSO}_2\text{Me}
\]

Scheme 82

In this case, reaction of methanesulfonyl azide with pyridine gave 1-mesylimidopyridinium imide and unsubstituted methanesulfonamide.\(^{75}\)

Recent work in this department has shown that pyridinium imides can be prepared by reaction of the 3-acetoxyaminquinazolinone (14) with pyridine and substituted pyridines.\(^{76}\) For example, pyridinium imides (138) and (139) can be prepared by the reaction of Q\(^{1}\)NHOAc (14) with pyridine and 2-methylpyridine respectively (Scheme 83).
In the NMR spectrum of imide (138), broadened signals are observed at room temperature for the methyl groups of the quinazolinone 2-isopropyl substituent and from the two ortho protons on the pyridine ring. The two dynamic processes responsible for this broadening will be discussed later.

These imides are not stable to silica chromatography and were purified by crystallisation after removal of the bulk of the pyridine. They function as aziridinating agents, e.g. heating the imide (138) with styrene at 135 °C gave the aziridine (140) in 44% yield (Scheme 84).

Similarly, aziridination of diethyl fumarate at 150 °C gave the corresponding aziridine (141) in 56% yield (Scheme 85).
It was of interest to see if formation of pyridinium imides would occur with pyridines bearing electron donating or withdrawing groups on the ring and if so, to test the ability of the resultant pyridinium imides to aziridinate alkenes.

5.2 Oxidation of 3-Aminoquinazolinones (8) and (17) with LTA in the Presence of Substituted Pyridines

The preparation of the pyridinium imide from dimethylaminopyridine and Q1NHOAc (14) was attempted but the only product isolated from this reaction was 2-isopropylquinazolinone (104) (identical in all respects to that isolated previously) (Scheme 86). Either the 3-acetoxyaminquinazolinone (14) does not react with DMAP to give the imide, or the imide is too unstable to be identified.
The pyridinium imide (142) was prepared in 37% yield by the reaction of (20) with 4-cyanopyridine. Its ability to aziridinate alkenes was tested by heating with both styrene and diethyl fumarate. In both cases, no aziridine products were formed even on heating to 200 °C (in the case of diethyl fumarate) and only partial decomposition of the imide occurred (Scheme 88).
5.3 Measurement of Rotational Barriers around each N-N bond in Pyridinium Imides (138) and (142)

Edwards\textsuperscript{76} has examined a number of NMR spectra of imide (138) at 400 MHz between -95 °C and room temperature and has identified two dynamic processes responsible for the broadening of the signals from the isopropyl methyl groups and from the two ortho protons on the pyridinium ring. The preferred stereostructure (138a,b) proposed for this imide is shown in Scheme 89.
From the coalescence temperature and chemical shift difference of the two ortho protons of the pyridinium ring, a barrier of $\Delta G^\circ = 48$ kJ / mol has been calculated (see Appendix 2) which has been assigned to that for $N_\beta - N_\gamma$ bond rotation. Assignment of this barrier to that for inversion at $N_\beta$ is ruled out since in such process interconversion of the magnetic environments of the isopropyl methyl groups would also occur which is not observed.

Similarly, a barrier of $\Delta G^\circ = 60$ kJ / mol has been calculated from the coalescence temperature and $\Delta \delta$ of the isopropyl methyl signals (see Appendix 2) and this has been assigned to that for rotation around the $N_\alpha - N_\beta$ bond. Inversion at $N_\beta$ via (A) could in principle give rise to the observed changes in the NMR spectra but it would require a higher energy sp-hybridisation of $N_\beta$ in the transition state and also unfavourable interaction between the lone pairs contained in p orbitals on $N_\alpha$ and $N_\beta$. Whereas rotation around the $N_\alpha - N_\beta$ bond can proceed via conformation (B) having sp$^3$ hybridisation for $N_\beta$ and less unfavourable interactions between lone pairs on $N_\alpha$ and $N_\beta$. Further support for this interpretation of the dynamic processes involved has been obtained from measurement of the corresponding barriers in p-cyanopyridinium imide (142).

Measurement of Rotational Barriers around each N-N Bond in p-Cyanopyridinium Imide (142)

The NMR spectrum of (142) at 233 K shows sharp signals for both the two ortho protons of the p-cyanopyridinium ring ($\delta$ 7.38 and 7.30) and also for the methylene protons of the ethyl group ($\delta$ 2.83 and 2.74). At 263 K the signals for the ortho protons become
broad and coalesce at 296 K. From these values, a barrier of $\Delta G^\neq = 62$ kJ / mol was calculated for rotation around the $N_p-N_y$ bond. This barrier is higher than that in imide (138) (48 kJ / mol) corresponding to greater $N_p$ lone pair resonance delocalisation with the pyridine ring and hence more double bond character in the $N_p-N_y$ bond.

The proton NMR spectrum of imide (142) even at 373 K shows that the signals for the methylene protons have not quite coalesced, giving a value of $\Delta G^\neq > 77$ kJ / mol for $N_g-N_p$ bond rotation. This barrier is also larger than in imide (138) which can be accounted for by a coupling of the rotation around the $N_g-N_p$ bond with that for rotation around the $N_p-N_y$ bond, i.e. the transition state for the $N_g-N_p$ rotation has an orientation around the $N_p-N_y$ bond as illustrated in (B) in Scheme 89.

The greater $N_p$ lone pair resonance delocalisation with the pyridine ring in imide (142) results in more double bond character in the $N_p-N_y$ bond as described previously. As a consequence cleavage of this $N_p-N_y$ bond would be more difficult: this accounts for the fact that this imide does not aziridinate styrene or diethyl fumarate (see below).

5.4 Preparation of Triethylammonium Imide (143)

Since the 3-acetoxyaminoquinazolinone (14) reacts with substituted pyridines to give the corresponding imides (138) and (139), it seemed likely that similar reactions may occur with different trialkylamines. This in fact proved to be the case.

Addition of triethylamine to acetic acid-free solutions of the 3-acetoxyaminoquinazolinone (14) at -20°C results in complete conversion to
triethylammonium imide (143) from examination of the solution at -20°C by NMR spectroscopy (Scheme 90).

The three methylene groups in the imide (143) appear as two broad signals in the NMR spectrum at -20 °C at δ 3.45 and 3.82 each consisting of three protons; the Q-N chiral axis renders the protons in each of these equivalent methylene groups diastereotopic. The methyl groups in the 2-isopropyl substituent are also diastereotopic. Addition of styrene (10 mol equiv.) to a solution of the imide at -20 °C and then allowing it to warm to room temperature gives the aziridine (140) in 77% isolated yield. Similarly, addition of diethyl fumarate (10 mol equiv.) to a solution of the imide gives the corresponding aziridine (141) in 83% yield. Methyl acrylate is also aziridinated by the imide (143) to give (144) in 63% yield (Scheme 91).
The efficiency of this new aziridinating agent was tested by its reaction with hex-1-ene, an alkene which gives low yields in its reaction with 3-acetoxyaminoquinazolinone (14). Aziridination of hex-1-ene (10 mol equiv.) with the triethylammonium imide (143) occurs to give the aziridine (145) in 11% yield and also the imine (146) in 35% yield (Scheme 92). 3-Acetoxyaminoquinazolinone (14) reacts with this alkene to give 15% of aziridine (145), so therefore (143) appears to give slightly lower yields than Q\(^{1}\)NHOAc (14) in this reaction.

An authentic sample of the imine (146) was obtained by the reaction of (8) with acetaldehyde. This compound presumably arises from a Stevens rearrangement,\(^ {78}\) the mechanism of which is believed to involve a radical pair as in Scheme 93.
The radicals do not drift apart because they are held together by the solvent cage.

5.5 Investigation into the Mechanism of Aziridination using Trialkylammonium Imides

Two obvious mechanisms for the title aziridination may involve either direct reaction of the imide (143) with the alkene, or alternatively, decomposition of the imide to the azaimide (N-nitrene) (147) and subsequent reaction with the alkene (Scheme 94).

either
Attempts to Identify the Mechanism of Aziridination by Competition Experiments with Different Alkenes

A variety of other amines can be used in place of triethylamine to give the corresponding imides. These include 1,4-diazabicyclooctane (DABCO) and N,N-dimethyl-α-methylbenzylamine. In each case, aziridination of a 1:1 mixture of diethyl fumarate and styrene using these imides gave approximately the same ratio of aziridines (140) : (141). The results are illustrated in Table 4 and include the same reactions using the imines derived from pyridine and 2-methylpyridine which require heating at 80°C (see earlier). The conclusion to be drawn from the identity of the ratios in Table 4 is that the nature of the trialkylamine does not affect the ratio of aziridines obtained and that this is in better agreement with an azaimide intermediate which is common to all the reactions.
Table 4: Illustrates the ratio of aziridines produced from competition experiments using different imides.

<table>
<thead>
<tr>
<th>Imide</th>
<th>Ratio of aziridines (140) and (141)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \text{Ph} )</td>
</tr>
<tr>
<td>(143)</td>
<td>1</td>
</tr>
<tr>
<td>(148)</td>
<td>1</td>
</tr>
<tr>
<td>(149)</td>
<td>1</td>
</tr>
<tr>
<td>(138)</td>
<td>1.1</td>
</tr>
<tr>
<td>(139)</td>
<td>1.1</td>
</tr>
</tbody>
</table>
Sulphimide (150) was prepared by reaction of $Q^1\text{NHOAc}$ (14) with dimethylsulphide (Scheme 95). Since the corresponding N-phthalimido-substituted sulphimide has previously been used to generate phthalimido-nitrene on heating, it was anticipated that thermolysis of this sulphimide (150) would generate the corresponding quinazolinonylnitrene.

![Scheme 95](image)

This sulphimide was also heated in the presence of the 1:1 mixture of the two alkenes described previously. Direct observation of the aziridine products by NMR was not possible due to the small yield of aziridines (~10%) and the large amounts of 2-isopropylquinazolinone (104) produced. It was therefore necessary to purify the mixture by column chromatography. A 300 MHz proton NMR spectrum of the eluted products indicated a 1.3 : 1 ratio of the aziridines to be present. This somewhat different ratio to those above in Table 4 cannot be regarded as strong evidence against an azaimide (N-nitrene) intermediate. Apart from the grossly inferior yield of product in this aziridination method, chromatography may have altered the ratio of aziridines by comparison with the ratio present in the crude reaction mixture. By contrast, the other ratios in the Table 4 were measured using crude reaction products. In contrast 3-acetoxyaminoquinazolinone (14) reacts (in the absence of tertiary amine) exclusively with styrene in a competition experiment using the 1:1 mixture of styrene and diethyl fumarate used above.

Aziridination of phenanthrene using the 3-acetoxyaminoquinazolinone (14) gave the aziridine (151) in 43% yield. It was hoped that on heating the aziridine it would
decompose to the azainide (N-nitrene). Unfortunately this did not occur, since no aziridine products were obtained in the presence of the two alkenes used above.

![Structure](image)

(151)

**Attempted Asymmetric Induction using Enantiopure Imides**

![Scheme](image)

(140)

(141)

Both aziridines show no optical activity

Scheme 96

Aziridinations analogous to those described above could also be carried out using enantiopure tertiary amines including (R)-\(N,N\)-dimethyl-\(\alpha\)-methylbenzylamine and quinine.

In aziridinations of styrene and diethyl fumarate with trialkylammonium imides derived
from these enantiopure amines, the product aziridines were devoid of optical activity (Scheme 96). This lack of asymmetric induction is also consistent with the absence of the chiral amine in the transition state for alkene aziridination.

**Stereospecificity in Reactions with Alkenes**

The reaction of triethylammonium imide (143) with cis- and trans- alkenes is stereospecific (Scheme 97). This indicates that the azaimide (N-nitrene) is reacting in the singlet ground state (as discussed previously for phthalimido nitrene in Chapter 1).
Kinetic Studies

Reactions zero order with respect to alkene

Scheme 98

Kinetic studies using the triethylammonium imide (143) in reaction with styrene were monitored by proton NMR spectroscopy. Initially, 6 mol equivalents of styrene were used, and the rate of appearance of aziridine was monitored with respect to time. This gave a rate constant of \( k = 1.1 \times 10^{-4} \text{ s}^{-1} \) (see Appendix 3). This experiment was repeated using 3 mol equiv. of styrene and this gave a rate constant of \( k = 9.4 \times 10^{-5} \text{ s}^{-1} \). Since the rate constant for formation of the aziridine is independent of the concentration of styrene this supports a mechanism involving azaimide (N-nitrene) formation from the imide (Scheme 98). When this experiment was repeated using diethyl fumarate, the rate constants obtained were again independent of the alkene concentration supporting the mechanism above.
5.6 Analogy with Phthalimido-nitrene: Syn Selectivity in Reaction with Styrene

Further support for the azaimide as the aziridinating agent in reactions using the trialkylammonium imides above comes from analogy with aziridination of alkenes using phthalimido-nitrene which is thought to be the common intermediate from a number of chemically different precursors. In competition experiments using a mixture of methyl acrylate and styrene, this azaimide (147) exhibited a greater preference for methyl acrylate than the presumed N-acetoxyphthalimide intermediate generated in situ from N-aminophthalimide by oxidation with LTA i.e. it is also more nucleophilic (see Chapter 1). Also, in aziridination of e.g. styrene by oxidative addition of N-aminophthalimide, in which N-acetoxyaminophthalimide (23) is believed to be the aziridinating agent, the cis-N-invertomer of the aziridine is the kinetically formed product (see Chapter 1).

Formation of the corresponding cis-invertomer as the kinetically formed product also occurs in aziridination of styrene using 3-acetoxyaminquinazolinone (14) but because the rate of inversion at the aziridine ring nitrogen is faster with a quinazolinone as the N-substituent, it has not been possible to show experimentally that aziridination is completely syn selective. Aziridination of styrene via the azaimide (N-nitrene) (147) proceeds at a sufficiently lower temperature for the application of NMR spectroscopy to reveal that not only is the kinetically formed product the cis-invertomer, but also that this reaction is completely syn-selective (> 20 : 1). After 1 h at -40 °C, signals at δ 3.20 (heptet, J 6.8 Hz, CH₃CH₂CH₂), δ 3.36, 3.45 and 3.72 (azir. ring-H) were visible from the kinetically formed cis-invertomer (140a). When this solution was allowed to warm to room temperature, then
re-cooled to -40 °C, these signals were replaced by those at δ 2.88, 2.94, and 3.41-3.58 corresponding to the thermodynamically preferred trans-invertomer (140b) (Scheme 99).

The same preference for syn-aziridination for the two aziridinating agents, the 3-acetoxyaminoquinazolinone (14) and the azaimide (147), can be accounted for in terms of two similar transition states (Figure 11). In both there is an attractive interaction between the quinazolinone carbonyl carbon and the phenyl ring of styrene which leads to the above syn-selectivity.79
5.7 Diastereoselectivity in Aziridinations via N-(Quinazolinonyl)azainiides (N-nitrenes)

Reaction of (154) and (156) with Styrene

Aziridination of styrene using the enantiopure ammonium imide (154) gave aziridine (155) in 63% yield and a 300 MHz proton NMR spectrum on the crude product indicated a 9 : 1 ratio of diastereoisomers present. When this experiment was repeated using the DABCO-derived QN-imide (156) a 9.6 : 1 ratio of diastereoisomers was obtained. The similarity in these ratios and the lack of dependence on the nature of the amine is further evidence for an azainide intermediate (Scheme 100).
In contrast, the 3-acetoxyaminoquinazolinone (157)\textsuperscript{80} reacts with styrene to give a 4.6 : 1 ratio of diastereoisomers of (155) (identical by NMR comparison with a spectrum of the same ratio of these diastereoisomers obtained by Williams).\textsuperscript{80} Therefore in this case, the stereoselectivity of the aziridination is higher using the QN-imide (155).

**Reaction of (158) with Cyclohexen-ol**

\[
\begin{align*}
\text{Q}^2 & \quad \text{N}^+ \\
(158) & \quad \text{AcCl} \\
\text{Pyridine} & \quad \text{AcCl} \\
\text{AcCl} & \quad \text{Pyridine}
\end{align*}
\]

\[
\begin{align*}
\text{OH} & \quad \text{Ac}_{2}O \\
(159a) & \quad (159b) \\
9.3 : 1 & \quad 20 : 1
\end{align*}
\]

Scheme 101

Aziridination of cyclohexenol with Q\textsuperscript{2}N-imide (158) followed by acetylation gave aziridine (159) as a 9.3 : 1 mixture of diastereoisomers (159a : 159b) (cis : trans) (Scheme 101). By comparison, reaction of (20) with cyclohexenol followed by acetylation gave (159) in a ~ 20 : 1 ratio\textsuperscript{81} which has been rationalised by the transition state shown in Figure 12 and which is analogous to that used to account for the syn-selectivity of cyclohexenols upon epoxidation with peroxyacids. The hydrogen bonding present in the transition state for the epoxidation appears to be easier with the hydroxyl group equatorially disposed.\textsuperscript{27}
The stereoselective formation of the cis-aziridine in the reaction of azaindole with cyclohexenol is at first surprising. However, Adam and Nestler have shown that using certain allyl alcohols, epoxidation using m-chloroperoxybenzoic acid and the ene reaction using singlet oxygen (via a peroxide intermediate) show very similar diastereoselectivities. Since the azaindole is isoelectronic at nitrogen with singlet oxygen at oxygen and since 3-acetoxyaminoquinazolinone (20) is a nitrogen analogue of a peroxy acid, similar diastereoselectivities in their reactions with cyclohexenol is less surprising.

**Conclusion:** The rotational barriers around each N-N bond in 4-cyanopyridinium imide (142) have been measured. The reaction of 3-acetoxyaminoquinazolinones with tertiary amines results in the formation of imides. These compounds react with alkenes at -30 °C to give aziridines. The reactivity of the aziridinating intermediate is consistent with its formulation as an azaindole (N-nitrene). This azaindole appears to be more nucleophilic than the 3-acetoxyaminoquinazolinone but has an aziridination reactivity profile remarkably similar to it.
CHAPTER SIX
6.1 Introduction

The previous chapter dealt with the aziridination of alkenes via in situ generation of the quinazoline N-nitrene. The work contained in this chapter is concerned with the aziridination of alkenes using 3-acetoxyaminoquinazolinones in the presence of HMDS or its analogues and the increased yields associated with the use of these silylamine derivatives.

Increased yields of aziridines, or aziridine-derived products from the oxidation of 3-aminoquinazolinones with LTA can be brought about in one of two ways. The first involves the use of 3-acetoxyamino-2-trifluoromethylquinazoline (160) as the aziridinating agent. This compound is much more stable than other 2-substituted-3-acetoxyaminoquinazolinones where the 2-substituent is e.g. Et, t-Bu, CO₂Et and CMeCl₂. It is isolated as a crystalline solid and is stable at room temperature for several days. The higher yields of aziridines obtained with this compound are thought to be a consequence of its lack of basicity and hence relative stability towards acetic acid which is known to accelerate the decomposition of these 3-acetoxyaminoquinazolinones.

![Scheme 102](image-url)
For example, hex-1-ene reacts with the 3-acetoxyamino-2-trifluoromethylquinazolinone (160) to give the aziridine (161) in 51% yield (Scheme 102), but when the 2-ethyl analogue is used aziridine (162) is produced in only 11% yield.

The second way in which aziridination yields can be increased involves the addition of trifluoroacetic acid to the aziridination mixture. Aziridination of hex-1-ene in the presence of 3 mol equiv. of TFA gives aziridine (162) and the ring-opened trifluoroacetate (163) in 64% and 11% yields respectively (Scheme 103).

When 6 mol equiv. of TFA are used, aziridine (162) and ring-opened product (163) are both obtained in 35% yield since more of the aziridine (162) is ring-opened by trifluoroacetic acid. However, there are other aziridines which are stable under these conditions, e.g. (164)
In these reactions, the TFA is believed to protonate the quinazolinone amide carbonyl oxygen and assists in the departure of the acetoxy group (see Figure 13).

![Figure 13](image)

### 6.2 Aziridination of Alkenes in the Presence of HMDS

Preliminary studies involved the aziridination of styrene using 3-acetoxyaminoquinazolinone (14) in the presence and absence of HMDS.

![Scheme 104](image)
The results showed a slight increase in yield of aziridine (140) in the presence of HMDS (2 mol equiv.) (Scheme 104).

\[
\begin{array}{c}
\text{Q}^1 \\
\text{NHOAc} \\
(14)
\end{array}
\xrightarrow{\text{HMDS}}
\begin{array}{c}
\text{Q}^1 \\
\text{N} \\
(145)
\end{array}
\]

Scheme 105

More impressive increases in yield are obtained using hex-1-ene (3 mol equiv.) (Scheme 105). In the absence of HMDS a 22% yield was obtained (from NMR). When HMDS (2 mol equiv.) was present a 78% yield (NMR) was obtained; an increase from 2 to 10 mol equiv. of HMDS has no effect on the yield of aziridine (145).

Naphthalene is particularly difficult to aziridinate with the 3-acetoxyaminoquinazolinone (14) and a yield of ~14% of the bis-aziridine (165) is obtained. Aziridination of naphthalene (3 mol equiv.) using Q^1NHOAc (14) in the presence of HMDS (2 mol equiv.) gave both the mono-aziridinated product (166) (Figure 14) and also the di-aziridinated product (165) in 20% and 11% yields respectively (Scheme 106).
The proton NMR spectrum of (166) shows inter alia diastereotopic methyl groups from the isopropyl group (δ 1.46 and 1.50, 2 x d, J 6.7 Hz, CH\textsubscript{3}CHCH\textsubscript{3}). The di-aziridine (165) has two doublets for each equivalent isopropyl containing diastereotopic methyl groups and two doublets for two pairs of equivalent aziridine protons in its NMR spectrum (δ 3.74 d, J 8.3 Hz, NCH\textsubscript{3}, δ 4.18 d, J 8.3 Hz, NCH\textsubscript{3}). The significant yield of di-aziridine (165) in this reaction is not unexpected since the mono-aziridine (166) would be expected to be more reactive than naphthalene towards aziridination by virtue of the styrenoid unit that it contains.

When the aziridination is carried out using 0.5 mol equiv. of naphthalene, the only product present was the di-aziridine (165) in 68% yield by NMR spectroscopy and isolated in 46% yield after column chromatography: presumably the reduced yield is due to its instability to chromatography.

Oxidation of 3-aminoquinazolinone (8) in the presence of allyl chloride (3 mol equiv.) gave no aziridine product from examination of the proton NMR spectrum of the crude reaction mixture. However, when the reaction was repeated in the presence of HMDS, aziridine (167) was obtained in 34% isolated yield (Scheme 107).
The NMR spectrum of aziridine (167) showed the protons within the chloromethyl group and also the isopropyl methyl groups to be diastereotopic. In the presence of HMDS, therefore, aziridination of otherwise wholly unreactive alkenes can be brought about.

Another example involves the aziridination of phenol. In the presence of HMDS, Q\(^{1}\)NHOAc (14) reacts with phenol to give the substituted trimethylsilyl ether (168) in 61% yield (Scheme 108), whereas in the absence of HMDS, no reaction occurs with phenol.

Presumably, silylation of phenol is the first reaction that occurs and then aziridination followed by ring-opening / aromatisation gives the o-substituted product only (168).
Stereospecificity in Reaction of (14) with HMDS

Reaction of Q^NHOAc (14) with diethyl maleate in the presence of HMDS gave only the cis-aziridine (169) in 33% yield. (A 13% yield of aziridine (169) is obtained in the absence of HMDS). Under the same conditions, reaction with diethyl fumarate gave only the trans-aziridine (141), indicating that the reactions are stereospecific with retention of the alkene configuration in the product (Scheme 109).

The NMR spectrum of (169) shows the methyl groups of the isopropyl group to be equivalent. This is consistent with the plane of symmetry present.
Comparison of Yields (by NMR) in Aziridination Reactions using O$_2$NHOAc (14) in the Presence or Absence of HMDS

<table>
<thead>
<tr>
<th>Substrate</th>
<th>HMDS (mol equiv.)</th>
<th>NMR yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>styrene</td>
<td>–</td>
<td>86</td>
</tr>
<tr>
<td>styrene</td>
<td>2</td>
<td>89</td>
</tr>
<tr>
<td>hex-1-ene</td>
<td>–</td>
<td>22</td>
</tr>
<tr>
<td>hex-1-ene</td>
<td>2</td>
<td>78</td>
</tr>
<tr>
<td>hex-1-ene</td>
<td>10</td>
<td>78</td>
</tr>
<tr>
<td>naphthalene</td>
<td>–</td>
<td>14</td>
</tr>
<tr>
<td>naphthalene</td>
<td>2</td>
<td>68</td>
</tr>
<tr>
<td>allyl chloride</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>allyl chloride</td>
<td>2</td>
<td>34</td>
</tr>
<tr>
<td>phenol</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>phenol</td>
<td>2</td>
<td>61</td>
</tr>
<tr>
<td>diethyl maleate</td>
<td>–</td>
<td>13</td>
</tr>
<tr>
<td>diethyl maleate</td>
<td>2</td>
<td>41</td>
</tr>
</tbody>
</table>

Table 5: Summarises the yields (by NMR) in several aziridination reactions.
6.3 Investigation into the Stability of $Q^1\text{NHOAc}$ (14) in the presence of HMDS

A solution of the 3-acetoxyaminoquinazolinone (14) was prepared and divided into two and HMDS (2 mol equiv.) was added to one of them. After leaving both solutions at 5 °C for 10 min, styrene (3 mol equiv.) was added to each and the percentage yields of aziridine (140) present after work up measured by NMR spectroscopy. For the reactions carried out with and without HMDS the yields of aziridine were 52% and 69% respectively.

It is known that base-washed solutions of $Q^1\text{NHOAc}$ (14) are more stable than in the presence of acetic acid. In the presence of HMDS the acetic acid will be removed by reaction with HMDS. In spite of this the $Q^1\text{NHOAc}$ (14) decays faster in the presence of HMDS. The fact that this solution is less stable therefore rules out the possibility that HMDS is simply removing the acetic acid.

**Low Temperature NMR Studies**

A solution of 3-acetoxyaminoquinazolinone (14) in the presence of HMDS was monitored by proton NMR spectroscopy between -20 °C and room temperature. The only new signals to appear were those assignable to 2-isopropylquinazolinone (104) (Scheme 110).

\[
\begin{align*}
Q^1_{\text{NHOAc}} \quad (14) & \quad + \quad [(\text{Me})_3\text{Si}]_2\text{NH} \\
\text{at } -20^\circ\text{C} \quad \text{to} \quad \text{RT} & \quad \rightarrow \\
Q^1_{\text{H}} \quad (104)
\end{align*}
\]

Scheme 110
6.4 Investigation into Asymmetric Induction in Aziridinations using Q\textsuperscript{NHOAc} (157) and HMDS

It was of interest to examine reagent-controlled diastereoselectivity in the aziridination of alkenes in the presence of HMDS to provide evidence for the nature of the species involved. For this purpose, aziridination of styrene using Q\textsuperscript{NHOAc} (157) in the presence of HMDS was carried out and gave a 4.5 : 1 ratio of diastereoisomers of (155) (Scheme 111). This ratio is almost identical to that obtained in the same reaction carried out by Williams\textsuperscript{80} in the absence of HMDS which suggests that we are dealing with a modified 3-acetoxyaminoquinazolinone species and not a new aziridinating agent.
6.5 Reactions of $\text{Q}^1\text{NHOAc}$ (14) with Hex-1-ene in the Presence of HMDS, its Analogues and Silylated Amines

Since the yields of aziridines are significantly increased in the presence of HMDS it was of interest to examine analogues of similar compounds to HMDS and determine their effect on aziridination. The results are summarised in Table 6.

<table>
<thead>
<tr>
<th>HMDS analogue or amine</th>
<th>2 mol equiv. (g)</th>
<th>NMR yield (%) of (145)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMDS</td>
<td>0.8</td>
<td>78</td>
</tr>
<tr>
<td>[PhMe$_2$Si]$_2$NH</td>
<td>1.41</td>
<td>52</td>
</tr>
<tr>
<td>t-BuNSiMe$_3$</td>
<td>0.72</td>
<td>16</td>
</tr>
<tr>
<td>—</td>
<td>—</td>
<td>22</td>
</tr>
<tr>
<td>Me$_3$SiOC(CH$_3$)=NSiMe$_3$</td>
<td>1.0</td>
<td>10</td>
</tr>
<tr>
<td>NH$_3$</td>
<td>0.08 (in CH$_2$Cl$_2$)</td>
<td>17</td>
</tr>
</tbody>
</table>

Table 6: Illustrates the effectiveness of different silylamines on aziridination of an alkene.

From these results it is evident that using hex-1-ene as the alkene the best yield is obtained with HMDS.

In competitive aziridinations of styrene and diethyl fumarate using $\text{Q}^1\text{NHOAc}$ (14) in the presence of HMDS and its analogues the ratios of products obtained (between 3.5 : 1 and 2.7 : 1) are very similar (Table 9) (see Experimental). It is significant that the ratios in each case differ from those obtained either in the absence of any silylamine (reaction only
with styrene) or from reactions in which the azaimide (Q\(\tilde{N}\)) is believed to be an intermediate (1 : 1).

6.6 Discussion of the Mechanism of Aziridination in the Presence of HMDS

In the presence of acetic acid, HMDS is a trimethylsilylating agent for alcohols. Although it is not clear at present what the involvement of HMDS and (14) is, one of the most likely explanations is that the HMDS-derived trimethylsilyl group is playing a similar role to TFA and trimethylsilylating the carbonyl group of the 3-acetoxyaminoquinazolinone. Unpublished observations\(^8\) support this explanation except that the coordination of the trimethylsilyl is with the Q carbonyl oxygen only and not with the acetoxy group also as is believed to be the case when TFA is used (Figure 15).

**Figure 15**

**Conclusion:** Aziridination of alkenes by the oxidative addition of N-aminoquinazolinones in the presence of HMDS results in increased yields of aziridine products compared to those in the absence of HMDS.
GENERAL EXPERIMENTAL
General Experimental

All 90 MHz proton NMR spectra were recorded on a Varian EM 390 spectrometer. High field proton NMR spectra were recorded on a Bruker AM 300 spectrometer at room temperature, unless stated otherwise. 400 MHz proton NMR spectra were recorded (courtesy of O. Howarth) at the University of Warwick. Infra-red spectra of crystalline compounds were determined using Nujol mulls and of liquids as dichloromethane solutions, using a Perkin-Elmer 298 spectrometer. Standard mass spectra were recorded on either a Micromass 16B spectrometer or a Kratos 'concept' 1H. Accurate mass measurements were made on the latter. Elemental analysis was carried out by CHN analysis, Wigston, Leicester. Melting points were determined on a Kofler hot stage and are uncorrected. Optical rotations were determined on a Perkin-Elmer 141 polarimeter. X-ray crystal structures were carried out by Dr J. Fawcett at the University of Leicester. Flash chromatography was carried out according to the method of Still et al\textsuperscript{85} using silica gel manufactured by Merck and Co. or Kieselgel 60 (230-400 mesh). Purifications by Chromatotron were performed using model 7924T and Kieselgel 60 (PF 254) silica plates (Merck and Co.). T.l.c. was conducted on pre-coated alumina sheets (60-254) with a 0.2 mm layer of thickness, manufactured by Merck and Co.

Light petroleum refers to the 40 - 60 °C fraction unless otherwise stated. Dry tetrahydrofuran (THF) and benzene were obtained by distillation from sodium metal in the presence of benzophenone. Dry pyridine, diisopropylamine, triethylamine, 2-methylpyridine and dichloromethane were obtained by distillation from calcium hydride. Ether refers to diethyl ether and was sodium dried prior to use. Methanol and ethanol were dried by distillation from magnesium and iodine. Routine drying of organic solutions was carried out using magnesium sulphate.
n-Butyllithium (2.5 M) and samarium diiodide (2.5 M) were used as received from Aldrich Chemical Co. Sodium hydride was purchased (Aldrich) as a dispersion in mineral oil, and was washed with dry, distilled light petroleum before use. Lead tetra-acetate was purchased as a solid under acetic acid and was filtered and freed from residual acetic acid under reduced pressure prior to use. Alkenes used in aziridination reactions were distilled prior to use. All other reactants e.g. α-methylbenzylamine, trimethylsilyl triflate, 1,4-diazabicyclo[2.2.2]octane, N,N-dimethyl-N-α-methylbenzylamine, 4-cyanopyridine, hexamethyldisilazane etc. were reagent grade unless otherwise stated and were used as received. Base washed in work up of reactions means washing with saturated aqueous sodium carbonate.

**Physical Data**

Infra-red (IR) spectra are measured in units of cm⁻¹. The abbreviations used in determining IR data are: s – strong; m – medium; w – weak; br – broad.

In nuclear magnetic resonance (NMR) spectra, chemical shifts are expressed in p.p.m. on the δ scale relative to the internal standard (TMS). The following abbreviations are used: s – singlet; d – doublet; t – triplet; q – quartet; m – multiplet; dd – doublet of doublets; ddd – doublet of doublet of doublets; dq – doublet of quartets; br – broad; Ar – aryl; azir. – aziridine; Ph – phenyl; pyrid. – pyridine; Q – quinazolinone (see list of abbreviations); DHQ – dihydroquinazolinone; J – coupling constant (Hz).

Mass spectra were determined in units of mass relative to charge (m/z) unless stated otherwise.
EXPERIMENTAL

CHAPTER TWO
Preparation of 3-amino-2-(diphenylmethyl)quinazolin-4(3H)-one (69)

Stage 1: Preparation of methyl-N-(diphenylethanoyl)anthranilate (71)

Diphenylacetic acid (30 g, 0.14 mol) was added to freshly distilled thionyl chloride (60 ml) and one drop of DMF added as catalyst. The solution was heated at 40 °C for 4 h (with exclusion of moisture), cooled to room temperature and excess thionyl chloride was removed under reduced pressure. The acid chloride was diluted with dry ether (25 ml) then added briskly to an efficiently stirred solution of methyl anthranilate (70) (47.01 g, 0.31 mol) in dry ether (800 ml). After stirring for 3 h, the insoluble methyl anthranilate hydrochloride was filtered off, the ether solution washed with hydrochloric acid (2 M, 200 ml) (twice), then water, dried and the solvent evaporated under reduced pressure. The product was crystallised from light petroleum to give colourless crystals (33.16 g, 69%) of anthranilate (71) m.p 58-60 °C (Found: C, 76.55; H, 5.65; N, 3.9. C_{22}H_{19}N_{1}O_{3} requires C, 76.5; H, 5.55; N, 4.05%); \( \nu_{\text{max}} \) / cm\(^{-1}\) 3260w, 1680s, 1605m and 1590s; \( \delta_{\text{H}} \) (d\(_6\)-DMSO, 300 MHz) 3.71 (3H, s, OC\(_2\)Me), 5.36 (1H, s, (Ph)\(_2\)CH), 7.16 (1H, ddd, J 8.0, 7.0 and 1.0 Hz, CH(Ar)), 7.25-7.49 (10H, m, 10 x CH(Ph), 7.58 (1H, ddd, J 7.8, 7.0 and 1.5 Hz, CH(Ar)), 7.89 (1H, dd, J 8.0 and 1.5 Hz, CH(Ar)), 8.40 (1H, d, J 7.8 Hz, CH(Ar)) and 10.97 (1H, s, br, NH); \( \delta_{\text{C}} \) (d\(_6\)-DMSO, 75 Mz) 52.09 (OCH\(_3\)), 58.50
((Ph)₂CH), 117.72 (CCO₃Me), 121.03, 123.24, 126.87, 128.34, 128.62, 130.41, 133.71
(7 x CH(Ar)), 139.33 (2 x C(Ph)), 167.26 and 170.19 (2 x CO); m/z (%) 345 (M⁺, 9),
178 (80), 167 (42), 165 (34) and 146 (100).

Stage 2: Preparation of 2-(diphenylethanoyl)aminobenzoic acid hydrazide (72)

\[
\begin{align*}
\text{NH}_2\text{NH}_2 & \quad \begin{array}{c}
\text{Ph} \\
\text{HN} \\
\text{Ph}
\end{array} \\
\text{HN} & \quad \begin{array}{c}
\text{Ph} \\
\text{CONHNHPh} \\
\text{Ph}
\end{array}
\end{align*}
\]

Methyl-N-(diphenylethanoyl)anthranilate (71) (31.91 g, 0.092 mol) was dissolved
in ethanol (60 ml) and hydrazine monohydrate (12.41 ml, 0.046 mol) added. The reaction
mixture was heated under reflux for 2 h then cooled to room temperature and excess
ethanol removed under reduced pressure. On cooling, the product crystallised.
Recrystallisation from ethanol gave a colourless solid (28.87 g, 91%) of 2-
diphenylethanoyl)aminobenzoic acid hydrazide (72) m.p 179-181 °C (Found: C, 72.75; H,
5.7; N, 11.95. C₂₇H₂₉N₃O₂ requires C, 73.05; H, 5.55; N, 12.15%); νmax / cm⁻¹ 3230m,
br, 1660s, 1630w and 1600s; δH (d₆-DMSO, 300 MHz) 4.70 (2H, s, NH₂NH), 5.23
(1H, s, (Ph)₂CH), 7.14 (1H, dd, J 7.8 and 1.4 Hz, CH(Ar)), 7.25-7.49 (10H, m, 10 x
CH(Ph), NHCO), 7.58 (1H, dd, J 7.9 and 1.4 Hz, CH(Ar)), 7.72 (1H, dd, J 7.9 and 1.4
Hz, CH(Ar)), 8.51 (1H, d, J 7.8 Hz, CH(Ar)) and 11.61 (1H, s, NHCO); δC (d₆-DMSO,
75 MHz) 58.82 ((Ph)₂CH), 119.92 (CCO(Ar)), 120.40, 122.82, 126.85, 127.50, 128.35,
128.54, 131.58 (7 x CH(Ar)), 138.52, 139.40 (2 x C(Ph), CONH), 166.92, 169.92 (2 x
CO); m/z (%) 345 (M+, 4), 313 (24), 312 (20), 212 (11), 178 (55), 168 (31), 167 (100), 166 (27), 165 (70), 152 (26), 149 (20) and 146 (89).

Stage 3: Preparation of 3-amino-2-(1'-phenylbenzyl)quinazolin-4(3H)-one (69)

![Chemical structure of 72 and 69](image)

2-(Diphenylethanoxy)aminobenzoic acid hydrazide (72) (27.16 g, 0.079 mol) was dissolved in ethanol (100 ml) and heated in a sealed tube at 185 °C for 2 days. On cooling to room temperature and standing overnight, the product crystallised out. Recrystallisation from ethanol gave colourless crystals of the title compound (69) (22.38 g, 87%) m.p 211-213 °C (Found: C, 77.0; H, 5.3 ; N, 12.8. C_{21}H_{17}N_{3}O requires C, 77.05; H, 5.25; N, 12.85%); ν max / cm⁻¹ 3290w, 1675s, 1600m and 1590m; δ_H (d_6-DMSO, 300 MHz) 4.80 (2H, s, br, NH₂), 6.31 (1H, s, (Ph)₂CH), 7.22-7.37 (10H, m, 10 x CH(Ph)), 7.44 (1H, ddd, J 7.9, 6.6 and 1.7 Hz, Q^4 6-H), 7.62-7.71 (2H, m, Q^4 8- and 7-H), 8.22 (1H, ddd, J 7.9, 1.4 and 0.7 Hz, Q^4 5-H); δ_C (d_6-DMSO, 75 MHz) 53.76 ((Ph)₂CH), 119.87 (CCO (Q^4)), 126.30, 126.64, 127.07, 127.99, 128.51, 129.43, 134.01 (7 x CH(Ar)), 139.78 (2 x C(Ph)), 146.39 (CN=C(Q^4)), 157.83 (CN(Q^4)), 161.55 (CO(Q^4)); m/z (%) 327 (M+, 100), 311 (24), 310 (29), 235 (39), 167 (26), 165 (37) and 152 (16).
General Procedure (A) for the Mono-Acylation of N-Aminoquinazolinones

To the given carboxylic acid (1 mol equiv.) an excess of freshly distilled thionyl chloride and 1 drop of DMF were added and the mixture was then heated at 40 °C until the reaction was complete, (1-2 h, as shown by the appearance of bands at 1835 and 1780 cm⁻¹ in the IR spectrum). Excess thionyl chloride was then removed under reduced pressure, the residual acid chloride diluted with dichloromethane (~1 ml / 1 g) and added dropwise with stirring over 2 min. to the 3-aminoquinazolinone (0.9 mol equiv.) in dichloromethane (~2 ml / 1 g) containing pyridine (1 mol equiv.) The resulting mixture was then stirred at room temperature for approximately 5 h. Further dichloromethane (40 ml) was added and the solution washed with sodium hydrogen carbonate solution, then water, dried and the solvent evaporated.

General Procedure (B) for Preparation of 3-Di-acylaminoquinazolinones from 3-Mono-acylaminoquinazolinones

To a solution of the 3-acylaminoquinazolinone (1 mol equiv.) prepared as described above, in pyridine (~3 ml / 1 g) was added the acid chloride (2-3 mol equiv.) (dropwise) over 10 min., and the reaction mixture was then stirred for 1-2 days at room temperature. Dichloromethane (40 ml) was added, the solution washed twice with sodium hydrogen carbonate solution, then water, dried and the dichloromethane removed under reduced pressure. The bulk of the pyridine was removed from the residual product on a
rotary evaporator at room temperature and oil pump pressure (0.5 mmHg), and the residue further purified by flash column chromatography on silica gel.

Acylation of 3-amino-2-isopropylquinazolin-4(3H)-one (8) using pivaloyl chloride

\[
\begin{align*}
\text{O}^1 & \underset{\text{NH}_2}{\text{Q}^1} \\
\text{OCl} & \rightarrow \\
\text{NH}_3 & \underset{\text{Cl}}{\text{Q}^1} \\
\text{(8)} & \rightarrow \\
\text{(45)} & 
\end{align*}
\]

The general procedure (A) was followed using 3-amino-2-isopropylquinazolin-4(3H)-one (8) (3 g, 0.015 mol), pyridine (1.3 ml, 0.016 mol), dichloromethane (6 ml), and pivaloyl chloride (1.64 g, 0.016 mol; prepared from the corresponding acid). The oil obtained on work-up solidified on standing overnight (4.07 g). Recrystallisation from ethyl acetate gave amide (45) as colourless crystals (2.32 g, 55%) m.p 168-170 °C (Found: C, 66.85; H, 7.35; N, 14.65. \(\text{C}_{16}\text{H}_{21}\text{N}_3\text{O}_2\) requires C, 66.9; H, 7.35; N, 14.6 %); \(\nu_{\text{max}}/\text{cm}^{-1}\) 3285m, 1715m, 1675s and 1600s; \(\delta_{\text{H}}\) (CDCl\(_3\), 300 MHz) 1.16, 1.24 (6H, 2 x d, J 6.8 Hz, CH\(_2\)CHCH\(_3\)), 1.33 (9H, s, (CH\(_3\))\(_3\)C), 3.01 (1H, heptet, J 6.8 Hz, CH\(_2\)CHCH\(_3\)), 7.36 (1H, ddd, J 8.0, 7.9 and 1.1 Hz, Q\(^1\) 6-H), 7.60 (1H, d, J 7.6 Hz, Q\(^1\) 5-H), 7.68 (1H, ddd, J 7.9, 7.6 and 1.1 Hz, Q\(^1\) 7-H), 8.10 (1H, dd, J 8.0 and 1.1 Hz, Q\(^1\) 5-H) and 8.63 (1H, s, NH, exchangeable with D\(_2\)O); \(\delta_{\text{C}}\) (CDCl\(_3\), 75 MHz) 20.13 (CH\(_2\)CHCH\(_3\)), 20.97 (CH\(_2\)CHCH\(_3\)), 27.12 ((CH\(_3\))\(_3\)C), 30.92 (CH\(_2\)CHCH\(_3\)), 38.83 ((CH\(_3\))\(_3\)C), 120.40 (CCO(Q\(^1\))), 126.31, 126.44, 127.52, 134.54, (4 x CH(Q\(^1\))), 147.04 (CN=C(Q\(^1\))), 160.58, 161.78 (CN(Q\(^1\)), CO(Q\(^1\))) and 179.06 ((CH\(_3\))\(_3\)CCON); m/z (%) 287 (M\(^+\), 53), 230 (50),
The general procedure (A) was followed using 3-amino-2-isopropylquinazolin-4(3H)-one (8) (3.85 g, 0.019 mol), pyridine (2 ml, 0.021 mol), dichloromethane (8 ml), and 2-phenylpropionyl chloride (3.16 g, 0.021 mol; prepared from the corresponding acid). The yellow oil obtained on work-up solidified on standing overnight (7.17 g). Trituration using ethyl acetate-light petroleum followed by crystallisation from ethyl acetate gave a 2 : 1 mixture of diastereoisomers (from comparison of the signals at δ 3.93 and δ 3.88 in the proton NMR spectrum below). This mixture (46) was obtained as a colourless crystalline hydrate (3.62 g, 57%) m.p 73.5-76 °C (Found: C, 67.8; H, 6.55; N, 11.9. C_{20}H_{21}N_{3}O_{2}·H_{2}O requires C, 67.95; H, 6.55; N, 11.9 %); v_{max} / cm^{-1} 3480m, 3410m, 1685s, 1670s and 1610s; δ_{H} (CDCl_{3}, 300 MHz) major diastereoisomer: 0.98, 1.15 (6H, 2 x d, J 6.7 Hz, CH_{3}CHCH_{3}), 1.57 (3H, d, J 7.1 Hz, CH_{3}CHPh), 1.90 (2H, s, br, H_{2}O), 2.70 (1H, heptet, J 6.7 Hz, CH_{3}CHCH_{3}), 3.93 (1H, q, J 7.1 Hz, CH_{3}CHPh), 7.27-7.46 (6H, m, O^{1} 6-H, 5 x CH(Ph)), 7.62-7.74 (2H, m, Q^{1} 7- and 8-H), 8.14 (1H, dd,
J 8.0 and 1.0 Hz, Q¹ 5-H) and 8.56 (1H, s, NH); minor diastereoisomer (observable peaks): 1.21, 1.31 (6H, 2 x d, J 6.8 Hz, CH₃CHCH₃), 1.66 (3H, d, J 7.2 Hz, CH₃CHPh), 3.07 (1H, heptet, J 6.8 Hz, CH₃CHCH₃), 3.88 (1H, q, J 7.2 Hz, CH₃CHPh) and 8.20 (1H, s, NH); δC (CDCl₃, 75 MHz) major diastereoisomer: 17.65, 19.90, 20.83 (3 x CH₃), 30.76 (CH₃CHCH₃), 45.04 (NCQCHCH₃), 120.45 (CO(Q¹)), 126.41, 126.45, 126.57, 126.61, 127.51, 127.63, 127.81, 128.85, 128.91, 134.73 (10 x CH(Ar)), 140.10 (C(Ph)), 147.10 (CN=C(Q¹)), 160.94, 161.93 (CN(Q¹), CO(Q¹)) and 174.24 (NCOCHPh); minor diastereoisomer (observable peaks): 18.62, 20.19, 21.13 (3 x CH₃), 31.01 (CH₃CHCH₃), 45.36 (NCQCHCH₃), 120.50 (CO(Q¹)), 134.65 (C(Ar)), 139.30 (C(Ph)), 147.04 (CN=C(Q¹)), 160.50 (CN(Q¹)), 161.75 (CO(Q¹)) and 174.80 (NCOCHPh); m/z (%) 335 (M⁺, 30), 230 (99), 132 (19) and 105 (100).

Low temperature NMR studies were carried out on a crystallised sample of (46) from ethyl acetate and dissolved in d₄-methanol at the temperatures indicated in Table 7.

<table>
<thead>
<tr>
<th>Compound dissolved at temperature / °C</th>
<th>Temperature of NMR spectra obtained / °C</th>
<th>Ratios of diastereoisomers (H₅ signal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-50</td>
<td>-50</td>
<td>1 : 7</td>
</tr>
<tr>
<td>-50</td>
<td>-40</td>
<td>1 : 5</td>
</tr>
<tr>
<td>-50</td>
<td>+25</td>
<td>1 : 2</td>
</tr>
<tr>
<td>-50</td>
<td>-40</td>
<td>1 : 2</td>
</tr>
</tbody>
</table>

Table 7: Shows the variation in ratios of diastereoisomers with temperature.
These results suggest that in crystallisation of this compound from ethyl acetate a second-order asymmetric transformation is taking place.

Acylation of 3-amino-2-(1,1-dimethylethyl)quinazolin-4(3H)-one (47) using 2-phenylpropionyl chloride

\[ O^3 \begin{array}{c} \text{NH} \end{array} HN \begin{array}{c} \text{Ph} \end{array} \]

The general procedure (A) was followed using 3-amino-2-t-butylquinazolin-4(3H)-one (47) (0.82 g, \(3.7 \times 10^{-3}\) mol), pyridine (0.34 ml, \(4.2 \times 10^{-3}\) mol), dichloromethane (2 ml), and 2-phenylpropionyl chloride (0.63 g, \(4.2 \times 10^{-3}\) mol). The solid obtained after work-up was triturated with ice cold ether, then crystallised to give the amide (48) as a colourless solid (0.9 g, 68%) m.p 167-171 °C (from ethanol / water). (Found: C, 72.05; H, 6.7; N, 12.05. \(C_{21}H_{23}N_3O_2\) requires C, 72.2; H, 6.65; N,12.05%); \(\nu\)\text{max} / cm\(^{-1}\) 3275m, 1710s, 1675s and 1595s; This compound exists as a 2.4 : 1 mixture of diastereoisomers from comparison of the integration of signals in its NMR spectrum below at \(\delta\) 3.95 and \(\delta\) 3.83. \(\delta\)\text{H} (CDCl\(_3\), 300 MHz) major diastereoisomer: 1.09 (9H, s, (CH\(_3\)_3C), 1.58 (3H, d, J 7.1 Hz, CH\(_3\)CHPh), 3.95 (1H, q, J 7.1 Hz, CH\(_3\)CHPh), 7.24-7.43 (6H, m, Q\(^3\) 6-H, 5 x CH\(_3\)(Ph)), 7.58-7.62 (1H, m, Q\(^3\) 7-H), 7.69 (1H, dd, J 7.1 and 1.4 Hz, Q\(^3\) 8-H), 8.14 (1H, dd, J 8.0 and 1.1 Hz, Q\(^3\) 5-H) and 8.46 (1H, s, NH); minor diastereoisomer (observable peaks): 1.33 (9H, s, ((CH\(_3\))\(_3\)C), 1.66 (3H, d, J 7.2 Hz,
CH₃(CHPh), 3.83 (1H, q, J 7.2 Hz, CH₃CHPh), 8.04 (1H, s, NH) and 8.16 (1H, dd, J 8.0
and 1.2 Hz, Q₃ 5-H); δC (CDCl₃, 75 MHz) major diastereoisomer: 17.50 (CH₃CHPh),
28.38 ((CH₃)₂C), 38.64 ((CH₃)₂C), 45.44 (NCOCHCH₃), 120.26 (CO(Q₃)), 126.61,
127.60, 127.72, 127.90, 128.83, 129.01, 134.69 (7 x CH(Ar)), 139.25 (C(Ph)), 146.55
(CN=C(Q₃)), 161.70, 162.00 (CN(Q₃), CO(Q₃)) and 175.05 (NCOCHPh); minor
diastereoisomer (observable peaks): 18.35 (CH₃CHPh), 28.83 ((CH₃)₂C), 38.88
((CH₃)₂C), 45.88 (NCOCHCH₃), 120.41 (CO(Q₃)), 134.58 (CH(Ar)), 139.04 (C(Ph)),
146.49 (CN=C(Q₃)), 161.28, 161.78 (CN(Q₃), CO(Q₃)) and 175.84 (NCOCHPh); m/z
(%) 349 (M+, 30), 292 (28), 202 (19), 201 (50), 188 (13), 187 (20), 175 (13), 132 (23),
105 (100), 104 (13), 103 (12) and 77 (10).
NMR spectra of a crystalline sample of (48) (from ethanol / water) were obtained in d₄-
methanol at the temperatures shown in Table 8 below.

<table>
<thead>
<tr>
<th>Temperature / °C</th>
<th>Ratio of diastereoisomers (H₅ signal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>2.4 : 1</td>
</tr>
<tr>
<td>35</td>
<td>1.8 : 1</td>
</tr>
<tr>
<td>55</td>
<td>1.5 : 1</td>
</tr>
<tr>
<td>65</td>
<td>1.5 : 1</td>
</tr>
<tr>
<td>85</td>
<td>1.5 : 1</td>
</tr>
</tbody>
</table>

Table 8: Shows the variation in ratios of diastereoisomers with temperature.

Equilibration of both diastereoisomers occurs at a temperature between 35 and 55 °C.
Acetylation of 3-(2'-phenylpropionyl)amino-2-isopropylquinazolin-4(3H)-one (46)

The general procedure (B) was followed using (46) (1 g, 2.99 x 10^-3 mol) and acetyl chloride (0.47 g, 5.98 x 10^-3 mol) in pyridine (4 ml). The black oil obtained after work-up was purified by column chromatography using silica, eluting with light-petroleum:ethyl acetate (5:1) to give (49) as a colourless solid (0.69 g, 61%) which consisted of a 1.8:1 mixture of diastereoisomers (from comparison of the signals at δ 4.08 and δ 4.91 in the NMR spectrum below). Separation was achieved using a Chromatotron with light petroleum:ether (7:1) as eluant. This gave the major imide diastereoisomer (49a) (Rf 0.20) m.p. 129-132 °C (from ethanol). (Found: C, 70.0; H, 6.2; N, 11.1. C_{22}H_{23}N_{3}O_{3} requires C, 70.0; H, 6.15; N, 11.15%; ν_{max} / cm^{-1} 1745s, 1735s, 1705s, 1600s and 1570m; δ_{H} (CDCl_{3}, 300 MHz) 0.77 (3H, d, J 6.7 Hz, CH_{3}(CH)), 1.12 (3H, d, J 6.7 Hz, CH_{3}(CH)), 1.54 (3H, d, J 6.6 Hz, CH_{3}(CHPh)), 2.45 (1H, heptet, J 6.7 Hz, CH_{3}(CHCH_{3})), 2.59 (3H, s, CH_{3}CO), 4.08 (1H, q, br, J 6.6 Hz, CH_{3}(CHPh)), 7.10-7.13 (2H, m, 2 x CH(Ph)), 7.25-7.35 (3H, m, 3 x CH(Ph)), 7.54 (1H, ddd, J 8.2, 7.1 and 1.3 Hz, Q^{1} 6-H), 7.73 (1H, ddd, J 8.2, 1.3 and 0.5 Hz, Q^{1} 8-H), 7.85 (1H, ddd, J 8.2, 7.1 and 1.6 Hz, Q^{1} 7-H) and 8.34 (1H, ddd, J 8.2, 1.6 and 0.5 Hz, Q^{1} 5-H); In d_{4}-methanol at -20 °C, there is broadening of the quartet at δ 4.05 (CH_{3}(CHPh)). δ_{C} (CDCl_{3}, 75 MHz) 20.36, 21.21, 21.80, 25.27 (4 x CH_{3}), 30.84 (CH_{3}(CHCH_{3})), 45.53 (NCO(CHCH_{3})), 120.44 (CCO(Q^{1})).
This compound was crystallised from ethanol and a single crystal X-ray structure determination carried out (see Appendix 1).

Further elution gave the minor imide diastereoisomer (49b) m.p. 144-147°C (from ethanol) Rf 0.14 (Found: C, 69.95; H, 6.15; N, 11.10. C\textsubscript{23}H\textsubscript{23}N\textsubscript{3}O\textsubscript{3} requires C, 70.0; H, 6.15; N, 11.15%); v\textsubscript{max} / cm\textsuperscript{-1} 1740s, 1705s and 1605s; δ\textsubscript{H} (CDCl\textsubscript{3}, 300 MHz) 1.14, 1.16 (6H, 2 x d, J 6.6 Hz, CH\textsubscript{3}CHCH\textsubscript{3}), 1.59 (3H, d, J 6.9 Hz, CH\textsubscript{3}CHPh), 2.20 (3H, s, CH\textsubscript{3}CO), 2.49 (1H, heptet, J 6.6 Hz, CH\textsubscript{3}CHCH\textsubscript{3}), 4.91 (1H, q, br, CH\textsubscript{3}CHPh), 7.27-7.33 (5H, m, 5 x CH(Ph)), 7.48 (1H, ddd, J 8.0, 7.2 and 1.2 Hz, Q\textsubscript{1} 6-H), 7.71 (1H, ddd, J 8.1 and 0.4 Hz, Q\textsubscript{1} 8-H), 7.81 (1H, ddd, J 8.1, 7.2 and 1.2 Hz, Q\textsubscript{1} 7-H) and 8.19 (1H, ddd, J 8.0 and 1.2 Hz, Q\textsubscript{1} 5-H); δ\textsubscript{C} (CDCl\textsubscript{3}, 300 MHz) 19.48, 21.43, 21.58, 24.16 (4 x CH\textsubscript{3}), 30.08 (CH\textsubscript{3}CHCH\textsubscript{3}), 46.34 (NCOCHPh), 120.63 (CO(Q\textsubscript{1})), 126.83, 127.21, 127.49, 127.53, 128.01, 128.58, 135.12 (7 x CH(Ar)), 139.21 (CH(Ph)), 146.87 (CN=C(Q\textsubscript{1})), 159.55 (CN(Q1)), 161.32 (CO(Q1)) and 170.80, 173.85 (2 x CO); m/z (%) 377 (M\textsuperscript{+}, 4), 230 (35), 228 (25), 132 (100) and 105 (63).

This compound was crystallised from ethanol and a single crystal X-ray structure determination carried out (see Appendix 1).

Diastereoisomer (49b) was heated in boiling d\textsubscript{8}-toluene (109 °C) and the rate of its interconversion with the other diastereoisomer was measured by changes in integration of the signal at δ 4.91 compared to the signal at δ 4.08 with time. This gave a ∆G\textsuperscript{o} value for N-N bond rotation of 121 kJ/mol (see Appendix 2).
Diacetylation of 3-amino-2-ethylquinazolin-4(3H)-one (17)

\[
\begin{array}{c}
\text{Q}^2 \\
\text{NH}_2
\end{array}
\xrightarrow{\text{Ac}_2\text{O}}
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{O}
\end{array}
\begin{array}{c}
\text{Q}^2
\end{array}
\]

(17) \rightarrow (51)

Compound (17) (2 g, 0.01 mol) was dissolved in acetic anhydride (5.7 ml, 0.06 mol) and pyridine (2.45 ml, 0.03 mol). The reaction mixture was heated at 50 °C for 24 h, then left to stir at room temperature overnight. Water was added and the mixture stirred for 30 min. before the product was extracted into dichloromethane (60 ml). The organic layer was washed with saturated sodium hydrogen carbonate solution (x 3), water, dried and the solvent removed. The bulk of the pyridine was removed on a rotary evaporator under reduced pressure (0.5 mm Hg), to yield a yellow oil (2.27 g). This oil solidified on standing and crystallisation from ethanol gave imide (51) as a colourless solid (1.94 g, 67%). m.p. 75-76 °C. (Found: C, 61.4; H, 5.6; N, 15.35. C\textsubscript{14}H\textsubscript{15}N\textsubscript{3}O\textsubscript{3} requires C, 61.5; H, 5.5; N, 15.4%); \( \nu_{\text{max}} / \text{cm}^{-1} \) 1740s, 1700s, 1605s and 1570w; \( \delta_{\text{H}} \) (d\textsubscript{6}-DMSO, 300 MHz) 1.27 (3H, t, br, J 7.2 Hz, CH\textsubscript{3}CH\textsubscript{2}), 2.41 (6H, s, 2 x CH\textsubscript{3}CO), 2.68 (2H, q, br, J 7.2 Hz, CH\textsubscript{3}CH\textsubscript{2}), 7.56-7.60 (1H, m, Q\textsuperscript{2} 6-H), 7.76 (1H, d, J 7.9 Hz, Q\textsuperscript{2} 8-H), 7.88-7.93 (1H, m, Q\textsuperscript{2} 7-H) and 8.17 (1H, d, J 7.7 Hz, Q\textsuperscript{2} 5-H); \( \delta_{\text{C}} \) (d\textsubscript{6}-DMSO, 75 MHz) 9.72 (CH\textsubscript{3}CH\textsubscript{2}), 24.28 (2 x CH\textsubscript{3}CO), 25.14 (CH\textsubscript{3}CH\textsubscript{2}), 120.08 (CO(CQ\textsuperscript{2})), 126.62, 127.09, 127.33, 135.50 (4 x CH(Q\textsuperscript{2})), 146.24 (CN=C(Q\textsuperscript{2})), 157.23 (CN(Q\textsuperscript{2})), 158.80 (CO(Q\textsuperscript{2})) and 170.12 (2 x CH\textsubscript{3}CO); m/z (%) 273 (M\textsuperscript{+}, 33), 231 (26), 214 (52), 189 (100), 173 (20), 130 (22) and 119 (26). A proton NMR spectrum at -83 °C in d\textsubscript{6}-acetone shows two
broadened signals at $\delta$ 2.85 and 2.60 for the non-equivalent methylene protons HCH(CH$_3$)$_2$ indicating the presence of an N-N chiral axis. Two broadened singlets are also observed at $\delta$ 2.60 and $\delta$ 2.20 for the COCH$_3$ groups which are of equal intensity. This indicates that the two imide conformations that are in equilibrium are the two (identical) exo-endo and endo-exo conformations.

**Di-acetylation of 3-aminoquinazolinone (69)**

![Di-acetylation reaction scheme]

To the 3-aminoquinazolinone (69) (1 g, 3.06 x $10^{-3}$ mol) in pyridine (0.27 ml, 3.36 x $10^{-3}$ mol) and dichloromethane (20 ml) was added acetyl chloride (0.24 ml, 3.36 x $10^{-3}$ mol) in dichloromethane (1 ml) as described in the procedure (B). The colourless oil obtained was purified by column chromatography with light petroleum : ethyl acetate (3 : 1) as eluant. This gave imide (52) as a white crystalline solid $R_f$ 0.52 (0.54 g, 43%) m.p. 155-156.5 °C (from ethanol) (Found: C, 72.95; H, 5.2; N, 10.2. C$_{25}$H$_{21}$N$_3$O$_3$ requires C, 73.0; H, 5.15; N, 10.2%); $\delta_H$ (d$_6$-DMSO, 300 MHz) 2.07 (6H, s, 2 x CH$_3$CO), 5.68 (1H, s, (Ph)$_2$CH), 7.28-7.41 (10H, m, 10 x CH(Ph)), 7.61 (1H, ddd, J 8.0, 7.6 and 1.0 Hz, Q$^4$ 6-H), 7.68 (1H, d, J 7.8 Hz, Q$^4$ 8-H), 7.90 (1H, ddd, J 7.8, 7.6 and 1.1 Hz, Q$^4$ 7-H) and 8.16 (1H, dd, J 8.0 and 1.1 Hz, Q$^4$ 5-H); $\delta_C$ (d$_6$-DMSO, 75 MHz) 23.96 (2 x CH$_3$CO), 51.94 ((Ph)$_2$CH), 120.05 (CCO(Q$^4$)), 126.71, 127.21, 127.72, 128.37, 128.56, 129.21, 135.74 (7 x CH(Ar)), 138.43 (2 x CH(Ar)).
\[ \text{C(Ph)}, 145.71 (\text{CN=C(Q^4)}), 157.34 (\text{CN(Q^4)}), 159.07 (\text{CO(Q^4)}) \text{ and } 170.36 (2 \times \text{CO}); \]
m/z (%) 411 (M^+, 100), 370 (11), 369 (44), 368 (11), 352 (37), 328 (11), 327 (45), 326 (10), 311 (35), 310 (35), 309 (22), 235 (23), 202 (12), 167 (43), 166 (18), 165 (55) and 152 (22).

**Mono-acetylation of 3-aminquinazolinone (69)**

\[ \text{Q}^4 \quad \text{NH}_2 \quad \overset{\text{Ac}_2\text{O}}{\longrightarrow} \quad \text{Q}^4 \quad \text{NH}_2 \text{C}^2 \text{O} \]

(69) (53)

To the 3-aminquinazolinone (69) (1 g, 3.06 x 10^{-3} mol) in dichloromethane (15 ml) was added acetyl chloride dropwise (0.24 ml, 3.36 x 10^{-3} mol) and the mixture stirred for one day. The mixture was then washed with saturated aqueous sodium bicarbonate, water, dried and the solvent removed to give a white solid. Recrystallisation from ethanol gave amide (53) (1.05 g, 93%) m.p. 228-230 °C (Found: C, 74.6; H, 5.3; N, 11.3. C_{23}H_{19}N_{3}O_{2} requires C, 74.8; H, 5.2; N, 11.4%); \( \nu_{\text{max}} \) / cm\(^{-1}\) 3070w, br, 1745s, 1725s, 1640s, 1600m and 1570m; \( \delta_{\text{H}} \) (\( \text{d}_5\)-DMSO, 300 MHz) 2.13 (3H, s, CH\(_3\)CO), 5.83 (1H, s, (Ph)\(_2\)CH), 7.20-7.44 (10H, m, 10 x CH(Ph)), 7.54 (1H, ddd, J 8.0, 7.3 and 1.0 Hz, Q\(^4\) 6-H), 7.61 (1H, d, J 7.9 Hz, Q\(^4\) 8-H), 7.82 (1H, ddd, J 7.9, 7.3 and 1.2 Hz, Q\(^4\) 7-H), 8.15 (1H, dd, J 8.0 and 1.2 Hz, Q\(^4\) 5-H), 11.01 (1H, s, br, NH); \( \delta_{\text{C}} \) (\( \text{d}_5\)-DMSO, 75MHz) 20.41 (CH\(_3\)CO), 52.25 ((Ph)\(_2\)CH), 120.48 (C(CO(Q\(^4\))), 126.27, 126.55, 126.99, 127.03, 127.39, 127.90, 128.10, 128.90, 129.16, 134.84 (10 x CH(Ar)), 139.27, 139.94 (2 x C(Ph)), 145.88 (C(N=C(Q\(^4\))), 158.70, 158.84 (C(N(Q\(^4\)), C(O(Q\(^4\)))) and 169.44 (CO); m/z
(% 369 (M+, 100), 328 (11), 327 (50), 326 (13), 311 (34), 310 (38), 309 (17), 235 (31), 167 (35), 166 (17), 165 (53) and 152 (21).

**General Procedure (C) for the Selective Acetylation of Amines**

To the amine(s) (1 mol equiv.) in dichloromethane (2ml) was added the imide (0.5 mol equiv.) in dichloromethane (1 ml / 100mg) and the solution stirred at room temperature for 2 h. Further dichloromethane (~10 ml) was added, the solution washed with water and the solvent removed under reduced pressure. The results are illustrated in Table 2 (see Chapter Two).

**Reaction of Imide (52) With Spermidine**

The general procedure (C) was followed using (52) (0.67 g, $2.34 \times 10^{-3}$ mol) and spermidine (0.17 g, $1.17 \times 10^{-3}$ mol) in dichloromethane (8 ml). In this case the organic layer was washed with 0.1M HCl to separate the acetylated spermidine (54) from (53). The aqueous layer was freeze-dried to give the HCl salt of (54) as a colourless solid (0.28 g, 90%); $\delta_H$ (D$_2$O, 250 MHz) 1.50-1.76 (m, 4H), 1.77-1.91 (m, 2H), 1.91 (s, 2 x CH$_3$CO), 2.96-3.05 (m, 4H) and 3.13-3.26 (m, 4H). This spectrum is very similar to a sample reported previously.$^{86}$

The same procedure was followed using imide (11) (0.67 g, $2.34 \times 10^{-3}$ mol). In this case a 92% yield of (54) was obtained.
Reaction of (11) with a 1 : 1 mixture of two amines

1) The general procedure (C) was followed using (11) (0.1 g, 3.48 x 10^-4 mol), diethylamine (0.025 g, 3.48 x 10^-4 mol) and piperidine (0.03 g, 3.48 x 10^-4 mol) in dichloromethane (2 ml). A proton NMR spectrum of the crude mixture (0.1 g) showed the presence of (9) and acetylated piperidine in a 1 : 1 ratio (by comparison with spectra of authentic samples).

2) The above procedure (C) was followed using (11) (0.1 g, 3.48 x 10^-4 mol), piperidine (0.03 g, 3.48 x 10^-4 mol) and 2-methylpiperidine (0.034 g, 3.48 x 10^-4 mol) in dichloromethane (2 ml). A proton NMR spectrum of the crude mixture (0.11 g) showed the presence of (9) and acetylated piperidine in a 1 : 1 ratio (by comparison with spectra of authentic samples).

3) The general procedure (C) was followed using (11) (0.1 g, 3.48 x 10^-4 mol), diethylamine (0.025 g, 3.48 x 10^-4 mol) and dimethylamine (0.016 g, 3.48 x 10^-4 mol) in dichloromethane (2 ml). A proton NMR spectrum of the crude mixture (0.09 g) showed the presence of (9) and acetylated dimethylamine in a 1 : 1 ratio (by comparison with spectra of authentic samples).

4) The general procedure (C) was followed using (11) (0.1 g, 3.48 x 10^-4 mol), dimethylamine (0.016 g, 3.48 x 10^-4 mol) and N-ethyl,N-methylamine (0.021 g, 3.48 x 10^-4 mol) in dichloromethane (2 ml). A proton NMR spectrum of the crude mixture (0.09 g)
showed the presence of (9) and the two acetylated amines and in a ratio of $> 9 : 1$ respectively (by comparison with spectra of authentic samples).

5) The procedure (C) was followed using (11) (0.1 g, $3.48 \times 10^{-4}$ mol), sec-butylamine (0.025 g, $3.48 \times 10^{-4}$ mol) and t-butylamine (0.025 g, $3.48 \times 10^{-4}$ mol) in dichloromethane (2 ml). A proton NMR spectrum of the crude mixture (0.1 g) showed the presence of (9) and the two acetylated amines and in a ratio of $> 10 : 1$ respectively (by comparison with spectra of authentic samples).

6) The procedure was followed using N-methoxydiacetamide$^{52}$ (55) (0.1 g, $7.63 \times 10^{-4}$ mol), 2-methyl piperidine (0.076 g, $7.63 \times 10^{-4}$ mol) and piperidine (0.065 g, $7.63 \times 10^{-4}$ mol) in water (5 ml). The mixture was extracted with dichloromethane, dried and the solvent removed under reduced pressure. A proton NMR spectrum of the crude mixture (0.08 g) showed the presence of acetylated piperidine only (by comparison with spectra of authentic samples).

7) The procedure was followed using (55) (0.1 g, $7.63 \times 10^{-4}$ mol), sec-butylamine (0.056 g, $7.63 \times 10^{-4}$ mol) and t-butylamine (0.056 g, $7.63 \times 10^{-4}$ mol) in water (5 ml). A proton NMR spectrum of the crude mixture (0.07 g) showed the presence of acetylated sec-butylamine only (by comparison with spectra of authentic samples).

Control experiments in which mixtures of these amines competed for acetic anhydride showed some selectivity but nothing like comparable with those using imides.
The general procedure (B) was followed using 3-aminoquinazolinone (8) (0.25 g, 1.23 x 10^{-3} mol), (S)-2-acetoxypropionyl chloride (0.93 g, 6.16 x 10^{-3} mol) in dichloromethane (0.5 ml) and pyridine (1 ml). The black oil obtained after work-up was purified by flash column chromatography using light petroleum : ethyl acetate (2 : 1) as eluant. This gave imide (59) (R_f 0.63) as a colourless oil (0.41 g, 77%) [α]_D = -46, (c = 12, CH_2Cl_2) (Found: M^+ 431.1691. C_{21}H_{25}N_3O_7 requires M^+ 431.1693); ν max / cm^{-1} 1740s, 1700s and 1600s; δ_H (CDCl_3, 300 MHz) 1.18 (3H, d, J 6.6 Hz, CH_3CH), 1.36 (3H, d, J 6.6 Hz, CH_3CH), 1.42 (3H, d, J 6.7 Hz, CH_3CH), 1.63 (3H, d, J 6.7 Hz, CH_3CH), 2.10, 2.11 (6H, 2 x s, 2 x CH_3CO), 3.43 (1H, heptet, J 6.6 Hz, CH_3CHCH_3), 4.87 (1H, q, J 6.7 Hz, CH_3CHOAc), 6.00 (1H, q, J 6.7 Hz, CH_3CHOAc), 7.47 (1H, ddd, J 8.1, 7.1 and 1.3 Hz, Q_1^1 6-H), 7.72 (1H, dd, J 8.2, 1.3 Hz, Q_1^1 8-H), 7.80 (1H, ddd, J 8.2, 7.1 and 1.0 Hz, Q_1^1 7-H) and 8.19 (1H, dd, J 8.1 and 1.0 Hz, Q_1^1 5-H); δ_C (CDCl_3, 75 MHz) 15.91, 16.33, 20.01, 20.04, 21.73, 22.35 (6 x CH_3), 30.04 (CH_3CHCH_3), 68.37 (CH_3CHOAc), 70.89 (CH_3CHOAc), 120.15 (CCO(Q^1)), 126.89, 126.93, 127.56, 135.37 (4 x CH(Q^1)), 146.71 (CN=C(Q^1)), 160.08 (CN(Q^1)), 162.84 (CO(Q^1)) and 169.87, 170.04, 170.80, 171.93 (4 x CO); m/z (%) 431 (M^+, 15), 300 (52), 274 (26), 230 (100), 188 (20), 187 (23), 173 (24), 115 (83) and 87 (93).
Acylation of 3-amino-2-isopropylquinazolin-4(3H)-one (8) using
(S)-2-acetoxypropionyl chloride

\[
\begin{align*}
\text{Q}^1 \text{NH}_2 & \quad \text{MeOCO} \quad \text{Cl} \quad \text{O} \\
\text{Q}^1 & \quad \text{H} \quad \text{N} \quad \text{OCOMe}
\end{align*}
\]

The general procedure (A) was followed using 3-aminoquinazolinone (8) (3 g, 1.48 x 10⁻² mol) and (S)-2-acetoxypropionyl chloride (2.47 g, 1.64 x 10⁻² mol) in dichloromethane (6 ml) and pyridine (1.4 ml, 1.64 x 10⁻² mol). The brown / black oil obtained was purified by column chromatography using silica, with light petroleum : ethyl acetate (2 : 1) as eluant. The product (60) was obtained as a 1.55 : 1 ratio of diastereoisomers (from comparison of signals at δ 5.50 and δ 5.45 in the NMR spectrum below) as a pale orange oil (3.52g, 75%) (Rf 0.15) (Found: M⁺ 317.1373. C₁₆H₁₉N₅O₄ requires M⁺ 317.1376); νmax / cm⁻¹ 3380w, 1740s, 1690s and 1600s; δH (CDCl₃, 300 MHz)

major diastereoisomer: 1.25-1.33 (6H, 2 x d (overlapping), CH₃CH(CH₃)), 1.70 (3H, d, J 6.9 Hz, CH₃CHOAc), 2.24 (3H, s, CH₃CO), 3.10 (1H, heptet, J 6.7 Hz, CH₃CHCH₃), 5.50 (1H, q, J 6.9 Hz, CH₃CHOAc), 7.34-7.44 (1H, m, Q¹ 6-H), 7.60-7.76 (2H, m, Q¹ 7- and 8-H), 8.05 (1H, dd, J 7.9, 1.0 Hz, Q¹ 5-H) and 9.50 (1H, s, NH); δC (CDCl₃, 75 MHz) major diastereoisomer: 17.29, 20.00, 20.80, 21.02 (4 x CH₃), 30.91 (CH₃CHCH₃),
69.78 (CH$_3$CHOAc), 120.13 (CCO(Q$^1$)), 126.33, 126.46, 127.55, 134.75 (4 x CH(Q$^1$)),
146.94 (CN=C(Q$^1$)), 160.63 (CN(Q$^1$)), 161.44 (CO(Q$^1$)) and 170.28, 171.12 (2 x CO);
minor diastereoisomer (observable peaks): 17.51, 20.16, 21.60 (3 x CH$_2$), 30.83
(CH$_3$CHCH$_3$), 69.56 (CH$_3$CHOAc), 120.32 (CCO(Q$^1$)), 146.98 (CN=C(Q$^1$), 160.63
(CN(Q$^1$), 161.71 (CO(Q$^1$)) and 169.90, 170.95 (2 x CO); m/z (%) 317 (M$^+$, 51), 231
(11), 230 (80), 203 (20), 188 (56), 187 (67), 186 (18), 175 (31), 174 (13), 173 (85), 160
(19), 146 (15), 145 (13), 130 (23), 119 (26), 115 (58), 103 (15), 92 (13), 90 (31), 87
(100), 77 (18) and 76 (23).

Acylation of 3-(2-acetoxypropionyl)amino-2-isopropylquinazolin-4(3H)-one (60)
using isobutyryl chloride

To the N-acylaminoquinazolinone (60) (0.20 g, 6.31 x 10$^{-4}$ mol) in pyridine (2 ml),
was added isobutyryl chloride (0.22 g, 2.1 x 10$^{-3}$ mol) in dry dichloromethane (0.5 ml) as
described in general procedure (B). The resulting black oil obtained was purified by
column chromatography using light petroleum : ethyl acetate (2 : 1) as eluant. This gave
imide (61) (0.19 g, 78%) as a 1.8 : 1 mixture of diastereoisomers (from comparison of the
signals at 5.35 and 6.00 in the NMR spectrum below). Separation was achieved using a
chromatotron with light petroleum : ether (7 : 1) as eluant. Imide diastereoisomer (61a)
(Rf 0.32) was isolated as a yellow oil (0.08 g, 33%) \([\alpha]_D = -1\) (c = 2, CH\(_2\)Cl) (Found: M\(^+\) 387.1791. C\(_{20}\)H\(_{25}\)N\(_3\)O\(_5\) requires M\(^+\) 387.1794); \(\nu_{max} / \text{cm}^{-1}\) 1740s, 1700s and 1600s; 
\(\delta_H\) (CDCl\(_3\), 300 MHz) 1.13 (3H, d, J 6.7 Hz, CH\(_3\)CH), 1.18, 1.22 (6H, 2 x d, J 6.7 Hz, 2 x CH\(_3\)CH), 1.36 (3H, d, J 6.7 Hz, CH\(_3\)CH), 1.64 (3H, d, J 6.7 Hz, CH\(_3\)CH), 2.10 (3H, s, CH\(_3\)CO), 2.54 (1H, heptet, J 6.7 Hz, (CH\(_3\))\(_2\)CH), 3.06 (1H, heptet, J 6.7 Hz, CH\(_3\)CH), 6.00 (1H, q, J 6.7 Hz, CH\(_3\)CHOAc), 7.47 (1H, ddd, J 8.0, 7.0 and 1.2 Hz, Q\(_1^6\)-H), 7.73 (1H, dd, J 7.7 and 1.2 Hz, Q\(_1^8\)-H), 7.80 (1H, ddd, J 7.7, 7.0 and 1.1 Hz, Q\(_1^7\)-H), 8.20 (1H, dd, J 8.0 and 1.1 Hz, Q\(_1^5\)-H); In d\(_6\)-acetone at -20 °C, significant broadening of the heptet at \(\delta\) 2.80 ((CH\(_3\))\(_2\)CHCO) and the quartet at \(\delta\) 5.97 (CH\(_3\)CHOAc) is observed by comparison with their appearance at room temperature. \(\delta_C\) (CDCl\(_3\), 75 MHz) 16.24, 19.64, 19.77, 20.48, 21.63, 22.14 (6 x CH\(_3\)), 30.21, 32.83 (2 x CH\(_3\)CHCH\(_3\)), 71.36 (CH\(_3\)CHOAc), 120.50 (COO(Q\(_1\))), 126.95, 127.20, 127.61, 135.32 (4 x CH(Q\(_1\))), 146.92 (CN=C(Q\(_1\))), 159.87 (CN(Q\(_1\))), 162.33 (CO(Q\(_1\))) and 170.70, 171.82, 179.11 (3 x CO); m/z (%) 387 (M\(^+\), 16), 301 (10), 300 (53), 274 (17), 256 (13), 231 (15), 230 (100), 187 (12), 149 (18), 115 (10), 87 (12), 71 (20), 57 (19) and 55 (11). Further elution gave diastereoisomer (61b) (Rf 0.27) as a yellow oil (0.075 g, 31%) \([\alpha]_D = -12\) (c = 10, CH\(_2\)Cl) (Found: M\(^+\) 387.1791. C\(_{20}\)H\(_{25}\)N\(_3\)O\(_5\) requires M\(^+\) 387.1794); \(\nu_{max} / \text{cm}^{-1}\) 1740s, 1700s and 1600s; \(\delta_H\) (CDCl\(_3\), 300 MHz) 1.25-1.30 (9H, m, 3 x CHCH\(_3\)), 1.36 (3H, d, J 6.7 Hz, CHCH\(_3\)), 1.50 (3H, d, J 6.5 Hz, CH\(_3\)CH), 2.14 (3H, s, CH\(_3\)CO), 3.14 (1H, heptet, J 6.7 Hz, (CH\(_3\))\(_2\)CH), 3.32 (1H, heptet, J 6.7 Hz, CH\(_3\)CHCH\(_3\)), 5.35 (1H, q, br, CH\(_3\)CHOAc), 7.50 (1H, ddd, J 8.1, 8.0 and 1.3 Hz, Q\(_1^6\)-H), 7.74 (1H, d, J 7.4 Hz, Q\(_1^8\)-H), 7.82 (1H, ddd, J 8.0, 7.4 and 1.1 Hz, Q\(_1^7\)-H), 8.25 (1H, dd, J 8.1 and 1.1 Hz, Q\(_1^5\)-H); In d\(_6\)-acetone at -20 °C, significant broadening
of the heptet at δ 3.30 \(((\text{CH}_3)_2\text{CHCO})\) and the quartet at δ 5.50 \((\text{CH}_3\text{CH}_2\text{OAc})\) was observed. δ\textsubscript{C} (CDCl\textsubscript{3}, 75 MHz) 16.67, 19.04, 19.46, 20.49, 21.70, 21.79 (6 x CH\textsubscript{3}), 30.41, 34.63 (2 x CH\textsubscript{3}CHCH\textsubscript{3}), 69.68 (CH\textsubscript{3}CH\text{OAc}), 120.62 (CO(Q\textsubscript{1})), 126.99, 127.41, 127.62, 135.30 (4 x CH(Q\textsubscript{1})), 146.85 (CN=CH(Q\textsubscript{1})), 160.00 (CN(Q\textsubscript{1})), 162.08 (CO(Q\textsubscript{1})) and 170.20, 171.62, 177.37 (3 x CO); m/z (%) 387 (M\textsuperscript{+}, 13), 300 (51), 274 (12), 256 (10), 231 (14), 230 (100), 211 (21), 187 (13), 182 (11), 173 (11), 115 (10), 87 (18) and 71 (15).

**Reaction of 3-aminoquinazolinone (8) with benzenesulphonyl chloride**

\[
\begin{align*}
&\text{O}^1 \quad \text{NH}_2 \\
\text{PhSO}_2\text{Cl} &\quad \text{Pyridine} \\
\text{(8)} &\quad \text{PhO}_2\text{S}^+\text{N}_2\text{O}_2\text{Ph} \\
\text{(63)}
\end{align*}
\]

Benzenesulphonyl chloride (0.96 g, 5.42 x 10\(^{-3}\) mol) was diluted with dichloromethane (1 ml) then added dropwise to 3-aminoquinazolinone (8)(1 g, 4.93 x 10\(^{-3}\) mol) in pyridine (0.44 ml, 5.42 x 10\(^{-3}\) mol) and dichloromethane (2 ml). The reaction mixture was left to stir overnight. Further dichloromethane (40 ml) was added, the solution washed with saturated sodium hydrogen carbonate solution, water, dried and the solvent removed under reduced pressure. On standing, the product crystallised. The crystals of the N,N-disulphonylaminoquinazolinone (63) were washed with cold ethanol (0.96 g, 40%) m.p. 180-183 °C. (Found: C, 56.95; H, 4.4; N, 8.65%. C\textsubscript{23}H\textsubscript{21}N\textsubscript{3}O\textsubscript{5}S\textsubscript{2} requires: C, 57.15; H, 4.4; N, 8.7 %); \(\nu\)\textsubscript{max} / cm\(^{-1}\) 1710s and 1610s; δ\textsubscript{H} (CDCl\textsubscript{3}, 300 MHz) 1.47 (6H, d, J 6.5 Hz, CH\textsubscript{3}CHCH\textsubscript{3}), 3.60 (1H, heptet, J 6.5 Hz, CH\textsubscript{3}CHCH\textsubscript{3}),
7.38-7.50 (5H, m, 5 x CH(Ph)), 7.67-7.83 (8H, m, 5 x CH(Ph), Q1 6-, 7-, and 8-H) and 7.98 (1H, ddd, J 8.0, 1.4 and 0.6 Hz, Q1 5-H); δC (CDCl3, 75 MHz) 22.26 (CH3CHCH3), 30.80 (CH3CHCH3), 120.80 (CCO(Q1)), 126.72, 126.99, 127.45, 128.66, 129.85, 134.77, 135.21 (7 x CH(Ar)), 137.06 (Q(Ph)), 146.22 (CN=C(Q1)), 159.23 (CN(Q1)) and 164.31 (CCO(Q1)); m/z (%) 483 (M+, 76), 343 (27), 342 (22), 278 (25), 202 (30), 200 (13), 188 (13), 187 (18), 174 (21), 173 (45), 146 (15), 145 (77), 144 (22), 141 (22), 131 (11), 130 (79), 125 (100), 104 (20), 103 (39), 90 (11), 86 (13), 84 (16), 78 (14), 77 (86), 76 (38) and 51 (20).

When this reaction was carried out in the absence of pyridine, no reaction occurred.

**Attempted reaction of N-acylaminoquinazolinone (9) with benzenesulphonyl chloride**

![Diagram](image)

To N-acylaminoquinazolinone (9) (0.31 g, 1.26 x 10^-3 mol) in pyridine (2 ml) was added benzenesulphonyl chloride (0.25 g, 1.39 x 10^-3 mol) as described in general procedure (B) for further acylation with carboxylic acid chlorides. After the same work up the black oil obtained was identified as unreacted starting material (0.24 g).
Mono-acetylation of 3-amino-2-(1,1-dimethylethyl)quinazol-4(3H)-one (47)

\[
\begin{align*}
\text{3-Amino-2-(1,1-dimethylethyl)quinazol-4(3H)-one (47)} & \quad \text{(1 g, 4.61 x 10}^{-3} \text{ mol), was dissolved in acetic anhydride (3 ml) and heated at 50 °C for 8 h. Water was then added, the organic layer separated and washed with saturated aqueous sodium hydrogen carbonate (x 3), water, dried and the solvent evaporated under reduced pressure to give a pale yellow oil (0.94 g), which solidified on standing overnight. Crystallisation of this solid from ethanol / water gave the amide (65) as a colourless solid hydrate (0.84 g, 71%). m.p 90-92 °C (Found: C, 60.75; H, 6.90; N, 15.15. C\textsubscript{14}H\textsubscript{17}N\textsubscript{3}O\textsubscript{2}.H\textsubscript{2}O requires C, 60.65; H, 6.90; N, 15.15%); ν\textsubscript{max} / cm\textsuperscript{-1} 3460m, 3380m, 3180w, 1695s, 1670s, 1610m and 1590s; δ\textsubscript{H} (d\textsubscript{6}-DMSO, 300 MHz) 1.48 (9H, s, (CH\textsubscript{3})\textsubscript{3}C), 2.22 (3H, s, CH\textsubscript{3}CO), 7.62 (1H, ddd, J 7.9, 7.3 and 1.1 Hz, Q\textsuperscript{3} 6-H), 7.75 (1H, d, J 7.7 Hz, Q\textsuperscript{3} 8-H), 7.93 (1H, ddd, J 7.7, 7.3 and 1.3 Hz, Q\textsuperscript{3} 7-H), 8.19 (1H, dd, J 7.9 and 1.3 Hz, Q\textsuperscript{3} 5-H), 10.92 (1H, s, NH); δ\textsubscript{C} (d\textsubscript{6}-DMSO, 75 MHz) 20.78 (CH\textsubscript{3}CO), 28.64 ((CH\textsubscript{3})\textsubscript{3}C), 38.58 ((CH\textsubscript{3})\textsubscript{3}C), 120.28 (CCO(Q\textsuperscript{3})), 126.17, 126.82, 127.57, 134.74 (4 x CH(Q\textsuperscript{3})), 145.87 (CN=C(Q\textsuperscript{3})), 159.88 (CN(Q\textsuperscript{3})), 162.58 (CO(Q\textsuperscript{3})) and 170.50 (NHCOCH\textsubscript{3}); m/z (%) 259 (M\textsuperscript{+}, 47), 202 (100), 201 (77), 187 (23), 175 (68), 160 (30), 132 (35), 119 (20), 103 (20) and 77 (11).}
\end{align*}
\]
Reaction of (S)-2-acetoxypropionyl chloride with 3-acetylamino-2-(1,1-dimethylethyl)quinazolin-4(3H)-one (65)

\[
\text{MeOCO} \quad \text{Cl} \\
\text{HN} \quad \text{Pyridine} \\
\text{O} \\
\text{O} \\
(65)
\]

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{N} & \quad + \\
(68)
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad + \\
(66)
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{N} \\
\text{O} & \quad \text{COMe} \\
(67)
\end{align*}
\]

General procedure (B) was followed using 3-acetylaminoquinazolinone (65) (0.5 g, 1.93 x 10^{-3} mol) and (S)-2-acetoxypropionyl chloride (0.87 g, 5.79 x 10^{-3} mol) in dichloromethane (1 ml) and pyridine (2 ml). The black oil obtained was purified by flash column chromatography using light petroleum : ether (7:1) as eluant to give, in order of elution; acetate (66) as a colourless solid (R_f 0.47) (0.045 g, 8%) m.p. 117-120 °C (Found: M^+ 283.1317, C_{16}H_{17}N_{3}O_{2} requires M^+ 283.1321); \nu_{\text{max}} / \text{cm}^{-1} 1770s, 1620m and 1600m; \delta_\text{H} (\text{CDCl}_3, 300 MHz) 1.68 (9H, s, (\text{CH}_3)_3C), 2.42 (3H, s, \text{CH}_3\text{CO}), 6.92 (1H, s, C=\text{CH}), 7.52 (1H, ddd, J 7.8, 7.3 and 1.2 Hz, CH(Ar)), 7.62 (1H, ddd, J 7.8, 7.2 and 1.6 Hz, CH(Ar)) and 7.88-7.95 (2H, m, 2 x CH(Ar)); \delta_\text{C} (\text{CDCl}_3, 75 MHz) 21.25
(CH₃CO), 27.68 (°CH₃)C), 38.85 (°CH₃)C), 88.24 (C-CH), 118.89 (CCN), 122.69, 127.20, 128.65, 129.73 (4 x CH(Ar)), 139.21, 141.59, 155.09, 156.78 (4 x C) and 167.80 (COCH₃); m/z (%) 283 (M⁺, 32), 241 (37), 240 (22), 226 (40) and 199 (100); 2-acetoxypropionate (67) as a colourless oil (Rf 0.29) (0.022 g, 3%) (Found: M⁺ 355.1532. C₁₉H₂₁N₃O₄ requires M⁺ 355.1532); νmax / cm⁻¹ 1780m, 1745m, 1710s, 1620m and 1605m; δH (CDCl₃, 300 MHz); 1.81 (9H, s, (CH₃)₂C), 1.85 (3H, d, J 7.0 Hz, CH₃CHO), 2.34 (3H, s, CH₃CO), 5.50 (1H, q, J 7.0 Hz, CH₃CHOAc), 7.10 (1H, s, C=CH), 7.62 (1H, ddd, J 7.7, 6.5 and 1.2 Hz, CH(Ar)), 7.66 (1H, ddd, J 7.7, 6.5 and 1.2 Hz, CH(Ar)) and 7.73-8.07 (2H, m, 2 x CH(Ar)); m/z (%) 355 (M⁺, 26), 241 (45), 240 (24), 226 (39) and 199 (100); followed by the 3-diacetylaminquinazolinone (68) as a colourless oil Rf 0.24 (0.05 g, 9%) (Found: M⁺ 301.1427. C₁₆H₁₉N₃O₃ requires M⁺ 301.1426); νmax / cm⁻¹ 1740s, 1690s, 1605m and 1590s; δH (CDCl₃, 300 MHz); 1.41 (9H, s, (CH₃)₂C), 2.42 (6H, s, 2 x CH₃CO), 7.49 (1H, ddd, J 7.9, 7.0 and 1.4 Hz, Q3 6-H), 7.71 (1H, ddd, J 8.2, 1.4 and 0.5 Hz, Q3 8-H), 7.80 (1H, ddd, J 8.2, 7.0 and 1.5 Hz, Q3 7-H) and 8.21 (1H, ddd, J 7.9, 1.5 and 0.5 Hz, Q3 5-H); δC (CDCl₃, 75 MHz) 24.85 (2 x CH₃CO), 29.51 ((CH₃)₂C), 39.65 ((CH₃)₂C), 120.25 (CCO(Q3)), 126.97, 127.16, 128.08, 135.09 (4 x CH(Q3)), 146.22 (C=N=C(Q3)), 160.43, 160.69 (C(N=CO(Q3)) and 171.51 (2 x CH₂CO); m/z (%) 301 (M⁺, 1), 244 (16), 203 (12), 202 (100), 201 (13), 175 (11) and 160 (12).
Mono-acylation of 3-aminoquinazolinone (69) using (S)-2-acetoxypropionylic chloride

\[
\begin{align*}
\text{Q}^4 & \quad \text{MeOCO} \quad \text{Cl} \\
\text{NH}_2 & \quad \text{HNN} \quad \text{OOCMe}
\end{align*}
\]

(69) (73)

The general procedure (A) was followed using 3-aminoquinazolinone (69) (1.73 g, 5.3 x 10^{-3} mol), (S)-2-acetoxypropionyl chloride (0.88 g, 5.83 x 10^{-3} mol), dichloromethane (5 ml) and pyridine (0.43 ml, 5.3 x 10^{-3} mol). The pale green solid obtained on work-up was purified by flash chromatography using silica and light-petroleum : ethyl acetate (2 : 1) as eluant. This gave colourless crystals of N-acylaminoquinazolinone (73) as a 1.8 : 1 mixture of diastereoisomers (from comparison of the signals at \( \delta \) 5.12 and \( \delta \) 5.22 in the NMR spectrum below) (Rf 0.32) (1.82 g, 78%). m.p. 181-184 °C (from ethanol) (Found: C, 70.4; H, 5.3; N, 9.45. C_{26}H_{23}N_{3}O_{4} requires C, 70.7; H, 5.25; N, 9.5%); \( \nu_{\text{max}} \) / cm^{-1} 3320w, 1720s, 1690s and 1595s; \( \delta_{\text{H}} \) (d_{6}-DMSO, 300 MHz) major diastereoisomer: 1.54 (3H, d, J 6.8 Hz, CH\textsubscript{3}CH), 2.19 (3H, s, CH\textsubscript{3}CO), 5.12 (1H, q, J 6.8 Hz, CH\textsubscript{3}CH), 5.85 (1H, s, (Ph)\textsubscript{2}CH), 7.23-7.50 (10H, m, 10 x CH(Ph)), 7.54-7.59 (1H, m, Q\textsuperscript{4} 6-H), 7.64 (1H, d, J 7.9 Hz, Q\textsuperscript{4} 8-H), 7.84 (1H, ddd, J 8.2, 7.9 and 1.4 Hz, Q\textsuperscript{4} 7-H), 8.11-8.18 (1H, m, Q\textsuperscript{4} 5-H) and 11.46 (1H, s, NH); minor diastereoisomer (observable peaks): 2.17 (3H, s, CH\textsubscript{3}CO), 5.22 (1H, q, J 6.8 Hz, CH\textsubscript{3}CH), 5.70 (1H, s, (Ph)\textsubscript{2}CH) and 11.37 (1H, s, NH); \( \delta_{\text{C}} \) (d_{6}-DMSO, 75 Mz) major diastereoisomer: 16.63, 20.43, (2 x CH\textsubscript{3}), 51.67 ((Ph)\textsubscript{2}CH), 58.54 (CH\textsubscript{3}CHOAc), 120.31 (CO(Q\textsuperscript{4})), 126.29, 126.51, 127.19, 127.63, 128.48, 128.73, 129.12, 129.31, 135.01,
135.97, (10 x CH(Ar)), 139.09, 139.96 (2 x C(Ph)), 145.82 (CN=C(Q4)), 158.56, 158.75 (CN(Q4), CO(Q4)) and 170.05, 171.00 (2 x CO); minor diastereoisomer (observable peaks): 17.27, 20.38 (2 x CH3), 51.76 ((Ph)2CH), 69.58 (CH3CHOAc), 123.77 (CCO(Q4)), 139.05, 140.12 (2 x C(Ph)), 145.42 (CN=C(Q4)), 158.65 (CO(Q4)) and 170.02, 170.07 (2 x CO); m/z (%) 441 (M+, 100), 328 (151), 327 (59), 312 (21), 311 (50), 310 (30), 309 (20), 167 (48), 165 (56), 152 (22), 115 (22) and 87 (43).

Acylation of (73) using isobutyryl chloride

\[
\begin{align*}
\text{HN}^4\text{C} \quad &\quad \text{O} \quad \text{COMe} \\
\text{(73)} &\quad \text{O} \quad \text{COMe} \\
\text{Pyridine} &\quad \text{O} \quad \text{COMe} \\
\text{(74)} &\quad \text{O} \quad \text{COMe} \\
\end{align*}
\]

(75a) and (75b)

(76)

General procedure (B) was followed using 3-acylaminoquinazolinone (73) (1 g, 2.27 x 10^{-3} mol) and isobutyryl chloride (1.08 g, 1.02 x 10^{-2} mol) in dichloromethane (1 ml) and pyridine (2 ml). The dark brown oil obtained on work-up was purified by column
chromatography using light petroleum : ethyl acetate (5 : 1) as eluant. This gave 3-
diacylaminoquinazolinone (74) as a colourless solid (0.11 g, 10 %), \( R_f \) 0.38 m.p. 154-
156 °C (from ethanol) (Found: \( M^+ \) 467.2206. \( C_{29}H_{29}N_3O_3 \) requires \( M^+ \) 467.2209); \( \nu_{\text{max}} \)
/ cm\(^{-1} \) 1730s, 1690s, 1610s and 1600s; \( \delta_H \) (CDCl\(_3\), 300 MHz) 0.85, 1.23 (12H, 2 x d, J
6.8 Hz, 2 x CH\(_3\)CHCH\(_3\)), 2.98-3.03 (2H, m, 2 x CH\(_2\)CH(CH\(_3\))), 5.32 (1H, s, (Ph)\(_2\)CH),
7.24-7.42 (10H, m, 10 x CH(Ar)), 7.48 (1H, ddd, J 8.0, 6.8 and 1.2 Hz, Q\(_4\) 6-H), 7.68-
7.78 (2H, m, Q\(_4\) 7- and 8-H) and 8.25 (1H, ddd, J 8.0, 1.2 and 0.4 Hz, Q\(_4\) 5-H); \( \delta_C \)
(CDCl\(_3\), 75 MHz) 18.65, 19.92 (4 x CH\(_3\)), 34.46 (2 x CH\(_2\))CH\(_2\)), 52.93 (CH(Ph)\(_2\)),
120.79 (CCO(Q\(_4\))), 127.08, 127.23, 127.38, 128.11, 128.55, 129.16, 134.99 (7 x
CH(Ar)), 138.60 (2 x C(Ph)), 146.21 (CN=C(Q\(_4\))), 157.26 (CN(Q\(_4\))), 159.81 (CO(Q\(_4\)))
and 178.38 (2 x CO); m/z (%) 467 (M\(^+\), 100), 397 (65), 380 (55), 354 (22), 327 (30), 311
(34), 310 (28), 309 (26), 306 (20), 230 (38), 167 (55), 165 (39) and 71 (27).

Further elution with the same solvent mixture gave one diastereoisomer of 3-
diacylaminoquinazolinone (75a) as a pale pink oil (\( R_f \) 0.30) (0.30 g, 26 %) [\( \alpha \)]\(_D\) = -336 (c
= 4, CH\(_2\)Cl\(_2\)). (Found: \( M^+ \) 511.2106. \( C_{30}H_{29}N_5O_5 \) requires \( M^+ \) 511.2107); \( \nu_{\text{max}} \) /
cm\(^{-1} \) 1730s, 1700m, 1605m and 1595m; \( \delta_H \) (CDCl\(_3\), 300 MHz) 0.19 (3H, d, J 6.7 Hz,
CH\(_3\)CHCH\(_3\)), 0.94 (3H, d, J 6.7 Hz, CH\(_3\)CHCH\(_3\)), 1.64 (3H, d, J 6.2 Hz, CH\(_3\)CHOAc),
2.02-2.07 (1H, m, br, CH\(_3\)CHCH\(_3\)), 2.15 (3H, s, CH\(_3\)CO), 5.61 (1H, s, PhCH(Ph)), 6.07
(1H, q, br, J 6.2 Hz, CH\(_3\)CHOAc), 7.13-7.38 (10H, m, 10 x CH(Ph)), 7.42 (1H, ddd, J
8.1, 7.7 and 1.4 Hz, Q\(_4\) 6-H), 7.59 (1H, d, J 7.7 Hz, Q\(_4\) 8-H), 7.70 (1H, ddd, J 8.1, 7.7
and 1.4 Hz, Q\(_4\) 7-H) and 8.18 (1H, d, J 7.7 Hz, Q\(_4\) 5-H); Double irradiation of the signal
at \( \delta \) 6.07 (CH\(_3\)CHOAc) caused the collapse of the doublet at \( \delta \) 1.64 (CH\(_3\)CHOAc). \( \delta_C \)
(CDCl\(_3\), 75 MHz) 16.74, 19.25, 21.06, 21.19 (4 x CH\(_3\)), 34.10 (CH\(_3\)CHCH\(_3\)), 52.58
Further elution gave the second diastereoisomer of 3-diacylaminquinazolinone (75b) as a colourless oil containing ~10% of (76) (see below) (from comparison of peaks in the NMR spectrum at δ 0.98 and δ 1.27) (Rf 0.20) (0.36 g, 31 %) (Found: M⁺ 511.2105. C_{30}H_{29}N_{3}O_{5} requires M⁺ 511.2107); ν_{max} / cm⁻¹ 1730s, 1700s and 1600s; δ_{H} (CDCl₃, 300 MHz) 0.60 (3H, d, J 6.7 Hz, CH₃CHCH₃), 0.98 (3H, d, J 6.7 Hz, CH₂CHCH₂), 1.58 (3H, d, J 6.7 Hz, CH₃CHOAc), 2.11 (3H, s, CH₃CO), 2.61-2.75 (1H, m, br, CH₂CHCH₂), 5.51 (1H, s, PhCHPh), 5.70-5.75 (1H, m, br, CH₃CHOAc), 7.16-7.37 (10H, m, 10 x CH(Ph)), 7.44 (1H, ddd, J 8.0, 7.0 and 0.9 Hz, Q₄ 6-H), 7.64 (1H, dd, J 8.1 and 0.9 Hz, Q₄ 8-H), 7.71 (1H, ddd, J 8.1, 7.0 and 1.0 Hz, Q₄ 7-H) and 8.24 (1H, dd, J 8.0 and 1.0 Hz, Q₄ 5-H); Double irradiation of the signal at δ 5.70-5.75 (CH₃CHOAc) caused the collapse of the doublet at δ 1.58 (CH₃CHOAc). δ_{C} (CDCl₃, 75 MHz) 16.45, 18.45, 19.77, 20.50 (4 x CH₃), 34.06 (CH₂CHCH₂), 52.88 ((Ph)₂CH), 70.13 (CH₃CHOAc), 120.70 (CCO(Q₄)), 126.92, 127.28, 127.44, 127.71, 128.07, 128.12, 128.90, 129.26, 129.43, 135.16 (10 x CH(Ar)), 137.51, 139.75 (2 x C(Ph)), 145.97 (CN=C(Q₄)), 156.73 (CN(Q₄)), 159.76 (CO(Q₄)) and 169.96, 171.51, 177.55 (3
1.53 \times 10^{-3} \text{ mol}) and isobutyryl chloride (0.24 ml, 1.68 \times 10^{-3} \text{ mol}) in dichloromethane (2 ml) and pyridine (0.2 ml) following general procedure (A). The solid obtained was crystallised from ethanol to give colourless crystals of imide (76) (0.44 g, 73 %), m.p. 78-80 °C. (Found: C, 75.2; H, 5.9; N, 10.5. \text{C}_{25} \text{H}_{23} \text{N}_{3} \text{O}_{2} \text{ requires } C, 75.5; H, 5.85; N, 10.55\%); v_{\text{max}} / \text{cm}^{-1} 3240\text{w}, 1720\text{m}, 1660\text{s and 1600s}; \delta_{H} (\text{CDCl}_3, 300 \text{ MHz}) 1.27, 1.32 (6H, 2 \times d, J 6.8 \text{ Hz}, \text{CH}_3\text{CHCH}_3), 2.69 (1H, heptet, J 6.8 \text{ Hz}, \text{CH}_3\text{CHCH}_3), 5.66 (1H, s, (\text{Ph})_2\text{CH}), 7.26-7.40 (10H, m, 10 \times \text{CH(Ar)}), 7.44 (1H, ddd, J 8.0, 7.0 and 1.2 \text{ Hz}, Q^4 6-H), 7.66 (1H, dd, J 7.7 and 1.2 \text{ Hz}, Q^4 8-H), 7.73 (1H, ddd, J 7.7, 7.0 and 1.1 \text{ Hz}, Q^4 7-H), 8.11 (1H, dd, J 8.0 and 1.1 \text{ Hz}, Q^4 5-H) and 8.30 (1H, s, NH); \delta_{C} (\text{CDCl}_3, 75 \text{ MHz}) 18.73, 19.41 (\text{CH}_3\text{CHCH}_3), 33.63 (\text{CH}_3\text{CHCH}_3), 53.76 ((\text{Ph})_2\text{CH}), 120.57 (\text{CCO}(Q^4)), 126.59, 126.70, 126.63, 127.25, 127.89, 128.11, 128.77, 128.79, 129.63, 134.54 (10 \times \text{CH(Ar)}), 139.05, 139.56 (2 \times \text{C(Ph)}), 146.44 (\text{CN}=\text{C}(Q^4)), 157.65 (\text{CN}(Q^4)), 160.44 (\text{CO}(Q^4)) and 177.12 (\text{NHCO}); m/z (%) 397 (M^+, 100), 327 (69), 311 (24), 310 (26), 235 (20), 167 (24), 165 (30) and 152 (14).
General Procedure (D) for Kinetic Resolution of Racemic α-Methylbenzylamine

To the imide (0.5 mol equiv.) dissolved in the chosen solvent (100 mg / 1ml) was added racemic α-methylbenzylamine (1 mol equiv.) and the solution stirred for between 15 min. and 24 h (dependent on temperature). The bulk of the solvent was removed under reduced pressure, the residue diluted with dichloromethane, washed with 2M HCl, water, dried and the solvent removed. The results are illustrated in Table 3 (see Chapter Two).

An analogous experiment was carried out using (S)-2-acetoxypropionyl chloride (0.5 mol equiv.) and racemic methylbenzylamine (1 mol equiv.). After the same work-up described above, amide diastereoisomers (58a) and (58b) were obtained in a 1.05 : 1 ratio.

Preparation of authentic samples of the enantiopure amides (58a) and (58b)

To (S)-2-acetoxypropionyl chloride (1.24 g, 8.25 x 10^-3 mol) in dichloromethane (2 ml) was added a solution of (R)-α-methylbenzylamine (57) (1 g, 8.25 x 10^-3 mol) in pyridine (0.74 ml, 8.25 x 10^-3 mol) and dichloromethane (2 ml). After 1 h, further dichloromethane (30ml) was added, the solution then washed successively with saturated aqueous sodium hydrogen carbonate, 2M HCl, water, then dried and the solvent removed under reduced pressure to give an orange solid. Crystallisation twice from ethyl acetate.
gave pale yellow crystals of \( \alpha\text{-}(R),2\text{-}(S)-N\text{-}(2\text{-acetooxpropiony})\text{-}\alpha\text{-methylbenzylamine} \) (58a) (1.67 g, 86%) \([\alpha]_D = +14^\circ\) \((c = 6, \text{CH}_2\text{Cl}_2)\) (Found: \(\text{MH}^+ 236.1286\)). \(\text{C}_{13}\text{H}_{18}\text{N}_{2}\text{O}_{3}\) requires \(\text{MH}^+ 236.1287\); \(\nu_{\text{max}} / \text{cm}^{-1} 3440\text{m}, 1750\text{s} \text{and} 1680\text{s}; \delta_{\text{H}} \) (\(\text{CDCl}_3, 300 \text{MHz}\) 1.44 (3H, d, \(J 6.9 \text{ Hz}, \text{CH}_3\text{CH}\), 1.49 (3H, d, \(J 7.0 \text{ Hz}, \text{CH}_3\text{CH}\)), 2.10 (3H, s, \text{CH}_3\text{CO}), 5.07-5.16 (1H, m, \text{CH}_3\text{CHNH}), 5.19 (1H, q, \(J 6.9 \text{ Hz}, \text{CH}_3\text{CHCO}), 6.48 (1H, d, br, \(J 7.0 \text{ Hz}, \text{NHCHCH}_3\)) and 7.19-7.42 (5H, m, 5 x \text{CH(Ph)}); \delta_{\text{C}} \) (\(\text{CDCl}_3, 75 \text{ MHz}\) 18.3, 21.5, 22.0 (3 x \text{CH}), 48.8, 71.1 (2 x \text{CH}_2\text{CH}), 126.5, 127.9, 129.1 (5 x \text{CH(Ph)}), 143.1 (\text{C(Ph)}) and 169.9, 170.0 (2 x CO); m/z (%) \(\text{Cl} / \text{NH}_3 253 \text{(M+NH}_4^+), 236 \text{(MH}^+, 100)\).

The \(-\alpha\text{-}(S),2\text{-}(S)-\text{diastereoisomer} \) (58b) was prepared as described above using \((S)-\alpha\text{-methylbenzylamine} \) to give the product (58a) as a yellow oil (1.71 g, 88%) \([\alpha]_D = -78^\circ\) \((c = 6, \text{CH}_2\text{Cl}_2)\) (Found: \(\text{MH}^+ 236.1286\)). \(\text{C}_{13}\text{H}_{18}\text{N}_{2}\text{O}_{3}\) requires \(\text{MH}^+ 236.1287\); \(\nu_{\text{max}} / \text{cm}^{-1} 3440\text{m}, 1745\text{s} \text{and} 1630\text{s}; \delta_{\text{H}} \) (\(\text{CDCl}_3, 300 \text{ MHz}\) 1.47 (3H, d, \(J 6.9 \text{ Hz}, \text{CH}_3\text{CH}), 1.52 (3H, d, \(J 7.0 \text{ Hz}, \text{CH}_3\text{CH}), 2.11 (3H, s, \text{CH}_3\text{CO}), 5.08-5.20 (2H, m, 2 x \text{CH}_3\text{CH}), 6.39 (1H, d, br, \(J 6.8 \text{ Hz}, \text{NHCHCH}_3\)) and 7.23-7.37 (5H, m, 5 x \text{CH(Ph)}); \delta_{\text{C}} \) (\(\text{CDCl}_3, 75 \text{ MHz}\) 18.2, 21.5, 22.1 (3 x \text{CH}), 48.8, 71.0 (2 x \text{CH}_2\text{CH}), 126.5, 127.8, 129.1 (5 x \text{CH(Ph)}), 143.2 (\text{C(Ph)}) and 169.9, 170.0 (2 x CO); m/z (%) \(\text{Cl} / \text{NH}_3 253 \text{(M+NH}_4^+), 236 \text{(MH}^+, 100)\).
Attempts at kinetic resolution by reaction of imides (75a) and (75b) with other racemic amines

Reaction of imides (75a) and (75b) with different racemic amines were carried out. The amines used and the approximate ratios of diastereoisomeric amides produced are as follows: sec-butylamine (1.4 : 1), 2-amino-1-methoxypropane (1 : 1), exo-2-aminonorbornane (1.1 : 1), and 2-ethylhexylamine (both diastereoisomers overlapped in NMR spectrum). In these cases, the ratios of diastereoisomers were lower than with \( \alpha \)-methylbenzylamine.
General Procedure (E) for the Reaction of β-Ketoesters, β-Diketones and Silyl Enol Ethers with 3-Acetoxyminoquinazolione (14)

3-Aminoquinazoline (1 mol equiv.) and lead tetra-acetate (1.05 mol equiv.) were added alternately in small portions over 15 min. to a stirred solution of dry dichloromethane (1 ml / 100 mg of 3-aminoquinazoline) cooled at -20 °C to -25 °C with a dry ice-acetone bath. The β-ketoester (1.5 - 3.5 mol equiv.) was then added at this temperature and the mixture then allowed to warm to room temperature. Insoluble lead di-acetate was separated, washed with dichloromethane, then the dichloromethane solution washed with saturated aqueous sodium hydrogen carbonate, water, dried (MgSO₄) and the solvent removed.
Reaction of 3-Acetoxyaminoquinazolinone (14) with

Ethyl 2-oxocyclohexane-1-carboxylate

\[ \overset{\text{O}}{\text{O}} \text{CO}_2\text{Et} \quad \overset{\text{NHOAc}}{\text{-20 °C to RT}} \quad \overset{\text{O}}{\text{O}} \text{CO}_2\text{Et} \text{NH}^+\overset{\text{Ql}}{\text{Ql}} \]

(14) (85)

The general procedure (E) was followed using 3-aminoquinazolinone (8) (3.17 g, 0.016 mol), LTA (7.27 g, 0.016 mol) and ethyl 2-oxocyclohexane-1-carboxylate (7.97 g, 0.047 mol) in dichloromethane (32 ml). After the work up, the bulk of the unchanged β-ketoester was removed by distillation (Kugelrohr) under reduced pressure (0.5 mm Hg) and the product purified by column chromatography over silica with light petroleum : ethyl acetate (4 : 1) as eluant. The α-QlNH-β-ketoester (85) (Rf 0.21) was obtained as colourless crystals (3.82 g, 66%) m.p. 79-81 °C (from ethanol) (Found: C, 64.5; H, 6.75; N, 11.25. C\text{20H25N3O4} requires C, 64.65; H, 6.8; N, 11.3%); \nu_{\text{max}} / \text{cm}^{-1} 3260 \text{m}, 1740 \text{m}, 1680 \text{s} \text{ and} 1590 \text{s}; \delta_{\text{H}} (\text{CDCl}_3, 300 \text{ MHz}) 1.26-1.35 (9 \text{H}, 6 \text{ lines}, \text{CH}_3\text{CHCH}_3, \text{CH}_3\text{CH}_2), 1.59-1.83 (4 \text{H}, m, 2 \times \text{CH}_2), 2.01-2.07 (1 \text{H}, m, \text{CH}), 2.30-2.33 (1 \text{H}, m, \text{CH}), 2.46-2.57 (1 \text{H}, m, \text{CH}), 2.70-2.75 (1 \text{H}, m, \text{CH}), 3.70 (1 \text{H}, \text{heptet}, J 6.5 \text{ Hz}, \text{CH}_3\text{CHCH}_3), 4.18-4.34 (2 \text{H}, m, 2 \times \text{CH}), 6.94 (1 \text{H}, s, \text{br}, \text{NH}), 7.44 (1 \text{H}, \text{ddd}, J 8.0, 6.8 \text{ and} 1.5 \text{ Hz}, \text{Ql} \text{ 6-H}), 7.68-7.78 (2 \text{H}, m, \text{Ql} \text{ 7- and} 8-H) \text{ and} 8.17 (1 \text{H}, \text{ddd}, J 8.0, 1.5 \text{ and} 0.6 \text{ Hz}, \text{Ql} \text{ 5-H}); \delta_{\text{C}} (\text{CDCl}_3, 75 \text{ MHz}) 13.84, 20.80, 20.86 (3 \times \text{CH}_3), 22.03, 25.97 (2 \times \text{CH}_2), 30.57 (\text{CH}_2\text{CHCH}_3), 39.79, 62.27 (2 \times \text{CH}_2), 69.27 (\text{CO}_2\text{CH}_2\text{CH}_3), 71.90 (\text{CNH(Ql)}), 120.34 (\text{CCO(Ql)}), 126.14, 126.52, 127.26, 134.31 (4 \times \text{CH(Ql)}), 146.96 (\text{CN=C(Ql)}), 163.11,
164.13 (CN(Q1), CO(Q1)), 168.83 (CO\_2\CH\_3) and 203.03 (CH\_2\CO); m/z (%) 371 (M\^+, 1), 298 (16), 270 (40), 189 (71), 188 (100), 187 (14), 173 (48), 160 (15), 156 (10) and 82 (29).

**Oxidation of α-Q\^NH-β-Ketoester (85) with LTA in Dichloromethane**

![Chemical structure](image)

To a solution of α-Q\^NH-β-Ketoester (85) (4.54 g, 0.012 mol) in dry dichloromethane (33 ml) was added LTA (5.69 g, 0.013 mol) and the solution stirred at room temperature for 3 days. Insoluble lead di-acetate was separated, washed with dichloromethane (40 ml) and the combined dichloromethane solutions washed with saturated aqueous sodium hydrogen carbonate, then water, dried, and evaporated under reduced pressure. Chromatography of the crude product over silica using light petroleum : ethyl acetate (3 : 1) gave the benzoxazinone (87) as a colourless solid (R\_f 0.37) (0.52 g) m.p. 102-106 °C (from ethanol) (Found: C, 69.55; H, 5.95; N, 7.4. C\(_{11}\)H\(_{11}\)N\(_{1}\)O\(_{2}\) requires: C, 69.85; H, 5.85; N, 7.4%); \(\nu\)\_max / cm\(^{-1}\) 1770s and 1640s; \(\delta\)\_H (CDCl\(_3\), 300 MHz) 1.38 (6H, d, J 6.9 Hz, CH\(_3\)CHCH\(_3\)), 2.94 (1H, heptet, J 6.9 Hz, CH\(_3\)CHCH\(_3\)), 7.48 (1H, ddd, J 7.9, 7.3 and 1.1 Hz, Ar 6-H), 7.56 (1H, dd, J 8.1 and 0.5 Hz, Ar 8-H) and 7.78 (1H, ddd, J 8.1, 7.3 and 1.5 Hz, Ar 7-H), 8.17 (1H, ddd, J 7.9, 1.5 and 0.5 Hz, Ar 5-H); \(\delta\)\_C (CDCl\(_3\), 75 MHz) 19.44 (CH\(_3\)CHCH\(_3\)), 33.92 (CH\(_3\)CHCH\(_3\)), 116.68 (C=O), 126.43,
127.61, 128.07, 136.12 (4 x CH(Ar)), 146.24 (C=N=C(Ar)), 159.63 (CN(Ar)) and 166.40 (CO(Ar)); m/z (%) 189 (M+, 37), 174 (11), 161 (11), 146 (100), 119 (11) and 90 (32).

Further elution gave unreacted starting material (2.36 g).

**Reaction of Q\(^{1}\)NHOAc (14) with 1-Methyl-2-trimethylsilyloxy-cyclohexene**

The general procedure (E) was followed using 3-aminoquinazolinone (8) (1 g, 4.93 \(\times\) 10\(^{-3}\) mol), LTA (2.3 g, 5.17 \(\times\) 10\(^{-3}\) mol) and the silyl enol ether (2.72 g, 0.0148 mol) in dry dichloromethane (10 ml). The product was purified by column chromatography using light petroleum : ethyl acetate (4 : 1) as eluant, to give the \(\alpha\)-Q\(^{1}\)NH-\(\alpha\)-methylcyclonexanone (88) as a colourless solid (0.95 g, 62%) (R\(_f\) 0.34) m.p. 102-104 °C (from ethanol) (Found: C, 68.85; H, 7.4; N, 13.4. C\(_{18}\)H\(_{23}\)N\(_3\)O\(_2\) requires C, 69.0; H, 7.4; N, 13.4%); \(\nu\)\(_{\text{max}}\) / cm\(^{-1}\) 3300m, 1700m, 1670s and 1610m; \(\delta\)\(_{\text{H}}\) (CDCl\(_3\), 300 MHz) 1.15 (3H, s, CH\(_3\)), 1.30, 1.34 (6H, 2 x d, J 6.7 Hz, CH\(_3\)CH\(_2\)CH\(_3\)), 1.73-1.93 (5H, m, 5 x CH), 2.04-2.15 (1H, m, CH), 2.49-2.58 (1H, m, CH), 2.98-3.03 (1H, m, CH), 3.69 (1H, heptet, J 6.7 Hz, CH\(_2\)CH\(_2\)CH\(_3\)), 6.39 (1H, s, NH), 7.41 (1H, ddd, J 8.0, 6.8 and 1.4 Hz, Q\(^1\) 6-H), 7.65-7.75 (2H, m, Q\(^1\) 7- and 8-H) and 8.17 (1H, dd, J 8.0 and 1.4 Hz, Q\(^1\) 5-H); \(\delta\)\(_{C}\) (CDCl\(_3\), 75 MHz) 20.55 (br), 20.91 (br) (2 x CH\(_3\)), 21.34, 26.54 (2 x CH\(_2\)).
30.77 (CH₂CH₂CH₃), 38.14 (CH₂), 65.44 (CCH₃), 120.15 (CCO(Q)), 126.04, 126.52, 127.14, 134.16 (4 x CH(Q)), 146.69 (CN=C(Q)), 163.12, 163.86 (CN(Q), CO(Q)) and 210.26 (CO), (one CH₂ and one CH₃ not visible); m/z (%) 313 (M⁺,1), 285 (20), 270 (13), 229 (16), 228 (100), 203 (14), 189 (10), 188 (25), 187 (21), 175 (26) and 173 (18).

LTA Oxidation of α-Methyl-α-Q₁NH-cyclohexanone (88) in Dichloromethane

To a solution of α-Q₁NH-cyclohexanone (88) (0.2 g, 4.94 x 10⁻⁴ mol) in dry dichloromethane (2 ml) was added LTA (0.23 g, 5.2 x 10⁻⁴ mol) and the solution stirred at room temperature for 3 days. Insoluble lead di-acetate was separated, washed with dichloromethane (20 ml) and the combined dichloromethane solutions washed with saturated sodium hydrogen carbonate solution, then water, dried, and evaporated under reduced pressure. Chromatography of the crude product over silica using light petroleum : ethyl acetate (3 : 1) gave benzoazinone (87) (0.02 g) (Rf 0.37) identical with that isolated previously. Further elution gave unreacted starting material (0.1 g).
Reaction of Q\(^1\)NHOAc (14) with the \(\beta\)-Ketoester

The general procedure (E) was followed using 3-aminoquinazolinone (8) (0.56 g, 2.78 \(\times\) 10\(^{-3}\) mol), LTA (1.29 g, 2.92 \(\times\) 10\(^{-3}\) mol) and \(\beta\)-ketoester\(^{88}\) (1.7 g, 8.33 \(\times\) 10\(^{-3}\) mol) in dichloromethane (6 ml). After work up, the residue was purified by chromatography over silica using light petroleum : ethyl acetate (3 : 1) as eluant to give the \(\alpha\)-Q\(^1\)NH-\(\beta\)-ketoester (89) (R\(_f\) 0.41) as a white solid (0.78 g, 69\%) m.p. 164-165 °C (from ethanol) (Found: M\(^+\) 405.1686. C\(_{23}\)H\(_{23}\)N\(_3\)O\(_4\) requires M\(^+\) 405.1689); \(\nu\)\(_{\text{max}}\) / cm\(^{-1}\) 3280w, 1730s, 1705s; \(\delta\)\(_H\) (CDCl\(_3\), 300 MHz) 1.32, 1.34 (6H, 2 x d, J 6.8 Hz, CH\(_3\)CHCH\(_3\)), 2.11-2.14 (1H, m, CH), 2.34-2.41 (1H, m, CH), 2.78-3.05 (2H, m, 2 x CH), 3.67 (3H, s, OCH\(_3\)), 3.89 (1H, heptet, J 6.8 Hz, CH\(_3\)CHCH\(_3\)), 7.03 (1H, s, NH), 7.17 (1H, d, J 7.5 Hz, CH\(_3\)(Ar)), 7.34-7.41 (2H, m, 2 x CH\(_3\)(Ar)), 7.49 (1H, ddd, J 7.8, 1.5 and 0.8 Hz, CH\(_3\)(Ar)), 7.66-7.74 (2H, m, 2 x CH\(_3\)(Ar)), 8.11 (1H, ddd, J 7.8, 1.5 and 0.8 Hz, CH\(_3\)(Ar)) and 8.20 (1H, dd, J 7.8 and 1.1 Hz, CH\(_3\)(Ar)); \(\delta\)\(_C\) (CDCl\(_3\), 75 MHz) 20.37, 21.03 (CH\(_3\)CHCH\(_3\)), 25.63 (CH\(_2\)), 28.61 (CH\(_2\)), 30.36 (CH\(_3\)CHCH\(_3\)), 53.11 (OCH\(_3\)), 66.90(CNH(Q\(^1\))), 120.26 (CCO(Q\(^1\))), 126.07, 126.41, 126.74, 126.99, 127.15, 128.40 (6 x CH\(_3\)(Ar)), 130.45 (C(Ar)), 133.39, 134.24 (2 x CH(Ar)), 142.24 (C(Ar)), 146.66 (C(Ar)), 163.13, 164.12, (C\(_\text{CN}(Q^1))$, CO(Q\(^1\))) and 191.12 (CO(Ar)), (one CO not visible);
m/z (%) 405 (M+, 2), 347 (10), 346 (42), 218 (22), 203 (11), 189 (37), 188 (68), 187 (18), 173 (55), 160 (17), 159 (17), 158 (100), 131 (13), 130 (28), 118 (13), 103 (15) and 90 (10).

LTA Oxidation of α-Q^NH-β-ketoester (89) in Dichloromethane

![Reaction Scheme]

To a solution of α-Q^NH-β-ketoester (89) (0.2 g, 6.4 x 10^-4 mol) in dry dichloromethane (2 ml) was added LTA (0.3 g, 6.7 x 10^-4 mol) and the solution stirred at room temperature for 12 h. Insoluble lead di-acetate was separated, washed with dichloromethane (20 ml) and the combined dichloromethane solutions washed with saturated aqueous sodium hydrogen carbonate, then water, dried, and evaporated under reduced pressure. Chromatography of the crude product over silica using light petroleum : ethyl acetate (3 : 1) gave benzoxazinone (87) (0.7 g) identical with that isolated previously. Further elution gave unreacted starting material (0.06 g).
Reaction of \( Q' \)NHOAc (14) with Methyl Indan-1-one-2-carboxylate

\[
\begin{align*}
\text{Q'} &\quad \text{NHOAc} \\
-20 \, ^\circ \text{C} &\to \text{RT} \\
\end{align*}
\]

The general procedure (E) was followed using 3-aminoquinazolinone (8) (0.61 g, \( 2.98 \times 10^{-3} \) mol), LTA (1.39 g, \( 3.13 \times 10^{-3} \) mol) and methyl indan-1-one-2-carboxylate (1.7 g, \( 8.95 \times 10^{-3} \) mol) in dichloromethane (6 ml). After the work up, the oil was purified by chromatography using light petroleum : ethyl acetate (3 : 1) as eluant. This gave the \( Q' \)N-H \( \beta \)-ketoester (91) (Rf 0.31) as a colourless solid (0.75 g, 64%) m.p. 142-145 \(^\circ\)C (from ethanol) (Found: C, 67.15; H, 5.5; N, 10.6. \( C_{22}H_{31}N_3O_4 \) requires C, 67.5; H, 5.4; N, 10.75%); \( \nu_{\text{max}} \) / cm\(^{-1}\) 3320m, 1720s, 1680s and 1595m; \( \delta_H \) (CDCl\(_3\), 300 MHz) 1.05, 1.25 (6H, 2 x d, J 6.8 Hz, \( \text{CH}_3\text{CHCH}_3 \)), 2.83 (1H, d, J 17.4 Hz, HCH), 3.50 (1H, heptet, J 6.8 Hz, \( \text{CH}_3\text{CHCH}_3 \)), 3.68 (1H, J 17.4 Hz, HCH), 3.85 (3H, s, \( \text{CH}_3\text{O} \)), 6.49 (1H, s, NH), 7.33-7.50 (3H, m, 3 x CH(Ar)), 7.57 (1H, ddd, J 7.5, 7.4 and 1.0 Hz, CH(Ar)), 7.65 (1H, d, J 7.4 Hz, CH(Ar)), 7.74 (1H, ddd, J 8.0, 7.6 and 1.0 Hz, CH(Ar)), 7.81 (1H, d, J 7.6 Hz, CH(Ar)) and 8.16 (1H, dd, J 8.0 and 1.0 Hz, CH(Ar)); \( \delta_C \) (CDCl\(_3\), 75 MHz) 20.28, 20.99 (\( \text{CH}_3\text{CHCH}_3 \)), 30.61 (\( \text{CH}_3\text{CHCH}_3 \)), 32.62 (\( \text{CH}_2 \)), 53.46 (\( \text{CO}_2\text{CH}_3 \)), 75.57 (CNH(Q\(^1\))), 120.10 (CCO(Q\(^1\))), 125.09, 126.05, 126.20, 126.47, 127.22, 128.10 (6 x CH(Ar)), 133.30 (C(Ar)), 134.42, 135.80 (2 x CH(Ar)), 146.67, 151.16, 163.09, 163.86, 169.37, (C(Ar), CN=C(Q\(^1\)), CN(Q\(^1\)), CO(Q\(^1\)), CO) and 198.67 (CO); m/z (%) 391 (M\(^+\)), 332 (23), 204 (27), 203 (100), 189 (41), 188 (62), 187 (22), 175 (17), 174 (12), 173
Oxidation of \( \alpha \)-Methyl-\( \alpha \)-Q\(^1\)NH-indanone (91) in Dichloromethane:

Ring Expansion to Isoquinolone (92)

A solution of (91) (0.2 g, 5.12 \( \times \) 10\(^{-4} \) mol) and LTA (0.24 g, 5.37 \( \times \) 10\(^{-4} \) mol) in dry dichloromethane (2 ml) was stirred at room temperature for 24 h. Insoluble lead diacetate was separated, washed with dichloromethane (20 ml) and the combined dichloromethane solutions washed with saturated aqueous sodium hydrogen carbonate, then water, dried, and evaporated under reduced pressure. Chromatography of the crude product over silica with light petroleum : ethyl acetate (3 : 1) gave the isoquinolone (92) (R\(_f\) 0.21) as a colourless oil (0.12 g, 60\%) (Found: M\(^+\) 389.1376. \( \text{C}_{22}\text{H}_{19}\text{N}_{3}\text{O}_{4}\) requires M\(^+\) 389.1376); \( \nu \)\(_{\text{max}} \) / cm\(^{-1}\) 1740s, 1705m, 1685s and 1600s; \( \delta \)\(_{\text{H}} \) (CDCl\(_3\), 300 MHz) 1.34, 1.35 (6H, 2 x d, J 6.7 Hz, CH\(_3\)CHCH\(_3\)), 2.87, (1H, heptet, J 6.7 Hz, CH\(_3\)CHCH\(_3\)), 3.76 (3H, s, CH\(_3\)O), 7.41-7.46 (1H, m, CH(Ar)), 7.60 (1H, s, C=CH), 7.65-7.85 (5H, m, 5 x CH(Ar)), 8.21 (1H, dd, J 8.0 and 1.4 Hz, CH(Ar)) and 8.46 (1H, dd, J 7.5 and 0.4 Hz, CH(Ar)); \( \delta \)\(_{\text{C}} \) (CDCl\(_3\), 75 MHz) 21.15, 21.73 (CH\(_3\)CHCH\(_3\)), 31.51 (CH\(_3\)CHCH\(_3\)), 53.14
(CO₂CH₃), 115.28 (C=CH), 121.00 (CCO(Q¹)), 126.69, 127.23, 127.47 (3 x CH(Ar)),
127.98 (C), 128.23 (CH(Ar)), 129.07 (CH(Ar)), 130.07 (CH(Ar)), 130.70 (C(Ar)),
134.10 (CH(Ar)), 134.29 (C(Ar)), 135.06 (CH(Ar)), 145.5 (CN=C(Q¹)), 160.44, 163.16
(CN(Q¹) and CO(Q¹)) (two CO signals not visible); m/z (%) 389 (M⁺, 10), 331 (23) and
330 (100).

Reaction of Q¹NHOAc (14) with 1-Methyl-2-trimethylsilyloxycclopentene

![Reaction Scheme](image)

The general procedure (E) was followed using 3-aminoquinazolinone (8) (1 g,
4.93 x 10⁻³ mol), LTA (2.29 g, 5.17 x 10⁻³ mol) and the silyl enol ether⁸⁹ (2.51 g, 0.015
mol) in dichloromethane (10 ml). After work up, an orange oil was obtained which was
purified by chromatography over silica using light petroleum : ethyl acetate (3 : 1). This
gave the α-Q¹NH-α-methylcyclcopentanone (93) (Rf 0.51) as a colourless solid (0.87 g,
59%) m.p. 128-130 °C (from ethanol) (Found: C, 68.0; H, 7.05; N,14.0. C₁₇H₂₁N₃O₂
requires C, 68.20; H, 7.05; N,14.05%); νmax / cm⁻¹ 3320m, 1740s, 1670s and 1590s; δH
(CDCl₃, 300 MHz) 1.21 (3H, s, CH₃C), 1.28, 1.33 (6H, 2 x d, J 6.7 Hz, CH₃CHCH₃),
1.83-2.20 (4H, m, 4 x CH), 2.22-2.31 (1H, m, CH), 2.53-2.62 (1H, m, CH), 3.79 (1H,
heptet, J 6.7 Hz, CH₃CHCH₃), 5.70 (1H, s, NH), 7.40 (1H, d, J 8.1, 6.6 and 1.5 Hz,
Q¹ 6-H), 7.65-7.73 (2H, m, Q¹ 7- and 8-H) and 8.13 (1H, dd, J 8.1 and 1.1 Hz, Q¹ 5-H);
\[ \delta_C (\text{CDCl}_3, 75 \text{ MHz}) \begin{array}{c}
18.17 \text{ (CH}_2\text{), 20.45, 20.86, 21.41 (3 x CH}_3\text{), 30.52 (CH}_3\text{CHCH}_2\text{), 35.82 (CH}_2\text{), 65.31 (CNH(Q^1))}, 120.22 (\text{CCO(Q^1)}), 126.00, 126.32, 127.13, 134.13 (4 x \text{CH(Q^1)}), 146.64 (\text{CN=C(Q^1)} \text{ and 163.18, 163.53 (CN(Q^1), CO(Q^1))}, (\text{one CH}_2 \text{ and one CO not visible}); \text{m/z} (%) 299 (M^+, 1), 256 (10), 229 (16), 228 (100), 189 (11), 188 (20), 187 (24) \text{ and 173 (15)}. \end{array} \]

**LTA Oxidation of (93) in Dichloromethane: Ring Expansion to Enamido-ester (94)**

![Chemical Structure](image)

The ketone (93) (0.1 g, 3.34 x 10^{-4} mol) and LTA (0.16 g, 3.51 x 10^{-4} mol) in dry dichloromethane (2 ml) were stirred at room temperature for 12 h. Insoluble lead diacetate was separated, washed with dichloromethane (20 ml) and the combined dichloromethane solution washed with saturated aqueous sodium hydrogen carbonate, then water, dried, and evaporated under reduced pressure. The residue was purified by chromatography over silica using light petroleum : ethyl acetate (2 : 1) to give enamido-ester (94) as a colourless oil (0.06 g, 60%) (Found: M^+ 297.1475, C_{17}H_{19}N_{3}O_{2} requires M^+ 297.1477, \nu_{max} / \text{cm}^{-1} 1730s, 1715s, 1690s \text{ and 1600s}; \delta_H (\text{CDCl}_3, 300 \text{ MHz}) 1.33, 1.39 (6H, 2 x d, J = 6.8 \text{ Hz, CH}_3\text{CHCH}_2\text{), 1.70 (3H, d, J = 1.5 \text{ Hz, CH}_3\text{C=CH}), 2.43-2.50, 2.72-2.92 (4H, 2 x m, 2 x CH}_2\text{) 3.03 (1H, heptet, J = 6.8 \text{ Hz, CH}_3\text{CHCH}_2\text{), 5.26-5.30 (1H, m, C=CH) \text{, 7.47 (1H, ddd, J = 8.0, 6.9 and 1.5 Hz, Q^1 6-H), 7.74 (1H, dd, J = 8.3 and 1.5 Hz, Q^1 7-H) and 8.25 (1H, ddd, J = 8.0, 1.5 and} \]
Reaction of Q¹NHOAc (14) with 2-Acetylcyclopentanone

The general procedure (E) was followed using 3-aminoquinazolinone (8) (1 g, 4.93 x 10⁻³ mol), LTA (2.29 g, 5.17 x 10⁻³ mol) and 2-acetylcyclopentanone (1.86 g, 0.015 mol) in dichloromethane (10 ml). The residue was purified by column chromatography using light petroleum : ethyl acetate (3 : 1) as eluant to give α-Q¹NH₂-β-diketone (95) (Rf 0.39) as a colourless solid (1.06 g, 66%) m.p. 130-132 °C (from ethanol) (Found: C, 65.95; H, 6.5; N, 12.8. C₁₈H₂₁N₃O₃ requires C, 66.05; H, 6.45; N, 12.85%); v_max / cm⁻¹ 3260m, 1750s, 1715s, 1670s and 1600s; δ_H (CDCl₃, 300 MHz) 1.30, 1.35 (6H, 2 x d, J 6.8 Hz, CH₃CH₂CH₃), 1.81-2.01 (2H, m, CH₂), 2.33-2.65 (4H, m, 2 x CH₂), 2.44 (3H, s, OCH₃), 3.25 (1H, heptet, J 6.8 Hz, CH₃CH₂CH₃), 6.21 (1H, s, br, NH), 7.43 (1H, ddd, J 8.0, 6.9 and 1.3 Hz, Q¹ 6-H), 7.70 (1H, ddd, J 8.2, 1.3 and 0.5 Hz, Q¹ 8-H), 7.75 (1H, ddd, J 8.2, 6.9 and 1.5 Hz, Q¹ 7-H) and 8.14 (1H, ddd, J 8.0, 1.5 and...
0.5 Hz, Q{\textsuperscript{1}} 5-H; \delta_{C} (CDCl_{3}, 75 MHz) 18.71 (CH_{2}), 20.10, 20.97, 25.42 (3 x CH{\textsubscript{3}}), 26.57 (CH_{2}), 31.22 (CH_{3}CHCH_{3}), 35.35 (CH_{2}), 78.40 (CNH(Q{\textsuperscript{1}})), 119.85 (CCO(Q{\textsuperscript{1}})), 126.37, 126.39, 127.37, 134.48 (4 x CH(Q{\textsuperscript{1}})), 146.80 (CN=C(Q{\textsuperscript{1}})), 162.70, 162.97 (CN(Q{\textsuperscript{1}}), CO(Q{\textsuperscript{1}})) and 202.89, 213.07 (2 x CO); m/z (%) 327 (M\textsuperscript{+}, 1), 287 (23), 244 (19), 201 (21), 190 (13), 189 (100), 188 (51), 187 (18), 173 (68), 160 (15), 96 (16), 90 (11), 84 (12), 68 (11) and 55 (14).

LTA Oxidation of \(\alpha\)-Q{\textsuperscript{1}}NH-\(\beta\)-diketone (95)

\[
\begin{array}{c}
\text{O} \\
\text{\textbf{NH}Q^1} \\
\text{COCH_3} \\
(95)
\end{array}
\xrightarrow{\text{LTA}}
\begin{array}{c}
\text{CH}_2\text{Cl}_2
\end{array}
\]

Mixture of many products

The \(\alpha\)-Q{\textsuperscript{1}}NH-\(\beta\)-diketone (95) (0.3 g, 9.17 x 10\textsuperscript{-4} mol) and LTA (0.43 g, 9.63 x 10\textsuperscript{-4} mol) in dry dichloromethane (1 ml) were stirred at room temperature for 12 h. Insoluble lead di-acetate was separated, washed with dichloromethane (20 ml) and the combined dichloromethane solutions washed with saturated aqueous sodium hydrogen carbonate, then water, dried, and evaporated under reduced pressure. A proton NMR spectrum and t.l.c. of the crude reaction mixture suggested many products had formed and their separation was not attempted.
Reduction of $\alpha$-Q$^1$NH-β-ketoester (82) with Sodium Borohydride

To the $\alpha$-Q$^1$NH-β-ketoester (82) (0.5 g, 1.40 x 10$^{-3}$ mol) in dry ethanol (5 ml) was added an excess of sodium borohydride until the solution remained cloudy. After stirring for 30 min. at room temperature it was neutralised with 2M HCl and the solvent removed under reduced pressure. The residue was diluted with ether (30 ml), washed with water, dried (MgSO$_4$) and the solvent removed. Column chromatography of the residue with light petroleum : ethyl acetate (2 : 1) as eluant gave (97) (Rf 0.47) as a single diastereoisomer and as a colourless oil (0.29 g, 58%) (Found: C, 63.5; H, 7.0; N, 11.7. C$_{19}$H$_{25}$N$_3$O$_4$ requires C, 63.5; H, 7.0; N, 11.7%). $\nu_{max}$ / cm$^{-1}$ 3420m,br, 3290m,br, 1740s, 1610m and 1595s; $\delta_{H}$ (CDCl$_3$, 300 MHz) 0.99 (3H, t, J 7.2 Hz, CH$_3$CH$_2$), 1.25, 1.36 (6H, 2 x d, J 6.8 Hz, CH$_3$CHCH$_3$), 1.58-1.90 (5H, m, 5 x CH), 2.19-2.26 (1H, m, CH), 3.69 (1H, heptet, J 6.8 Hz, CH$_3$CHCH$_3$), 4.02 (2H, ABX$_3$, J 7.2 Hz, CH$_2$CH$_3$), 4.25-4.30 (1H, m, CHOH), 4.70 (1H, s, br, CHOH), 5.94 (1H, s, NH), 7.43 (1H, ddd, J 8.0, 6.8 and 1.0 Hz, Q$^1$ 6-H), 7.67 (1H, dd, J 8.2 and 1.0 Hz, Q$^1$ 8-H), 7.74 (1H, ddd, J 8.2, 6.8 and 1.1 Hz, Q$^1$ 7-H) and 8.18 (1H, dd, J 8.0 and 1.1 Hz, Q$^1$ 5-H); $\delta_{C}$ (CDCl$_3$, 75 MHz) 13.44 (CH$_3$), 18.74 (CH$_2$), 19.44, 21.52 (2 x CH$_3$), 29.85 (CH$_2$), 30.66 (CH$_3$CHCH$_3$), 30.92 (CH$_2$), 60.21 (CH$_2$), 74.80 (CNH), 75.46 (CHOH), 120.09
(\text{CCO}(Q^1)), 126.16, 126.35, 127.14, 134.36 (4 \times \text{CH}(Q^1)), 146.80 (\text{CN}=\text{C}(Q^1)), 163.64, 163.70 (\text{CN}(Q^1), \text{CO}(Q^1)) and 171.65 (\text{CO}_2\text{CH}_2\text{CH}_3); m/z (%) \text{ FAB} \ 360 (M+H)^*.

**Acetylation of Alcohol (97)**

\[
\begin{align*}
\text{OH} & \quad \text{NHO}^1 \\
\text{CO}_2\text{Et} & \quad \text{O} \\
\text{Pyridine} & \quad \text{Ac} \\
\end{align*}
\]

To alcohol (97) (0.44 g, 1.23 \times 10^{-3} \text{ mol}) dissolved in dichloromethane (3 ml) and pyridine (0.2 ml) was added a solution of acetyl chloride (0.05 g, 1.23 \times 10^{-3} \text{ mol}) in dichloromethane (1 ml). After stirring for 3 h. the mixture was diluted with dichloromethene, washed with saturated aqueous sodium bicarbonate, water, dried and the solvent removed under reduced pressure. Purification by column chromatography using light petroleum : ethyl acetate (3 : 1) as eluant gave acetate (98) (R_f 0.45) as a colourless oil (0.31 g, 63\%) (Found: M^+ 401.1953. C_{21}H_{27}N_3O_5 \text{ requires } M^+ 401.1951); v_{max} / cm^{-1} 3300w, 1740s, 1680s, 1610m and 1595s; δ_H (CDCl_3, 300 MHz) 1.22 (3H, t, J 7.2 Hz, CH_3CH_2), 1.24, 1.39 (6H, 2 x d, J 6.7 Hz, CH_3CHCH_3), 1.64-2.11 (6H, m, 6 x CH), 2.16 (3H, s, CH_3CO), 3.92 (1H, heptet, J 6.7 Hz, CH_3CHCH_3), 4.22 (2H, ABX_3, J 7.2 Hz, CH_3CH_2), 5.44-5.47 (1H, m, CHOAc), 6.00 (1H, s, NH), 7.39 (1H, ddd, J 8.0, 6.8 and 1.5 Hz, Q^1 6-H), 7.63-7.73 (2H, m, Q^1 7- and 8-H) and 8.16 (1H, dd, J 8.0 and 0.8 Hz, Q^1 5-H); δ_C (CDCl_3, 75 MHz) 13.72 (CH_3), 19.42 (CH_2), 19.55, 21.01, 21.53 (3 x CH_3), 28.04, 29.46 (2 x CH_2), 30.14 (CH_3CHCH_3), 61.69 (OCH_2CH_3), 72.95
(CO₂Et), 78.03 (CHOAc), 120.30 (CCO(Q¹)), 125.97, 126.45, 127.02, 134.14 (4 x CH(Q¹)), 146.79 (CN=C(Q¹)), 162.94 (CN(Q¹)), 163.76 (CO(Q¹)) and 169.84, 171.68 (2 x CO); m/z (%) 401 (M⁺, 19), 328 (37), 269 (100), 189 (47), 188 (55), 187 (21), 174 (10), 173 (60), 171 (10), 160 (15), 130 (15), 129 (12), 90 (12) and 55 (10).

**Attempted Thermal Elimination of Acetic Acid from Acetate (98)**

![Diagram of thermal elimination](image)

The acetate (98) (0.1 g, 2.49 x 10⁻⁴ mol) was heated at 250 °C and 0.2 mmHg pressure for 3 h. A proton NMR spectrum of this material showed that elimination of acetic acid had not occurred; some decomposition of (98) was observed.

**Aziridination of Ethyl Cyclopentene 1-Carboxylate using**

3-Acetoxyaminoquinazolinone (14)

![Diagram of aziridination](image)
The general procedure (E) was followed using 3-aminoquinazolinone (8) (0.24 g, 1.17 x 10^{-3} mol), LTA (0.54 g, 1.23 x 10^{-3} mol) and ethyl cyclopentene 1-carboxylate (0.49 g, 3.5 x 10^{-3} mol) in dichloromethane (3 ml). After work up, the residue was purified by column chromatography using light petroleum : ethyl acetate (3 : 1) as eluant to give aziridine (101) (R_f 0.54) as a colourless solid (0.25 g, 63%) m.p. 108-110 °C (from ethanol) (Found: C, 66.65; H, 6.8; N,12.2. C_{19}H_{24}N_{3}O_{3} requires C, 66.85; H, 6.8; N,12.3%); v\text{max} / cm^{-1} 1720s, 1670s and 1590s; δ_H (CDCl_{3}, 300 MHz) 0.92 (3H, t, J 7.1 Hz, CH_{3}CH_{2}), 1.34, 1.37 (6H, 2 x d, J 6.7 Hz, CH_{3}CHCH_{3}), 1.63-1.84, 1.91-2.02, 2.17-2.29, 2.37-2.51 (6H, 4 x m, 6 x CH), 3.34 (1H, heptet, J 6.7 Hz, CH_{3}CHCH_{3}), 3.95 (2H, ABX_{3}, J 7.1 Hz, CH_{3}CH_{2}), 4.00-4.03 (1H, m, NCH), 7.38 (1H, ddd, J 8.0, 6.3 and 1.4 Hz, Q_{1} 6-H), 7.60-7.69 (2H, m, Q_{1} 7- and 8-H) and 8.17 (1H, ddd, J 8.0, 1.4 and 0.6 Hz, Q_{1} 5-H); δ_C (CDCl_{3}, 75 MHz) 13.41, 19.89, 20.79 (3 x CH_{3}), 20.90, 27.83, 28.55 (3 x CH_{2}), 31.16 (CH_{2}CHCH_{3}), 55.02 (NCH), 59.42 (CO_{2}CH_{2}CH_{3}), 61.51 (CH_{2}CH_{2}), 120.96 (CO \text{(Q}_{1})), 125.86, 126.63, 126.90, 133.20 (4 x CH(Q_{1})), 145.82 (CN=\text{C(Q}_{1})), 159.79, 159.92 (CN=\text{Q}_{1}), 166.86 (CO_{2}CH_{2}CH_{3}); m/z (%) 341 (M^+, 11), 268 (21), 241 (26), 240 (44), 189 (31), 188 (31), 187 (44), 173 (83), 172 (14), 171 (26), 160 (15), 154 (25), 146 (16), 145 (100), 144 (24), 130 (92), 129 (18), 108 (18), 104 (19), 103 (33), 95 (15) and 76 (26).
Aziridine (101) (0.17 g, 4.99 x 10⁻⁴ mol) was dissolved in ether (10 ml), the solution cooled to 0 °C and concentrated hydrochloric acid (0.1 ml) added. The mixture was stirred at 0 °C for 3 h. Further ether (20 ml) was added, the solution was washed with water, dried and the solvent removed. Separation of the two regioisomers (i.e. ring-opened chloroesters) was carried out by using a chromatotron and light petroleum : ethyl acetate (3 : 1) as eluant. This gave the α-chloroester (102) (Rₙ 0.24) as a colourless oil (0.09 g, 48%) (Found: M⁺ 377.1507. C₁₉H₂₄N₃O₃Cl requires M⁺ 377.1506); νₘₐₓ / cm⁻¹ 3290w, 1740s,br, 1680s and 1595s; δH (CDCl₃, 300 MHz) 1.27-1.38 (9H, m, CH₃CHCH₃, CH₃CH₂), 1.60-1.80 (1H, m, br, CH), 1.87-2.10 (3H, m, 3 x CH), 2.23-2.32, 2.64-2.75 (2H, 2 x m, 2 x CH), 3.66 (1H, heptet, J 6.7 Hz, CH₂CHCH₃), 4.22-4.39 (3H, m, CH₂CH₂, CHNH), 5.95 (1H, d, J 5.8 Hz, NH(Ch)), 7.42 (1H, ddd, J 8.0, 6.4 and 1.5 Hz, Q₁ 6-H), 7.67-7.75 (2H, m, Q₁ 7- and 8-H) and 8.20 (1H, ddd, J 8.0, 1.5 and 0.7 Hz, Q₁ 5-H); δC (CDCl₃, 75 MHz) 14.01 (CH₃), 20.53 (CH₂), 21.05 (br) (2 x CH₃, CH), 20.53 (CH₂), 30.36 (CH), 37.73, 62.41 (2 x CH₂), 74.60 (CCO₂Et), 120.53 (CCO(Q₁)), 126.27, 126.50, 127.26, 134.30 (4 x CH(Q₁)), 146.93 (CN=C(Q₁)), 162.07 (CN(Q₁)), 163.27 (CO(Q₁)) and 169.24 (CO); m/z (%) 377 (M⁺, 2), 342 (10), 341 (41), 326 (11),
Further elution gave \( \beta \)-chloroester (100) \((R_f 0.18)\) as a colourless solid \((0.03 \, \text{g}, 16\%)\) m.p. 119-121.5 °C \(\text{from ethanol}\) \((\text{Found } M^+ 377.1506, C_{19}H_{24}N_3O_3Cl_1 \text{ requires } M^+ 377.1506); \nu_{\text{max}} \, \text{cm}^{-1} 3300w, 1735s, 1680s \text{ and } 1595s; \delta_H \, (\text{CDCl}_3, 300 \, \text{MHz}) 1.26 (3H, d, J 6.8 Hz, CH\_3CH\_CH\_3), 1.32 (3H, t, J 7.2 Hz, CH\_3CH\_2), 1.36 (3H, d, J 6.8 Hz, CH\_3CH\_CH\_3), 2.05-2.19 (3H, m, 3 x CH), 2.39-2.54 (3H, m, 3 x CH), 3.62 (1H, heptet, J 6.8 Hz, CH\_3CH\_CH\_3), 4.28-4.47 (3H, m, CH\_3C\%. CH\_3), 6.01 (1H, s, NH), 7.41 (1H, ddd, J 7.9, 6.8 and 1.4 Hz, Q\_1 6-H), 7.66-7.75 (2H, m, Q\_1 7- and 8-H) and 8.18 (1H, dd, J 7.9 and 0.8 Hz, Q\_1 5-H); m/z (%) 377 (M\(^+\) 24), 306 (33), 305 (19), 304 (100), 269 (17), 268 (11), 203 (56), 190 (14), 189 (81), 188 (18), 187 (29), 175 (25), 174 (12), 173 (12), 173 (49), 160 (13), 145 (10), 130 (22), 129 (13), 119 (12), 118 (12) and 116 (27).

Reconversion of \( \alpha \)-Chloroester (102) to Aziridine (101)

\[
\begin{align*}
\text{NH}_2\text{H}^+ & \quad \text{CO}_2\text{Et} & \xrightarrow{\text{NaH, DMF}} & \quad \text{N}^1 \text{CO}_2\text{Et} \\
\text{(102)} & & & \text{(101)}
\end{align*}
\]

To sodium hydride \((0.011 \, \text{g}, 8.74 \times 10^{-5} \, \text{mol})\) \((60\% \text{ dispersion in mineral oil})\) in dry DMF \((0.5 \, \text{ml})\) was added the \( \alpha \)-chloroester (102) \((0.03 \, \text{g}, 7.95 \times 10^{-5} \, \text{mol})\) and the mixture stirred at room temperature under a nitrogen atmosphere for 3h. Water \((2 \, \text{ml})\) was then added, then the product extracted into ethyl acetate \((10 \, \text{ml})\). This solution was washed with water, dried, and the solvent evaporated under reduced pressure.
Crystallisation of the residue from ethanol gave aziridine (101) (0.021 g, 78%) identical in all respects with the sample prepared previously.

Treatment of β-chloroester (100) with LTA in Dichloromethane

\[
\begin{align*}
\text{Cl} & \quad \text{NH}_2^1 \\
\text{CO}_2\text{Et} & \quad \text{LTA} \\
\text{CH}_2\text{Cl}_2 & \quad \text{No reaction}
\end{align*}
\]

(100)

To a solution of β-chloroester (100) (0.02 g, 5.3 x 10^{-5} mol) in dry dichloromethane (1 ml) was added LTA (0.025 g, 5.56 x 10^{-5} mol) and the solution stirred at room temperature for 2 days. Insoluble lead di-acetate was separated, washed with dichloromethane (15 ml) and the combined dichloromethane solutions washed with saturated aqueous sodium hydrogen carbonate, then water, dried, and evaporated under reduced pressure. A 300 MHz NMR spectrum showed only unreacted starting material to be present (0.01 g).
Reduction of Enamide-ester (84) with Samarium Diiodide

\[ \text{O} \begin{array}{c} \text{H} \\ \text{CO}_2\text{Et} \end{array} + \text{O}^\dagger \quad \text{SmI}_2 \quad \text{THF} \quad \text{O} \begin{array}{c} \text{H} \\ \text{CO}_2\text{Et} + Q^\dagger \end{array} \]

(84) \quad (103) \quad (104)

The enamide-ester (84) (0.23 g, 6.48 x 10^{-4} mol) was dissolved in dry THF (10 ml) containing dry t-butanol (1 ml) and the solution purged with argon using a 3-way tap connected to a vacuum pump and an argon supply. A solution of samarium diiodide (0.1M in THF, 14.3 ml, 1.4 x 10^{-3} mol) was added and the mixture stirred at room temperature for 20 min. during which time the solution turned from blue to green. The bulk of the solvent was removed under reduced pressure, the residue dissolved in dichloromethane (30 ml) and this solution washed with saturated aqueous sodium hydrogen carbonate, water, dried, then evaporated. The residue was purified by column chromatography using light petroleum : ethyl acetate (2 : 1) as eluant. This gave the enamido-ester (103) as a colourless oil (0.06 g, 51%) (Found: M⁺ 169.0739. C₉H₁₁N₁O₃ requires M⁺ 169.0740);

\[ \nu_{\text{max}} / \text{cm}^{-1} \quad 3390\text{m}, \quad 1685\text{s} \quad \text{and} \quad 1660\text{s}; \quad \delta_{\text{H}} \quad (\text{CDCl}_3, \quad 300 \text{ MHz}) \quad 1.34 \text{ (3H, t, J 7.1 Hz, CH}_3\text{CH}_2), \quad 2.50-2.53 \text{ (4H, m, 2 x CH}_2), \quad 4.30 \text{ (2H, q, J 7.1 Hz, CH}_2\text{CH}_3), \quad 6.26-6.30 \text{ (1H, m, C=CH) \ and \ 7.57 \text{ (1H, s, br, NH); } \delta_{\text{C}} \quad (\text{CDCl}_3, \quad 75 \text{ MHz}) \quad 14.01 \text{ (CH}_2\text{CH}_3), \quad 20.64, \quad 29.04 \text{ (2 x CH}_2), \quad 61.68 \text{ (CH}_2\text{CH}_3), \quad 113.78 \text{ (C=CH), \ 128.74 \text{ (C=CO}_2\text{Et) \ and \ 161.47, \ 169.43 \text{ (2 x CO; m/z (%) 169 (M}^+\text{, 100), 157 (73), 140 (70), 113 (30), 112 (52), 97 (18), 96 (69), 95 (21), 94 (19), 69 (16), 68 (61), 67 (40), 66 (11), 55 (18) and 54 (59). Further elution gave unreacted starting material (0.06 g).} \]
LTA Oxidation of (85) in Methanol:

Ring Cleavage to Imino-diesters (107) and (108)

A solution of α-Q1NH-ester (85) (0.33 g, 8.89 x 10^-4 mol) and LTA (0.41 g, 9.34 x 10^-4 mol) in dry methanol (3 ml) was stirred overnight. The insoluble lead di-acetate was separated and the bulk of the solvent removed under reduced pressure. The residue was diluted with dichloromethane (30 ml), which was washed with saturated aqueous sodium hydrogen carbonate, then water, dried and evaporated under reduced pressure. Chromatography of the residue over silica, using light petroleum : ethyl acetate (4 : 1) gave imino-diester (107) (R_f 0.42) (2.4 : 1 mixture of imine double bond isomers) as a yellow oil (0.08g, 22%) (Found: M+ 401.1953. C_{21}H_{27}N_{3}O_{5} requires M+ 401.19510);

υ_{max} / cm^{-1} 1740s, 1680s and 1590s; δ_{H} (CDCl_{3}, 300 MHz) major isomer: 1.10 (3H, t, J 7.2 Hz, CH_{3}CH_{2}), 1.36 (6H, d, J 6.7 Hz, CH_{3}CHCH_{3}), 1.60-1.62, 1.81-1.83, 2.24-2.29, 2.39-2.43, 2.89-2.93 (8H, 5 x m, 8 x CH), 3.37 (1H, heptet, J 6.7 Hz, CH_{3}CHCH_{3}), 3.68 (3H, s, CH_{3}O), 4.15 (2H, q, J 7.2 Hz, CH_{3}CH_{2}), 7.37-7.48 (1H, m, Q1 6-H), 7.67-7.78 (2H, m, Q1 7- and 8-H) and 8.17 (1H, ddd, J 8.0, 1.0 and 0.7 Hz, Q1 5-H); minor isomer (observable peaks): 1.31 (6H, d, J 6.7 Hz, CH_{3}CHCH_{3}), 1.43 (3H, t, J 7.2 Hz, CH_{3}CH_{2}).
3.21 (1H, heptet, J 6.7 Hz, CH$_3$CH($CH_3$)$_2$), 3.61 (3H, s, CH$_3$O), 4.44 (2H, q, J 7.2 Hz, CH$_2$CH$_2$) and 8.26 (1H, ddd, J 8.5, 1.3 and 0.8 Hz, Q$_1$ 5-H); $\delta_C$ (CDCl$_3$, 75 MHz) major isomer: 13.95, 20.05 (2 x CH$_3$), 24.22, 24.72, 30.80 (3 x CH$_2$), 31.57 (CH$_3$CH$_3$), 33.18 (CH$_2$), 51.33 (CH$_3$O), 62.54 (CH$_2$O), 120.45 (CCO(Q$_1$)), 126.28, 126.97, 127.25, 134.03 (4 x CH(Q$_1$)), 146.67 (CN=C(Q$_1$)) and 155.71, 158.99, 162.91, 172.72, 173.11 (2 x CN, 3 x CO); minor isomer (observable peaks): 13.56, 21.10 (2 x CH$_3$), 24.15, 25.03 (2 x CH$_2$), 31.78 (CH$_3$CH$_3$), 33.47, 34.47 (2 x CH$_2$), 51.38 (CH$_3$O), 61.83 (CH$_2$O), 120.36 (CCO(Q$_1$)), 126.00, 127.16, 133.87 (4 x CH(Q$_1$)), 146.51 (CN=C(Q$_1$)) and 158.83, 160.21, 168.65, 173.59 (2 x CN, 2 x CO); m/z (%) 401 (M+, 1), 329 (21), 328 (100), 317 (16), 230 (26), 188 (30), 187 (38), 175 (11), 173 (50), 160 (12), 130 (11), 119 (13), 115 (18), 90 (17), 87 (28), 76 (10) and 55 (15).

Further elution gave imino-diester (108) (R$_f$ 0.32) (4.1 : 1 mixture of imine double bond isomers) as an oil (0.05 g, 15%) (Found: M$^+$ 387.1795. C$_{20}$H$_{25}$N$_3$O$_5$ requires M$^+$ 387.1794); $\nu_{\text{max}}$ / cm$^{-1}$ 1740s, 1680s and 1600s; $\delta_H$ (CDCl$_3$, 300 MHz) major isomer: 1.30 (6H, d, J 6.7 Hz, CH$_3$CH($CH_3$)$_2$), 1.55-1.65, 1.79-1.82, 2.24-2.29, 2.41-2.44, 2.87-2.92 (8H, 5 x m, 8 x CH), 3.20 (1H, heptet, J 6.7 Hz, CH$_3$CH($CH_3$)$_2$), 3.61, 3.98 (6H, 2 x s, 2 x CH$_3$O), 7.38-7.49 (1H, m, Q$_1$ 6-H), 7.69-7.78 (2H, m, Q$_1$ 7- and 8-H) and 8.26 (1H, dd, J 7.9 and 0.8 Hz, Q$_1$ 5-H); minor isomer (observable peaks): 1.35 (6H, d, J 6.7 Hz, CH$_3$CH($CH_3$)$_2$), 3.38 (1H, heptet, J 6.7 Hz, CH$_3$CH($CH_3$)$_2$), 3.69, 3.71 (6H, 2 x s, CH$_3$O) and 8.17 (1H, m, Q$_1$ 5-H); $\delta_C$ (CDCl$_3$, 75 MHz) major isomer: 20.30 (2 x CH$_3$), 24.43, 24.90, 31.00 (3 x CH$_2$), 31.73 (CH$_2$CH($CH_3$)$_2$), 33.37 (CH$_2$), 51.53, 53.33 (2 x CH$_3$O), 120.60 (CCO(Q$_1$)), 126.48, 127.19, 127.43, 134.24 (4 x CH(Q$_1$)), 146.84 (CN=C(Q$_1$))
and 155.85, 159.13, 163.50, 172.61, 173.32 (2 x CN, 3 x CO); minor isomer (observable peaks): 20.22 (2 x CH₃), 24.31, 25.18, 31.09 (3 x CH₂), 32.04 (CH₃CHCH₃), 33.65 (CH₂), 53.81, 53.83 (2 x CH₂O), 126.19, 134.10 (2 x CH(Q₁)) and 173.59 (CO); m/z (%) 387 (M⁺, 1), 329 (21), 328 (100), 188 (21), 187 (19) and 173 (48).

LTA Oxidation of α-Methyl-α-Q₁NH-cyclohexanone (93) in Methanol:

Ring Cleavage to Imino-ester (110)

The ketone (88) (0.31 g, 9.24 x 10⁻⁴ mol) and LTA (0.45 g, 1.02 x 10⁻³ mol) were stirred in dry methanol (3 ml) for 12 h. After the work up as described previously, the product was purified by chromatography using light petroleum : ethyl acetate (5 : 1) as eluant. This gave a single imino-ester (109) (Rₚ 0.18) as a colourless oil (0.24 g, 71%) (Found: M⁺ 343.1898. C₁₅H₂₅N₃O₃ requires M⁺ 343.1896); νmax / cm⁻¹ 1730s, 1670s and 1590s; δH (CDCl₃, 300 MHz) major isomer: 1.18, 1.37 (6H, 2 x d, J 6.5 Hz, CH₃CH₂), 1.81-1.93 (4H, m, 4 x CH), 1.84 (3H, s, CH₃C=N), 2.38-2.42 (2H, m, CH₂), 2.62-2.65 (2H, m, 2 x CH), 3.20 (1H, heptet, J 6.5 Hz, CH₃CHCH₃), 3.67 (3H, s, CH₃O), 7.41 (IH, ddd, J 8.1, 7.1 and 1.0 Hz, Q₁ 6-H), 7.67-7.72 (2H, m, Q₁ 7- and 8-H) and 8.21 (1H, dd, J 8.1 and 1.0 Hz, Q₁ 5-H); δC (CDCl₃, 75 MHz) major isomer: 19.12, 19.55, 20.58 (3 x CH₃), 24.23, 25.36 (2 x CH₂), 31.12 (CH₃CHCH₃), 31.42, 33.51 (2 x
CH$_2$), 51.36 (CH$_2$O), 120.79 (CCO(Q$^1$)), 125.85, 126.60, 127.08, 133.52 (4 x CH(Ar)), 146.65 (CN=C(Q$^1$)), 156.56 (CN(Q$^1$)), 159.30 (CO(Q$^1$)) and 173.54, 181.10 (C=N, C=O); m/z (%) 343 (M$^+$, 7), 328 (11), 229 (15), 228 (100) and 187 (11).

**LTA Oxidation of α-Methyl-α-$Q^1$NH-cyclopentanone (93):**

**Ring Cleavage to Imino-ester (110)**

The ketone (93) (0.09 g, $3.01 \times 10^{-4}$ mol) and LTA (0.14 g, $3.16 \times 10^{-4}$ mol) were stirred in dry methanol (2 ml) for 12 h. After work up, the crude reaction mixture was purified by chromatography using light petroleum : ethyl acetate (2 : 1) as eluant. This gave imino-ester (110) (R$_f$ 0.13) (5.2 :1 mixture of imine double bond isomers) as a colourless oil (0.046 g, 47%) (Found: M$^+$ 329.1738. C$_{19}$H$_{23}$N$_3$O$_3$ requires M$^+$ 329.1739); $\nu_{\text{max}}$ / cm$^{-1}$ 1730s, 1670s and 1590s; $\delta_H$ (CDCl$_3$, 300 MHz) major isomer: 1.25, 1.38 (6H, 2 x d, J 7.0 Hz, CH$_3$CHCH$_3$), 1.85 (3H, s, CH$_3$C=N), 2.08-2.27, 2.21-2.35, 2.51-2.57, 2.63-2.69 (6H, 4 x m, 6 x CH), 3.20 (1H, heptet, J 7.0 Hz, CH$_3$CHCH$_3$).
3.69 (3H, s, CH$_3$O), 7.42 (1H, ddd, J 8.1, 7.7 and 1.6 Hz, Q$^1$ 6-H), 7.67-7.74 (2H, m, Q$^1$ 7- and 8-H) and 8.22 (1H, d, J 8.1 and 0.4 Hz, Q$^1$ 5-H); minor isomer (observable peaks): 1.25, 1.38 (6H, 2 x d, J 6.6 Hz, CH$_3$CH$_2$), 2.15-2.20, 2.25-2.32, 2.55-2.60, 2.66-2.72 (6H, 4 x m, 6 x CH), 2.35 (3H, s, CH$_3$C=), 3.17 (1H, heptet, J 6.6 Hz, CH$_3$CH$_2$) and 3.56 (3H, s, CH$_3$O); $\delta$C (CDCl$_3$, 75 MHz) major isomer: 19.32, 19.58, 20.57 (3 x CH$_3$), 21.02 (CH$_2$), 31.18 (CH$_3$CH$_2$), 32.84, 37.82 (2 x CH$_2$), 51.48 (CH$_3$O), 120.80 (CO(Q$^1$)), 125.90, 126.65, 127.13, 133.57 (4 x CH(Q$^1$)), 146.88 (CN=C(Q$^1$) and 156.56, 159.29, 173.42, 180.53 (2 x CN, 2 x CO); m/z (%) 329 (M+, 5), 229 (15), 228 (100), 187 (18) and 130 (10).

An authentic sample of imino-ester (110) was prepared by heating 3-aminoquinazolinone (8) (0.5 g, 2.46 x 10$^{-3}$ mol) and the ketoester (111) (0.36 g, 2.46 x 10$^{-4}$ mol) together at 130 °C for 4 h. The residue was purified by column chromatography using light petroleum : ethyl acetate (3 : 1) as eluant. The white solid obtained (R$_f$ 0.13) was recrystallised to give only the minor isomer of imino-ester (110) (0.49 g, 59%) m.p. 49-51 °C (from ethanol).
EXPERIMENTAL

CHAPTER FOUR
Reaction of 3-Aminoquinazolinone (17) with Heptan-2-one

![Chemical Structure](image)

3-Aminoquinazolinone (17) (0.2 g, 1.06 x 10^{-3} mol) was dissolved in 2-heptanone (1 ml) and heated at 130 °C for 6 h. After cooling, the bulk of the heptan-2-one was removed under reduced pressure (Kugelrohr at 0.5 mm Hg). A 300 MHz proton NMR spectrum of the crude product indicated a 7.7 : 1 ratio of double bond isomers (from comparison of the signals at δ 0.93 and δ 0.78 (CH$_2$CH$_3$)). The residue was purified by column chromatography using light petroleum : ethyl acetate (4 : 1) as eluant and this gave the major isomer of the imine (115) (Rf 0.28) as a colourless oil (0.22 g, 72%) (Found: M$^+$ 285.1843. C$_{17}$H$_{23}$N$_3$O requires M$^+$ 285.1841); $\nu_{\text{max}}$ / cm$^{-1}$ 1670s and 1590s; δ$_H$ (CDCl$_3$, 300 MHz) major isomer: 0.93 (3H, t, J 6.9 Hz, CH$_3$CH$_2$), 1.29 (3H, t, J 7.4 Hz, CH$_3$CH$_2$), 1.36-1.50 (4H, m, 4 x CH), 1.76 (2H, sextet, J 7.4 Hz, CH$_3$CH$_2$CH$_2$), 1.83 (3H, s, CH$_3$CN), 2.59 (2H, ABX$_3$, J 7.4 Hz, CH$_3$CH$_2$), 2.66-2.81 (2H, m, 2 x CH), 7.42 (1H, ddd, J 8.1, 6.1 and 1.0 Hz, Q$_2$ 6-H), 7.66-7.74 (2H, m, Q$_2$ 7- and 8-H) and 8.25 (1H, ddd, J 8.1, 1.0 and 0.6 Hz, Q$_2$ 5-H); δ$_C$ (CDCl$_3$, 75 MHz) major isomer: 10.55, 13.81, 18.81 (3 x CH$_3$), 22.25, 25.76, 27.70, 31.24, 38.69 (5 x CH$_2$), 120.90 (CCO(Q$_2$)), 125.90, 126.65, 126.84, 133.59 (4 x CH(Q$_2$)), 146.87 (CN=C(Q$_2$)), 156.09, 156.52 (CN(Q$_2$), CO(Q$_2$)) and 182.15 (CN); m/z (%) 285 (M$^+$, 9), 270 (10), 215 (14) and 214 (100).
Reaction of 3-Aminoquinazolinone (8) with Heptan-2-one

3-Aminoquinazolinone (8) (0.2 g, 9.85 x 10^{-4} mol) was dissolved in heptan-2-one (1 ml) and the solution heated at 130 °C for 6 h. After cooling, the bulk of the heptan-2-one was removed under reduced pressure. A 300 MHz proton NMR spectrum of the crude product indicated a 9.6 : 1 ratio of double bond isomers (from comparison of the signals at δ 0.96 and δ 0.85 (CH₂CH₃)). The residue was purified by column chromatography using light petroleum : ethyl acetate (2 : 1) as eluant to give the major isomer of the imino (120) (R₉ 0.35) as a colourless oil (0.19 g, 64%) (Found: M⁺ 299.1997. C₁₈H₂₅N₃O requires M⁺ 299.1998); v_max / cm⁻¹ 1680 s, 1630 w and 1595 s; δ_H (CDCl₃, 300 MHz) 0.96 (3H, t, J 7.1 Hz, CH₃CH₂), 1.20-1.23 (3H, m, 3 x CH), 1.41, 1.44 (7H, 2 x d, J 6.7 Hz, CH₂CH₂CH₃ , m, CH), 1.79 (2H, sextet, J 7.1 Hz, CH₃CH₂CH₂), 1.86 (3H, s, CH₃CN), 2.62 (2H, ABX₂, J 7.4 Hz, CH₂CN), 3.25 (1H, heptet, J 6.7 Hz, CH₂CH₂CH₃), 7.44 (1H, ddd, J 8.0, 7.6 and 0.9 Hz, Q² 6-H), 7.70-7.73 (2H, m, Q¹ 7- and 8-H) and 8.26 (1H, dd, J 8.0 and 0.9 Hz, Q¹ 5-H); δ_C (CDCl₃, 75 MHz) 13.69, 19.05, 19.64, 20.66 (4 x CH₃), 22.34, 25.87 (2 x CH₂), 31.16 (CH₂CH₂CH₃), 31.34, 38.81 (2 x CH₂), 120.91 (QCO(Q¹)), 125.88, 126.69, 127.14,
133.54 (4 x CH(Q^1)), 146.96 (CN=C(Q^1)), 156.69, 159.45 (CN(Q^1), CO(Q^1)) and 181.85 (CN); m/z (%) 299 (M^+, 7), 284 (13), 229 (15) and 228 (100).

The major isomer above was heated at 200 °C for 1 h. A 300 MHz proton NMR spectrum of the product indicated the ratio of isomers to be 5.4 : 1 (from comparison with the signals at δ 0.96 and δ 0.85).

**Reduction of Imine (120) with Sodium Borohydride**

\[
\begin{align*}
\text{O}^1 & \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \ quad
room temperature, water was added, the methanol removed under reduced pressure, the residue diluted with dichloromethane (10 ml) and the solution washed with water, dried and the solvent removed. The residue was purified by column chromatography using light petroleum : ethyl acetate (7 : 1) as eluant. This gave \( \text{N-(quinazolinonyl)amine} \) (121) \((R_f \, 0.24)\) as a colourless oil \((0.026 \, g, 26\%)\) (Found: \(M^+ \, 301.2154\). \(C_{18}H_{27}N_2O\) requires \(M^+ \, 301.2154\)); \(\nu_{\max} / \text{cm}^{-1} \, 3280 \text{w}, 1670 \text{s}, 1610 \text{m} \) and \(1585 \text{s}; \delta_H \) \((\text{d}_{3}-\text{toluene}, \, 300 \, \text{MHz,} \, \text{378K}) \, 0.83 \) \((3H, \, t, \, J \, 7.2 \, \text{Hz,} \, \text{CH}_3\text{CH}_2)\), \((0.86 \) \((3H, \, d, \, J \, 6.4 \, \text{Hz,} \, \text{CH}_3\text{CH})\), \(1.19-1.42 \) \((14H, \, m, \, 8 \times \text{CH})\), \(2 \times \text{d,} \, J \, 6.7 \, \text{Hz,} \, \text{CH}_3\text{CHCH}_3)\), \(3.19-3.27 \) \((1H, \, m, \, \text{CH}_3\text{CHNH})\), \(3.81 \) \((3H, \, \text{d,} \, J \, 6.7 \, \text{Hz,} \, \text{CH}_3\text{CHCH}_3)\), \(5.33 \) \((3H, \, d, \, J \, 4.3 \, \text{Hz,} \, \text{NHCH})\), \(7.34 \) \((1H, \, ddd, \, J \, 8.1, \, 7.6 \) and \(1.4 \, \text{Hz,} \, \text{Q}_1 \, \text{6-H})\), \(7.57-7.69 \) \((2H, \, m, \, \text{Q}_1 \, 7-\text{and} \, 8-\text{H})\) and \(8.15 \) \((1H, \, ddd, \, J \, 8.1 \) and \(0.8 \, \text{Hz,} \, \text{Q}_1 \, 5-H)\); \(\delta_C \) \((\text{CDCl}_3, \, 75 \, \text{MHz}) \, 14.4 \) \((\text{CH}_3)\), \(18.5 \) \((\text{br} \, \times \, \text{CH}_2)\), \(23.0, \, 26.0 \) \((2 \times \text{CH}_2)\), \(30.80 \) \((\text{CH}_2\text{CHCH}_3)\), \(32.4, \, 36.0 \) \((2 \times \text{CH}_2)\), \(40.0 \) \((\text{CH})\), \(120.2 \) \((\text{CO}(\text{Q}_1))\), \(126.4, \, 126.8, \, 127.7, \, 134.5 \) \((4 \times \text{CH}(\text{Q}_1))\), \(147.7 \) \((\text{CN}=\text{C}(\text{Q}_1))\) and \(160.8, \, 162.6 \) \((\text{CN}(\text{Q}_1)), \, \text{CO}(\text{Q}_1))\); \(m/z \) \((\%) \, 301 \) \((M^+, \, 1)\), \(230 \) \((28)\), \(189 \) \((37)\), \(188 \) \((32)\), \(187 \) \((11)\), \(173 \) \((52)\), \(160 \) \((13)\) and \(114 \) \((100)\).

A \(\text{300 MHz proton NMR spectrum at 298K} \) showed most peaks to be broadened. Maximum broadening of the heptet at \(\delta \, 3.81 \) (the coalescence temperature) was observed at this temperature \((298K)\). An NMR spectrum at \(235K\) showed two heptets at \(\delta \, 3.93 \) and \(3.82 \) assigned to two \(N-N\) bond rotamers. A value of \(60 \, \text{kJ} / \text{mol} \) was calculated for the barrier to this \(N-N\) bond rotation (see Appendix 2).

Further elution gave \(\text{N-(dihydroquinazolinonyl)amine} \) (122) \((\text{which appears to be a single diastereoisomer}) \) \((R_f \, 0.20)\) as a colourless oil \((0.017 \, g, 17\%)\) (Found: \(M^+ \, 304.2381\). \(C_{18}H_{20}N_2O\) requires \(M^+ \, 304.2389\)); \(\nu_{\max} / \text{cm}^{-1} \, 3420 \text{m}, \, 1640 \text{s} \) and \(1610 \text{m} \).
Further elution gave a product (0.019 g) possibly the other diastereoisomer of (122) \( (R_f 0.19) \) although complete separation from the first diastereoisomer was not obtained.

Further elution gave the imine (123) \( (R_f 0.16) \) as a colourless oil (0.02 g, 20%) (Found: \( \text{MH}^+ 302.2236 \). \( \text{C}_{18}\text{H}_{27}\text{N}_2\text{O}_1 \) requires \( \text{MH}^+ 302.2232 \)); \( \nu_{\text{max}} / \text{cm}^{-1} \) 3420m, 1650s and 1610s; \( \delta_{\text{H}} \) (CDCl\(_3\), 250 MHz) 0.81-0.86 (3H, m, \text{CH}_3, d, J 7.2 Hz, \text{CH}_3\text{CHCH}_3), 0.99 (3H, d, J 7.2 Hz, \text{CH}_3\text{CHCH}_3), 1.26-1.34, 1.54-1.63 (6H, 2 x m, 6 x CH), 1.86 (3H, s, \text{CH}_3\text{C}=\text{N}), 2.30-2.39 (3H, m, 3 x CH), 4.17 (1H, s, br, NH), 5.00-5.03 (1H, m, CH), 6.59 (1H, d, J 8.1 Hz, DHQ\(_1^1\) 8-H), 6.76 (1H, ddd, J 7.8, 7.0 and 0.9 Hz, DHQ\(_1^1\) 6-H), 7.18-7.24 (1H, m, DHQ\(_1^1\) 7-H) and 7.83 (1H, dd, J 7.8 and 1.2 Hz, DHQ\(_1^1\) 5-H); \( \delta_{\text{C}} \) (CDCl\(_3\), 75 MHz) 14.40, 15.35, 18.53, 20.09, 22.85, 26.93, 30.91, 31.87, 39.19, 39.44, 113.00, 114.43, 119.31, 129.27, 133.77, 146.76, 161.00 and 176.54; \( m/z \) (%) FAB 304 (\( \text{MH}^+ \)).
Reduction of N-(Dihydroquinazolinonyl)-Imine (123)

The imine (123) (0.02 g, 6.64 x 10^{-5} mol) was dissolved in dry methanol (1 ml) and treated with sodium borohydride as described above. After work up, a proton NMR spectrum was obtained. The product appeared to be a mixture of diastereoisomers of (122) from comparison of the NMR spectrum of (122). The mixture was purified using a chromatotron with light petroleum : ethyl acetate (7 : 1) as eluant to give (122) (0.006 g) identical to that isolated previously.
Reaction of 3-Aminoquinazolinone (69) with the Ketoester

The 3-aminoquinazolinone (69) (0.2 g, 6.12 x 10^-4 mol) and the ketoester (0.09 g, 6.12 x 10^-4 mol) were heated at 210 °C for 1.5 h. A 300 MHz proton NMR spectrum of the crude product indicated a 6.7 : 1 ratio of double bond isomers to be present (from comparison of the signals at δ 1.12 and δ 2.19 (CH3CN)). Purification by column chromatography using light petroleum : ethyl acetate (7 : 1) as eluant, gave the major double bond isomer of the imine (124) (Rf 0.25) as a colourless oil (0.2 g, 73%) (Found: M+ 453.2053. C28H27N3O3 requires M+ 453.2052; νmax / cm^-1 1730s, 1675s, 1590s; δH (CDCl3, 250 MHz) major isomer: 1.12 (3H, s, CH3CN), 1.95-2.14, 2.40-2.49, 2.52-2.57 (6H, 3 x m, 6 x CH), 3.74 (3H, s, CH3O), 5.84 (1H, s, (Ph)_2CH), 7.28-7.37 (10H, m, 10 x CH(Ar)), 7.47 (1H, ddd, J 8.2, 7.7 and 1.1 Hz, Q^4 6-H), 7.67-7.75 (2H, m, Q^4 7- and 8-H) and 8.27 (1H, ddd, J 8.2, 1.1 and 0.8 Hz, Q^4 5-H); δC (CDCl3, 75 MHz) major isomer: 18.25 (CH3CN), 20.84, 32.82, 37.57 (3 x CH2), 51.48 (CH3O), 54.16 ((Ph)_2CH), 120.89 (CCO(Q^4)), 126.36, 126.55, 127.82, 128.70, 129.11, 129.79, 133.52 (7 x CH(Ar)), 138.96, 139.53 (2 x C(Ph)), 146.45 (CN=C(Q^4)), 155.06, 156.72 (CCN(Q^4), CCO(Q^4)) and 173.45, 182.11 (CN, CO2Me); m/z (%) 453 (M+, 28), 353 (13), 352 (49), 312 (37), 311 (100), 310 (25), 167 (36), 165 (28) and 152 (12).
Reduction of \( N-(\text{Quinazolinonyl})\)-imine (124) with Sodium Borohydride

\[
\begin{align*}
\text{MeO}_2\text{C} & \xrightarrow{\text{NaBH}_4} \text{OH} & \text{OH} \\
(124) & \xrightarrow{} (125) & (126)
\end{align*}
\]

The imine (124) (0.15 g, \(3.31 \times 10^{-4}\) mol) was dissolved in dry distilled methanol (3 ml) and sodium borohydride added until the solution remained cloudy. After 30 min. at room temperature, water was added, the methanol removed under reduced pressure, and the residue diluted with dichloromethane (15 ml). The solution was washed with water, dried and the solvent removed. The residue was purified by column chromatography using light petroleum : ethyl acetate (2 : 1) as eluant. This gave \( \text{N-(quinazolinonyl)} \)-amine (126) (\(R_f 0.25\)) as a colourless oil (0.038 g, 27\%) (Found: \(M^+ 427.2259\). C\(_{27}\)H\(_{29}\)N\(_3\)O\(_2\) requires \(M^+ 427.2260\); \(\nu_{\text{max}} / \text{cm}^{-1}\) 3040w, 1680s, 1590s and 1570m; \(\delta_H\) (d\(_8\)-toluene, 300 MHz, 378K) 0.71-0.85 (2H, m, 2 x CH), 1.12 (3H, d, J 6.7 Hz, CH\(_3\)CH), 1.17-1.63 (5H, m, 5 x CH), 3.26-3.31 (1H, m, CH), 3.52-3.61 (2H, m, OH, CH), 5.24 (1H, d, J 4.5 Hz, NHCH), 6.41 (1H, s, (Ph)\(_2\)CH), 7.14-7.40 (11H, m, 11 x CH(Ar)), 7.58-7.68 (2H, m, 2 x CH(Ar)) and 8.14 (1H, d, J 8.2 Hz, Q\(_4\) 5-H); A 300 MHz proton NMR spectrum at 298K showed most peaks broadened. \(\delta_C\) (CDCl\(_3\), 75 MHz) 18.68, 22.00, 33.06, 35.14, 41.00, 52.65, 62.99, 121.18, 126.79, 126.98, 127.24, 127.31, 128.40, 128.69, 128.81, 129.76, 129.90, 134.57, 141.13, 147.10, 157.00 and 162.72; \(m/z\) (%) 427 (M\(^+\), 10), 314 (11), 313 (57), 312 (100), 311 (83), 310 (26), 167 (31), 165 (20), 149 (13) and 116 (35).
Further elution gave imine (125) (Rf 0.17) as a colourless oil (0.05 g, 36%)
(Found: M+ 425.2103. C_{27}H_{27}N_{3}O_{2} requires M+ 425.2103); ν_{max} / cm^{-1} 1680s and
1590s; δ_{H} (CDCl₃, 250 MHz) 0.74-0.83 (2H, m, 2 x CH), 1.03 (3H, s, CH₃CN), 1.52-
1.76 (3H, m, 3 x CH), 2.15-2.41 (2H, m, 2 x CH), 3.60-3.68 (2H, m, OH, CH), 5.74
(1H, s, (Ph)₂CH), 7.17-7.29 (10H, m, 10 x CH(Ar)), 7.37 (1H, ddd, J 8.2, 7.2 and 1.5 Hz,
Q⁴ 6-H), 7.56-7.64 (2H, m, Q⁴ 7- and 8-H) and 8.18 (1H, d, J 8.2 Hz, Q⁴ 5-H); m/z (%) 425 (M⁺, 5), 352 (39), 327 (53), 313 (37), 312 (82), 311 (100), 310 (28), 167 (59), 165
(42), 149 (59), 99 (83), 83 (31), 71 (51) and 69 (43).

Reduction of N-(Quinazolinonyl)-Imine (125)

\[
\begin{align*}
\text{(125)} & \quad \xrightarrow{\text{NaBH}_4} \quad \text{(126)} \\
\end{align*}
\]

The imine (125) (0.015 g, 3.53 x 10⁻⁵ mol) was dissolved in dry methanol (1 ml)
and treated with sodium borohydride as described previously. After work up, the product
was purified by column chromatography using light petroleum : ethyl acetate (2 : 1) as
eluant to give (126) (0.01 g, 66%) identical to that isolated previously.
Reaction of 3-Aminoquinazolinone (127) with Butyraldehyde

\[
\begin{align*}
\text{OH} & \quad \text{NH}_2 \\
\text{N} & \quad \text{N} \\
\text{O} & \\
(127) & \\
\end{align*}
\]

3-Aminoquinazolinone (127) (0.14 g, 6.83 x 10^{-4} mol) was dissolved in ethanol (2 ml) and butyraldehyde added (0.1 g, 1.37 x 10^{-3} mol). The mixture was heated under reflux for 1.5 hr. The bulk of the solvent was then removed, dichloromethane added (15 ml), the solution washed with water, dried and the solvent evaporated to give a white solid (0.16 g, 90%). A 300 MHz proton NMR spectrum indicated a 1.8 : 1 ratio of diastereoisomers to be present (from comparison of the signals at δ 6.01 and δ 5.58).

Fractional crystallisation of the major diastereoisomer was achieved using ethanol / water to give (128) (0.06 g, 33%) m.p 74-80 °C [α]D = -93 (c = 6, CH₂Cl₂) (Found: C, 64.55; H, 6.6; N, 16.1. C₁₄H₁₇N₃O₂ requires C, 64.85; H, 6.6; N, 16.2%); νmax / cm⁻¹ 3240s, 1670s and 1600s; δH (CDCl₃, 300 MHz) 1.00 (3H, t, J 7.3 Hz, CH₃CH₂), 1.57 (2H, sextet, J 7.3 Hz, CH₃CH₂CH₂), 1.73 (3H, d, J 6.7 Hz, CH₃CHCN), 1.72-1.79 (2H, m, CH₂CH₂CH₂), 4.63-4.71 (1H, m, CH₂CHNH), 5.05 (1H, q, J 6.7 Hz, CH₂CHO), 6.05 (1H, d, J 6.6 Hz, CH₂CHNH), 7.44 (1H, dd, J 8.1 and 1.1 Hz, Q₅ 6-H), 7.63 (1H, d, J 7.7 Hz, Q₅ 8-H), 7.71 (1H, ddd, J 8.1, 7.7 and 1.1 Hz, Q₅ 7-H), 8.23 (1H, dd, J 8.1 and 1.1 Hz, Q₅ 5-H); Double irradiation of the signal at δ 6.05 caused the signal at δ 4.69 to collapse to a triplet. δC (CDCl₃, 75 MHz) 13.71 (CH₃CH₂), 17.39 (CH₂CH₃), 17.57...
(CH₃CHO), 34.68 (CH₃CH₂CHO), 69.12 (CH₃CHO), 82.81 (CHNH), 119.99 (CCO
(Q5)), 126.24, 126.31, 127.02, 133.85, (4 x CH(Q5)), 146.15 (C=N(Q5)), 151.73
(CN(Q5)), 157.74 (CO(Q5)); m/z (%) 259 (M+, 12), 216 (100), 188 (20), 186 (19), 172
(11), 146 (14).

Reaction of (129) with Heptan-2-one

\[ \begin{array}{c}
\text{Q}^6 \\
\text{NH}_2 \\
\text{(129)}
\end{array} \xrightarrow{130 \degree C} \begin{array}{c}
\text{O}^6 \\
\text{N} \\
\text{(130a) and (130b)}
\end{array} \]

The 3-aminoquinazolinone (129) (0.44 g, 2.0 x 10⁻³ mol) was dissolved in heptan-
2-one (3 ml) and heated at 130 °C for 6 h. After removal of the bulk of the heptan-2-one
(Kugelrohr at 0.5 mmHg) a 250 MHz proton NMR spectrum of the crude product
indicated a 4.8 : 1 ratio of double bond isomers (from comparison of the signals at δ 1.77
and δ 2.27 (CH₃CN). The residue was purified by column chromatography using light
petroleum : ethyl acetate (4 : 1) as eluant. This gave the major double bond isomer of
imine (130a) as a 1 : 1 ratio of rotamers (Rf 0.36) as a colourless oil (0.38 g, 60%) [α]D
= -42 (c = 3, CH₂Cl₂) (Found M⁺ 315.1947. C₁₈H₂₂N₃O₂ requires M⁺ 315.1947); νₘₐₓ / cm⁻¹ 1670s and 1590s; δH (CDCl₃, 250 MHz) rotamer A: 0.85 (3H, t, J 6.9 Hz,
CH₃(CHO), 1.26-1.41 (6H, m, 3 x CH, CH₃CH₂CH₂), 1.46-1.55 (1H, m, CH), 1.60-1.73 (2H,
m, 2 x CH), 1.77 (3H, s, CH₃CN), 2.52 (2H, t, J 7.2 Hz, CH₂CH₂), 3.26 (3H, s, br,
CHOCH₃), 4.46-4.49 (1H, m, br, CHOCH₃), 7.39 (1H, ddd, J 8.1, 7.0 and 1.2 Hz, Q₆ 6-
H), 7.61-7.79 (2H, m, Q₆ 7- and 8-H) and 8.19 (1H, dd, J 8.1 and 1.0 Hz, Q₆ 5-H);
rotamer B (observable peaks): 3.35 (3H, s, br, CHOCH$_3$) and 4.60-4.66 (1H, m, br, CHOCH$_3$); $\delta$C (CDCl$_3$, 75 MHz) rotamer A: 14.3, 16.7, 19.6 (3 x CH$_2$), 22.8, 26.3, 31.8, 39.3 (4 x CH$_2$), 56.7 (br, OCH$_3$), 74.9 (br, CHOCH$_3$), 121.6 (CCO(OQ$_6$)), 127.1, 127.2, 128.2, 134.3 (4 x CH(Q$_6$)), 147.1 (CN=Cl(Q$_6$)), 156.1, 157.1 (CN(Q$_6$), CO(Q$_6$)) and 183.3 (CN); rotamer B (observable peaks): 58.0 (br, OCH$_3$) and 75.7 (br, CHOCH$_3$); m/z (%) 315 (M$^+$, 13), 245 (15), 244 (100), 229 (14), 218 (36), 203 (31), 188 (13), 186 (34), 174 (12) and 173 (20).

A 300 MHz proton NMR spectrum at 308K showed coalescence of the CHOCH$_3$ signals. At 343K (in d$_8$-toluene) the CHOCH$_3$ signal appears as a sharp quartet ($\delta$ 4.58) and one signal at $\delta$ 3.09 is apparent for CHOCH$_3$. i.e at this temperature N-N bond rotation is fast so only one time averaged rotamer is seen. From these values $\Delta G^e = 65$ kJ / mol (see Appendix 2).

Further elution gave the minor double bond isomer of imine (130b) as a 1.3 : 1 ratio of rotamers (R$_f$ 0.28) and as a colourless oil (0.07 g, 11%) [$\alpha$]$_D$ = +6 (c = 2, CH$_2$Cl$_2$) (Found: M$^+$ 315.1947. C$_{18}$H$_{25}$N$_3$O$_2$ requires M$^+$ 315.1947); $\nu_{\text{max}} / \text{cm}^{-1}$ 1670s and 1590s; $\delta$H (CDCl$_3$, 250 MHz) major rotamer: 0.75 (3H, t, J 6.9 Hz, CH$_3$CH$_2$), 1.11-1.28 (3H, m, 3 x CH), 1.34-1.44 (2H, m, 2 x CH), 1.51-1.64 (4H, m, 4 x CH), 2.07-2.11 (2H, m, CH$_2$CN), 2.27 (3H, s, CH$_3$CN), 3.27 (3H, s, br, OCH$_3$), 4.43-4.46 (1H, m, CHOCH$_3$), 7.42 (1H, ddd, J 8.1, 6.8 and 1.2 Hz, Q$^6$-H), 7.64-7.81 (2H, m, Q$^6$ 7- and 8- H) and 8.22 (1H, dd, J 8.1 and 1.1 Hz, Q$^6$ 5-H); minor rotamer (observable peaks): 3.36 (3H, s, br, CHOCH$_3$) and 4.61-4.67 (1H, m, CHOCH$_3$); m/z (%) 315 (M$^+$, 10), 256 (14), 245 (11), 244 (100), 218 (83), 203 (24), 186 (32), 173 (13), 97 (10), 83 (15), 73 (19), 71 (18) and 69 (25).
Reduction of N-(Quinazolinonyl)-Imine (130a) with Sodium Borohydride

The imine (130a) (0.3 g, 9.5 x 10^-4 mol) was dissolved in dry distilled methanol (3 ml) and sodium borohydride added until the solution remained cloudy. After stirring at room temperature for 1 h, water was added, the methanol removed under reduced pressure, and the residue diluted with dichloromethane (20 ml). The solution was washed with water, dried and the solvent removed under reduced pressure. Chromatography of the residue over silica using light petroleum : ethyl acetate (5 : 1) as eluant gave what appears to be a single diastereoisomer of the imine (131) (R_f 0.34) as a colourless oil (0.09 g, 29%) [α]D = +13 (c = 2, CH2Cl2) (Found: M+ 317.2103. C18H27N3O2 requires M+ 317.2103); ν_max / cm^-1 3020 w, 1720 m, 1660 s, 1610 m; δ_H (CDCl3, 250 MHz) 0.80-0.88 (3H, m, CH3CH2), 1.22 (3H, d, J 6.3 Hz, CH3CH), 1.27-1.34, 1.56-1.64 (6H, 2 x m, 6 x CH), 1.84 (3H, s, CH3CN), 2.35 (2H, t, J 7.2 Hz, CH2CH2), 3.23 (3H, s, OCH3), 3.73 (1H, dq, J 6.3, 5.4 Hz, CHOCH3), 4.55-4.59 (1H, m, CH), 4.74 (1H, s, br, NH), 6.65 (1H, d, J 8.0 Hz, DHQ^6 8-H), 6.79 (1H, ddd, J 7.8, 7.3 and 0.9 Hz, DHQ^6 6-H), 7.22-7.26 (1H, m, DHQ^6 7-H) and 7.82 (1H, dd, J 7.8 and 1.4 Hz, DHQ^6 5-H);
irradiation of the signal at $\delta$ 4.55-4.59 (CH) caused the collapse of the signal at $\delta$ 3.73 (CHOCH$_3$) to a quartet. $\delta_C$ (CDCl$_3$, 75 MHz) 19.8, 20.2, 22.8, 26.7, 31.8, 39.2, 39.6, 57.4, 75.9, 76.1, 115.8, 117.4, 120.0, 128.9, 133.6, 146.1, 157.0 and 178.0; m/z (%) Cl 318 (M+1). Further elution with the same solvent mixture gave a mixture of unidentified compounds (0.12 g).

**Reaction of 3-Aminoquinazolinone (133) with Heptan-2-one**

To the 3-aminoquinazolinone (133) (0.27 g, 1.1 x 10$^{-3}$ mol) was added heptan-2-one (1 ml) and the mixture heated at 130 °C for 8 h. The bulk of the heptan-2-one was removed (Kugelrohr at 0.5 mmHg) and the residue was purified by column chromatography using light petroleum : ethyl acetate (7 : 1) as eluant. This gave the major double bond isomer of the imine (132) in a 1 : 1 ratio of rotamers (Rf 0.28) as a colourless oil (0.38 g, 84%) (Found: M$^+$ 341.2467. C$_{21}$H$_{31}$N$_3$O requires M$^+$ 341.2467);

$\nu_{\text{max}}$ / cm$^{-1}$ 1670s, 1610w and 1590s; $\delta_H$ (CDCl$_3$, 250 MHz) **rotamer A**: 0.77 (3H, t, J 7.2 Hz, CH$_3$CH$_2$), 0.85 (9H, s, (CH$_3$)$_3$C), 1.07 (3H, d, J 7.1 Hz, CH$_3$CH), 1.22-1.35 (4H, m, 4 x CH), 1.63 (3H, s, CH$_3$CN), 1.66-1.69 (1H, m, CH), 2.21-2.30 (1H, m, CH), 2.38-2.52 (2H, m, CH$_2$CH$_2$), 2.90 (1H, q, br, J 7.1 Hz, CHCH$_3$), 7.26 (1H, ddd, J 7.9, 7.4 and 1.4 Hz, Q$^7$ 5-H), 7.49-7.58 (2H, m, Q$^7$ 7- and 8-H) and 8.08 (1H, d, J 7.9 Hz, Q$^7$ 5-H); **rotamer B** (observable peaks): 0.90 (9H, s, (CH$_3$)$_3$C), 1.16 (3H, d, J 6.8 Hz, Q$^7$ 5-H).
CH$_3$(CH), 1.65 (3H, s, CH$_3$CN) and 3.08 (1H, q, J 6.8 Hz, CHCH$_3$); $\delta_C$ (CDCl$_3$, 75 MHz) rotamer A: 14.4, 15.4, 19.2 (3 x CH$_3$), 22.9, 26.3 (2 x CH$_2$), 28.1 ((CH$_3$)$_3$C), 31.7 (CH$_2$), 35.4 ((CH$_3$)$_3$C), 39.2 (CH$_2$), 44.1 (CH), 121.5 (CO(Q$^7$)), 126.3, 127.2, 127.8, 134.0 (4 x CH(Q$^7$)), 147.3 (CN=CH(Q$^7$)), 157.3, 158.7 (CN(Q$^7$), CO(Q$^7$)) and 181.3 (CN); rotamer B (observable peaks): 15.5, 20.3 (2 x CH$_3$), 23.9, 26.6 (2 x CH$_2$), 28.3 ((CH$_3$)$_3$C), 31.9 (CH$_2$), 35.0 ((CH$_3$)$_3$C), 40.2 (CH$_2$), 44.4 (CH), 159.4 (C) and 182.3 (CN); m/z (%) 341 (M$, 11), 326 (15), 285 (16), 271 (19), 270 (100), 256 (15), 229 (13), 215 (13), 214 (33), 188 (12), 174 (15), 173 (21), 158 (10) and 57 (12).

Reduction of Imine (132) with Sodium Borohydride

![Reduction of Imine (132) with Sodium Borohydride](image)

To the imine (132) (0.1 g, 2.93 x 10$^{-4}$ mol) in dry distilled methanol (1 ml) was added sodium borohydride until the solution remained cloudy. After stirring at room temperature for 1 h, water was added, the methanol removed under reduced pressure, and the residue diluted with dichloromethane (10 ml). The solution was washed with water, dried and the solvent removed. Chromatography of the residue over silica using light petroleum : ethyl acetate (10 : 1) as eluant gave N-(quinazolinonyl)amine (134) as a colourless oil (0.08 g, 74%) (Found: M$^+$ 343.2624. C$_{21}$H$_{33}$N$_3$O requires M$^+$ 343.2624); $\nu_{max}$ / cm$^{-1}$ 3270w, 1720s, 1670s and 1580m; $\delta_H$ (d$_8$-toluene, 250 MHz, 373K) (1.2 : 1 mixture of diastereoisomers) major diastereoisomer: 0.79 (3H, t, J 7.0 Hz, CH$_3$CH$_2$), 0.86 (3H, d, J 6.4 Hz, CH$_3$CH), 1.00 (9H, s, (CH$_3$)$_3$C), 1.13-1.32 (8H, m, 8 x CH), 1.34 (3H,
d, J 7.0 Hz, CH₃CH₂), 3.07-3.16 (1H, m, br, NHCH₂CH₂), 3.80 (1H, q, J 7.0 Hz, CHCH₃),
5.50 (1H, d, J 6.3 Hz, CHNH), 7.41 (1H, ddd, J 8.0, 7.4 and 1.2 Hz, Q₇ 6-H), 7.65-7.76
(2H, m, Q₇ 7- and 8-H) and 8.23 (1H, d, J 8.0 Hz, Q₇ 5-H); minor diastereoisomer
(observable peaks): 0.83 (3H, t, J 7.0 Hz, CH₂CH₃), 0.84 (3H, d, J 6.4 Hz, CH₃CH₂),
1.02 (9H, s, (CH₃)₃C), 1.37 (3H, d, J 7.0 Hz, CH₃CH₂), 3.23-3.29 (1H, m, br,
NHCH₂CH₂), 3.88 (1H, q, J 7.0 Hz, CH₂CH₃) and 5.45 (1H, d, J 4.2 Hz, CHNH); δC
(CDCl₃, 75 MHz) major diastereoisomer: 14.5, 18.6, 18.7 (3 x CH₃), 23.0, 25.9 (2 x
CH₂), 27.9 ((CH₃)₂C), 32.4, 35.3 (2 x CH₂), 35.6 ((CH₃)₃C), 42.6, 55.1 (2 x CH), 120.8
(CO(Q₇)), 126.4, 126.7, 127.9, 134.4 (4 x CH(Q₇)), 147.2 (CN=C(Q₇)) and 161.2,
161.5 (CN(Q₇), CO(Q₇)); minor diastereoisomer (observable peaks): 14.8, 18.8 (2 x
CH₃), 26.1 (CH₂), 32.4, 35.6 (2 x CH₂), 36.0 ((CH₃)₂C) and 121.0 (CCO(Q₇)); m/z (%)
343 (M⁺, 3), 272 (20), 231 (19), 189 (12), 175 (35), 174 (100), 173 (18), 114 (68), 57
(20) and 55 (11).

Reduction of 3-Acetylaminoquinazolinone (9) with Sodium Borohydride

\[
\text{O}^1 \quad \text{H} \quad \text{N} \quad \text{C} \quad \text{O} \quad \text{NaBH}_4 \quad \text{H} \quad \text{N} \quad \text{C} \quad \text{O} \quad \text{O}
\]

To the 3-acetylaminoquinazolinone (9) (0.1 g, 4.08 x 10⁻⁴ mol) in dry distilled
methanol (2 ml) was added sodium borohydride until the solution remained cloudy. After
stirring at room temperature for 30 min. water was then added, the methanol removed
under reduced pressure, and the residue diluted with dichloromethane (10 ml). The
solution was washed with water, dried and the solvent removed under reduced pressure. Chromatography of the residue over silica using light petroleum : ethyl acetate (2 : 1) as eluant gave dihydroquinazolinone (135) (Rf 0.32) as a colourless oil (0.077 g, 76%) (Found: M+ 248.1400. C_{13}H_{17}N_{3}O_{2} requires M+ 248.1400); ν_{max} / cm\(^{-1}\) 3400w, 3190w, 1700m, 1650s and 1610m; δ_H (CDCl\(_3\), 250 MHz) 0.83, 0.92 (6H, 2 x d, J 6.7 Hz, CH\(_3\)CHCH\(_3\)), 2.04 (3H, s, COCH\(_3\)), 2.15-2.22 (1H, m, CH\(_3\)CHCH\(_3\)), 4.59-4.61 (1H, m, NH), 4.86-4.89 (1H, m, CH\(_{2}\)NH), 6.57 (1H, d, J 8.1 Hz, DHQ\(_{1}\) 8-H), 6.70 (1H, dd, J 7.8, and 7.6 Hz, DHQ\(_{1}\) 6-H), 7.20 (1H, ddd, J 8.1, 7.6 and 1.3 Hz, DHQ\(_{1}\) 7-H), 7.72 (1H, d, J 7.8 Hz, DHQ\(_{1}\) 5-H) and 9.16 (1H, s, br, NH); δ_C (CDCl\(_3\), 75 MHz) 16.3, 18.0, 21.0 (3 x CH\(_3\)), 31.8 (CH\(_3\)CHCH\(_3\)), 76.1 (CH), 114.8 (CH(Q\(_{1}\))), 117.1 (C=O(Q\(_{1}\))), 118.8, 128.7, 134.3 (3 x CH(Q\(_{1}\))), 146.00 (CNH(Q\(_{1}\))), 157.0 (C=O(Q\(_{1}\))) and 173.4 (C=O); m/z (%) FAB 248 (MH+) Elimination of 2-Isopropylquinazolinone (104) from 3-Acetylamidodihydroquinazolinone (135)

![Reaction Diagram](image)

Amide (135) (0.05 g, 2.02 x 10^{-4} mol) was heated at 250 °C under reduced pressure (0.2 mmHg) for 2 h. The residue obtained was triturated with ice cold ether to give 2-isopropylquinazolinone (104) (0.02 g, 62%) identical in all respects to that isolated previously.\(^{16}\)
EXPERIMENTAL

CHAPTER FIVE
General Procedure (F) for the preparation of 

N-acetoxyaminoquinazolinones

3-Aminoquinazolinone (1 mol equiv.) and lead tetra-acetate (1.05 mol equiv.) were added alternately in small portions over 15 min. to a stirred solution of dry dichloromethane (1 ml / 100 mg of 3-aminoquinazolinone) cooled at -20 °C to -25 °C with a dry ice-acetone bath. The mixture was stirred for a further 5 min. at this temperature, then the insoluble lead di-acetate separated and washed with cold dichloromethane.

Reaction of (20) with 4-Cyanopyridine

\[
\begin{align*}
\text{Reaction of (20) with 4-Cyanopyridine} \\
\text{The general procedure (F) was followed using 3-aminoquinazolinone (17) (1 g, 5.29 \times 10^{-3} \text{ mol}) and LTA (2.47 g, 5.57 \times 10^{-3} \text{ mol}) in dry dichloromethane (10 ml). 4-Cyanopyridine (1.65 g, 0.016 mol) was then added and the solution allowed to warm to room temperature. The solid / oil mixture obtained was triturated with cold ether to remove some 4-cyanopyridine and 2-isopropylquinazolinone. After removal of the ether, the remaining 4-cyanopyridine in the crude reaction mixture was dissolved in light petroleum (100 ml) which was decanted off. Trituration of the residue with further ether (10 ml), followed by crystallisation from ethanol gave pyridinium imide (142) as a pale brown solid (0.57 g, 37%), m.p. 155-157 °C (from ethanol) (Found: M^+ 292.1193)}
\end{align*}
\]
\( \text{C}_{16} \text{H}_{13} \text{N}_2 \text{O} \) requires \( M^+ \ 292.1198 \); \( \nu_{\text{max}} \ / \ cm^{-1} \ 1690 \text{s}, 1620 \text{w} \text{ and } 1590 \text{s}; \delta_2 (\text{CDCl}_3, 250 \text{ MHz}) \ 1.28 \ (3 \text{H}, \text{ t}, J \ 7.4 \text{ Hz}, \text{ CH}_2 \text{CH}_2), \ 2.80 \ (2 \text{H}, \text{ ABX}\text{x}, \ J \ 15.3, \ 7.4 \text{ Hz}, \text{ CH}_3 \text{CH}_2), \ 7.25-7.42 \ (2 \text{H}, \text{ m, br, } 2 \times \text{ CH(Ar)}), \ 7.43-7.56 \ (1 \text{H, m, CH(Ar)}, \ 7.69-7.83 \ (3 \text{H, m, } 3 \times \text{ CH(Ar)}) \text{ and } 8.19-8.27 \ (2 \text{H, m, } 2 \times \text{ CH(Ar)}); \delta_3 \ (\text{CDCl}_3, \ 75 \text{ MHz}) \ 11.10 \ (\text{CH}_3 \text{CH}_2), \ 27.52 \ (\text{CH}_2 \text{CH}_2), \ 103.14 \ (\text{C=O}), \ 116.50 \ (\text{C=N}), \ 120.90 \ (\text{C}=\text{O}(Q^2)), \ 126.61, \ 126.86, \ 127.29, \ 134.60 \ (8 \times \text{ CH(Ar)}), \ 147.09 \ (\text{C}=(\text{N}(Q^2)) \text{ and } 158.82, \ 158.94 \ (\text{CN}(Q^2), \ \text{CO}(Q^2)); \ m/z \ (%) \ \text{FAB} \ 292 \ (\text{MH}^+). \\
The barriers to \text{ N-N} \text{ bond rotation for the bonds } \text{N}_\text{c}-\text{N}_\text{p} \text{ and } \text{N}_\text{p}-\text{N}_\text{c} \text{ were measured from NMR spectra at } 400 \text{ MHz at various low temperatures (see Appendix 2), and were calculated to be } \Delta G^* > 77 \text{ and } 62 \text{ kJ / mol respectively.}

**Reaction of \text{Q}_1^1 \text{NHOAc} (14) with Triethylamine: Preparation of a Solution of**

\( \text{N-} \text{(Quinazolinonyl)-triethylammonium imide (143)} \)

\[ \begin{align*}
\text{Q}_1^1 \text{NHOAc} & \overset{\text{NET}_3}{\underset{-20 \text{ °C}}{\longrightarrow}} \text{Q}_1^1 \text{N}_\text{c}-\text{N}_\text{p} - \text{N}_\text{p}-\text{N}_\text{c} \\
(14) & \stackrel{(143)}{\longrightarrow}
\end{align*} \]

The 3-acetoxyaminoquinazolinone (14) was prepared using (8) (0.1 g, 4.93 x 10^-4 mol) and LTA (0.23 g, 5.17 x 10^-4 mol) in dry CDCl\(_3\) (1 ml) as described in the general procedure (F). Triethylamine (0.15 g, 1.48 x 10^-3 mol) was then added to the solution at -20 °C. A 300 MHz proton NMR spectrum at this temperature shows two broad signals of equal intensity at \( \delta \ 3.45 \) and \( \delta \ 3.82 \) for the three methylene groups in the triethylammonium residue of the imide (143).
General Procedure (G) for the Preparation of Trialkylammonium-NQ⁻²-Imide at -20 °C for Subsequent Aziridination Experiments

3-aminoquinazolinone (1 mol equiv.) and lead tetra-acetate (1.05 mol equiv.) were added alternately in small portions over 15 min. to a stirred solution of dry dichloromethane (1 ml / 100 mg of 3-aminoquinazolinone) cooled at -20 °C to -25 °C with a dry ice-acetone bath. The mixture was stirred for a further 5 min. at this temperature, then the insoluble lead di-acetate separated and washed with cold dichloromethane. The trialkylamine (10 mol equiv.) was added and the solution kept at -20 °C for 10 min. This solution of imide was then used in subsequent aziridination reactions.
Aziridination of Styrene using Triethylammonium NQ\(^1\)-Imide (143)

![Chemical structure](image)

A lead-free solution of triethylammonium imide (143) was prepared by the general procedure (G) described previously from 3-aminoquinazolinone (8) (0.1 g, 4.93 x 10\(^{-4}\) mol), LTA (0.23 g, 5.17 x 10\(^{-4}\) mol) and triethylamine (0.5 g, 4.93 x 10\(^{-3}\) mol) in dichloromethane (1 ml). Styrene (0.5 g, 4.93 x 10\(^{-3}\) mol) was added and the solution allowed to warm to room temperature. Further dichloromethane (20 ml) was added, the solution then washed with water, dried and the solvent removed under reduced pressure. The residue was purified by column chromatography using light petroleum : ethyl acetate (3 : 1) as eluant, to give (140) (R\(_f\) 0.20) as colourless crystals (0.12 g, 77\%), identical in all respects to a sample isolated previously.\(^{16}\)
Aziridination of Diethyl Fumarate using Triethylammonium NQ¹-Imide (143)

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{EtO}_2\text{C} \\
\text{N} & \quad \text{N} \\
\text{Q}^1 & \quad \text{Q}^1 \\
(143) & \quad (141)
\end{align*}
\]

A lead-free solution of triethylammonium imide (143) was prepared as described previously using 3-aminoquinazolinone (8) (0.1 g, 4.93 x 10⁻⁴ mol), LTA (0.23 g, 5.17 x 10⁻⁴ mol) and triethylamine (0.5 g, 4.93 x 10⁻³ mol) in dichloromethane (1 ml). Diethyl fumarate (0.87 g, 4.93 x 10⁻³ mol) was added and the solution allowed to warm to room temperature. Further dichloromethane (20 ml) was added, the solution then washed with water, dried and the solvent removed. The residue was purified by column chromatography using light petroleum : ethyl acetate (4 : 1) as eluant, to give (141) as a colourless oil (Rf 0.23) (0.14 g, 83%), identical in all respects to a sample isolated previously.¹⁶
Aziridination of Methyl Acrylate using Triethylammonium NQ¹-Imide (143)

A lead-free solution of triethylammonium imide (143) was prepared as described previously using 3-aminoquinazolinone (8) (0.5 g, 2.46 x 10⁻³ mol), LTA (1.15 g, 2.59 x 10⁻³ mol) and triethylamine (2.5 g, 2.46 x 10⁻² mol) in dichloromethane (5 ml). Methyl acrylate (2.1 g, 2.46 x 10⁻² mol) was added and the solution allowed to warm to room temperature. Further dichloromethane (50 ml) was added, the solution then washed with water, dried and the solvent removed under reduced pressure. The residue was purified by column chromatography using light petroleum : ethyl acetate (5 : 1) as eluant, to give aziridine (144) (R_f 0.28) as a colourless solid (0.45 g, 63%), m.p. 94-96 °C (from ethanol) (Found: C, 62.7; H, 6.0; N, 14.65. C₁₅H₁₇N₃O₃ requires C, 62.7; H, 5.95; N, 14.65%); ν_max / cm⁻¹ 1730m, 1660s and 1600m; δ_H (CDCl₃, 300 MHz) 1.34, 1.37 (6H, 2 x d, J 6.7 Hz, CH₃CHCH₃), 2.79 (1H, d, J 4.8 Hz, azir. ring H-3 trans to Q¹), 3.32 (1H, d, J 7.5 Hz, azir. ring H-3 cis to Q¹), 3.69 (1H, septet, J 6.7 Hz, CH₃CHCH₃), 3.80-3.84 (4H, m, CO₂CH₃, azir. ring CH gem to CO₂Me), 7.33 (1H, ddd, J 8.1, 6.9 and 1.4 Hz, Q¹ 6-H), 7.55-7.65 (2H, m, Q¹ 7- and 8-H) and 8.07 (1H, ddd, J 8.1 and 1.1 Hz, Q¹ 5-H); δ_C (CDCl₃, 75 MHz) 20.63, 20.96 (CH₂CHCH₂), 30.95 (CH₂CHCH₂), 36.67 (CH₂), 39.58 (CHCO₂CH₃), 52.47 (CO₂CH₃), 120.99 (CO(Q¹)), 125.83, 126.05, 126.64, 133.71 (4 x CH(Q¹)), 145.91 (CN=C(Q¹)), 160.34 (CN(Q¹)), 161.32 (CO(Q¹)) and 166.76 (CO₂CH₃); m/z (%) 287 (M⁺, 98), 272 (16), 259 (22), 256 (11), 201 (15),
Aziridination of Hex-1-ene using Triethylammonium NQ1-Imide (143)

A lead-free solution of triethylammonium imide (143) was prepared as described in procedure (G) using 3-aminoquinazolinone (8) (0.2 g, 9.85 x 10^-4 mol), LTA (0.46 g, 1.03 x 10^-3 mol) and triethylamine (0.99 g, 9.85 x 10^-3 mol) in dichloromethane (2 ml). Hex-1-ene (0.63 g, 9.85 x 10^-3 mol) was added and the solution allowed to warm to room temperature. Further dichloromethane (30 ml) was added, the solution then washed with water, dried and the solvent removed under reduced pressure. Purification of the residue by column chromatography using light petroleum : ethyl acetate (4 : 1) as eluant gave aziridine (145) (Rf 0.52) as a colourless oil (0.03 g, 11%) (Found; M+ 285.1842. C_{17}H_{23}N_{3}O requires M+ 285.1841); ν_{max} / cm^{-1} 1730w, 1670s and 1590s; δ_{H} (CDCl_{3}, 300 MHz) 0.98 (3H, t, J 7.1 Hz, CH_{3}CH_{2}), 1.40-1.57 (11H, m, CH_{3}CHCH_{3}, m, 5 x CH), 2.18-2.24 (1H, m, CH), 2.46-2.48 (2H, m, CH_{2}N), 2.84-2.91 (1H, m, CHN), 3.75 (1H, heptet, J 6.7 Hz, CH_{3}CHCH_{2}), 7.40 (1H, ddd, J 7.9, 6.6 and 1.4 Hz, Q1 6-H), 7.63-7.73 (2H, m, Q1 7-and 8-H) and 8.20 (1H, ddd, J 7.9, 1.4 and 0.8 Hz, Q1 5-H); δ_{C} (CDCl_{3}, 75 MHz) 13.87 (CH_{3}), 20.61, 21.26 (CH_{3}CHCH_{3}), 22.47, 28.03 (2 x CH_{2}), 30.64 (CH_{3}CHCH_{3}), 30.93, 41.34 (2 x CH_{3}), 46.29 (CHN), 121.10 (CCO(Q1)), 125.87,
Further elution gave imine (146) (R<sub>f</sub> 0.31) as a colourless oil (0.08 g, 35%) m.p. 60-62 °C (from ethanol) (Found: M<sup>+</sup> 229.1215. C<sub>13</sub>H<sub>14</sub>N<sub>3</sub>O requires M<sup>+</sup> 229.1215); <sup>1</sup>H max / cm<sup>-1</sup> 1730m, 1670s and 1590s; δ<sub>H</sub> (CDCl<sub>3</sub>, 300 MHz) 1.35 (6H, d, J 6.7 Hz, CH<sub>3</sub>CHCH<sub>3</sub>), 2.36 (3H, d, J 5.3 Hz, CH<sub>3</sub>CH), 3.44 (IH, heptet, J 6.7 Hz, CH<sub>3</sub>CHCH<sub>3</sub>), 7.46 (IH, ddd, J 8.2, 7.1 and 1.3 Hz, Q<sub>1</sub> 6-H), 7.70-7.78 (2H, m, Q<sub>1</sub> 7- and 8-H) and 8.23-8.29 (2H, m, Q<sub>1</sub> 5-H, CH=N); δ<sub>C</sub> (CDCl<sub>3</sub>, 75 MHz) 19.43 (CH<sub>3</sub>C=N), 20.17 (CH<sub>3</sub>CHCH<sub>3</sub>), 31.23 (CH<sub>3</sub>CHCHCH<sub>3</sub>), 121.25 (CCO(Q<sub>1</sub>)), 125.99, 126.86, 127.14, 133.61 (4 x CH(Q<sub>1</sub>)), 146.59 (CN=C(Q<sub>1</sub>)), 158.25 (CN(Q<sub>1</sub>)), 159.50 (CO(Q<sub>1</sub>)) and 171.39 (CH=N); m/z (%) 229 (M<sup>+</sup>, 27), 214 (54), 203 (13), 188 (33), 187 (42), 175 (20), 174 (13), 173 (100), 160 (18), 144 (11), 130 (20), 119 (13), 103 (12), 90 (12) and 76 (15).

**Reaction of 3-Aminoquinazolinone (8) with Acetaldehyde**

![Chemical structure](image)

3-Aminoquinazolinone (8) (0.45 g, 2.22 x 10<sup>-3</sup> mol) was dissolved in acetaldehyde (5 ml) and ethanol (5 ml) added. The mixture was then heated under reflux for 5 h. After
removal of the solvent under reduced pressure, the residue was diluted with
dichloromethane (50 ml) washed with water, dried and the solvent evaporated under
reduced pressure to give a colourless oil (146) (0.44 g, 87%) identical with the sample
obtained previously.

**Investigations into the Mechanism of Aziridination using**

**Trialkylammonium NQ¹-Imides:**

**Competition Experiments using Triethylammonium NQ¹-Imide (143)**

![Diagram](image)

(143)

A lead-free solution of triethylammonium imide (143) was prepared as described in
procedure (G) using 3-aminoquinazolinone (8) (0.2 g, 9.85 x 10⁻⁴ mol), LTA (0.46 g,
1.03 x 10⁻³ mol) and triethylamine (0.99 g, 9.85 x 10⁻³ mol) in dichloromethane (2 ml). A
1 : 1 mixture of styrene (0.31 g, 2.96 x 10⁻³ mol) and diethyl fumarate (0.51 g, 2.96 x 10⁻³
mol) was added and the solution allowed to warm to room temperature. Further
dichloromethane (30 ml) was added, the solution then washed with water, dried and the
solvent removed. A 300 MHz proton NMR spectrum of the crude mixture indicated a 1 : 1
mixture of aziridines (140) and (141) to be present (from comparison of the signals at δ
3.39 and δ 3.21 which correspond to those present in the NMR spectra of the respective
individual aziridines (see earlier)).
Using the NQ\textsuperscript{1}-Imide (148) derived from DABCO

\[ \text{Chemical Structure of NQ\textsuperscript{1}-Imide (148)} \]

The general procedure given earlier was repeated using 3-aminoquinazolinone (8) (0.2 g, 9.85 x 10\textsuperscript{-4} mol), LTA (0.46 g, 1.03 x 10\textsuperscript{-3} mol), DABCO (1.1 g, 9.85 x 10\textsuperscript{-3} mol), styrene (0.31 g, 2.96 x 10\textsuperscript{-3} mol) and diethyl fumarate (0.51 g, 2.96 x 10\textsuperscript{-3} mol) in dichloromethane (2 ml). A 300 MHz proton NMR spectrum of the crude mixture indicated a 1 : 1 mixture of aziridines (140) and (141) to be present (see previous experimental).

Using the NQ\textsuperscript{1}-Imide (149) derived from N,N-Dimethyl-N-\(\alpha\)-methylbenzylamine

\[ \text{Chemical Structure of NQ\textsuperscript{1}-Imide (149)} \]

The procedure was repeated using 3-aminoquinazolinone (8) (0.2 g, 9.85 x 10\textsuperscript{-4} mol), LTA (0.46 g, 1.03 x 10\textsuperscript{-3} mol), N,N-dimethyl-N-\(\alpha\)-methylbenzylamine (1.47 g, 9.85 x 10\textsuperscript{-3} mol), styrene (0.31 g, 2.96 x 10\textsuperscript{-3} mol) and diethyl fumarate (0.51 g, 2.96 x 10\textsuperscript{-3} mol) in dichloromethane (2 ml). A 300 MHz proton NMR spectrum of the crude mixture indicated a 1 : 1 mixture of aziridines (140) and (141) to be present (see previous two experiments).
Competitive Aziridination of Styrene and Diethyl Fumarate using the 3-
Acetoxyaminoquinazolinone (14)

The procedure (E) was followed using 3-aminoquinazolinone (8) (0.2 g, 9.85 x 10^-4 mol), LTA (0.46 g, 1.03 x 10^-3 mol), styrene (0.31 g, 2.96 x 10^-3 mol) and diethyl fumarate (0.51 g, 2.96 x 10^-3 mol) in dichloromethane (2 ml). A 300 MHz proton NMR spectrum of the crude mixture indicated the presence of aziridine (140) only from the absence of the signals at δ 3.39, 3.80, 4.08-4.10 and 4.35 from aziridine (141).

Competitive Aziridination of Styrene and Diethyl Fumarate using
Pyridinium NQ^I-Imides (138), (139) and (142)

Using the NQ^I-Imide (138) derived from Pyridine

Following the method of Edwards^{16} the pyridinium imide (138) (0.065g, 2.3 x 10^-4 mol) was added to a 1 : 1 mixture of styrene (0.24 g, 2.3 x 10^-3 mol) and diethyl fumarate (0.4 g, 2.3 x 10^-3 mol) in benzene (3 ml) and the solution heated under reflux under an argon atmosphere for 2 h. The benzene and the bulk of the olefins were removed under reduced pressure. A 300 MHz proton NMR spectrum of the crude mixture indicated the presence of a 1.1 : 1 ratio of aziridines (140) and (141) to be present (from comparison of the signals at δ 3.39 and δ 3.21): see previous experiments.
Using the NQ\(^1\)-Imide (139) derived from 2-Methylpyridine

Following the method of Edwards\(^{\text{a}}\) the pyridinium imide (139) (0.065 g, 2.2 x 10\(^{-4}\) mol) was dissolved in a 1 : 1 mixture of styrene (0.23 g, 2.2 x 10\(^{-3}\) mol) and diethyl fumarate (0.38 g, 2.2 x 10\(^{-3}\) mol) in benzene (3 ml) and heated under reflux under an argon atmosphere for 2 h. The benzene and the bulk of the olefins were removed under reduced pressure. A 300 MHz proton NMR spectrum of the crude mixture indicated the presence of a 1.1 : 1 ratio of aziridines (140) and (141) to be present (see experiments previously).

Using The NQ\(^1\)-Imide (142) derived from 4-Cyanopyridine

![Diagram](142)

The pyridinium imide (142) (0.05 g, 1.71 x 10\(^{-4}\) mol) was added to a 1 : 1 mixture of styrene (0.17 g, 1.71 x 10\(^{-3}\) mol) and diethyl fumarate (0.29 g, 1.71 x 10\(^{-3}\) mol) in benzene (2 ml) and the solution heated under reflux under an argon atmosphere for 2 h. Benzene and the bulk of the olefins were removed under reduced pressure. A 300 MHz proton NMR spectrum of the crude mixture indicated that partial decomposition of the imide had occurred with no reaction with either of the two alkenes.
Reaction of Q¹NHOAc (14) with Dimethylsulfide

\[ \begin{align*} 
Q^1 \text{NHOAc} & \xrightarrow{-20 \, ^\circ \text{C to RT}} Q^1 \text{N}^+ \text{SMe}_2 \\
(14) & \quad (150)
\end{align*} \]

The procedure (F) was followed using 3-aminoquinazolinone (8) (1 g, 4.93 x 10⁻³ mol) and LTA (2.29 g, 5.17 x 10⁻³ mol) in dichloromethane (10 ml). Dimethylsulfide (0.61 g, 9.85 x 10⁻³ mol) in dry dichloromethane (5 ml) was added and the solution allowed to warm to room temperature. The insoluble lead di-acetate was separated, washed with dichloromethane, then the dichloromethane solution washed with saturated aqueous sodium hydrogen carbonate, water, dried and the solvent removed under reduced pressure. The solid / oil mixture was triturated with ice-cold ether and insoluble 2-isopropylquinazolinone (104) (0.03 g) separated as white crystals. After removal of the solvent, crystallisation from ethanol gave sulphimide (150) as a white solid (0.75 g, 58%) m.p. 112-114 °C (from ethanol) (Found: M⁺ 263.1092. C₁₃H₁₇N₃O₁S₁ requires M⁺ 263.1093); νmax / cm⁻¹ 1680s, 1630m, 1610m and 1580m; δH (CDCl₃, 250 MHz) 1.32 (6H, d, J 6.9 Hz, CH₃CH₂CH₆), 2.88 (6H, s, S(CH₃)₂), 3.85 (1H, heptet, J 6.9 Hz, CH₃CH₂CH₂), 7.37 (1H, ddd, J 8.1, 7.9 and 1.0 Hz, Q¹ 6-H), 7.63-7.75 (2H, m, Q¹ 7- and 8-H) and 8.18 (1H, dd, J 7.9 and 1.0 Hz, Q¹ 5-H); m/z (%) 263 (M⁺, 21), 188 (50), 187 (27), 175 (15), 174 (15), 173 (100), 160 (15), 145 (32), 144 (13), 130 (35), 119 (12), 103 (11) and 76 (12).
Competitive Aziridination of Styrene and Diethyl Fumarate with Sulphimide (150)

The sulphimide (150) (0.1g, 3.8 x 10^{-4} mol) was added to a 1:1 mixture of styrene (0.4 g, 3.8 x 10^{-3} mol) and diethyl fumarate (0.65 g, 3.8 x 10^{-3} mol) in benzene (1 ml) and the solution heated under reflux under an argon atmosphere for 2 h. The benzene and the bulk of the olefins were removed under reduced pressure and the residue purified by column chromatography using light petroleum : ether (3:1). After elution of unreacted olefins, a fraction (R_f 0.15-0.25) was obtained containing aziridines (140) and (141) in a 1.3:1 ratio from comparison of peaks at δ 3.39 and δ 3.21 in its NMR spectrum (see previous experiments).
Aziridination of Phenanthrene using Q¹NHOAc (14)

\[
\begin{array}{c}
\text{Q}^1 \\
\text{N}
\end{array}
\]

The procedure (F) was followed using 3-aminoquinazoline (8) (0.2 g, 9.85 x 10⁻⁴ mol) and LTA (0.46 g, 1.03 x 10⁻³ mol) in dichloromethane (2 ml). Phenanthrene (0.53 g, 2.96 x 10⁻³ mol) was added and the solution allowed to warm to room temperature. The insoluble lead di-acetate was separated, washed with dichloromethane, then the dichloromethane solution washed with saturated aqueous sodium hydrogen carbonate, water, dried and the solvent removed. The solid / oil mixture was triturated with ice-cold ether and insoluble 2-isopropylquinazolinone (104) (0.045 g) separated as white crystals (identical with a sample prepared previously¹⁶). After removal of ether, the residue was purified by column chromatography using light petroleum : ethyl acetate (3 : 1) as eluant to give aziridine (151) (Rᶠ 0.37) as a white solid (0.16 g, 43%) m.p. 152-154 °C (from ethanol) (Found: C, 78.95; H, 5.70; N, 11.0. C₂₅H₂₁N₃O requires C, 79.15; H, 5.6; N, 11.05%); ν_max / cm⁻¹ 1670m, 1620w and 1590m; δ_H (CDCl₃, 300 MHz) 1.40 (6H, d, J 6.7 Hz, CH₃CHCH₃), 3.75 (1H, heptet, J 6.7 Hz, CH₃CHCH₃), 4.38 (2H, s, CHNCH), 7.44-7.53 (5H, m, 5 x CH(Ar)), 7.68-7.77 (2H, m, 2 x CH(Ar)), 7.73-7.89 (2H, m, 2 x CH(Ar)), 8.07-8.12 and 8.22-8.34 (3H, 2 x m, 3 x CH(Ar)); δ_C (CDCl₃, 75 MHz) 21.32 (CH₃CHCH₃), 30.95 (CH₃CHCH₃), 51.88 (2 x CH), 121.22 (CO(Q¹)), 123.41 (2 x CH(Ar)), 126.05, 126.16, 126.84 (3 x CH(Ar)), 127.48 (2 x CH(Ar)), 128.24
Thermolysis of Aziridine (151) in the presence of Styrene and Diethyl Fumarate

The aziridine (151) (0.05g, 1.31 x 10^{-4} mol) was added to a 1:1 mixture of styrene (0.14 g, 1.31 x 10^{-3} mol) and diethyl fumarate (0.23 g, 1.31 x 10^{-3} mol) in benzene (1 ml) and the solution heated under reflux under an argon atmosphere for 2 h. The benzene and the bulk of the olefins were removed under reduced pressure. A 300 MHz proton NMR spectrum of the crude mixture indicated that decomposition of the aziridine had occurred without formation of either of aziridines (140) or (141) from the signals at \( \delta 3.39 \) and \( \delta 3.21 \) respectively characteristic of these aziridines.
Attempted asymmetric induction in aziridination of alkenes
using the enantiopure NQ\(^1\)-imide (149)

![Chemical structures](image)

Both aziridines show no optical activity

**Reaction of NQ\(^1\)-Imide (149) with Styrene**

The procedure (G) was followed using 3-aminoquinazoline (8) (0.1 g, 4.93 x 10\(^{-4}\) mol), LTA (0.23 g, 5.17 x 10\(^{-4}\) mol) and (R)-N,N-dimethyl-N-\(\alpha\)-methylbenzylamine (0.88 g, 4.93 x 10\(^{-3}\) mol) in dichloromethane (2 ml). The solution was left at -20 °C for 30 min. then styrene (0.16 g, 1.48 x 10\(^{-3}\) mol) added and the solution allowed to warm to room temperature. Further dichloromethane (20 ml) was added, the solution then washed with water, dried and the solvent removed under reduced pressure. Purification of the residue by column chromatography using light petroleum : ethyl acetate (3 : 1) as eluant gave aziridine (140) as a colourless oil (0.09 g, 62%) \([\alpha]_D = 0\) (\(c=4,\ CH_2Cl_2\)).
Reaction of NQImide (149) with Diethyl Fumarate

The experiment above was repeated but after leaving for 30 min. at -20 °C, diethyl fumarate (0.25 g, 1.48 x 10^{-3} mol) was added and the solution allowed to warm to room temperature. Further dichloromethane (20 ml) was added, the solution then washed with water, dried and the solvent removed under reduced pressure. Purification of the residue by column chromatography using light petroleum : ethyl acetate (4 : 1) as eluant gave aziridine (141) as a colourless oil (0.12 g, 65%) \([\alpha]_D^0 = 0 \ (c= 3.5, \text{CH}_2\text{Cl}_2)\).
Stereospedfity of Aziridinations using NQ^1-Imide (143)

a) Aziridination of E-But-2-ene

The procedure (G) was followed using 3-aminoquinazolinone (8) (0.5 g, 2.46 x 10^{-3} mol), LTA (1.15 g, 2.59 x 10^{-3} mol), triethylamine (2.48 g, 2.46 x 10^{-2} mol) and E-but-2-ene (0.41 g, 7.39 x 10^{-3} mol) in dry dichloromethane (5 ml). After work up the residue was purified by column chromatography using light petroleum : ethyl acetate (2 : 1) as eluant, to give aziridine (152) (R_f 0.38) as a colourless solid (0.39 g, 62%), m.p. 84-86 °C (from ethanol) (Found: C, 69.95; H, 7.45; N, 16.15. C_{15}H_{19}N_{2}O requires C, 70.0; H, 7.45; N, 16.35%); \text{\nu}_{\text{max}} / \text{cm}^{-1} 1670 s and 1590 s cm^{-1}; \delta_H (\text{CDCl}_3, 300 MHz) 1.05 (3H, d, J 5.7 Hz, \text{CH}_3\text{CH}), 1.27, 1.45 (6H, 2 x d, J 6.7 Hz, \text{CH}_3\text{CHCH}_3), 1.53 (3H, d, J 5.7 Hz, \text{CH}_2\text{CH}), 2.50 (1H, quintet, J 5.7 Hz, azir. ring CH \text{trans} to Q^1), 2.76 (1H, quintet, J 5.7 Hz, azir. ring CH \text{cis} to Q^1), 3.49 (1H, heptet, J 6.7 Hz, \text{CH}_3\text{CHCH}_3), 7.37 (1H, ddd, J 8.1, 7.8 and 1.1 Hz, Q^1 6-H), 7.61-7.68 (2H, m, Q^1 7- and 8-H) and 8.17 (1H, ddd, J 8.1, 1.1 and 0.7 Hz, Q^1 5-H); \delta_C (\text{CDCl}_3, 75 MHz) 12.82, 16.96, 19.44, 21.37 (4 x \text{CH}_3), 31.14 (\text{CH}_3\text{CHCH}_3), 48.29, 48.44 (2 x \text{CH}), 121.15 (\text{CO}(Q^1)), 125.76, 125.82, 126.84, 133.11 (4 x \text{CH}(Q^1)), 146.12 (\text{CN=C}(Q^1)) and 160.72, 161.49
b) Aziridination of $\text{Z-But-2-ene}$

![Chemical structure](image)

The procedure (G) was followed using 3-aminoquinazolinone (8) (0.5 g, 2.46 x 10^{-3} mol), LTA (1.15 g, 2.59 x 10^{-3} mol), triethylamine (2.48 g, 2.46 x 10^{-2} mol) and $\text{Z-but-2-ene}$ (0.41 g, 7.39 x 10^{-3} mol) in dry dichloromethane (5 ml). The residue was purified by column chromatography using light petroleum : ethyl acetate (2 : 1) as eluant, to give aziridine (153) ($R_f$ 0.44) as a colourless solid (0.31 g, 48%), m.p. 86-88 °C (from ethanol) (Found: C, 69.95; H, 7.45; N, 16.35. $\text{C}_{15}\text{H}_{19}\text{N}_3\text{O}$ requires C, 70.0; H, 7.45; N, 16.35%); $\nu_{max}$ / cm^{-1} 1720s and 1590s; $\delta_H$ (CDCl$_3$, 300 MHz) 1.40 (6H, d, $J$ 6.7 Hz, CH$_3$CHCH$_3$), 1.45 (6H, d, $J$ 5.6 Hz, 2 x CH$_3$CH), 2.56-2.64 (2H, m, 2 x azir. ring CH), 3.55 (1H, heptet, $J$ 6.7 Hz, CH$_3$CHCH$_3$), 7.36 (1H, ddd, $J$ 8.1, 7.4 and 1.4 Hz, Q1 6-H), 7.57-7.66 (2H, m, Q1 7- and 8-H) and 8.14 (1H, ddd, $J$ 8.1, 1.4 and 0.8 Hz, Q1 5-H); $\delta_C$ (CDCl$_3$, 75 MHz) 11.48, 20.86 (4 x CH$_3$), 30.49 (CH$_3$CHCH$_3$), 46.93 (2 x CH), 120.96 ($\text{C}O(Q^1)$), 125.80, 126.40, 126.66, 133.19 (4 x CH(Car)), 145.86 ($\text{CN=C}(Q^1)$) and 159.88, 160.72 ($\text{CN}(Q^1)$, $\text{CO}(Q^1)$); m/z (%) 257 (M+, 45), 242 (29), 228 (14), 214 (12), 188 (14), 187 (15), 173 (30), 145 (35), 130 (39), 103 (16), 76 (22) and 70 (100).
Kinetic Studies of the Reaction of NQ₁-Imide (143) with Styrene or Diethyl Fumarate

Reactions zero order with respect to alkene

The procedure (G) was followed using 3-aminoquinazolinone (8) (0.33 g, 1.65 x 10⁻³ mol), LTA (0.76 g, 1.73 x 10⁻³ mol) and triethylamine (1.7 g, 1.65 x 10⁻² mol) in dichloromethane (1 ml). The solution was left at -20 °C for 10 min. then cooled to -40 °C and divided into two equal portions. To one portion was added 3 mol equiv. of the alkene, and to the other, 6 mol equiv. of the alkene. Aliquots of both portions were taken and quenched with hydrazine (0.2 ml) at intervals over 30 min. The rate of appearance of aziridine with respect to time was then measured by NMR spectroscopy (see Appendix 3).
Syn-Selectivity in Aziridination of Styrene with NQ1-Imide (143)

The procedure (G) was followed using 3-aminoquinazolinone (8) (0.1 g, 4.93 x 10^{-4} mol), LTA (0.23 g, 5.17 x 10^{-3} mol) and triethylamine (0.5 g, 4.93 x 10^{-3} mol) in dichloromethane (1 ml). The solution was left at -20 °C for 10 min. then cooled to -40 °C and styrene (0.15 g, 1.48 x 10^{-3} mol) added, and the reaction monitored by proton NMR at this temperature. After 1 h. signals at δ 3.20 (1H, heptet, J 6.8 Hz, CH_{3}CH_{2}CH_{3}), 3.36 (1H, dd, J 7.0, 2.4 Hz, azir. ring H-3 trans to Q1), 3.45 (1H, dd, J 5.4, 2.4 Hz, azir. ring H-3 cis to Q1), and 3.72 (1H, dd, J 7.0, 5.4 Hz, azir. ring H-2 gem to Ph) were assignable to the aziridine N-invertomer with Q1 and Ph cis (140a).

This solution was allowed to warm to room temperature then re-cooled to -40 °C. The NMR spectrum now showed these respective aziridine ring proton signals at δ 2.88, 2.94, and 3.41-3.58 corresponding to the thermodynamically stable N-invertomer having Q1 and Ph trans (140b) (described previously). These signals from the thermodynamically stable N-invertomer are absent in the spectrum above run at -40 °C.
Diastereoselectivity in Reactions of Chiral NQ₈-Imides with Achiral Alkenes

**Reaction of NQ₈-Imide (154) with Styrene**

The general procedure (G) was followed using 3-aminoquinazolinone (0.1 g, 3.13 x 10⁻⁴ mol), LTA (0.15 g, 3.29 x 10⁻⁴ mol), triethylamine (0.3 g, 3.13 x 10⁻³ mol) and styrene (0.1 g, 9.39 x 10⁻⁴ mol) in dry dichloromethane (1 ml). A 300 MHz NMR
spectrum of the crude product indicated a 9 : 1 mixture of diastereoisomers (from comparison of the signals at δ 5.46 and δ 5.58 (MeCHOSi)). Chromatography of the residue using light petroleum : ethyl acetate (4 : 1) gave the aziridine (155) as a colourless solid (0.08 g, 63%) identical in all respects to that isolated previously.\(^\text{80}\) \(\delta_H\) (CDCl\(_3\), 300 MHz) major diastereoisomer: 0.03 (6H, s, 2 x CH\(_3\)Si), 0.85 (9H, s, (CH\(_3\))\(_3\)C), 1.63 (3H, d, J 6.4 Hz, CH\(_3\)CH), 2.74 (1H, dd, J 5.0, 1.8 Hz, azir. ring H-3 trans to Q\(^\circ\)), 3.75 (1H, dd, J 7.7, 1.8 Hz, azir. ring H-3 cis to Q\(^\circ\)), 4.04 (1H, dd, J 7.7, 5.0 Hz, azir. ring H-2 gem to Ph), 5.46 (1H, q, J 6.4 Hz, CH\(_3\)CH), 7.36-7.50 (5H, m, 5 x CH(Ar), Q\(^\circ\)-H), 7.71-7.79 (2H, m, Q\(^\circ\) 7- and 8-H) and 8.22 (1H, dd, J 8.0 and 0.8 Hz, Q\(^\circ\) 5-H); minor diastereoisomer (observable peaks): 0.09 (6H, s, 2 x CH\(_3\)Si), 0.88 (9H, s, (CH\(_3\))\(_3\)C), 1.57 (3H, d, J 6.4 Hz, CH\(_3\)CH), 2.81 (1H, dd, J 5.0, 1.8 Hz, azir. ring H-3 trans to Q\(^\circ\)), 5.58 (1H, q, J 6.4 Hz, CH\(_3\)CH).

Reaction of NQ\(^\circ\)-Imide (156) with Styrene

The procedure (G) was followed using 3-aminooquinazolinone (0.1 g, 3.13 \times 10^{-4} mol), LTA (0.15 g, 3.29 \times 10^{-4} mol), DABCO (0.37 g, 3.13 \times 10^{-3} mol) and styrene (0.1 g, 9.39 \times 10^{-4} mol) in dry dichloromethane (1 ml). A 300 MHz NMR spectrum of the crude product indicated a 9.6 : 1 mixture of diastereoisomers (from comparison of the signals at δ 5.46 and δ 5.58). Chromatography of the residue using light petroleum : ethyl acetate (4 : 1) gave the aziridine (155) as a colourless solid (0.07 g, 53%) identical in all respects to that isolated previously.
Reaction of the 3-acetoxyaminoquinazolinone with styrene has been shown to give a 4.6 : 1 ratio of the corresponding diastereoisomers of (155). $^1$H (CDCl$_3$, 300 MHz)

**Major diastereoisomer:**
- 0.03 (6H, s, 2 x CH$_3$Si),
- 0.89 (9H, s, (CH$_3$)$_3$C),
- 1.65 (3H, d, J 6.5 Hz, CH$_3$CH),
- 2.73 (1H, dd, J 5.1 and 1.8 Hz, azir. ring H-3 *trans* to Q$^8$),
- 3.75 (1H, dd, J 7.8 and 1.8 Hz, azir. ring H-3 *cis* to Q$^8$),
- 4.04 (1H, dd, J 7.8, 5.1 Hz, azir. ring H-2 *gem* to Ph),
- 5.45 (1H, q, J 6.4 Hz, CH$_3$CH),
- 7.4 (5H, m, 5 x CH(Ar), Q$^8$-H),
- 7.7 (2H, m, Q$^8$ 7- and 8-H) and
- 8.2 (1H, dd, J 8 and 1 Hz, Q$^8$ 5-H).

**Minor diastereoisomer (observable peaks):**
- 0.08 (6H, s, 2 x CH$_3$Si),
- 1.57 (3H, d, J 6.4 Hz, CH$_3$CH),
- 2.8 (1H, dd, J 5.2 and 1.6 Hz, azir. ring H-3 *trans* to Q$^8$),
- 3.5 (1H, dd, J 7.2 and 1.6 Hz, azir. H-3 *cis* to Q$^8$),
- 5.59 (1H, q, J 6.4 Hz, CH$_3$CH),
- 8.23 (1H, d, J 8 Hz, Q$^8$ 5-H).

**Diastereoselectivity in reaction of achiral NQ$^2$-Imide (158) with chiral alkenes**

**Reaction of NQ$^2$-Imide (158) with Cyclohexenol**

The procedure (G) was followed using 3-aminoquinazolinone (17) (0.9 g, 4.93 x $10^{-4}$ mol), LTA (0.23 g, 5.17 x $10^{-4}$ mol), triethylamine (0.5 g, 4.93 x $10^{-3}$ mol) and
cyclohexenol (0.15 g, 1.48 x 10^{-3} \text{ mol}) in dry dichloromethane (1 ml). After the work up, the residue was dissolved in dry dichloromethane (1 ml) containing pyridine (1 ml) and acetic anhydride added (0.15 g, 1.48 x 10^{-3} \text{ mol}). The reaction mixture was left to stir overnight, then water was added and stirring continued for a further 30 min. Further dichloromethane (10 ml) was added, the solution then washed with saturated aqueous sodium hydrogen carbonate, dried and the solvent removed under reduced pressure. A 300 MHz NMR spectrum of the crude product indicated the presence of a 9.3 : 1 ratio of diastereoisomers (from comparison of the signals at $\delta$ 5.21 and $\delta$ 5.45). Chromatography of the residue using light petroleum : ethyl acetate (4 : 1) gave aziridine (159) (0.07 g, 53\%). The NMR spectrum showed peaks clearly at $\delta$ 5.21 (CHOAc), 2.23 (OCOCH$_3$) and 1.43 (CH$_2$CH$_3$) for the major diastereoisomer (159a) and peaks at $\delta$ 5.43 (CHOAc) and 2.11 (OCOCH$_3$) for the minor diastereoisomer (159b). These signals correlate well with NMR spectra for both compounds (159a) and (159b) previously isolated. 

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EXPERIMENTAL

CHAPTER SIX
General Procedure (H) for the Aziridination of Alkenes using Pre-formed 3-Acetoxyaminoquinazolinone (14) in the Presence of Hexamethyldisilazane (HMDS) (at -20 to -25 °C) followed by Addition of the Alkene

3-Acetoxyaminoquinazolinone (1 mol equiv.) and LTA (1.05 mol equiv.) were added alternately in small portions over 15 min. to a stirred solution of dry dichloromethane (1 ml / 100 mg of 3-aminoquinazolinone) cooled at -20 to -25 °C in a dry ice-acetone bath. The cold dichloromethane solution (~ -20 °C) was separated from the insoluble lead di-acetate and added with stirring to a mixture of HMDS (2 mol equiv.) and the alkene (3 mol equiv.) at -20 °C and the mixture allowed to warm to room temperature. Further dichloromethane (~30 ml) was added, the total solution washed with water, dried and the solvent removed.
Aziridination of Styrene using $Q^1\text{NHOAc}$ (14) / HMDS

The general procedure (H) was followed using 3-aminoquinazolinone (0.5 g, $2.46 \times 10^{-3}$ mol), LTA (1.15 g, $2.59 \times 10^{-3}$ mol), HMDS (0.8 g, $4.93 \times 10^{-3}$ mol) and styrene (0.38 g, $3.69 \times 10^{-3}$ mol) in dry dichloromethane (5 ml). A 300 MHz proton NMR spectrum of the crude product indicated a 8.1 : 1 ratio of aziridine (140) to 2-isopropylquinazolinone (104) (by comparison of the signals at $\delta$ 3.64 (CH$_3$)$_2$CH and $\delta$ 3.08 (CH$_3$)$_2$CH). Column chromatography of this material using light petroleum : ethyl acetate (4 : 1) gave the aziridine (140) (0.23 g, 78%) identical to that isolated previously.16

This reaction was repeated in the absence of HMDS and gave a 6.4 : 1 ratio of aziridine (140) to 2-isopropylquinazolinone (104). Purification was achieved by column chromatography as described above to give aziridine (140) (0.22 g, 74%).
The general procedure (H) was followed using 3-aminoquinazolinone (8) (0.2 g, 9.85 x 10^{-4} mol), LTA (0.46 g, 1.08 x 10^{-3} mol), HMDS (0.32 g, 1.97 x 10^{-3} mol) and hex-l-ene (0.25 g, 2.96 x 10^{-3} mol) in dry dichloromethane (2 ml). A 300 MHz proton NMR spectrum of the crude product indicated a 3.5 : 1 ratio of aziridine (145) to 2-isopropylquinazolinone (104) (by comparison of the signals at δ 3.75 (CH$_2$) and δ 3.08 (CH$_3$)$_2$CH). Column chromatography of this material using light petroleum : ethyl acetate (4 : 1) gave the aziridine (145) (0.2 g, 71%) identical to that isolated previously (Chapter 5).

The above reaction was repeated except (1.6 g, 9.85 x 10^{-3} mol) of HMDS was used and the same yield of aziridine as that isolated above was obtained.

In contrast, carrying out the above reaction with hex-1-ene in the absence of HMDS gave a 15% isolated yield of the aziridine (145).
Aziridination of Naphthalene using Q\(^\text{I}\)NHOAc (14) / HMDS

\[\begin{align*}
\text{Q}^\text{I} \text{NHOAc} & \xrightarrow{\text{HMDS}} \begin{array}{c}
\text{N} \\
1
\end{array} + \begin{array}{c}
\text{N} \\
1
\end{array} \\
(14) & \quad (166)
\end{align*}\]

The general procedure (H) was followed using 3-aminoquinazolinone (8) (0.5 g, 2.46 x 10\(^{-3}\) mol), LTA (1.15 g, 2.59 x 10\(^{-3}\) mol), HMDS (0.8 g, 4.93 x 10\(^{-3}\) mol) and naphthalene (0.95 g, 7.39 x 10\(^{-3}\) mol) in dry dichloromethane (5 ml). After the work up, the residue was purified by column chromatography over silica with light petroleum : ethyl acetate (6 : 1) as eluant and aziridine (166) (Rf 0.25) was obtained as a colourless oil (0.16 g, 20%) (Found: M\(^+\) 329.1528. C\(_{21}\)H\(_{19}\)N\(_3\)O requires M\(^+\) 329.1528); \(\nu_{\text{max}} / \text{cm}^{-1}\) 1675s, 1610 and 1590s; \(\delta_H\) (CDCl\(_3\), 250 MHz) 1.46, 1.50 (6H, 2 x d, J 6.7 Hz, CH\(_3\)CHCH\(_3\)), 3.75 (1H, heptet, J 6.7 Hz, CH\(_3\)CHCH\(_3\)), 3.86 (1H, dd, J 7.5, 4.6 Hz, NCH=C), 4.41 (1H, d, J 7.5 Hz, NCH), 6.55 (1H, dd, J 9.6, 4.6 Hz, NCH=CH), 6.78 (1H, d, J 9.6 Hz, NCH=CH), 7.25-7.37 (1H, m, CH(Ar)), 7.39-7.58 (3H, m, 3 x CH(Ar)), 7.68-7.80 (2H, m, 2 x CH(Ar)), 7.83-7.90 (1H, m, CH(Ar)) and 8.32 (1H, dd, J 7.7 and 0.9 Hz, CH(Ar)); \(\delta_C\) (CDCl\(_3\), 75 MHz) 21.5, 21.6 (2 x CH\(_3\)), 31.5 (CH\(_3\)CHCH\(_3\)), 50.8, 53.2 (2 x NCH), 121.0, 121.1 (2 x CH), 121.7 (COC(Q)), 126.4, 126.7, 126.9, 127.2 (4 x CH(Ar)), 127.4 (C), 129.2 (CH(Ar)), 129.5 (C), 130.5, 132.6, 135.0 (3 x CH(Ar)), 146.7 (CN=C(Q)) and 160.4, 162.0 (CN(Q), CO(Q)); m/z (%) 329 (M\(^+\),...
Further elution gave the di-aziridine (165) (R_f 0.14) as a colourless oil (0.15 g, 11%) (Found: M^+ 530.2431. C_{32}H_{30}N_6O_2 requires M^+ 530.2430); ν_max / cm\(^{-1}\): 1680 s, 1610 m and 1595 s; δ_H (CDCl\(_3\), 250 MHz) 1.28, 1.32 (12H, 2 x d, J 6.7 Hz, 2 x CH\(_3\)CHCH\(_3\)), 3.59 (2H, heptet, J 6.7 Hz, 2 x CH\(_3\)CHCH\(_3\)), 3.74 (2H, d, J 8.3 Hz, 2 x NCH), 4.18 (2H, d, J 8.3 Hz, 2 x NCH), 7.28-7.39 (4H, m, 4 x CH(Ar)), 7.52-7.69 (6H, m, 6 x CH(Ar)) and 8.11-8.27 (2H, m, 2 x CH(Ar)); δ_C (CDCl\(_3\), 75 MHz) 21.5, 21.6 (4 x CH\(_3\)), 31.6 (2 x CH\(_3\)CHCH\(_3\)), 46.6, 47.8 (4 x NCH), 121.6 (2 x CO(Q\(^1\))), 126.7, 126.8, 127.5, 129.7 (8 x CH(Ar)), 130.8 (2 x C), 131.6, 134.8 (4 x CH(Ar)), 146.6 (2 x CN=C(Q\(^1\))) and 160.6, 161.3 (2 x CO(Q\(^1\))); m/z (%): CI 531 (M+1).

This reaction was repeated under the same conditions but using 0.5 mol equiv. of naphthalene (0.48 g, 3.7 x 10\(^{-3}\) mol). A 250 MHz NMR spectrum of the crude product showed the presence of a 2.1 : 1 ratio of di-aziridine (165) to 2-isopropylquinazolinone (104) (from comparison of the signals at δ 3.59 and δ 3.08 in the respective spectrum above). Column chromatography (as described above) gave the product in 46% yield. Considerable loss of product appears to take place on chromatography.

In the absence of HMDS, a 250 MHz NMR spectrum of the crude product shows the presence of a 1 : 6.1 ratio of (165) to 2-isopropylquinazolinone (104) from comparison of signals at δ 3.75 (165) and δ 3.08 (104).
Aziridination of Allyl Chloride using \( \text{Q}^1 \text{NHOAc} \) (14) / HMDS

The general procedure (H) was followed using 3-aminoquinazolinone (8) (0.5 g, 2.46 x 10^{-3} mol), LTA (1.15 g, 2.59 x 10^{-3} mol), HMDS (0.8 g, 4.93 x 10^{-3} mol) and allyl chloride (0.57 g, 7.39 x 10^{-3} mol) in dry dichloromethane (5 ml). After work up, the residue was purified by column chromatography over silica with light petroleum : ethyl acetate (4 : 1) as eluant. The aziridine (167) \((R_f 0.34)\) was obtained as a pale yellow oil (0.23 g, 34%) \((\text{Found: } M^+ 277.0981. \text{C}_{14} \text{H}_{16} \text{N}_2 \text{O}_1 \text{Cl}_1 \text{H}_1 \text{ requires } M^+ 277.0982); \upsilon_{\text{max}}/\text{cm}^{-1} 1760\text{m}, 1680\text{s}, 1610\text{s} \text{ and } 1600\text{s}; \delta_{\text{H}} (\text{CDCl}_3, 250 \text{ MHz}) 1.55, 1.60 (6\text{H}, 2 \times \text{d}, J 6.7 \text{ Hz, CH}_3\text{CHCH}_3), 2.73 (1\text{H}, \text{dd}, J 5.1 \text{ and } 1.5 \text{ Hz, azir. ring H-3 cis to } \text{CH}_2\text{Cl}), 3.02 (1\text{H}, \text{dd}, J 7.4 \text{ and } 1.5 \text{ Hz, azir. ring H-3 trans to } \text{CH}_2\text{Cl}), 3.67, (1\text{H}, \text{ddddd}, J 7.4, 6.8, 5.1 \text{ and } 4.8 \text{ Hz, CHCH}_2\text{Cl}), 3.78 (1\text{H}, \text{dd}, J 11.2 \text{ and } 6.8 \text{ Hz, CHHCl}), 3.88 (1\text{H, heptet, J 6.7 Hz, CH}_3\text{CHCH}_3), 4.28 (1\text{H}, \text{dd}, J 11.2 \text{ and } 4.8 \text{ Hz, CHHCl}), 7.58 (1\text{H, ddd}, J 7.9, 7.6 \text{ and } 1.1 \text{ Hz, Q}^1 6-\text{H}), 7.78-7.87 (2\text{H, m, Q}^1 7- \text{ and } 8-\text{H}) \text{ and } 8.31 (1\text{H, dd, J 7.9 \text{ and } 1.1 \text{ Hz, Q}^1 5-\text{H}); \delta_{\text{C}} (\text{CDCl}_3, 75 \text{ MHz}) 21.0, 21.8 (2 \times \text{CH}_3), 31.3 (\text{CH}_3\text{CHCH}_3), 39.6 (\text{CH}_2), 44.0 (\text{CNH}), 44.6 (\text{CH}_2\text{Cl}), 121.6 (\text{C} \text{CO(Q}^1\)), 126.4, 126.7, 127.5, 134.2 (4 \times \text{CH(Q}^1\)), 146.6 (\text{CN=Cl(Q}^1\) and 161.0, 161.6 (\text{CN(Q}^1\), \text{CO(Q}^1\)); m/z (%) 277 (M*, 52), 242 (44), 214 (30), 187 (24), 173 (64), 146 (25), 145 (100), 144 (23), 130 (83), 104 (20), 103 (34), 90 (28), 77 (20), 76 (46) \text{ and } 75 (10).
When this reaction was carried out in the absence of HMDS, no aziridine product was detectable in the crude reaction mixture by NMR spectroscopy.

Reaction of Q1NHOAc (14) / HMDS with Phenol

\[
\begin{align*}
\text{Q1NHOAc} & \quad \text{HMDS} \quad \text{Phenol} \\
(14) & \quad \text{NHQ1} \quad \text{OSiMe3} \\
(14) & \quad (168)
\end{align*}
\]

The general procedure (H) was followed using 3-aminoquinazolinone (8) (0.2 g, 9.85 x 10^{-4} mol), LTA (0.46 g, 1.03 x 10^{-4} mol), HMDS (1.6 g, 9.85 x 10^{-3} mol) and phenol (0.28 g, 2.96 x 10^{-3} mol) in dry dichloromethane (2 ml). After work up, the residue was purified by column chromatography over silica with light petroleum : ethyl acetate (3 : 1) as eluant. The trimethylsilyl ether (168) (Rf 0.32) was obtained as a pale orange oil (0.22 g, 61%) (Found: M^+ 367.1714. C_{20}H_{25}N_{5}O_{2}Si requires M^+ 367.1716); \nu_{\text{max}} / \text{cm}^{-1} 1680 s and 1590 s; \delta_{H} (\text{CDCl}_3, 250 \text{ MHz}) 0.4 (9H, s, Si(CH_3)_3), 1.39 (6H, 2 x d, J 6.8 Hz, CH_3CH(CH_3)), 3.50 (1H, heptet, J 6.8 Hz, CH_3CH(CH_3), 6.27 (1H, dd, J 7.3, 1.6 Hz, CH(Ar)), 6.73-6.90 (3H, m, 3 x CH(Ar)), 7.36 (1H, s, NH), 7.38-7.43 (1H, m, CH(Ar)), 7.71-7.78 (2H, m, 2 x CH(Ar)) and 8.20 (1H, dd, J 7.9, 0.8 Hz, CH(Ar)); \delta_{C} (\text{CDCl}_3, 75 \text{ MHz}) 0.0 (Si(CH_3)_3), 19.6, 21.5 (CH_3CH(CH_3), 30.6 (CH_3CH(CH_3), 111.8, 118.2 (2 x CH(Ar)), 120.6 (C\text{C}(Q^1)), 121.4, 121.5, 125.8, 126.2, 127.0, 133.9 (6 x CH(Q^1)), 240
When the above reaction was carried out in the absence of HMDS, only 2-isopropylquinazolinone (104) (82%) was isolated.

Aziridination of Diethyl Maleate using Q\textsuperscript{1}NHOAc (14) / HMDS

The general procedure (H) was followed using 3-aminoquinazoline (8) (0.2 g, 9.85 x 10^{-4} mol), LTA (0.46 g, 1.03 x 10^{-3} mol), HMDS (0.32 g, 1.97 x 10^{-3} mol) and diethyl maleate (0.51 g, 2.96 x 10^{-3} mol) in dry dichloromethane (2 ml). After work up, the residue was purified by column chromatography over silica with light petroleum : ethyl acetate (3 : 1) as eluant. The aziridine (169) (R\textsubscript{f} 0.52) was obtained as a colourless oil (0.12 g, 33%) (Found: M\textsuperscript{+} 373.1638. C\textsubscript{19}H\textsubscript{23}N\textsubscript{3}O\textsubscript{5} requires M\textsuperscript{+} 373.1638); \nu_{\text{max}} / \text{cm}^{-1} 1730s, 1670w and 1600m; \delta\textsubscript{H} (CDCl\textsubscript{3}, 250 MHz) 1.24 (6H, t, J 7.2 Hz, 2 x CH\textsubscript{3}CH\textsubscript{2}), 1.34 (6H, d, J 6.8 Hz, CH\textsubscript{3}CHCH\textsubscript{3}), 3.97 (1H, heptet, J 6.8 Hz, CH\textsubscript{3}CHCH\textsubscript{3}), 4.18 (4H, q, J 7.2 Hz, 2 x CH\textsubscript{3}CH\textsubscript{2}), 4.78 (2H, s, 2 x CHCO\textsubscript{2}Et), 7.33 (1H, ddd, J 7.9, 6.9 and 1.4 Hz, Q\textsuperscript{1} 6-H), 7.55-7.70 (2H, m, Q\textsuperscript{1} 7- and 8-H) and 8.03 (1H, ddd, J 7.9, 1.4 and 0.4 Hz, Q\textsuperscript{1} 5-H); \delta\textsubscript{C} (CDCl\textsubscript{3}, 75 MHz) 14.5, 21.4 (4 x CH\textsubscript{3}), 31.6, 41.3 (2 x CH), 62.2 (2 x
CO₂CH₂CH₃), 121.8 (CCO(Q³)), 126.5, 126.9, 127.7, 134.9 (4 x CH(Q³)), 146.8 (CN=C(Q³)), 162.5, 163.7 (CN(Q³), CO(Q³)) and 166.6 (2 x COCH₂CH₂); m/z (%) 373 (M+, 21), 300 (60), 188 (22), 187 (23), 173 (60), 149 (30), 145 (100), 130 (57), 129 (20), 103 (23), 85 (21), 76 (23), 73 (26), 71 (24), 69 (48), 60 (23), 57 (48) and 55 (49).

In the absence of HMDS a yield of 13% was obtained for (169) (from NMR examination of the crude reaction product).

**Investigations into the Stability of the 3-Acetoxyaminoquinazolinone (14) in the Presence of HMDS**

The general procedure (F) for the preparation of the 3-acetoxyaminoquinazolinone (14) was followed using 3-aminoquinazolinone (8) (0.5 g, 2.46 x 10⁻³ mol), and LTA (1.15 g, 2.59 x 10⁻³ mol) in dry dichloromethane (5 ml). The cold (-20 °C) solution was divided into two equal portions, HMDS (0.4 g, 2.46 x 10⁻³ mol) added to one portion and both solutions were allowed to warm to +5 °C. After 10 min. at this temperature, styrene (0.19 g, 3.69 x 10⁻³ mol) was added to each solution and both were allowed to warm to room temperature. After the usual work up, 250 MHz proton NMR spectra of total products from both samples were obtained. The results are illustrated below.

<table>
<thead>
<tr>
<th>HMDS (g)</th>
<th>NMR yield (%) of (140)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.4</td>
<td>52</td>
</tr>
<tr>
<td>-</td>
<td>69</td>
</tr>
</tbody>
</table>
Low Temperature NMR Studies of the Decomposition of $Q^{1}$NHOOAc (14)
in the Presence of HMDS

The 3-acetoxyaminoquinazolinone (14) was prepared as described in procedure (F) from (8) ($0.1 \text{ g, } 4.93 \times 10^{-4} \text{ mol}$), and LTA ($0.23 \text{ g, } 5.17 \times 10^{-4} \text{ mol}$) in dry CDCl$_3$ (1 ml). HMDS was then added ($0.4 \text{ g, } 9.85 \times 10^{-4} \text{ mol}$) and the mixture monitored by proton NMR spectroscopy whilst warming to room temperature. The appearance of signals from 2-isopropylquinazolinone (104) were observed but none which could be assigned to a reaction product between (14) and HMDS were visible.
Aziridination of Styrene using $Q^N$NHOAc (157) / HMDS

The general procedure (H) was followed using 3-aminoquinazolinone (0.1 g, 3.13 x 10^{-4} mol), LTA (0.15 g, 3.29 x 10^{-4} mol), HMDS (0.10 g, 6.27 x 10^{-4} mol) and styrene (0.1 g, 9.4 x 10^{-4} mol) in dry dichloromethane (1 ml). After work up, a 4.5 : 1 ratio of diastereoisomers was obtained (from comparison of the signals at $\delta$ 5.4 and $\delta$ 5.47). The residue was purified by column chromatography over silica with light petroleum : ethyl acetate (3 : 1) as eluant. The aziridine (155) was obtained as a colourless oil (0.09 g, 74%) identical with that isolated previously.\textsuperscript{80}
Reactions of N-Acetoxyaminoquinazolinones with Hex-1-ene
in the Presence of HMDS Analogues or Amines

The general aziridination procedure (H) was followed using 3-aminooquinazolinone (8) (0.5 g, 2.46 x 10^{-3} mol), LTA (1.15 g, 2.59 x 10^{-3} mol), HMDS analogue (4.93 x 10^{-3} mol) and hex-1-ene (0.63 g, 7.39 x 10^{-3} mol) in dry dichloromethane (5 ml). Yields of product (145) relative to 2-isopropylquinazolinone (104) in the crude reaction mixture were measured by NMR spectroscopy from integration of signals at δ 3.64 (145) and δ 3.08 (104) and are given in Table 6 (Chapter 6).
Competitive Aziridination of Styrene and Diethyl Fumarate using Q\textsuperscript{1}NHOAc (14) and HMDS or other Analogues or Amines

Competition experiments were carried out as described previously, using 3-aminoquinazolinone (14) (0.2 g, 9.85 x 10\textsuperscript{-4} mol), LTA (0.46 g, 1.03 x 10\textsuperscript{-3} mol), HMDS analogue (1.97 x 10\textsuperscript{-3} mol) styrene (0.31 g, 2.96 x 10\textsuperscript{-3} mol) and diethyl fumarate (0.51 g, 2.96 x 10\textsuperscript{-3} mol) in dry dichloromethane (2 ml). After work up, the ratio of aziridines (140) and (141) were determined by integration of signals at δ 3.39 and δ 3.21 respectively in the NMR spectra of the crude reaction products (Table 9).

<table>
<thead>
<tr>
<th>HMDS analogue or amine</th>
<th>2 mol equiv. (g)</th>
<th>Ratio (140) : (141)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMDS</td>
<td>0.32</td>
<td>3.5 : 1</td>
</tr>
<tr>
<td>HMDS + base washed (14)</td>
<td>0.32</td>
<td>3.0 : 1</td>
</tr>
<tr>
<td>[PhMe\textsubscript{2}Si]\textsubscript{2}NH</td>
<td>0.56</td>
<td>2.8 : 1</td>
</tr>
<tr>
<td>t-BuNHSiNMe\textsubscript{3}</td>
<td>0.29</td>
<td>3.1 : 1</td>
</tr>
<tr>
<td>NH\textsubscript{3}</td>
<td>0.03 (in CH\textsubscript{2}Cl\textsubscript{2})</td>
<td>2.7 : 1</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>1.0 : 0</td>
</tr>
</tbody>
</table>

Table 9: Illustrates the ratios of aziridines (140) and (141) produced from competitive aziridination reactions using Q\textsuperscript{1}NHOAc in the presence of silylated amines.
APPENDIX ONE

N-(Quinazolinonyl)-Imide (49a) – X-Ray Crystal Structure Determination
Bond angles (°) with estimated standard deviations in parentheses

<table>
<thead>
<tr>
<th>Bond</th>
<th>Angle (°)</th>
<th>Standard Deviation (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C (2)–N (1)–C (10)</td>
<td>119.1 (2)</td>
<td>0.2</td>
</tr>
<tr>
<td>O (2)–C (16)–C (17)</td>
<td>122.8 (3)</td>
<td>0.3</td>
</tr>
<tr>
<td>N (3)–N (2)–C (4)</td>
<td>114.8 (2)</td>
<td>0.2</td>
</tr>
<tr>
<td>C (16)–C (17)–C (18)</td>
<td>107.9 (2)</td>
<td>0.3</td>
</tr>
<tr>
<td>N (2)–N (3)–C (14)</td>
<td>115.8 (2)</td>
<td>0.2</td>
</tr>
<tr>
<td>C (16)–C (17)–C (19)</td>
<td>110.9 (2)</td>
<td>0.3</td>
</tr>
<tr>
<td>C (14)–N (3)–C (16)</td>
<td>127.6 (2)</td>
<td>0.2</td>
</tr>
<tr>
<td>C (18)–C (17)–C (19)</td>
<td>111.9 (2)</td>
<td>0.3</td>
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<td>N (1)–C (2)–C (11)</td>
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<td>C (17)–C (18)–H (18B)</td>
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<td>0.3</td>
</tr>
<tr>
<td>N (2)–C (4)–O (3)</td>
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<td>0.2</td>
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<tr>
<td>C (17)–C (18)–H (18A)</td>
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<td>O (3)–C (4)–C (5)</td>
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<td>H (18B)–C (18)–H (18C)</td>
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<td>C (4)–C (5)–C (10)</td>
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<tr>
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<td>C (7)–C (8)–H (8A)</td>
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<td>0.3</td>
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<td>0.3</td>
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<tr>
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<td>C (2)–C (11)–C (13)</td>
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<tr>
<td>C (2)–N (2)–C (4)</td>
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<td>C (12)–C (11)–C (13)</td>
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<td>N (2)–N (3)–C (16)</td>
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<td>C (11)–C (12)–H (12B)</td>
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<td>0.3</td>
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<tr>
<td>H (12B)–C (12)–H (12C)</td>
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<td>0.3</td>
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<td>N (2)–C (4)–C (5)</td>
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<td>0.3</td>
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<td>C (11)–C (13)–H (13B)</td>
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<td>C (4)–C (5)–C (6)</td>
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<tr>
<td>H (13B)–C (13)–H (13C)</td>
<td>109.5</td>
<td>0.3</td>
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Bond lengths (Å) with estimated standard deviations in parentheses

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N-(Quinazolinonyl)-Imide (49b) – X-Ray Crystal Structure Determination

![Chemical Structure Diagram]
Bond angles (°) with estimated standard deviations in parentheses

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Angle values are in degrees, and standard deviations are given in parentheses.
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### Bond lengths (Å) with estimated standard deviations in parentheses

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N-(Quinazolinonyl)-Imide (75a) – X-Ray Crystal Structure Determination
Bond angles (°) with estimated standard deviations in parentheses

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<td>C (6)–C (7)–C (8)</td>
<td>119.9 (5)</td>
</tr>
<tr>
<td>C (8)–C (9)–C (10)</td>
<td>120.6 (5)</td>
</tr>
<tr>
<td>C (9)–C (10)–C (5)</td>
<td>118.8 (4)</td>
</tr>
<tr>
<td>N (3)–N (2)–C (11)</td>
<td>117.7 (4)</td>
</tr>
<tr>
<td>C (11)–N (2)–C (15)</td>
<td>127.8 (4)</td>
</tr>
<tr>
<td>C (2)–C (1)–C (21)</td>
<td>112.0 (3)</td>
</tr>
<tr>
<td>C (21)–C (1)–C (31)</td>
<td>112.3 (4)</td>
</tr>
<tr>
<td>O (2)–C (11)–C (12)</td>
<td>122.5 (5)</td>
</tr>
<tr>
<td>C (11)–C (12)–C (14)</td>
<td>109.0 (4)</td>
</tr>
<tr>
<td>C (14)–C (12)–C (13)</td>
<td>109.0 (5)</td>
</tr>
<tr>
<td>O (3)–C (15)–C (16)</td>
<td>122.7 (4)</td>
</tr>
<tr>
<td>O (4)–C (16)–C (17)</td>
<td>106.5 (4)</td>
</tr>
<tr>
<td>C (17)–C (16)–C (15)</td>
<td>109.1 (4)</td>
</tr>
<tr>
<td>O (5)–C (18)–C (19)</td>
<td>127.8 (9)</td>
</tr>
<tr>
<td>C (22)–C (21)–C (26)</td>
<td>117.8 (5)</td>
</tr>
<tr>
<td>C (26)–C (21)–C (1)</td>
<td>123.3 (5)</td>
</tr>
<tr>
<td>C (24)–C (23)–C (22)</td>
<td>121.2 (7)</td>
</tr>
<tr>
<td>C (24)–C (25)–C (26)</td>
<td>121.5 (7)</td>
</tr>
<tr>
<td>C (32)–C (31)–C (36)</td>
<td>118.9 (4)</td>
</tr>
<tr>
<td>C (36)–C (31)–C (1)</td>
<td>118.3 (4)</td>
</tr>
<tr>
<td>C (34)–C (33)–C (32)</td>
<td>119.3 (6)</td>
</tr>
<tr>
<td>C (34)–C (35)–C (36)</td>
<td>121.0 (6)</td>
</tr>
<tr>
<td>C (29)#1–C (27)–C (29)</td>
<td>122 (3)</td>
</tr>
<tr>
<td>C (29)#1–C (27)–O (7)</td>
<td>119 (2)</td>
</tr>
<tr>
<td>Bond Lengths (Å) with estimated standard deviations in parentheses</td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>N (1)–C (2)</td>
<td>1.277 (5)</td>
</tr>
<tr>
<td>C (2)–N (3)</td>
<td>1.399 (5)</td>
</tr>
<tr>
<td>N (3)–N (2)</td>
<td>1.394 (5)</td>
</tr>
<tr>
<td>C (4)–O (1)</td>
<td>1.214 (5)</td>
</tr>
<tr>
<td>C (5)–C (6)</td>
<td>1.392 (6)</td>
</tr>
<tr>
<td>C (6)–C (7)</td>
<td>1.362 (7)</td>
</tr>
<tr>
<td>C (8)–C (9)</td>
<td>1.376 (7)</td>
</tr>
<tr>
<td>N (2)–C (11)</td>
<td>1.428 (6)</td>
</tr>
<tr>
<td>O (2)–C (11)</td>
<td>1.189 (6)</td>
</tr>
<tr>
<td>O (4)–C (18)</td>
<td>1.342 (9)</td>
</tr>
<tr>
<td>O (5)–C (18)</td>
<td>1.215 (8)</td>
</tr>
<tr>
<td>C (1)–C (31)</td>
<td>1.537 (6)</td>
</tr>
<tr>
<td>C (12)–C (14)</td>
<td>1.508 (8)</td>
</tr>
<tr>
<td>C (15)–C (16)</td>
<td>1.520 (7)</td>
</tr>
<tr>
<td>C (18)–C (19)</td>
<td>1.485 (10)</td>
</tr>
<tr>
<td>C (21)–C (26)</td>
<td>1.392 (7)</td>
</tr>
<tr>
<td>C (23)–C (24)</td>
<td>1.351 (11)</td>
</tr>
<tr>
<td>C (25)–C (26)</td>
<td>1.415 (9)</td>
</tr>
<tr>
<td>C (31)–C (36)</td>
<td>1.388 (6)</td>
</tr>
<tr>
<td>C (33)–C (34)</td>
<td>1.384 (9)</td>
</tr>
<tr>
<td>C (35)–C (36)</td>
<td>1.378 (7)</td>
</tr>
<tr>
<td>C (27)–C (29)</td>
<td>1.17 (2)</td>
</tr>
<tr>
<td>C (27)–C (29)</td>
<td>1.17 (2)</td>
</tr>
</tbody>
</table>
APPENDIX TWO

Determination of the energy barrier separating the diastereoisomers (49a) and (49b)

In order to evaluate the energy barriers for the Q¹-imides (49a) and (49b), the following equations valid for first order reversible reactions were applied:

\[
\begin{align*}
\text{Isomer A} & \rightarrow \text{Isomer B} \\
K &= \frac{k_1}{k_{-1}} \\
(k_1 + k_{-1})t &= 2.303 \log_{10} \left( \frac{\%B \text{ in equilibrium}}{\%B \text{ in starting mixture}} - \frac{\%B \text{ in starting mixture}}{\%B \text{ at time } t} \right)
\end{align*}
\]

When the log term is plotted against time, a straight line with slope

\[
[k_1 + k_{-1} / 2.303] \text{ results.}
\]

The results from the graph in conjunction with relationship (a) enable the forward and reverse rate constants to be calculated at the temperature in question. A least squares line-fitting computer program was used to evaluate the rate constants.

The Arrhenius equation (c) was then employed to evaluate the activation energy:

\[
2.303 \log_{10} k = \left[ -\frac{E_A}{RT} \right]
\]
On plotting $\log_{10} k$ against $1/T$, the slope of the resulting straight line $= [-E_A / 2.303R]$ where $R$ is the gas constant.

The activation enthalpy, $\Delta H^*$ is then evaluated. The free energy of activation can be calculated using:

$$k = \frac{K_B T}{h} \exp\left(-\frac{\Delta G^*}{R T}\right)$$

Where $K_B$ = Boltzmann's constant, $h$ = Planck's constant, $R$ = gas constant.

$$\ln\left(\frac{k h}{K_B T}\right) = -\frac{\Delta G^*}{R T}$$

$$\Delta G^* = RT \ln\left(\frac{K_B T}{k h}\right) \quad (d)$$

Choosing one of the three temperatures, and substituting the appropriate rate constant, allows the $\Delta G^*$ value to be calculated from (d). The activation entropy $\Delta S^*$ can then be calculated using equation (e).

$$\Delta G^* = \Delta H^* - T \Delta S^* \quad (e)$$

**Experimental**

The imide (49b) (0.015 g) was dissolved in d$_8$-toluene (0.6 ml) and heated at a temperature of 120 °C. Samples were removed at different time intervals during the interconversion process which was monitored by proton NMR spectroscopy by integration of the PhCH$_2$CH$_3$ signals for (49a) and (49b) until equilibrium was achieved. This experiment was then repeated at temperatures of 105 °C and also 100 °C.
**Results**

**Imide (49b)**

<table>
<thead>
<tr>
<th>Isomer A</th>
<th>δ PhCMe</th>
<th>4.91 p.p.m</th>
<th>k₁</th>
</tr>
</thead>
<tbody>
<tr>
<td>A → B</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Isomer B</th>
<th>δ PhCMe</th>
<th>4.08 p.p.m</th>
<th>k₁</th>
</tr>
</thead>
</table>

In this case K = 2.38 (i.e. 29.4% A, 70.4% B at equilibrium).

(i) \( T = 120°C = 393K \)

<table>
<thead>
<tr>
<th>Time t/s</th>
<th>NMR Integration</th>
<th>%</th>
<th>%</th>
<th>[70.4 / (70.4 - x)]</th>
<th>[\log_{10}[70.4 (70.4 - x)]]</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>B</td>
<td>A</td>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>0</td>
<td>100.0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>120</td>
<td>178</td>
<td>36</td>
<td>83.2</td>
<td>16.8</td>
<td>1.3134</td>
</tr>
<tr>
<td>240</td>
<td>186</td>
<td>44</td>
<td>80.9</td>
<td>19.1</td>
<td>1.3723</td>
</tr>
<tr>
<td>360</td>
<td>199</td>
<td>56</td>
<td>78.0</td>
<td>22.0</td>
<td>1.4545</td>
</tr>
</tbody>
</table>

(ii) \( T = 105°C = 378K \)

<table>
<thead>
<tr>
<th>Time t/s</th>
<th>NMR Integration</th>
<th>%</th>
<th>%</th>
<th>[70.4 / (70.4 - x)]</th>
<th>[\log_{10}[70.4 (70.4 - x)]]</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>B</td>
<td>A</td>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>0</td>
<td>100.0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>900</td>
<td>187</td>
<td>19</td>
<td>90.8</td>
<td>9.2</td>
<td>1.0966</td>
</tr>
<tr>
<td>1500</td>
<td>205</td>
<td>34</td>
<td>85.8</td>
<td>14.2</td>
<td>1.2527</td>
</tr>
<tr>
<td>2100</td>
<td>129</td>
<td>23</td>
<td>84.9</td>
<td>15.1</td>
<td>1.2731</td>
</tr>
<tr>
<td>3300</td>
<td>224</td>
<td>78</td>
<td>74.2</td>
<td>25.8</td>
<td>1.5785</td>
</tr>
</tbody>
</table>
(iii) \( T = 100 ^\circ C = 373 K \)

<table>
<thead>
<tr>
<th>Time (s)</th>
<th>NMR</th>
<th>Integration</th>
<th>%</th>
<th>%</th>
<th>( 70.4 / (70.4 - x) )</th>
<th>( \log_{10} [70.4 (70.4 - x)] )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>0</td>
<td>100</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2400</td>
<td>174</td>
<td>29.5</td>
<td>85.5</td>
<td>14.5</td>
<td>1.2594</td>
<td>0.1002</td>
</tr>
<tr>
<td>3000</td>
<td>189.5</td>
<td>48</td>
<td>79.8</td>
<td>20.2</td>
<td>1.4024</td>
<td>0.1469</td>
</tr>
<tr>
<td>3600</td>
<td>200</td>
<td>59</td>
<td>77.2</td>
<td>22.8</td>
<td>1.4790</td>
<td>0.1700</td>
</tr>
</tbody>
</table>

**Evaluation**

<table>
<thead>
<tr>
<th>T</th>
<th>no. of points</th>
<th>r</th>
<th>( k_1 / 10^{-4} s^{-1} )</th>
<th>( k_{-1} / 10^{-4} s^{-1} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>120</td>
<td>4</td>
<td>0.997</td>
<td>2.9190</td>
<td>1.2264</td>
</tr>
<tr>
<td>105</td>
<td>5</td>
<td>0.988</td>
<td>0.9739</td>
<td>0.4088</td>
</tr>
<tr>
<td>100</td>
<td>4</td>
<td>0.995</td>
<td>0.8108</td>
<td>0.3407</td>
</tr>
</tbody>
</table>

\( r = \) correlation coefficient.

**Activation Parameters**

- Activation enthalpy \( \Delta H^o = 77 \text{ kJ/mol} \)
- Free energy of activation \( \Delta G^o = 121 \text{ kJ/mol} \)
- Activation entropy \( \Delta S^o = -118 \text{ J/K mol} \)
Determination of the energy barriers to $N\_N$ bond rotation

in compounds (121), (130a) and (142) by NMR spectroscopy

Compounds (121), (130a), and (142) were found to exhibit variable temperature NMR spectral behaviour. The equations below are valid for uncoupled signals.

$$K_c = \left[ \frac{3.14 \times \Delta v}{\sqrt{2}} \right]$$

$$\Delta G^\circ = \left[ 10.32 + \log T_c \right] \times 19.12 \times T_c$$

With $\Delta G^\circ$ in kJ / mol, where $\Delta v$ = frequency

Separation of coalescing signals (in Hz, measured at a temperature lower than $T_c$), and

$T_c$ = Coalescence temperature (in degrees Kelvin)
For \textit{N}-(Quinazolinonyl)-Amine (121)

\[ \Delta v = 31.38 \text{ Hz}, T_c = 298 \text{K for CH}_3\text{CH}=\text{CH}_3 \]

A 300 MHz proton NMR spectrum at 378K shows a sharp heptet for the CH$_3$CHCH$_3$ signal ($\delta$ 3.81) and at 298K (T$_c$) this signal is maximally broadened. At 235K, two sharp heptets are clearly visible ($\delta$ 3.93 and $\delta$ 3.82) for the two N-N bond rotamers. From these values, a barrier of $\Delta G^\ddagger = 60 \text{ kJ / mol}$ was calculated for rotation around this N-N bond.
For N-(Quinazoliny1)-Imine (130a)

\[ \Delta v = 29.06 \text{ Hz}, T_c = 308K \text{ for } \text{CHOCH}_3 \]

A 300 MHz proton NMR spectrum at 343K shows a sharp quartet for the \text{CHOCH}_3 signal (\delta 4.58). At 308K the signal is maximally broadened and the coalescence temperature has been reached. At 298K, two quartets are seen (\delta 4.48 and \delta 4.63) for the two N-N bond rotamers. From these values, a barrier of \( \Delta G^\# = 65 \text{ kJ / mol} \) was calculated for rotation around this N-N bond.
p-Cyanopyridinium NQ²-Imide (142)

\[
\begin{align*}
\text{O}^2 & \\
\text{I} & \\
\text{N}^+ & \\
\text{C} & \\
\text{N} & \\
\end{align*}
\]

(142)

\[\Delta \nu = 71.09 \text{ Hz}, T_c > 373K \text{ for CH}_2\text{CH}_3\]

\[\Delta \nu = 51.45 \text{ Hz}, T_c = 296K \text{ for pyridin. CH}_2\text{CH}_2\text{CH}_3\]

A 400 MHz proton NMR spectrum at 233K shows sharp signals for both ortho protons of the p-cyanopyridinium ring (δ 7.38 and δ 7.30) and also sharp signals for the Q² methylene protons (δ 2.83 and δ 2.74). At 263K the signals for the ortho protons broaden and coalesce at 296K. From these values, a barrier of \(\Delta G^\# = 62 \text{ kJ / mol}\) was calculated for rotation around the \(\text{N}_p-\text{N}_q\) bond. At 373K the signals for the methylene protons have not completely coalesced giving a value of \(\Delta G^\# > 77 \text{ kJ / mol}\) for \(\text{N}_m-\text{N}_o\) bond rotation.
APPENDIX THREE

Rates of aziridination of styrene and of diethyl fumarate by 
N-(quinazolinonyl)-imide (143)

A solution of triethylammonium imide (143) (0.5 g, 1.65 x 10^-3 mol) prepared in dry dichloromethane (10 ml) in the usual way (procedure G) was cooled to -40 °C with different concentrations of alkene. The solution was divided into two equal parts: 3 mol equiv. of alkene was added to one part, and 6 mol equiv. of alkene added to the other. Portions from each solution were taken and quenched with hydrazine (0.2 ml) at intervals over 30 min. The rate of appearance of aziridine with respect to time was then measured by proton NMR spectroscopy. This involved measuring the integrals of the signals for the aziridine relative to those of 2-isopropylquinazolinone (104).

![Diagram](image)

From the dependence of the rate constant of the reaction on the alkene concentration it is possible to determine whether the aziridine is the product of a direct exchange between the imide and styrene, or one mediated by a pre-equilibrium step, e.g. by reversible formation of an $N$-nitrene.
(1) A direct exchange

\[ k_1 \]

i.e. \[ A + B \rightarrow C + D \]  

(a)

From (a)

\[ \frac{d[C]}{dt} = k_1 [A][B] \text{ second order} \]  

(b)

Hence, if \( k_1 \) (i.e. \( k \) observed) above changes with increase or decrease in the concentration of \( [B] \) then a second order direct exchange is occurring as shown in (a).

(2) An exchange mediated by a pre-equilibrium step, e.g. reversible formation of an \( N \)-nitrene

\[ Q^1 \]
\[ \frac{k_1}{k_1} \]
\[ \text{N}_\text{Et}_3 \]

(A) \hspace{1cm} (E) \hspace{1cm} (D)

\[ Q^1 \]
\[ \text{N} \]

(E) \hspace{1cm} (B) \hspace{1cm} (C)

\[ k_1 \]

\[ [E] + [B] \rightarrow [C] \]  

(c)
From (c) \[ \frac{d[E]}{dt} = k_1 [A] - k_{-1} [E] [D] - k_2 [E] [B] \] (d)

assuming \( \frac{d[E]}{dt} = 0 \), (the steady state approximation) then:

\[ [E] = \frac{k_1 [A]}{k_{-1} [D] + k_1 [B]} \] (e)

The rate of formation of [C] is given by:

\[ \frac{d[C]}{dt} = k_1 [E] [B] \] (f)

Substituting (e) into (f) gives:

\[ \frac{d[C]}{dt} = k_1 \left( \frac{k_1 [A]}{k_{-1} [D] + k_1 [B]} \right) [B] \] (g)

Initially, [C] and [D] are small and (g) simplifies to:

\[ \frac{d[C]}{dt} = k_1 [A] \] first order

Hence, if \( k_1 (k_{obs}) \) remains constant with varying concentration of [B] then the possibility of reaction of the imide with an alkene via a pre-equilibrium, e.g. N-nitrene formation cannot be excluded.

(i) Using 3 mol equiv. of styrene

<table>
<thead>
<tr>
<th>Time (min.)</th>
<th>I (%)</th>
<th>ln (I)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>61.90</td>
<td>4.126</td>
</tr>
<tr>
<td>7</td>
<td>63.37</td>
<td>4.149</td>
</tr>
<tr>
<td>14</td>
<td>65.87</td>
<td>4.188</td>
</tr>
<tr>
<td>19</td>
<td>67.43</td>
<td>4.211</td>
</tr>
<tr>
<td>24</td>
<td>69.79</td>
<td>4.246</td>
</tr>
</tbody>
</table>

Where I represents the % of aziridine relative to 2-isopropylquinazolinone (104). A plot of time against ln (I) gave an initial first order rate constant of \( k = 9.4 \times 10^{-5} \text{ s}^{-1} \).
(ii) Using 6 mol equiv. of styrene

<table>
<thead>
<tr>
<th>Time (min.)</th>
<th>I (%)</th>
<th>ln (I)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>68.25</td>
<td>4.223</td>
</tr>
<tr>
<td>7</td>
<td>70.41</td>
<td>4.254</td>
</tr>
<tr>
<td>14</td>
<td>71.91</td>
<td>4.275</td>
</tr>
<tr>
<td>19</td>
<td>76.19</td>
<td>4.333</td>
</tr>
<tr>
<td>24</td>
<td>78.59</td>
<td>4.364</td>
</tr>
</tbody>
</table>

A plot of time against ln (I) gave an initial first order rate constant of $k = 1.1 \times 10^{-4} \text{ s}^{-1}$.

(iii) Using 3 mol equiv. of diethyl fumarate

<table>
<thead>
<tr>
<th>Time (min.)</th>
<th>I (%)</th>
<th>ln (I)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>47.37</td>
<td>3.858</td>
</tr>
<tr>
<td>7</td>
<td>49.75</td>
<td>3.907</td>
</tr>
<tr>
<td>18</td>
<td>54.55</td>
<td>3.999</td>
</tr>
<tr>
<td>30</td>
<td>58.51</td>
<td>4.069</td>
</tr>
</tbody>
</table>

A plot of time against ln (I) gave an initial first order rate constant of $k = 1.2 \times 10^{-4} \text{ s}^{-1}$.

(iv) Using 6 mol equiv. of diethyl fumarate

<table>
<thead>
<tr>
<th>Time (min.)</th>
<th>I (%)</th>
<th>ln (I)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>58.68</td>
<td>4.072</td>
</tr>
<tr>
<td>10</td>
<td>62.96</td>
<td>4.143</td>
</tr>
<tr>
<td>18</td>
<td>65.64</td>
<td>4.184</td>
</tr>
<tr>
<td>24</td>
<td>67.85</td>
<td>4.217</td>
</tr>
</tbody>
</table>

A plot of time against ln (I) gave an initial first order rate constant of $k = 1.1 \times 10^{-4} \text{ s}^{-1}$.
## Evaluation

<table>
<thead>
<tr>
<th>Experiment</th>
<th>no. of points</th>
<th>( r )</th>
<th>( k / 10^{-4} \text{ s}^{-1} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>(i)</td>
<td>5</td>
<td>0.998</td>
<td>0.94</td>
</tr>
<tr>
<td>(ii)</td>
<td>5</td>
<td>0.983</td>
<td>1.10</td>
</tr>
<tr>
<td>(iii)</td>
<td>4</td>
<td>0.992</td>
<td>1.20</td>
</tr>
<tr>
<td>(iv)</td>
<td>4</td>
<td>0.996</td>
<td>1.10</td>
</tr>
</tbody>
</table>

\( r \) = correlation coefficient.

From the initial slopes of the plots in (i) and (ii), and in (iii) and (iv), the rate constants observed were approximately the same and this indicates that the process for formation of the aziridine from either styrene or diethyl fumarate using triethylammonium N-Q1-imide cannot proceed via the direct exchange mechanism (1) but that a mechanism involving an N-nitrene is not excluded.


84) Sabri Ulukanli, unpublished results, Leicester University.


