

ASPECTS OF SUBSTITUTED HYDRAZINE
CHEMISTRY: THE N-N BOND AS A CHIRAL AXIS
IN 3-ACYLAMINOQUINAZOLIN-4(3H)-ONES

A thesis submitted for the degree of

Doctor of Philosophy

by

Paul John Edwards

in the

Faculty of Science

of the

Department of Chemistry

at the

University of Leicester



October 1992

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STATEMENT.

The accompanying thesis submitted for the degree of Doctor of Philosophy entitled "Aspects of Substituted Hydrazine Chemistry: the N-N Bond as a Chiral Axis in 3-Acylaminoquinazolin-4(3H)-ones" is based on work conducted by the author in the Department of Chemistry at the University of Leicester between the period October 1989 and September 1992.

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: Paul J. Edwards Date: 11th January 1993

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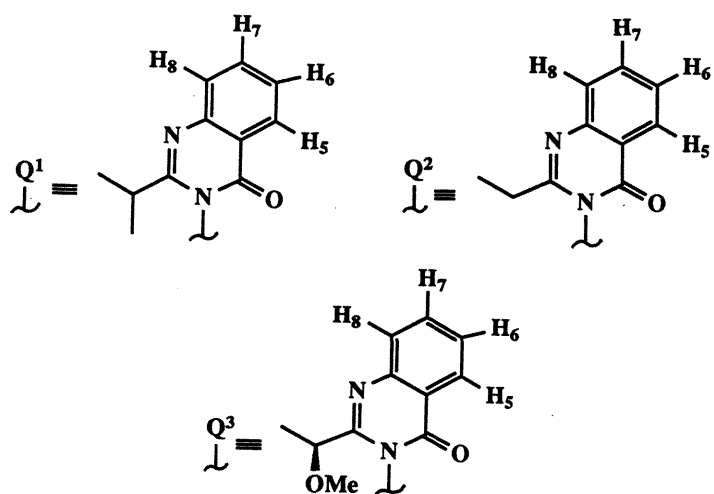
I would like firstly to thank Dr. R. S. Atkinson for his excellent supervision and guidance throughout my postgraduate studies. Also I would like to thank Dr G. A. Thomson for his help and I.C.I specialties for my CASE Award, Dr. J. Fawcett for recording the X-ray structures and Mick Lee for his technical assistance.

Also I would like to thank those who have made my stay in Leicester such a pleasurable one, namely Dave Dawkins, Mike Coogan, John Williams, Emma Barker, Paul Williams, Dave Justice, Keri Paul, Dave Baker, Paul Evans, Sab, Richard Weaver and Ramesh Menon.

ABBREVIATIONS.

Ac	- acetyl
Ar	- aryl
^t Bu	- tert-butyl
Decomp.	- decomposed
DMF	- <u>N,N</u> -dimethylformamide
DMSO	- dimethyl sulfoxide
Et	- ethyl
Ether	- diethyl ether
Equiv.	- equivalent
hr.	- hour
Het	- heterocycle
LTA	- lead tetra-acetate
mCPBA	- meta-chloroperbenzoic acid
Me	- methyl
min.	- minute
m.p.	- melting point
Ph	- phenyl
Phthal	- phthalimide
Pyrid.≡ Py	- pyridine
Q ¹ , Q ² , Q ³	- see below
TFA	- trifluoroacetic acid
THF	- tetrahydrofuran

Throughout this thesis



ASPECTS OF SUBSTITUTED HYDRAZINE
CHEMISTRY: THE N-N BOND AS A CHIRAL AXIS
IN 3-ACYLAMINOQUINAZOLIN-4(3H)-ONES
PAUL JOHN EDWARDS

ABSTRACT

The work contained in this thesis examines the aziridination of a number of β -diketones via their enol forms using oxidative addition of N-aminoquinazolin-4(3H)-ones, to give N-(quinazolinone-N'-yl)-N-acyl- α -aminoketones which result from C-C cleavage of the intermediate aziridine ring. Products which have the N-N bond diacylated are primed for reductive cleavage. One example has been studied in which reduction was successfully accomplished using aluminium amalgam to afford an N-acylated amino acid ester in good yield. The N-acetoxyaminoquinazolinone has been shown to function as an NH_2^+ equivalent.

Aziridination of 3-methylpentan-2,4-dione using oxidation of N-aminoquinazolinone in the presence of trifluoroacetic acid (TFA) afforded the aziridine C-N cleavage product.

The effects of retarded N-N bond rotation in many of the products from these aziridinations were observed in their n.m.r. spectra: the barriers involved were quantified in some cases but were too large to be measured in others.

The good leaving group ability of the quinazolinone ring was revealed in attempted alkylation reactions under basic conditions α - to the exocyclic nitrogen with the N-(quinazolinone-N'-yl)-N-acyl- α -aminoketones above. Synthesis of N-(2-isopropylquinazolin-4(3H)-one-3-yl)-6-ethoxycarbonyl-2-pyridone was accomplished with the expectation that elimination of the quinazolinone ring could be stereoelectronically inhibited. However, attempted methylation of this compound also resulted in elimination of the quinazolinone ring.

In their reactions with stabilised anions, the N-acetoxyaminoquinazolinones function as synthetic equivalents of the NH_2^+ synthon.

Oxidation of the N-aminoquinazolinones with lead tetraacetate (LTA) in the presence of pyridine and its derivatives gave N-(quinazolin-4(3H)-one-3-yl)pyridinium ylides. These pyridinium ylides, on heating, functioned as aziridinating agents e.g. for styrene and diethyl fumarate. From the n.m.r. spectra of one of these pyridinium ylides at various temperatures, the barrier to rotation around both N-N bonds could be calculated. An investigation of the possible mechanisms of aziridination of alkenes using these pyridinium ylides was undertaken.

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CHAPTER ONE-INTRODUCTION

1.1 INTRODUCTION

The concept of a chiral centre in a molecule and its association with optical activity was recognised by Pasteur, Van't Hoff and Le Bel as early as the nineteenth century. Most organic molecules which are resolvable into enantiomers contain one or more chiral centres which are usually sp^3 -hybridised carbon atoms substituted with four different atoms or groups. Far fewer organic molecules are known in which the chiral element is a chiral axis. In such molecules, chirality arises from the location of its atoms in two mutually perpendicular planes as in allenes (vide infra) but chiral centres are not present.

1.2. MOLECULES WITH A CHIRAL AXIS

Perhaps the best known examples of molecules which contain a chiral axis are allenes¹. In these molecules it is the electronic constraints within the molecule which give rise to optical activity. In allenes, the central carbon is sp - hybridised; the two p - orbitals are perpendicular to each other and each overlaps with a p - orbital of each terminal carbon atom, forcing the remaining bonds on each of these carbons into mutually perpendicular planes (Figure 1).

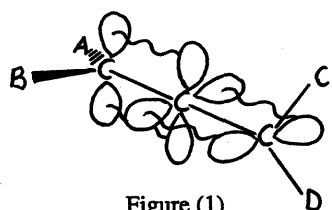
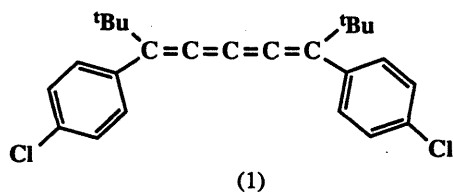
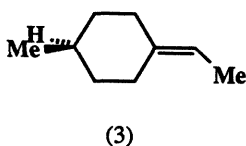
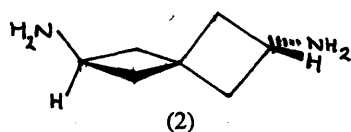


Figure (1)

Cumulenes may also contain a chiral axis. When three or more odd numbers of cumulated double bonds are present, orbital overlap causes the four groups on the terminal carbon atoms to occupy one plane and cis/trans isomerism is possible. When four or any greater even numbers of cumulated double bonds are present, the situation is analogous to that in allenes and so a chiral axis may be present and optical activity possible. For example, cumulene (1) has been resolved².

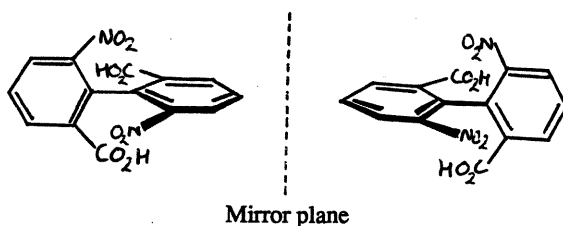


Spiranes, for example (2), are among other types of systems that can contain perpendicular disymmetric planes and are similarly chiral if both sides are disymmetric, as are compounds with exocyclic double bonds (3), if appropriately substituted.



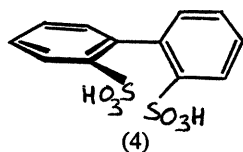
Also known to contain chiral axes are 1,1'-biphenyl and 1,1'-binaphthyl systems³. The chiral element in these molecules arises from steric factors which are present.

Biphenyl systems containing large groups in each of the four ortho positions cannot freely rotate around the central C-C bond because of steric hindrance which is present (Scheme 1) when both rings become coplanar.



SCHEME 1

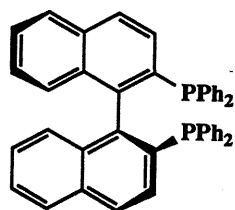
There is no plane or axis of symmetry in this molecule and the molecule is chiral. Isomers that can be separated only because rotation about single bonds is prevented or greatly slowed are called atropisomers⁴. The chiral axis in these compounds is a stereo-stable chiral element. It is, however, not always necessary for four bulky ortho substituents to be present. Biphenyls with three or even two groups, if large enough, can have hindered rotation and, if suitably substituted, can be resolved. An example of this is biphenyl-2,2'-bissulfonic acid (4)⁵.



However, the substituents may not always be large enough to prevent rotation completely, merely slow it. In

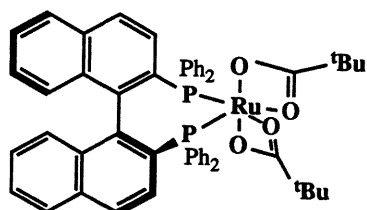
this case the biphenyls are said to contain a stereo-labile chiral axis. It may be possible to prepare optically active samples of such compounds but racemisation takes place on standing. The sulfonic acid (4) loses its optical activity with a half life of 9.4 min in ethanol at 25°C.

Binaphthyl derivatives, in enantiopure form have been extensively used as chiral auxiliaries. For example (S)-binap (5), coordinates to metal atoms and the reactions which the metal atom catalyses are rendered enantioselective by the presence of the chiral ligand.



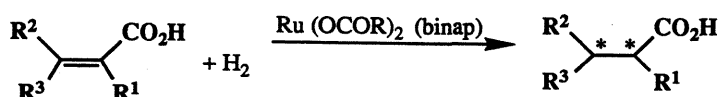
(5)

Binaphthyl systems have been widely used in enantioselective syntheses over the past decade with pioneering work by Noyori³. One example of BINAP's reactivity is the use of the BINAP-Ru dicarboxylate complexes of type (6).



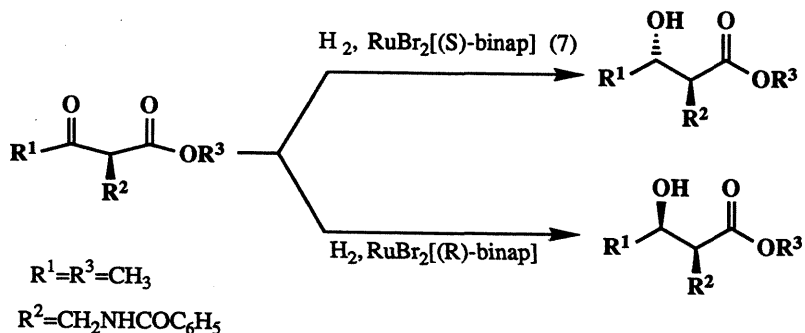
(s)-(6)

These systems hydrogenate prochiral α,β -or β,γ -unsaturated carboxylic acids to give optically active saturated carboxylic acids^{3a} (Scheme 2).



SCHEME 2

Chelate complexes in which carboxylate and alkene double bonds are coordinated to the ruthenium metal centre are considered to be reactive intermediates and enantiomeric excesses of 85-97% are routinely obtained. Ketones can also be reduced with up to 100% enantiomeric excess using halogen-containing ruthenium complexes, for example $\text{RuBr}_2[(\text{S})\text{-binap}]$ (7). These halogen-containing complexes are superior to the dicarboxylate complexes (6) mentioned above. Examples of highly enantio- and diastereoselective reductions of ketones are shown in Scheme 3.

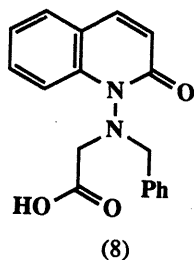


SCHEME 3

It is to be noted that different, virtually

enantio pure, diastereoisomers can be obtained upon hydrogenation depending on the "handedness" of the BINAP complex used. Thus, although in principle double asymmetric induction is possible here, in practice induction from the chiral catalyst is dominant.

An N-N chiral axis has been shown to exist in the N-benzyl-N-(1,2-dihydro-2-oxo-1-quinolyl)glycine (8) by B. Judkins in this department⁶.



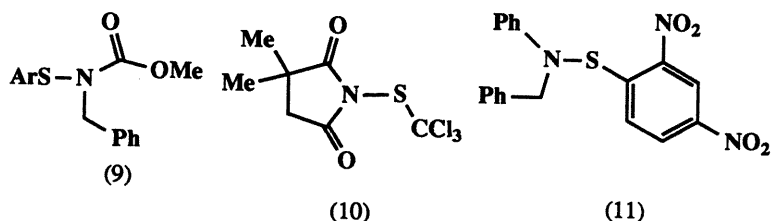
This compound (8) was resolved via its quinine salt and a barrier to rotation about the chiral N-N bond, $\Delta G^\ddagger = 26 \pm 0.5$ K cal mol⁻¹ was calculated from its rate of racemisation in boiling ethanol. The effects of the stereostable N-N chiral axis, which is the only chiral element in this molecule, are manifest in its proton n.m.r. spectrum: each methylene group shows an AB system for its diastereotopic protons.

Many other molecules containing single bonds about which rotation is sufficiently hindered could, in principle, be resolved. In hydroxylamines of the type (RO-NR¹R²), selenenamides (RSe-NR¹R²) and sulfenamides (RS-NR¹R²) the disposition of substituents on the heteroatoms in each

case means that the O-N, Se-N, or S-N bonds constitute chiral axes. The stereostructures of these compounds have been discussed by Raban⁷. Many of these compounds possess stereo-labile chiral axes which are not configurationally stable at room temperature.

Chiral Elements in Substituted Sulfenamides

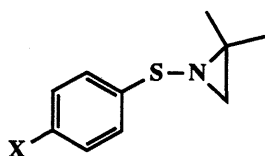
The chirality arising in substituted sulfenamides can be in principle a consequence of either slow rotation about the N-S bond or slow inversion of the pyramidal nitrogen. It is possible, in certain suitably substituted sulfenamides, to assign unambiguously which process is giving rise to chirality in the molecule. For example, when the sulfenamide nitrogen atom bears an acyl or aryl substituent, see (9), (10), and (11), chirality is usually the result of the barrier to rotation around the N-S bond. This assignment can be made because the inversion barrier at the nitrogen atom is known to be removed or lowered substantially due to conjugation, and so the chirality must be due to retarded N-S bond rotation.



Ar= 2,4-dinitrophenyl

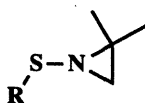
Ar= 3-nitrophenyl

Conversely, when the nitrogen atom is incorporated into an aziridine ring, for example (12) and (13), the rate of nitrogen inversion is lowered⁸⁻¹⁰. From the proton n.m.r. spectra of compounds (12) and (13) the coalescence of the signals from ring protons and/or geminal methyl groups can reasonably be supposed to be the result of barriers associated with inversion at the nitrogen chiral centres, *vide infra*.



X = OCH₃, CH₃, H, Cl, Br, NO₂

(12)

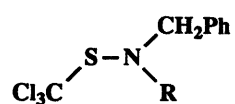


R = (a) CCl₃, (b) CF₃, (c) CH₃, (d) ^tBu

(13)

Steric Effects

With sulfenamides, as the size of the ligands at nitrogen increases so too does the barrier to S-N bond rotation, (see (14a-14d), Table 1). This corresponds to a steric destabilisation of the planar transition state which, consequently, raises the energy of the latter. However, the alkylsulfenylaziridines (13c) and (13d) show the opposite trend, the barrier decreasing as the steric bulk of the group on nitrogen increases: the bulkier groups increase the ground state energy relative to the (planar) transition state. This trend is consistent with an inversion barrier at the chiral nitrogen in each case.



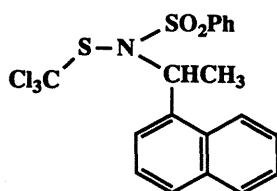
R=(a)Me, (b)Et, (c) ⁱPr,
(d)1-adamantyl

(14)

Compound	R	ΔG^\ddagger Kcalmol ⁻¹	Solvent	Reference
13c	Me	13.3	CDCl ₃	10
13d	^t Bu	12.2	CDCl ₃	10
14a	Me	14.4	CDCl ₃	11
14b	Et	15.6	CDCl ₃	11
14c	ⁱ Pr	16.0	CDCl ₃	11
14d	1-adamantyl	16.9	CDCl ₃	11

TABLE 1: Steric effects on inversion and rotation barriers in chiral sulfenamides.

A further case where the unambiguous assignment can be made involves (15), the crystal structure of which has been determined by X-ray diffraction¹¹.

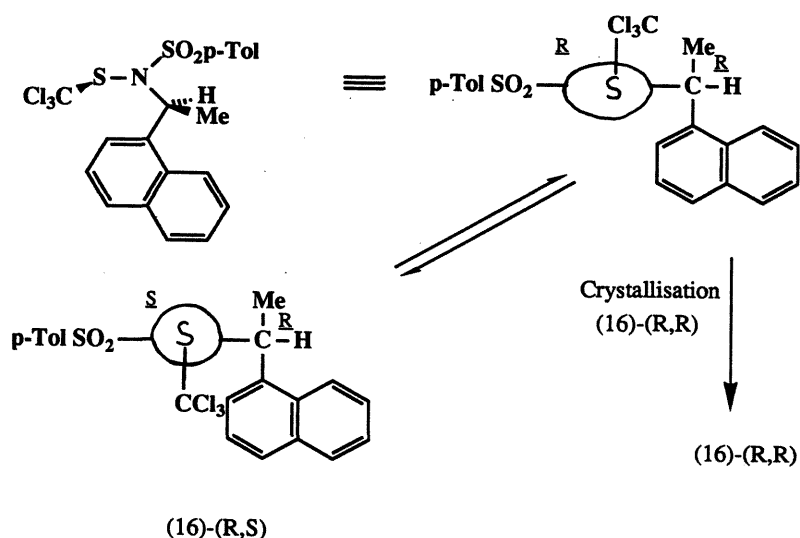


(15)

The geometry at nitrogen in this compound did not differ

greatly from planarity. The sum of the bond angles equalled 356.5° compared with the values of 328° and 360° which correspond to sp^3 and sp^2 hybridisation, respectively. Since this geometry at nitrogen is so close to planarity in the ground state, we can be sure that the substantial barrier measured by n.m.r. spectroscopy for the dynamic process taking place in this molecule, ($\Delta G^\ddagger = 18.3 \text{ K cal mol}^{-1}$)¹² cannot be a barrier to nitrogen inversion.

Raban has isolated a single sulfenamide diastereoisomer⁷ (16) which, in solution, exhibits the phenomenon of diastereoisomeric (asymmetric) transformation. Here the two stereoisomers are in mobile equilibrium but crystallisation of this mixture leads to a solid composed of a single diastereoisomer.



SCHEME 4

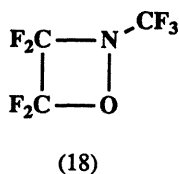
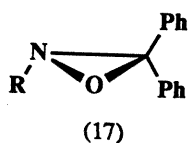
In Scheme 4, the asymmetric carbon atom of (16) has an absolute R- configuration and the sulfenamide exists in solution as a mixture of diastereoisomers (R,R) and (R,S), which differ in configuration at the sulfenamide chiral axis. Upon crystallisation, a sharp melting solid is obtained which has been shown by X-ray crystallography to have the (R,R)- configuration. However, the barrier to S-N bond rotation is such that this compound is stereo-labile in solution at room temperature. Crystallisation of the more abundant diastereoisomer of sulfenamide (16) perturbs the equilibrium in Scheme 4 and re-establishes the concentration of (16)-(R,R) which allows further crystallisation to occur. This continues until more or less all of the sulfenamide has crystallised as a single diastereoisomer. The barrier to S-N bond rotation for (16) in solution has been calculated at $\Delta G^\ddagger = 18.3 \text{ K cal mol}^{-1}$.

Chiral Elements in Substituted Hydroxylamines

Hydroxylamines represent a class of compounds in which the chiral element can be assigned as an N-O chiral axis or an N-chiral centre analogous to the case of sulfenamides. However, the barriers to N-O bond rotation in hydroxylamines are smaller than the corresponding barriers to N-S bond rotation in sulfenamides. In some hydroxylamines the nature of the molecule allows unambiguous assignment of the barrier, which may be quantified by n.m.r. spectroscopy.

Incorporation of the oxygen and nitrogen atoms into

small (3 or 4-membered) rings increases the barrier to N-inversion with a concomitant fixing of the C-O-N/O-N-C dihedral angle at or near the geometry of the transition state for N-O rotation.



In these cases, for example (17)¹³, (18)¹⁴, the barrier must be ascribed to inversion at nitrogen. The increase in the inversion barrier is great enough in oxaziridines to permit isolation of optical isomers which are stereostable at room temperature¹³.

1.3 N-N ROTATIONAL BARRIERS IN SUBSTITUTED HYDRAZINES

Rotation barriers about N-N bonds are increased by having both nitrogens sp^2 hybridised, Figure 2.

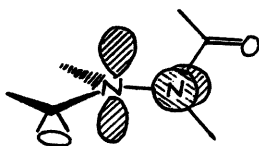
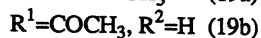
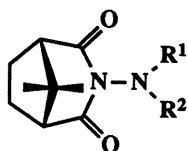


Figure (2)

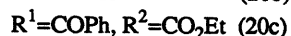
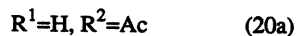
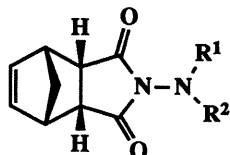
Hydrazine nitrogens are planarised by incorporating them into amides and rotation around the N-N bond is retarded because the lone pairs on the nitrogen have to

become eclipsed in order for rotation to occur. It is well known that the barrier to rotation around the N-N bond is greatly increased when both nitrogens are acylated¹⁵.

Verma¹⁶⁻²⁰ has prepared a number of mono, di, tri and tetra-acyl substituted hydrazine derivatives in which the effects of restricted rotation around the N-N bond have been observed by n.m.r. spectroscopy. Verma has shown in a number of N'-derivatives of N-amino-camphorimides (19) that retarded rotation around the N-N' bond is responsible for the temperature-dependent effects seen in the proton n.m.r. spectra of these compounds.



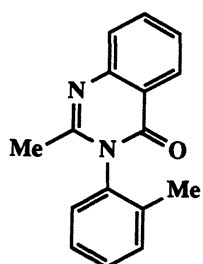
Verma has investigated a number of tetra-acyl substituted hydrazine derivatives, for example N-amino[2.2.1]bicyclo-5-heptene-2,3-endo-dicarboxylate (20b,c,d,e).



A barrier to rotation around the N-N bond $\Delta G^\ddagger = 20.3$ K cal mol⁻¹ for (20c) has been calculated from coalescence of ester methyl protons. However, (20b) and (20d) did not show coalescence of the two acetyl methyl singlets up to 110°C and therefore a minimum value for the free energy of activation would be of the order of 21 K cal mol⁻¹ for N-N bond rotation. Tri-acyl systems, for example (20e), also show temperature dependent proton n.m.r. spectra. A barrier to N-N bond rotation for (20e) has been calculated at around 20 K cal mol⁻¹. However, (20e) also exhibits amide (N-CO) bond rotation which has a barrier to rotation of 18.64 K cal mol⁻¹. It can be seen that in this molecule there are two identifiable barriers to rotation, one of which can be ascribed to N-N bond rotation and the other to amide (N-CO) rotation.

According to Verma, when the exocyclic nitrogen is mono-acylated, as with (20a), the temperature dependent effects one sees in its proton n.m.r. spectra are due, not to hindered N-N' bond rotation (as is believed for (19a)) but to hindered N-CO amide rotation: N-N' bond rotation in this compound (20b) is assumed to be fast. The barrier to amide rotation in this compound was calculated to be 17.7 K cal mol⁻¹.

Roussel *et al.*²¹ have estimated a barrier to N-C rotation of 28.14 K cal mol⁻¹ for the quinazolinone derivative (21).



(21)

1.4 N-N BOND CLEAVAGE IN N,N'-DI-ACETYLATED HYDRAZINES

When both nitrogens of a hydrazine are acylated (as in Figure 2), and hence both are sp^2 hybridised, the N-N bond is more easily cleaved reductively, as shown in work by Mellor and Smith²². These authors also showed that sulphonylation of nitrogen has a similar effect to that of acylation in facilitating reductive cleavage of N-N bonds. A variety of cyclic and acyclic hydrazines were examined, typified by those in Scheme 5, and the N-N bond could be reduced with aluminium amalgam, sodium in liquid ammonia, sodium in ethanol, zinc in glacial acetic acid or Raney nickel.



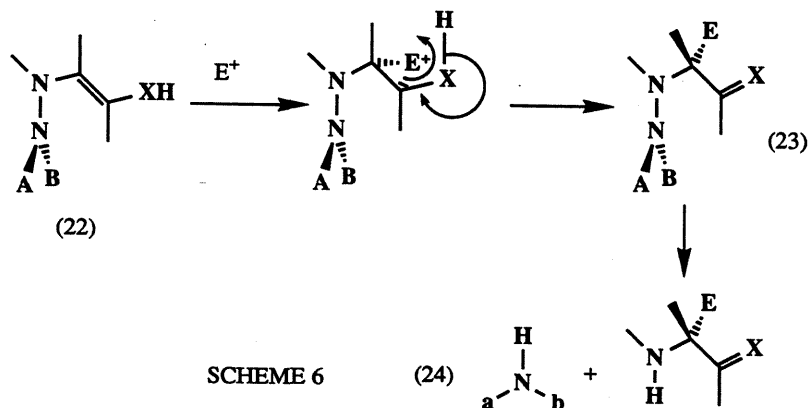
SCHEME 5

The acetylation can be seen to 'prime' the N-N bond for

reductive cleavage. Fortuitously, therefore, the factors which retard rotation about the N-N bond also make it more easily cleaved reductively.

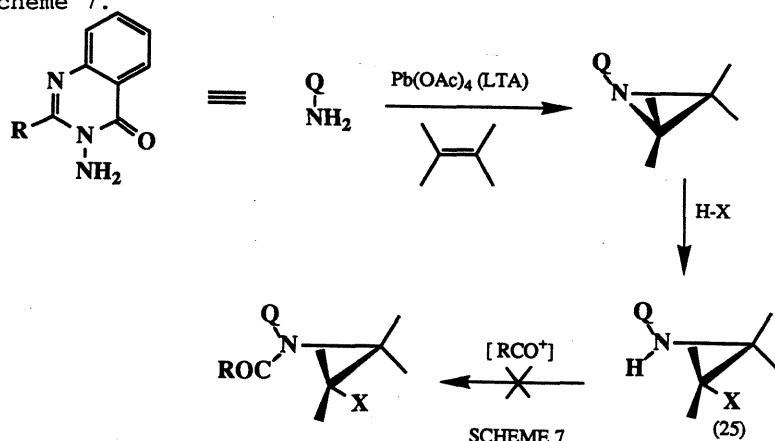
1.5 ASYMMETRIC INDUCTION MEDIATED BY AN N-N CHIRAL AXIS

The possibility of using an N-N bond as a chiral element to bring about asymmetric induction in addition to a prochiral double bond (Scheme 6) is attractive for two reasons. Firstly the prochiral double bond can be located adjacent to the chiral axis as in (22) thus maximising the differential effects of a and b on the accessibility of its two diastereofaces. Secondly, starting with (22) in enantiopure form, cleavage of the N-N bond in a single diastereoisomer of the product (23) should deliver a functionalised amine (24) in enantiopure form. Contrast this with chiral 1,1'-binaphthyl systems which are seldom used as sources of chiral naphthalenes not least because of the difficulty in selectively cleaving the 1,1' bond.



Diacetylated Hydrazines:

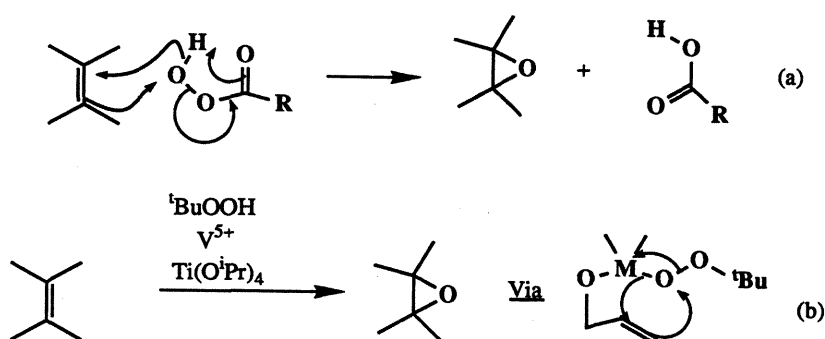
In principle, *N,N'*-diacyl-substituted hydrazines are available by ring-opening of *N*-(quinazolinone-*N*-yl)-substituted aziridines followed by acetylation, as shown in Scheme 7.



In practice however, this route fails because of the difficulty in acetylation of the secondary *N*-(quinazolinone-*N*-yl)-substituted amines (25), (see later).

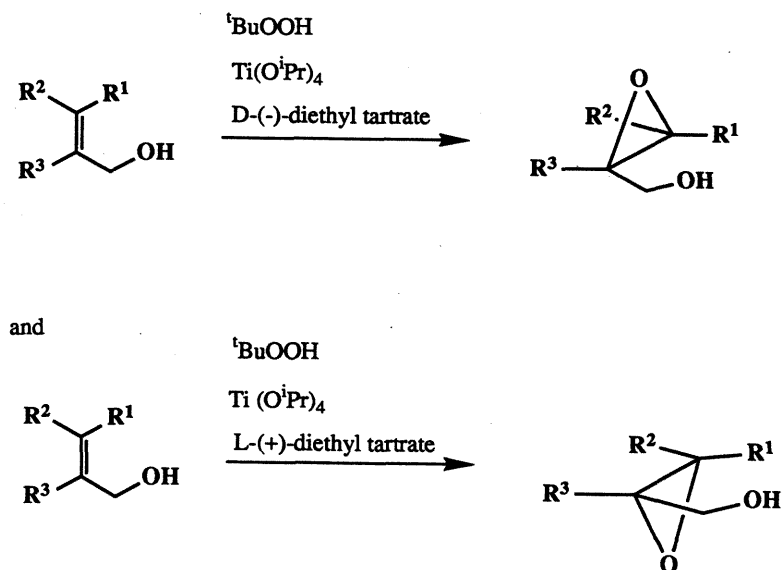
1.6 A COMPARISON BETWEEN EPOXIDATION AND AZIRIDINATION

Both epoxides and aziridines are useful as synthetic relay intermediates. Synthetic methods for the preparation of epoxides are well known^{23,24}. In particular, treatment of alkenes with peracids (method a)²³ or with *t*-butylperoxide-metal catalysts (method b)²⁴ yields epoxides, Scheme 8.



SCHEME 8

High enantioselectivity can be accomplished in, for example, the Sharpless epoxidation²⁵, Scheme 9.



SCHEME 9

Yields of 70-90% are obtainable with an enantiomeric excess of greater than 90% being routine in these

reactions.

Methods for aziridination of alkenes are fewer and less well developed²⁶. For example, there are no methods for aziridination analogous to those above for epoxidation using peracids or hydroperoxides/metal catalysts and few methods for direct conversion of alkenes into aziridines are in fact known²⁶.

This single fact has limited the growth and use of aziridine chemistry in spite of the fact that, in principle, aziridines are potentially valuable relay intermediates just like epoxides.

Direct conversion of alkenes into aziridines can be accomplished in one step using nitrenes but nitrene reactions are usually characterised by mixtures of products resulting from an absence of stereo- regio- and chemoselectivity. Nitrenes are generally unsuitable therefore as reagents for synthetically useful aziridination of alkenes.

However, over twenty years ago Rees and co-workers²⁷ discovered a method for generating what were presumed to be N-nitrenes whose behaviour was totally atypical by comparison with that normally associated with these intermediates. These nitrenes were generated in situ by oxidation of N-aminosubstituted heterocycles, typified by those shown in Figure 3. All these N-aminoheterocyclic compounds, when oxidised with lead tetra-acetate in the presence of alkenes, yielded aziridines²⁷⁻²⁹. They include N-aminophthalimide (26), N-aminobenzoxazolinone (27) N-

aminoquinazolinone (28), N-aminoquinolinone (29), N-aminopyrrole (30), N-aminotriazole (31), N-aminotriazolinone (32) and N-aminobenzimidazole (33).

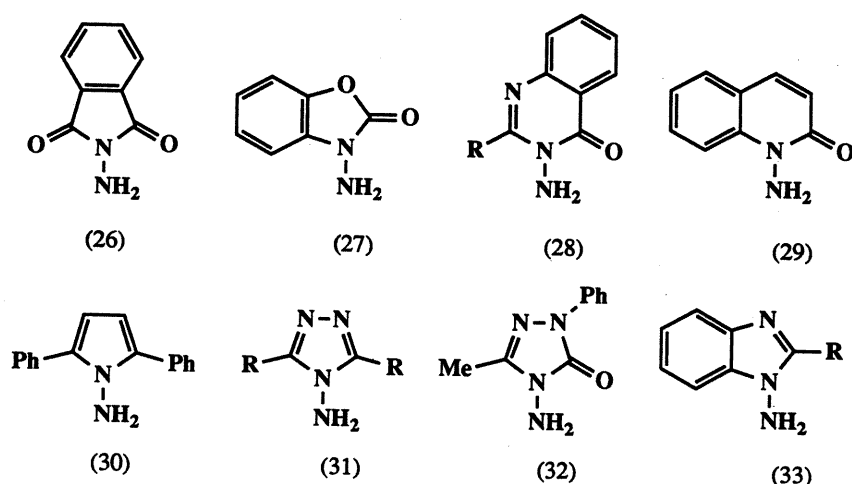


FIGURE 3

Examination of the heterocycles in Figure 3 reveals that they all contain features that will reduce the availability of the lone pair on the substituted trivalent nitrogen (N-1) for donation to, and stabilisation of, the adjacent univalent nitrogen of a nitrene. Thus either one or both of the N-1 substituents is a carbonyl or imino function or else the N-1 lone pair of electrons is part of an aromatic ring. Similar N-aminoheterocyclic compounds which, however, lack the features referred to above react with LTA and eliminate nitrogen intramolecularly. Although, therefore, the stabilising effect of these features on the putative N-nitrenes was hard to explain, at least the lesser double bond character of the N-N bond would reduce

the chances of nitrogen elimination.

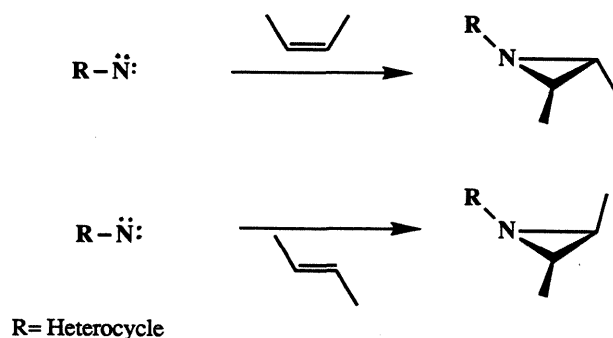
1.7 CHARACTERISTICS OF THE INTERMEDIATES

DERIVED FROM OXIDATIVE ADDITION OF (26)-(33) TO ALKENES

The so-called "nitrene" intermediates generated by oxidation of these N-aminoheterocycles (26)-(33) exhibit the following properties, some of which are atypical for these highly reactive intermediates²⁹.

(1) They react with electron-rich and electron-deficient double bonds to give aziridines often in excellent yields and thus they exhibit an ambiphilic nature; reaction occurs both with methyl acrylate and with styrene, two alkenes of very different electron availability.

(2) They appear to be completely stereoselective in their insertion into alkene π -bonds, even at low concentration of alkene, with retention of the alkene configuration in the product. For example, the insertion into cis-but-2-ene gives the cis-aziridine whereas insertion into trans-but-2-ene gives the trans-aziridine, Scheme 10.



SCHEME 10

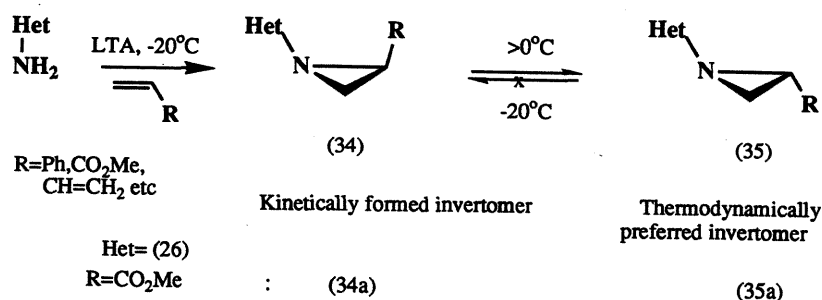
This suggested that the nitrenes were reacting via a singlet ground state.

(3) There are no products from competitive insertion into sigma (σ)-bonds in their reactions with alkenes.

(4) A single (aziridine ring) nitrogen pyramid is obtained on addition to monosubstituted alkenes which is often not the thermodynamically preferred nitrogen invertomer.

1.8 SYN-SELECTIVITY EFFECTS IN OXIDATIVE ADDITION OF N-AMINOHETEROCYCLES TO ALKENES

Oxidative addition of N-aminoheterocycles (26), (27), (28) and (33) to alkenes bearing a single π -electron containing substituent in conjugation with the double bond leads firstly to the kinetically-formed invertomer (Scheme 11). Those heterocycles shown in Figure 3 which have been studied show this same syn-selectivity in their oxidative addition to substituted alkenes.



SCHEME 11

The cis-aziridine (34) in many cases undergoes inversion at nitrogen at a measurable rate to the thermodynamically preferred trans-invertomer (35) at a temperature between -20°C and 0°C. For example, when this oxidation is performed using N-aminophthalimide (26) as the N-aminoheterocycle and methyl acrylate as the trap, signals from the cis-aziridine (34a) can be seen in the n.m.r. spectrum in CDCl₃ at -10°C (at this temperature, inversion at the aziridine ring nitrogen is negligible). As the temperature increases to ambient, formation of the trans-aziridine (35a) can be seen from the appearance of signals from this stereoisomer. When ambient temperature is reached, a 1:5 ratio of aziridines (34a):(35a) is seen. If the temperature is then returned to below -20°C, the 1:5 ratio of aziridines (34a):(35a) remains unchanged³⁰. The explanation for this kinetic preference for formation of the syn-invertomer (34a) is that in the transition state there is a favourable donor-acceptor effect indicated in Figure 4 between the ester carbonyl and the phthalimide carbonyl carbon, the planes of the heterocycle and the alkene being approximately parallel. It appears that the α,β -unsaturated ester is required to react via its s-cis conformation (vide infra).

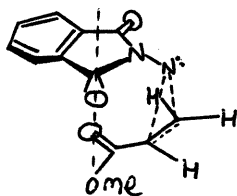
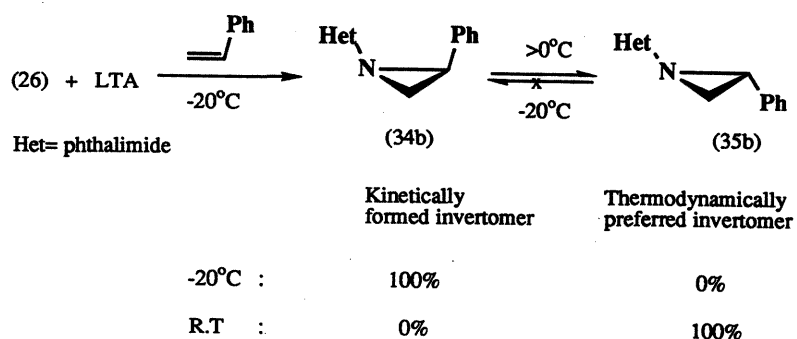


Figure (4)

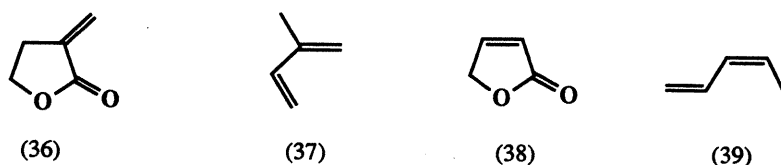
A similar explanation can be applied to aziridination of butadiene and styrene which also show the same syn-selectivity in the kinetically-formed invertomers. This oxidative addition of N-aminophthalimide (26) to styrene at -20°C results in the formation of only the syn-invertomer (34b) which on warming to ambient results in complete conversion to the anti-invertomer (35b) (Scheme 12). Again no inversion to the kinetically formed invertomer is seen on cooling the n.m.r. solution to -20°C . The π -electron containing substituent which acts as the donor in this 'secondary' interaction can also be a ketone carbonyl group



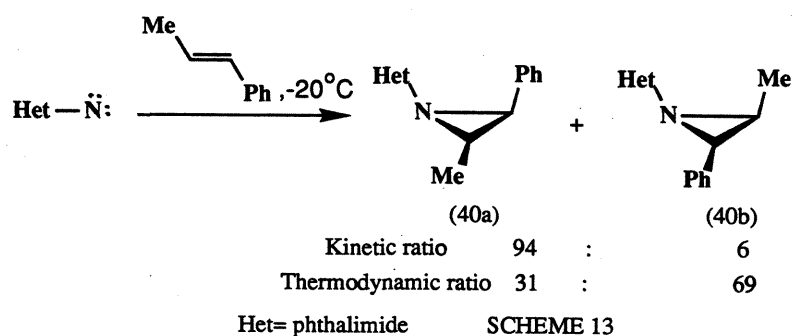
SCHEME 12

Whereas α -methylene- γ -butyrolactone (36) and isoprene (37) are aziridinated efficiently by oxidative addition of N-aminophthalimide (26); their s-trans counterparts, namely butenolide (38) and 4-methylpenta-1,3-diene (39) give no aziridine containing products at all under the same conditions^{31,32}. This result is rationalised by assuming that in the transition state for aziridination (Figure 4), the s-cis conformation of the α,β -unsaturated system is

required.



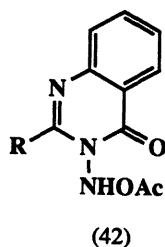
Aziridination of β -methylstyrene under the same conditions (Scheme 13) gave a kinetically-formed invertomer ratio of 94:6 for aziridines (40a) and (40b) respectively³⁰. This implies that the methyl group has a small attractive syn-interaction in the transition state for aziridination which is less than that of the phenyl group but larger than that of a hydrogen.



1.9 IDENTITY OF THE AZIRIDINATING AGENT IN THE OXIDATIVE ADDITION OF N-AMINOQUINAZOLINONES TO ALKENES:NON-INVOLVEMENT OF NITRENES

Following on some observations in these laboratories made by M. Grimshire³³, B. Kelly showed that the

intermediates formed from the lead tetra-acetate oxidation of N-aminoquinazolinones were not the presumed N-nitrenes (41) but N-acetoxyamino derivatives (42)³⁴, which were stable in dichloromethane solution at <-10°C.



N-acetoxyamino-heterocycles analogous to (42) are presumed to be intermediates in lead tetra-acetate (LTA)-mediated aziridinations of most, if not all, of the heterocycles in figure 3, but none examined thus far appears to be as stable as the N-acetoxyaminoquinazolinones (42). It is significant that the only reagents which accomplish oxidative addition of these heterocycles to alkenes are lead tetra-acetate or phenyl iodoso-diacetate.

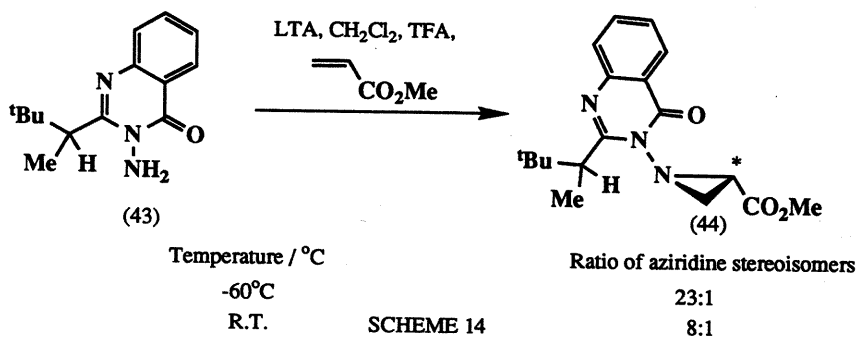
1.10 NITROGEN'S EXTRA VALENCY

One major difference between epoxidation and aziridination is the extra valency of nitrogen which results in an extra-annular substituent on this atom in the product aziridine. Bearing in mind that, as previously discussed, aziridines will, in general, find use as synthetic relay intermediates, to what use can this substituent be put both in the aziridination reaction

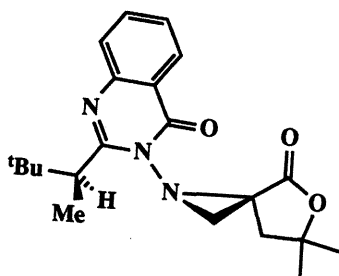
itself and in the chemistry of the aziridine ring?

Asymmetric Induction in Aziridination³⁵

When 3-amino-2-(1,2,2-trimethylpropyl)quinazolin-4(3H)-one (43) is oxidised with lead tetra-acetate in the presence of methyl acrylate and trifluoroacetic acid (TFA) at -60°C , a 23:1 ratio of diastereoisomers of aziridines (44) is obtained. An 8:1 ratio of aziridine diastereoisomers (44) is obtained when the reaction is carried out at room temperature (Scheme 14)³⁵



The relative configuration at the two chiral centres in this aziridine (44) is not known. However, a similar oxidation of (43) in the presence of 5,5-dimethyl-3-methylenebutyrolactone gave a single diastereoisomer whose relative configuration was shown by X-ray crystallography to be that shown in (45).³⁶



(45)

Clearly if this aziridination could be carried out using enantiopure N-aminoquinazolinones, for example, (43) and if cleavage of the N-N bond were possible with or without aziridine ring opening, a synthesis of enantiopure aziridines (or their ring-opened products) would be possible. There are, other than asymmetric induction from a chiral substituent in the heterocycle, other uses to which this heterocycle could be put: it may be used to direct the regioselectivity of aziridine ring-opening or to control the diastereoselectivity of attack on a prochiral aziridine ring substituent.

Effect of Trifluoroacetic Acid Upon the Aziridination of Alkenes Using N-acetoxyminoquinazolinones

The effect of adding trifluoroacetic acid to the solution prior to the aziridination is to produce higher yields of aziridines or aziridine-derived products, and even to bring about aziridination where none previously was found³². For example, alkyl-monosubstituted alkenes show poor reactivity in aziridination using N-

acetoxyaminoquinazolinones and yields of the corresponding aziridines are usually little better than 10% even with a large excess of alkene present. For example *N*-acetoxyaminoquinazolinone (47) reacts with hex-1-ene to give an 11% yield of aziridine. However, performing the reaction in the presence of TFA raises the yield of aziridine to 64%³⁷. TFA can also dramatically affect the diastereoselectivity of the reaction. The reaction shown in scheme 14 produces an 8:1 ratio of aziridine diastereoisomers (44) at room temperature in the presence of TFA. If this reaction is repeated in the absence of TFA, a 1:1.2 ratio of aziridine stereoisomers (44) is formed. TFA is believed to protonate the amide carbonyl oxygen on the quinazolinone ring and this accelerates the departure of the acetoxy group, as shown in Figure 5. The presence of TFA is presumed to accelerate the rate of aziridination to the point where this is much faster than inversion at the exocyclic nitrogen (*vide infra*) and so enhanced stereoselectivity is seen compared to the reaction where TFA is absent.

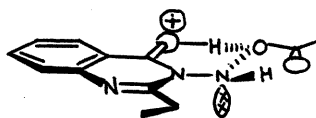
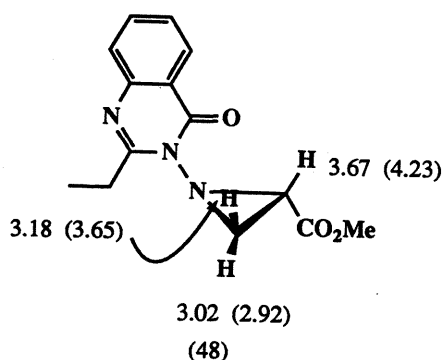


Figure (5)

Support for protonation on the quinazolinone amide carbonyl group by TFA comes from the n.m.r. spectrum of aziridine (48) in deuteriochloroform containing TFA, in

which the deshielding effects observed suggest that protonation on the amide carbonyl oxygen in this molecule is occurring.

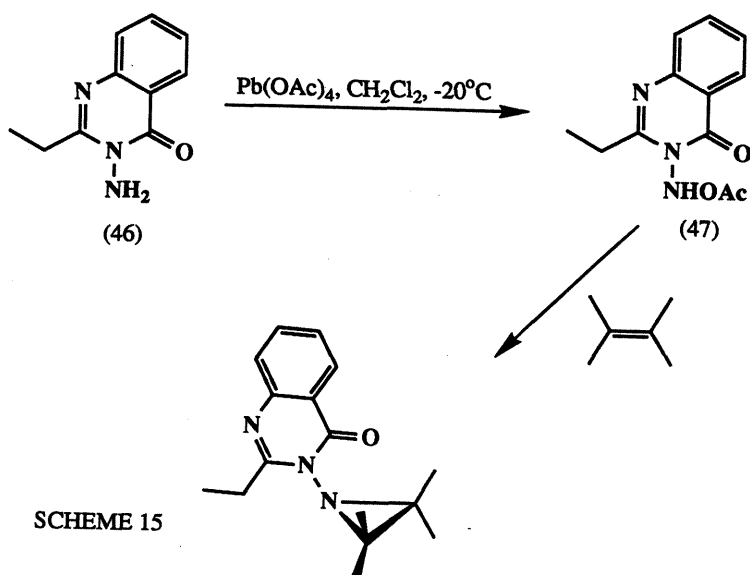


Thus the chemical shifts of the cis-aziridine ring protons shown in the structure (48) are shifted downfield to the positions indicated in brackets on addition of TFA. It is clear that the two aziridine ring hydrogens cis to the quinazolinone ring experience significantly greater deshielding relative to the trans ring proton as a result of the presence of a presumed increased aromatic ring current in the quinazolinone ring.

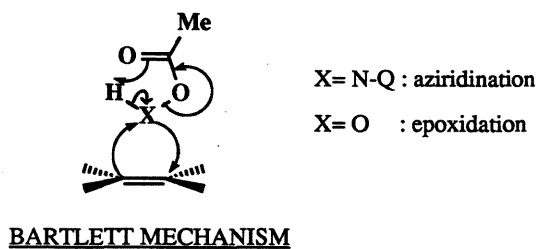
The potential uses of an N-substituent notwithstanding, it is clear that for this aziridination reaction to be of use to the synthetic chemist, ways must be found for eventually sloughing off the N-substituent. As mentioned earlier, the work of Mellor and Smith²² has shown that when the N-N bond is suitably substituted (that is, each is either part of an amide or sulphonamide), cleavage of the N-substituent is facilitated.

1.11 MECHANISM OF AZIRIDINATION

Observations made in this department by M. Grimshire³³ prompted B. Kelly to re-examine the mechanism of the oxidative addition of these N-aminoheterocycles to alkenes using LTA.³⁴ Kelly oxidised 3-amino-2-ethylquinazolin-4(3H)-one (46) in CDCl₃ with LTA at -20°C and washed the solution thus obtained with saturated sodium bicarbonate solution at this low temperature without allowing any intermediate warming of the solution. A 300MHz proton n.m.r. at -20°C of this solution showed the formation of a product in approximately 95% yield which contained only a methyl (acetoxyl) singlet and an NH singlet besides the quinazolinone ring protons. This spectrum and the corresponding ¹³C spectrum showed that the reactive intermediate, previously believed to be an N-nitrene, was in fact the N-acetoxaminoquinazolinone (47). Solutions of (47) could be used to aziridinate alkenes (Scheme 15). Yields of approximately 80% could be obtained on aziridination of, for example, styrene and methyl acrylate, two alkenes of very different electron availability.



The proposed transition state for aziridination using (47) now resembles that assumed for epoxidation (the Bartlett mechanism³⁸).

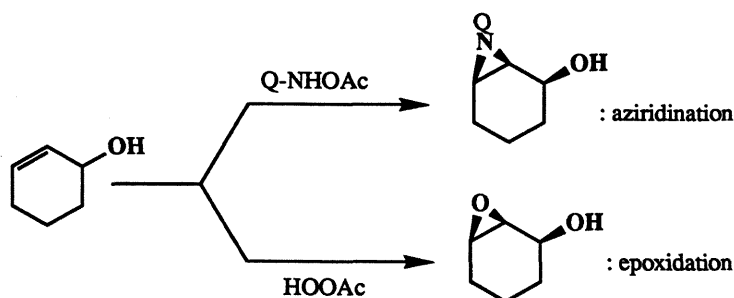


Thus the N-acetoxyaminoquinazolinone (47) is functioning as a nitrogen analogue of a peracid.

1.12 AZIRIDINATION OF CYCLIC ALLYLIC ALCOHOLS

Support for analogous mechanisms in epoxidation, using

peracids, and aziridination, using (47), comes from the epoxidation and aziridination of allylic alcohols, for example cyclohexenol. Aziridination of cyclic allylic alcohols gives the same syn-selectivity that is observed with epoxidation of these substrates^{23,38,39} (Scheme 16).



SCHEME 16

In the n.m.r. spectrum of N-acetoxyaminoquinazolinone (47) the two protons of the methylene group are diastereotopic. The chiral element responsible is thought to be the exocyclic nitrogen which is tetrahedral and inverting slowly, at least on the n.m.r. time scale. Not surprisingly, the presence of two chiral centres in the N-acetoxyaminoquinazolinone formed from LTA oxidation of (43) gives rise to diastereoisomers (Figure 5) which are present in a 4:1 ratio at -30°C from n.m.r. spectroscopy. The relevance of this diastereoisomer ratio to the diastereoselectivity of aziridination of prochiral alkenes with and without the presence of TFA is presently under investigation in these laboratories.

**Possible Transition State for the Aziridination of
Cyclohex-2-en-1-ol**

The stereoselectivity obtained in the aziridination of cyclohexenols may be rationalised by the transition state shown in Figure 6 which is analogous to that used to account for the syn-selectivity of cyclohexenols upon epoxidation with peracids.

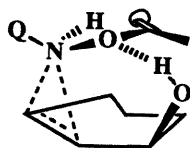
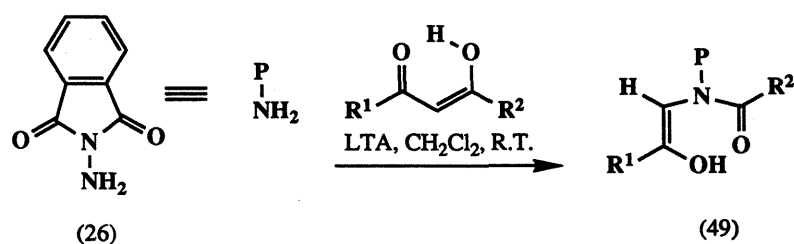


Figure 6

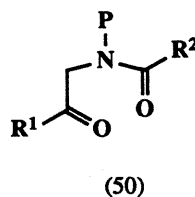
The hydrogen bonding present in the transition state in figure 6 appears to be easier with the hydroxyl group equatorially disposed. Whitham *et al*³⁹ have shown previously that an equatorially-fixed hydroxyl group brings about a greater acceleration in rate than an axial hydroxyl group in epoxidation of substituted cyclohexen-3-ols.

**1.13 REACTION OF N-AMINOPHTHALIMIDE WITH THE ENOLIC FORM OF
β-DIKETONES: THE UNREACTIVITY OF THE SECONDARY EXOCYCLIC NITROGEN
TOWARDS ACETYLATION IN 3-ALKYLAMINOQUINAZOLINONE DERIVATIVES**

In 1977, Foucaud *et al*⁴⁰ reported that the reaction of *N*-aminophthalimide (26) with LTA in the presence of 2,2,6,6-tetramethylheptan-3,5-dione, gave rise to *N*-acylated products, as shown in Scheme 17.



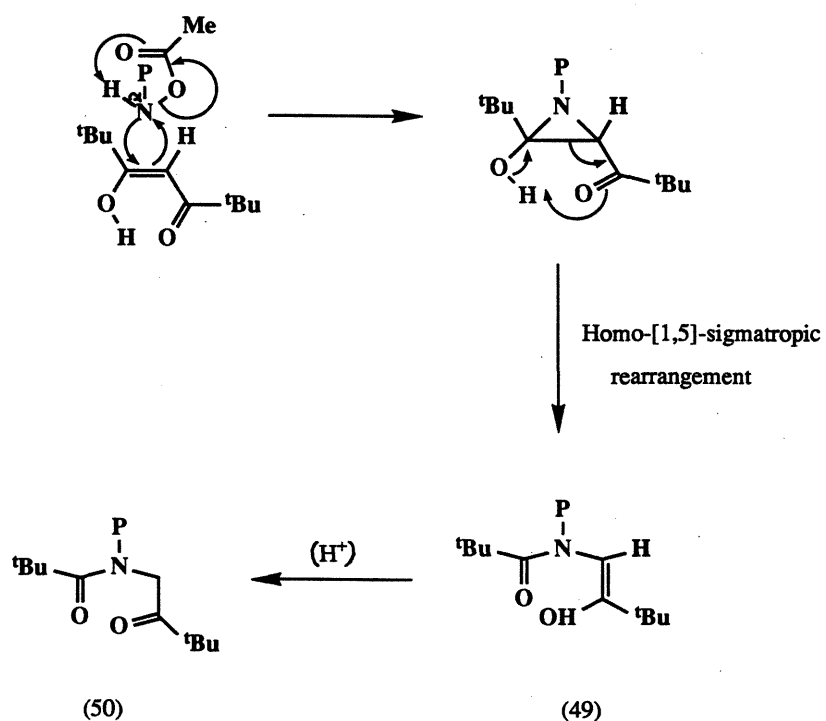
SCHEME 17



The reaction was assumed to occur via the enolic form of this β -diketone. Both the N-phthalimido-enol-amide (49) and the N-phthalimido-keto-amide (50) were of particular interest in that the exocyclic nitrogen was already acylated and therefore the N-N bond in these compounds was 'primed' for reduction (see earlier).

Foucaud used a number of β -diketones in reactions with N-aminophthalimide, and all except 2,2,6,6-tetramethylheptan-3,5-dione (Scheme 17) gave rise exclusively to the corresponding keto-amides [analogous to (50)]. However with the dione shown in Scheme 17, a 1:1.88 ratio of (49):(50) was obtained (after crystallisation). The mechanism proposed by Foucaud for aziridination of these β -dicarbonyl compounds in their enolic form involved an N-nitrene as the intermediate, formed by oxidation of N-aminophthalimide. However, the actual aziridinating agent is almost certainly N-acetoxyaminophthalimide

(Scheme 18), analogous to the N-acetoxyaminoquinazolinone intermediate described earlier.



SCHEME 18

The aziridine ring is opened via a homo-[1,5]-sigmatropic rearrangement. As postulated by Foucaud this constitutes an "unusual" C-C cleavage of the aziridine ring, the more usual cleavage occurring via the breaking of one of the C-N bonds.

CHAPTER TWO

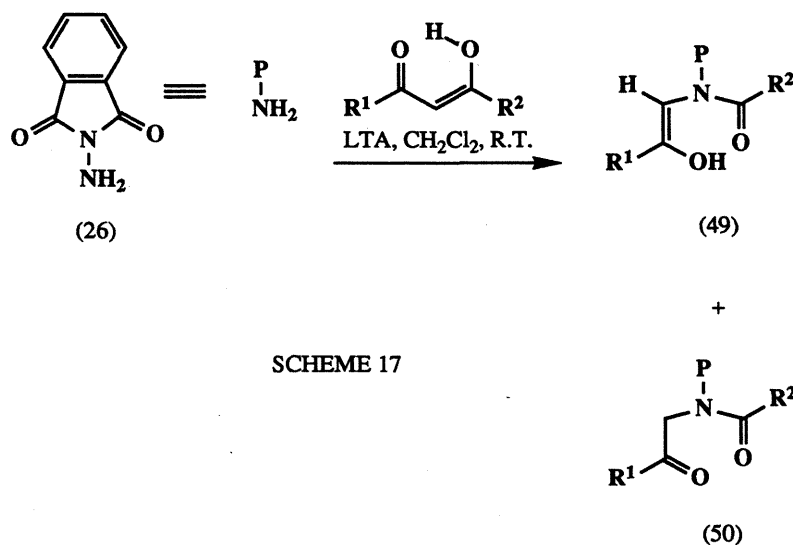
2.1 INTRODUCTION

For the aziridination procedure described in Chapter 1 to be of use to the synthetic chemist, the heterocyclic appendage on nitrogen needs eventually to be sloughed off. The work of Foucaud *et al*⁴⁰ prompted a study of the aziridination of β -dicarbonyl compounds by *N*-acetoxyamino-quinazolinones. The expected products would have the *N-N* bond diacylated and hence 'primed' for reductive cleavage²² and would provide model compounds with which to test the ease of reductive cleavage of the *N-N* bond in these compounds. There is no full paper on this work of Foucaud⁴⁰ and no other examples in the literature known to the author, in work related to this area which give compounds containing an *N-N* chiral axis. Also there are no other examples known to the author in the literature where asymmetric induction has been mediated by an *N-N* chiral axis.

2.2 AZIRIDINATION OF THE ENOLIC FORM OF β -DIKETONES

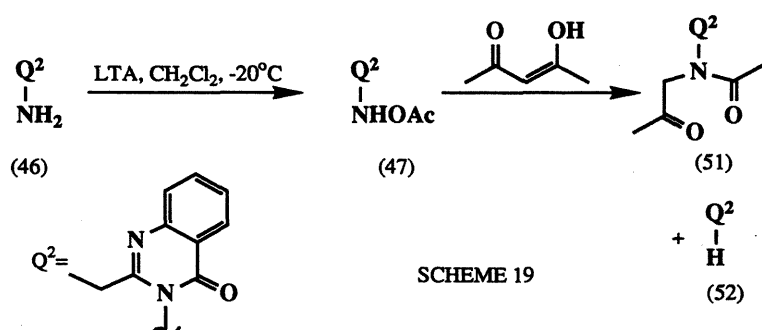
A repetition of the oxidation of *N*-aminophthalimide (26) with lead tetra-acetate (LTA) in the presence of 2,2,6,6-tetramethylheptan-3,5-dione as reported by Foucaud gave a mixture of two compounds (Scheme 17). The relatively stable *N*-phthalimido-enol-amide (49) was separated in 17% yield by fractional crystallisation using ethanol from the tautomeric *N*-phthalimido-keto-amide (50) (24%) derived from *in situ* protonation of the enol (49) by acetic acid. The proton n.m.r. data for these compounds agrees well with

that reported by Foucaud⁴⁰. Because of the symmetry of the phthalimide group, neither the enol-amide (49) nor the keto-amide (50) possess a chiral axis.



SCHEME 17

However, when pentan-2,4-dione was aziridinated using the N-aminoquinazolinone (46) then a 15% yield of the keto-amide (51) was obtained, the major product in this reaction being the de-aminated quinazolinone (52) (Scheme 19). In the proton n.m.r. spectra of this keto-amide (51), both pairs of protons in the methylene groups are diastereotopic (NCHH at δ 3.76 and 4.98, 2xd, J17.3Hz; CH₃CHH at δ 3.05, dq, J17.5,7.3Hz). This diastereotopicity is believed to result from retarded rotation around the N-N bond (at least on the n.m.r. time-scale) which endows the molecule with a chiral axis.



Keto-amide (51) also contains minor peaks for the methylene protons α to the exocyclic nitrogen at δ 3.76 and 4.98 which are assigned to an amide rotamer (ratio major:minor rotamer 7.6:1). From the gross difference in chemical shifts of the methylene protons α to the exocyclic nitrogen in both amide rotamers, it appears that there is a preferred rotamer about the exocyclic nitrogen-methylene carbon bond such that H_A is always found in the deshielding region of the quinazolinone carbonyl group (Figure 7).

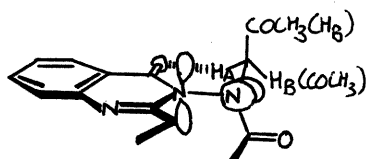


Figure (7)

The yield of keto-amide (51) is disappointingly low in that α,β -unsaturated esters normally give yields in excess of 70% on aziridination. Conceivably the donor-acceptor interaction (see Chapter 1) which assists in the

aziridination in the latter case is not present in the former, and the transition state assembly for aziridination could be that depicted in Figure 8 in which a less favourable methyl-quinazolinone donor-acceptor interaction is present.

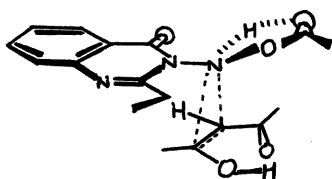
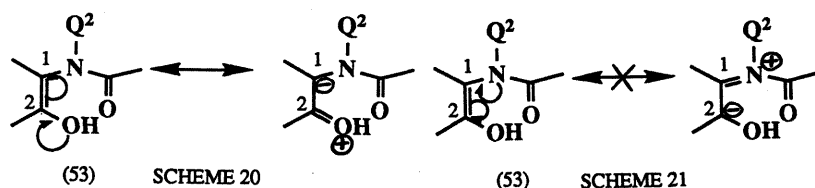


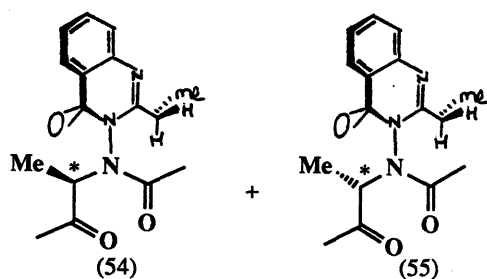
Figure (8)

When N-aminoquinazolinone (46) is oxidised with LTA and the intermediate N-acetoxyaminoquinazolinone (47) reacted at -20°C with 3-methylpentan-2,4-dione, a relatively stable enol-amide (53) is formed in 66% yield if the aziridination mixture is worked up as soon as ambient temperature is reached. Selected ^{13}C data show that carbon (1) ($\delta 107.7$) is at higher field than expected due to the resonance depicted in Scheme 20 which shields this position. The exocyclic nitrogen cannot efficiently contribute electrons in this way to carbon (2) ($\delta 158.0$) and so this latter carbon is considerably downfield (Scheme 21). These assignments agree with the (previously unreported) ^{13}C data for Foucaud's enol-amide with the corresponding carbons at δ 100.82 and 166.69.



In the proton n.m.r. spectrum of (53), the sharp singlet at $\delta 9.8$ suggests that the OH proton is not intramolecularly bonded. This molecule also possesses a chiral axis as can be seen from the diastereotopic nature of the methylene protons ($\delta 2.80$, CH_3CH_2 , ABX_3 , $J_{16.8,7.3\text{Hz}}$).

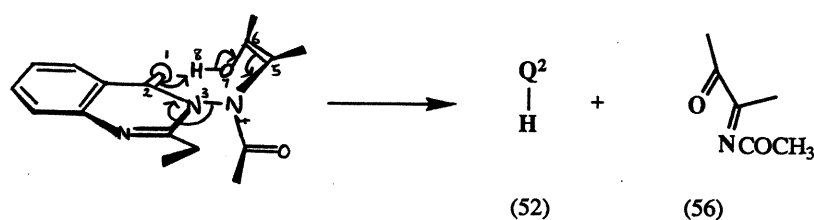
If the solution from attempted aziridination of 3-methylpentan-2,4-dione is left to stir at room temperature for more than an hour before work up, an approximately 1:1 mixture of tautomerised keto-amides (54) and (55) is isolated. These products can be separated by fractional crystallisation. The fact that these stereoisomers apparently do not interconvert shows that the rate of rotation around the chiral N-N axis is zero on the real time-scale. Both keto-amides (54) and (55) were heated to 200°C and no interconversion between these was detected from n.m.r. spectral comparison.



* Relative configuration arbitrarily assigned

However, it is possible to tautomerise the enol-amide (53) either by boiling briefly in ethanol, or by stirring overnight in glacial acetic acid, to give only the keto-amide diastereoisomer (54). Boiling briefly (for approximately one minute) in glacial acetic acid gave a 3:1 mixture of the two keto-amides (54):(55) respectively. The reason for this difference in ratio to the ratio obtained from letting the crude reaction mixture stand for more than one hour is not clearly understood. Setting aside a solution of the stereoisomer (54) in acetonitrile for three days resulted in conversion to the keto-amide (55). Both keto-amides (54) and (55) possess methylene (CH_3CH_2) protons which are diastereotopic (for (54): δ 2.80, CH_3CH_2 , ABX₃, J14.6, 7.3Hz, and for (55): δ 3.20, CH_3CH_2 , ABX₃, J17.8, 7.3Hz).

Heating the enol-amide (53) on a Kofler hot-stage gave a melting point of 114°C. However, re-solidification occurred and a temperature of 196-197°C is needed to re-melt this material. A proton n.m.r. spectrum of this material after heating to 197°C showed it to be identical with that of 2-ethylquinazolin-4(3H)-one (52). Heating either keto-amide (54) or (55) to 200°C did not result in the formation of 2-ethylquinazolin-4(3H)-one (52). The formation of (52) therefore is presumed to arise by elimination of the N-acylimine (56) via the 8-membered ring transition state shown in Scheme 22. It appears that neither (54) nor (55) are intermediates in this elimination.



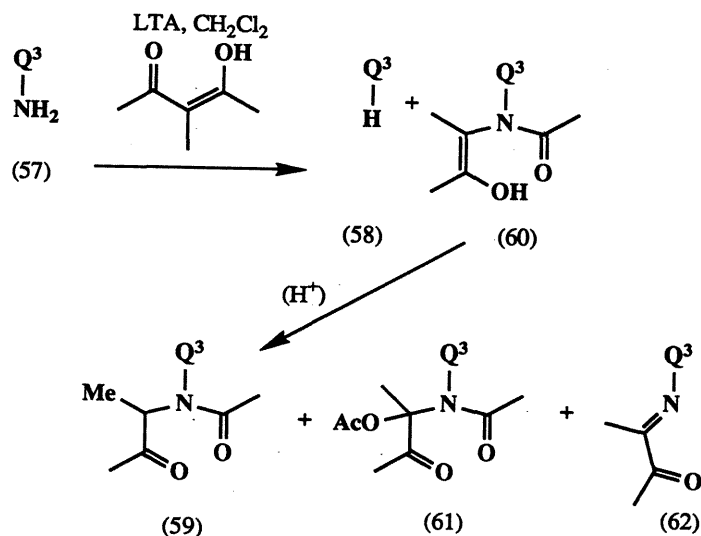
SCHEME 22

As drawn, atoms 1 to 4 and 8 are held in one plane and 4-7 in another. This conformational rigidity could explain why the elimination via the 8-membered transition state is so favourable.

Aziridination of 3-methylpentan-2,4-dione Using Oxidative Addition of an Enantiopure N-aminoquinazolinone

If the aziridination of 3-methylpentan-2,4-dione at room temperature is performed using the enantiopure N-aminoquinazolin-4(3H)-one (57) by addition of solid LTA and (57) in small portions to a solution of the dione (Method (2) see Experimental), the major product is the de-aminated quinazolinone (58) (63%). From the n.m.r. spectrum of the crude product after distillation of excess 3-methylpentan-2,4-dione and removal of the bulk of (58) but before chromatography, it is impossible to exclude the possibility that more than one keto-amide (59) is present due to the complexity of the spectrum. However, only stereoisomer (59) was isolated after chromatography. By analogy with the aziridination of 3-methylpentan-2,4-dione above, it was

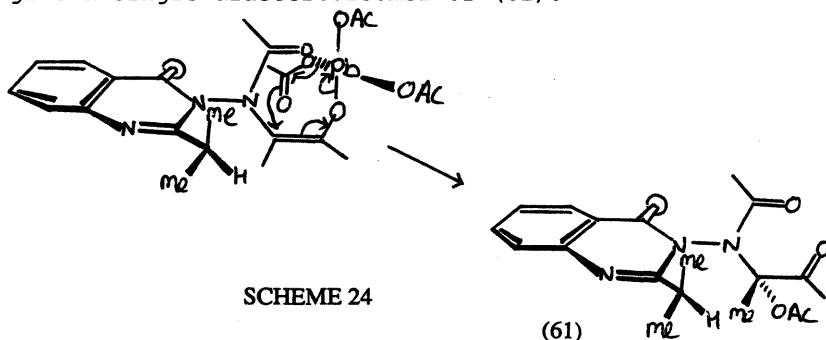
anticipated that at least two stereoisomers of keto-amide (59), epimeric at the position α - to the exocyclic nitrogen, would be obtained. The isolated stereoisomer (59) $[\alpha]_D = -83^\circ$ (Scheme 23) was isolated as an oil in only 2% yield whose ^1H and ^{13}C n.m.r. spectroscopic data in particular, suggested it was stereostructurally homogeneous.



SCHEME 23

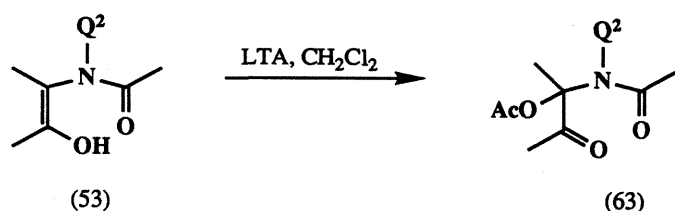
Also recovered from the above chromatography was unreacted starting *N*-aminoquinazolinone (57) (0.132g, 10%) and a single stereoisomer of α -acetoxy keto-amide (61) (12% based on the unreacted starting material obtained). This latter compound is presumed to arise by *in situ* oxidation of the enol-amide (60), which is not isolated, with lead tetra-acetate. Intramolecular delivery of an

acetoxy group from an enol-derived lead (IV) species onto one diastereoface only of the enol-amide (Scheme 24) would give a single diastereoisomer of (61).



This oxidation consumes some lead tetra-acetate. As only 1.05 equivalents of lead tetra-acetate were added to oxidise the N-aminoquinazolinone (57), not all the latter would be oxidised which accounts for the unreacted N-aminoquinazolinone (57) (10%) which is recovered. This in situ oxidation of enol-amide (60) with lead tetra-acetate was not detected when N-aminoquinazolinone (46) was used to aziridinate 3-methylpentan-2,4-dione, (see above and experimental relating to this Chapter), as the N-acetoxyaminoquinazolinone (47) is pre-formed in this case before addition of the β -dicarbonyl compound. This means there is essentially no lead tetra-acetate left to oxidise the enol-amide (53). However, it was found subsequently that taking a solution of enol-amide (53) and adding lead tetra-acetate to it, resulted in conversion to a single α -acetoxyated diastereoisomer (63) in 97% isolated yield (Scheme 25), presumably via a similar mechanism to that for the in situ oxidation postulated above (Scheme 24). This

compound (63) possesses a chiral element which is evident from the diastereotopic nature of the methylene protons (δ 3.21, CH_3CH_2 , ABX₃, J17.5, 7.4Hz).



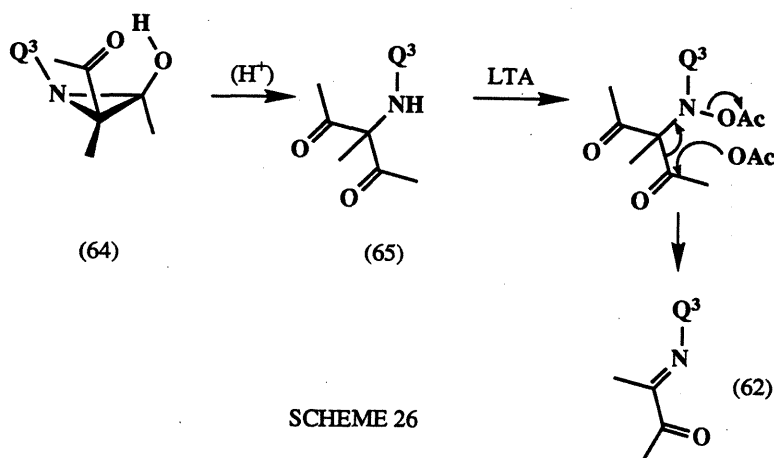
SCHEME 25

Attempts to thermally convert the isolated diastereoisomer of (63) (at least partially) into its other diastereoisomer by bringing about rotation around the N-N bond were unsuccessful. At 200°C the compound partially decomposed but none of the additional signals in the proton n.m.r. spectrum of this crude product could reasonably be assigned to a product diastereoisomeric with (63).

Presumably the same factors which make for high stereoselectivity in protonation of the enol (53) also control the stereoselective acetoxylation of (53).

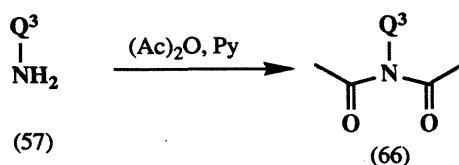
Also formed in the reaction using enantiopure N-aminoquinazolinone (57) and isolated by chromatography of the crude product in 2% yield was keto-imine (62). This is believed to result from the route shown in Scheme 26. Acetic acid which is formed in the initial lead tetraacetate oxidation of the N-aminoquinazolinone (57) and also in the aziridination of 3-methylpentan-2,4-dione, mediates C-N ring cleavage of the aziridine ring (64). The diketo-

amine (65) thus formed is then N-acetoxylation by the action of lead tetra-acetate and then elimination of this acetoxy is accompanied by deacetylation.



SCHEME 26

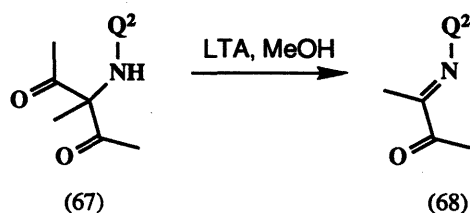
This compound (62) was at first thought to be the diacetylated quinazolinone (66). However, preparation of an authentic sample of the latter by addition of acetic anhydride and pyridine to N-aminoquinazolinone (57) (Scheme 27) showed this not to be the case when the proton n.m.r. spectra of (62) and (66) were compared.



SCHEME 27

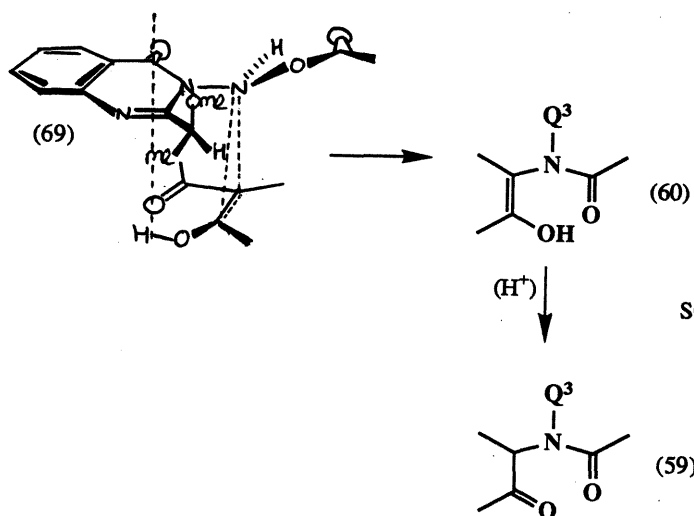
Taking a solution of keto-amine (67) in dry methanol and adding lead tetra-acetate furnished the keto-imine (68) in 31% yield (Scheme 28) which provides some support for

the mechanism outlined in Scheme 26.



SCHEME 28

In the oxidation of N-aminoquinazolinone (57) (Scheme 23) the first step is thought to be reaction of the N-acetoxyaminoquinazolinone (69) with the enolic form of 3-methylpentan-2,4-dione in which the α,β -unsaturated carbonyl is fixed in its s-cis conformation. Attack on this enol must be facially specific to give a single aziridine diastereoisomer (64). This then ring-opens via a homo-[1,5]-sigmatropic rearrangement and as the chiral elements in the aziridine ring (the two chiral centres) are destroyed they are transmuted completely stereoselectively into a single chiral element (the chiral axis) of enol-amide (60). This is then protonated by acetic acid present to give a single diastereoisomer of keto-amide (59) (Scheme 29).



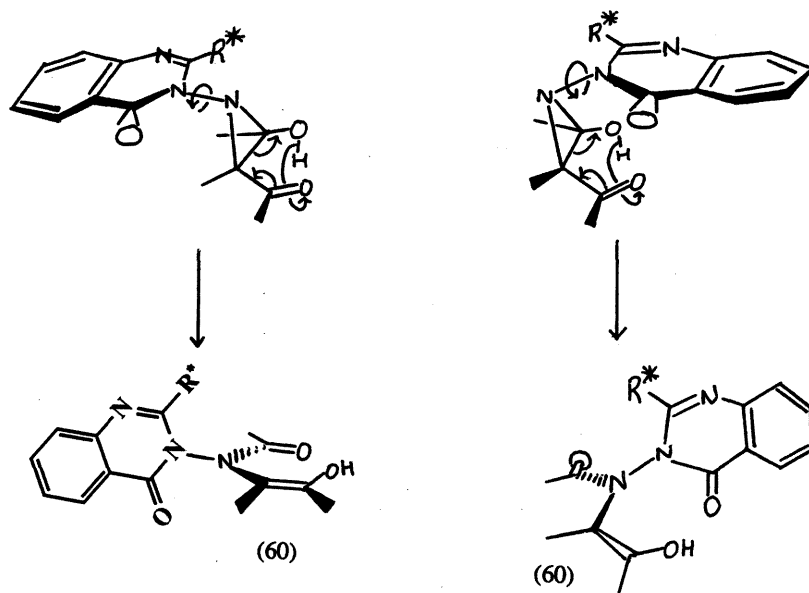
SCHEME 29

However, consider a 'worse case scenario' stereoselectively speaking: there is no facial specificity in the initial aziridination step and no stereoselectivity in the transmutation of the aziridine chiral centres into the chiral axis. As a result, both diastereoisomeric enol-amides (60) would be present in comparable amounts. The α -acetoxyated keto-amide (61), which is isolated as a single diastereoisomer, is believed to arise by LTA oxidation of (60). Just conceivably two diastereoisomeric enol-amides (60) were formed in the reaction mixture but only one reacted with lead tetra-acetate to give (61); the other tautomerised too rapidly to keto-amide (59) or reacted in some other way. Given the relatively small difference in stereostructure between both enol-amide diastereoisomers of

(60) however, the reaction of only one diastereoisomer with lead tetra-acetate seems as remarkable as diastereoselectivity in both the aziridination and aziridine ring-opening steps.

Similarly, it is conceivable that both diastereoisomers of (64) are in fact formed in the aziridination step but only one of these two diastereoisomers is in fact ring-opened (completely stereoselectively) to enol-amide (60): the other is ring-opened more rapidly to diketo-amine (65) (Scheme 26).

Transmutation of chirality in the ring-opening of aziridine (64), if it occurs, must presumably take place from one aziridine invertomer and with rotation of the N-N bond in a defined sense, e.g. with the more bulky R*-(R*=MeCH(OMe)-) containing half of the pyrimidinone ring moving away from the substituents on the exocyclic nitrogen as indicated in Scheme 30. Note that the N-N bond rotation in this same sense from both invertomers would produce both diastereoisomers of enol-amide (60) (Scheme 30).



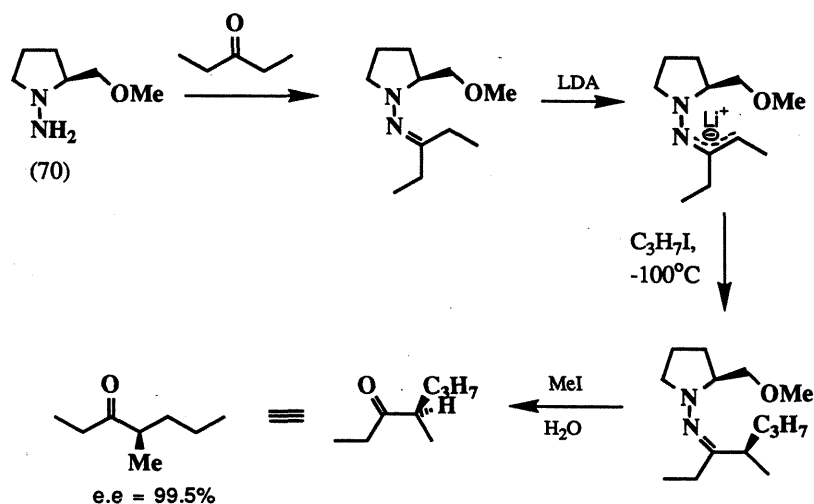
SCHEME 30

The factors which give rise to apparently complete stereoselectivity in the formation of keto-amide (59) deserve further investigation. Although the yield of the latter is poor it should be noted that this is largely the result of 'unproductive' oxidative de-amination of the *N*-aminoquinazolinone (57) to give (58). An intermediate chiral *N*-acetoxyaminoquinazolinone less prone to decompose in this way should give higher yields of aziridination products, and pre-forming this intermediate in solution (Method 1) would avoid the problems of competitive

oxidation of the aziridination products by lead tetraacetate encountered above.

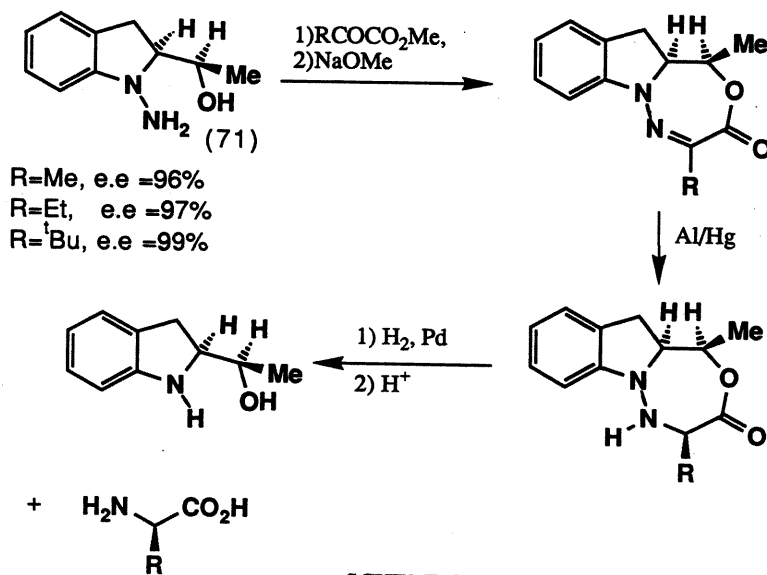
2.3 ASYMMETRIC INDUCTION IN SUBSTITUTED CHIRAL HYDRAZONES

Asymmetric induction in hydrazones has been studied by both Enders and Corey. Enders⁴¹ has used the hydrazine derivative (70) and formed the hydrazone derivative as shown in Scheme 31. Lithium diisopropylamide treatment followed by alkylation and cleavage of the auxiliary gave the enantiopurified ketones. For example,



SCHEME 31

Corey⁴² has used the chiral *N*-aminoindoline (71) as a chiral auxiliary to mediate asymmetric induction in the eventual formation of α -amino acids (Scheme 32).



SCHEME 32

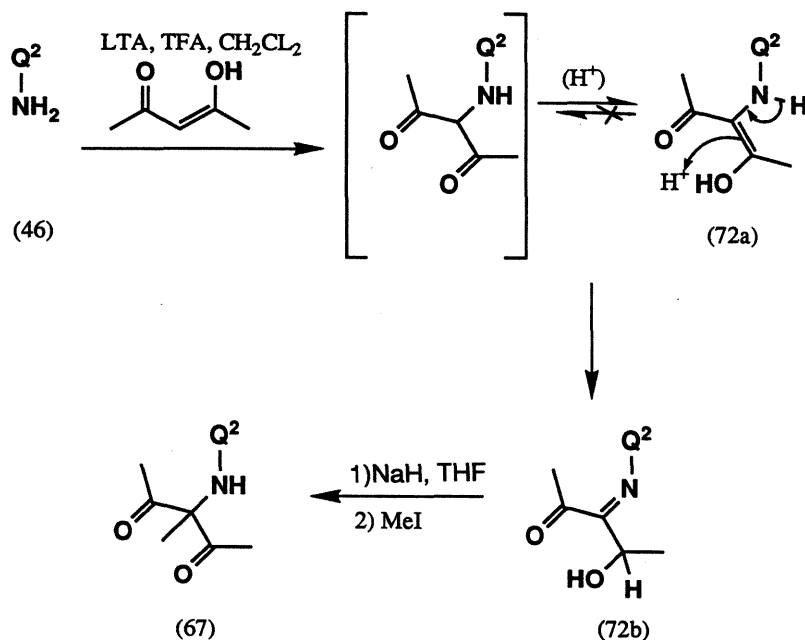
Formation of the chiral hydrazone from the indoline followed by aluminium amalgam reduction of the imine functionality and further reduction furnished the α -amino acid in high optical purity; regeneration of the chiral auxiliary was also possible. In both of these examples, asymmetric induction is mediated by the presence of chiral centres in the auxiliary and not dependent on hindered rotation around the N-N bond as is the case in the conversion of enol-amide (53) into keto-amide (54).

2.4 AZIRIDINATION OF THE ENOL FORM OF β -DIKETONES IN THE PRESENCE OF TFA

If the aziridination of pentan-2,4-dione using N-aminoquinazolinone (46) is performed in the presence of trifluoroacetic acid (TFA) then the reaction takes a different course and cleavage of the ring by C-N bond breakage of the intermediate aziridine is believed to occur. Subsequent tautomerisation gave a product (16%) to which the enol-amine structure (72a) is tentatively assigned (Scheme 33). This compound may have slowly tautomerised to its imine-alcohol tautomer (72b). The proton n.m.r spectral data is consistent with the enol-amine structure proposed (72a) with resonances at δ 5.38 (NH), 12.00 (bs, OH) and two non-equivalent methyl resonances (δ 1.77, (CH₃C(OH)=) and δ 2.15 (CH₃CO). However, on standing in the CDCl₃ (n.m.r.) solution a slow tautomerisation to the imine-alcohol (72b) may have occurred. The ¹³C n.m.r spectrum shows the presence of a CH resonance (δ 99.16) as well as a ketone-type carbonyl group (δ 197.36) and an imine carbon (δ 161.48) excluding those resonances attributable to the quinazolinone ring. This compound (72a/72b) possesses a chiral element, the effects of which are manifest in the diastereotopic nature of the methylene protons of the quinazolinone ethyl group (δ 2.85, CH₃CH₂, ABX₃, J16.2, 7.4Hz). A comparison of the high field ¹³C spectrum of this compound (72a/72b) with that of diketo-amine (67), after eliminating those signals assignable to the quinazolinone ring is instructive: compound (67) shows

one ketone carbonyl carbon peak at $\delta 204.46$ whereas compound (72a/72b) shows two signals, at $\delta 161.48$ and 197.36 . The chemical shift of the latter resonance is consistent with a ketone carbonyl carbon but the former would fit better for an imine carbon but not a ketone carbonyl carbon. This indicated that compound (72a/72b) does not have the diketamine type structure analogous to (67). Further work is needed to resolve this discrepancy between the ^{13}C and ^1H spectra.

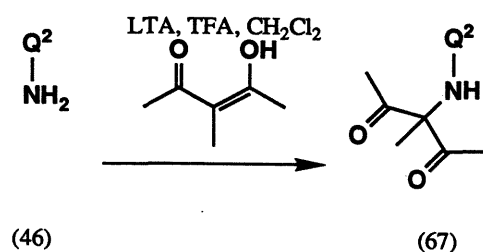
Compound (72a/72b) can be methylated with sodium hydride and methyl iodide in THF to give diketamine (67) in 10% yield (Scheme 33).



SCHEME 33

A single crystal X-ray structure of diketo-amide (67) was obtained from the methylation of (72a/72b), see Figure 9. The conversion of (72a/72b) into (67) albeit in low yield suggests that the carbon skeleton in both compounds (minus the added methyl group) is the same. The low yield in retrospect is not surprising (see Chapter 3).

Diketo-amine (67) was also produced directly in 63% yield from the oxidation of *N*-aminoquinazolinone (46) with lead tetra-acetate in the presence of 3-methylpentan-2,4-dione and trifluoroacetic acid (TFA) at room temperature (see Scheme 34).



SCHEME 34

When *N*-aminoquinazolinone (73) was oxidised with lead tetra-acetate at -20°C and reacted with pivaloylacetaldehyde the only homogeneous product isolated was the de-aminated quinazolinone (74) in 54% yield (Scheme 35). However, when the aziridination was repeated in the presence of trifluoroacetic acid then enamino-ketone (75) resulted in 50% yield (Scheme 35).

Diketo-amide (67)

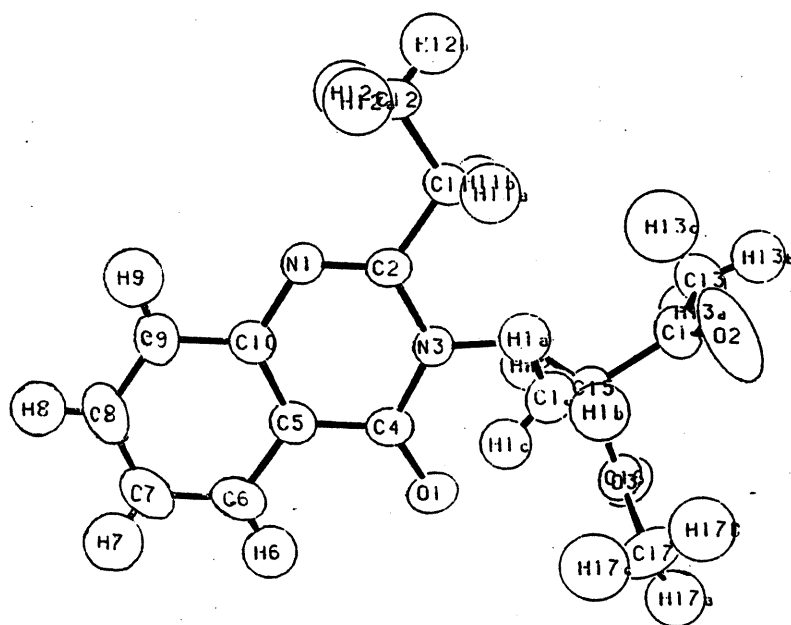
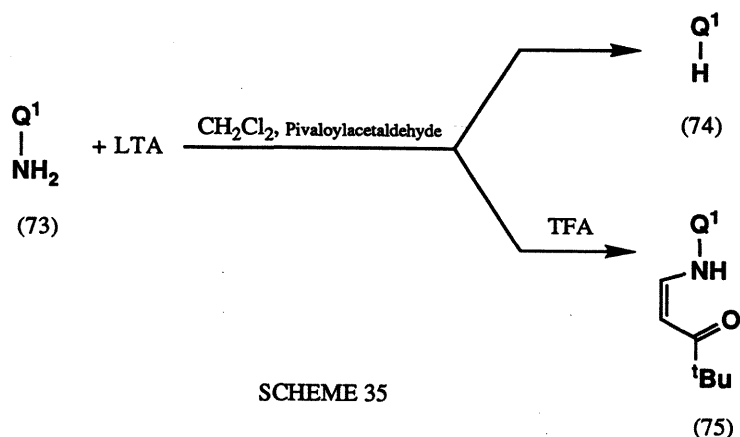


Figure 9



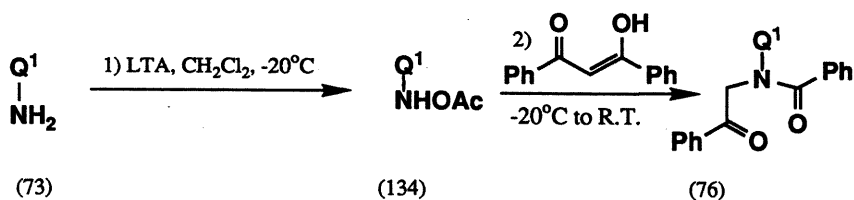
SCHEME 35

This product results from TFA-catalysed condensation of the N-aminoquinazolinone (73) with the aldehyde carbonyl group, this being more electrophilic than the ketone carbonyl group: unchanged lead tetra-acetate was converted to lead dioxide in the work up. The enamino-ketone (75) exists as a 6.7:1 ratio of double bond isomers, as can be seen from a doubling of signals in the proton n.m.r. spectrum. Proton decoupling experiments were performed on firstly the NH at $\delta 10.91$ with the result that the triplet at $\delta 6.68$ (CH=NH) collapsed to a singlet. Decoupling the triplet at $\delta 6.68$ collapsed the doublet at $\delta 10.91$ to a singlet and decoupling of the doublet at $\delta 5.62$ (CH=CO) reduced the triplet at $\delta 6.68$ to a doublet.

2.5 AZIRIDINATION OF THE ENOL FORM OF β -DIKETONES:

SELECTIVITY DERIVED FROM A DONOR-ACCEPTOR EFFECT

As mentioned earlier, the aziridination of pentan-2,4-dione with the *N*-acetoxyaminoquinazolinone (47) gave a low (15%) yield of keto-amide (51) (Scheme 19), which suggested that the transition state was one in which a favourable donor-acceptor relationship between the ketone and quinazolinone carbonyl was absent (Figure 8). A better yield of aziridinated product could be expected if dibenzoylmethane were to be substituted for pentan-2,4-dione in this aziridination. In the event when the 2-isopropyl-substituted *N*-aminoquinazolinone (73) was *N*-acetylated with lead tetra-acetate at low temperature and then reacted with dibenzoylmethane (Scheme 36), keto-amide (76) was isolated in 48% yield after crystallisation from ethanol.



SCHEME 36

The improved yield could be rationalised in terms of a more favourable donor-acceptor effect between the aromatic benzene ring and the carbonyl group of the quinazolinone, Figure 10, than between a methyl group and the quinazolinone in Figure 8. However, it is possible that the

increased yield is as much the result of a more nucleophilic (styrenoid) double bond with a donor-acceptor interaction between the ketone and the quinazolinone carbonyl preferred.

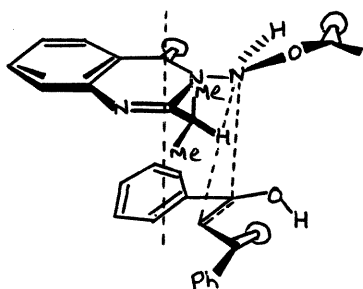
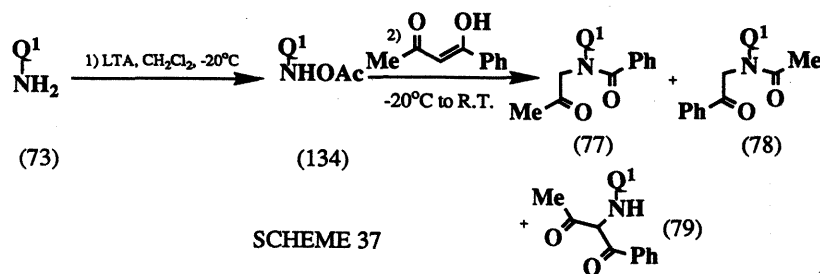


Figure (10)

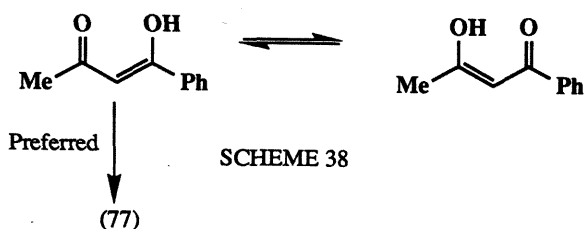
Keto-amide (76) exists in a 1.2:1 ratio of amide rotamers which can be seen from a doubling of the signals in the proton n.m.r. spectrum of this compound. The effects of the chiral axis in this molecule are evident from the diastereotopic nature of the isopropyl methyl groups, (δ 1.34, 2xd, CH_3CHCH_3 , J 6.8Hz) and methylene protons (δ 4.29 and 6.11, 2xd, CH_2N , J 17.5Hz). Again the gross difference in chemical shifts of the methylene protons (in both amide rotamers) as in the case of (51), is attributable to a preferred rotamer (see Figure 7) in which H_a is held in the deshielding region of the quinazolinone carbonyl group and is hence further downfield relative to H_b . It is noteworthy that the disparity in the ratio of amide rotamers in keto-amide (76) (1.2:1) is much less than for the corresponding ratio (7.6:1) in keto-amide (51).

Oxidation of *N*-aminoquinazolinone (73) with lead tetra-

acetate at low temperature and subsequent reaction with benzoyl-acetone gave a number of compounds, Scheme 37.



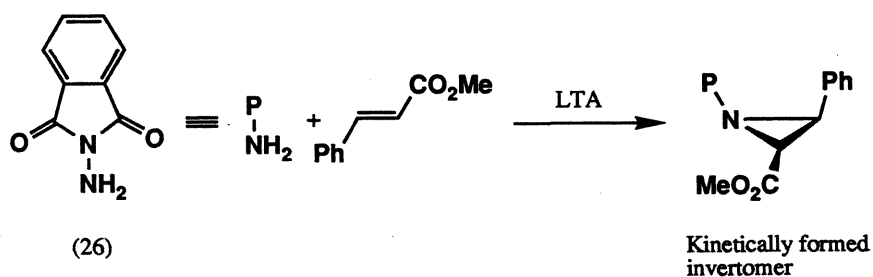
Enolisation of benzoyl-acetone (91% complete in CDCl_3 at 40°C)⁴³, gives rise to two enolic forms (Scheme 38) whose interconversion can be assumed to be fast by comparison with the rate of aziridination.



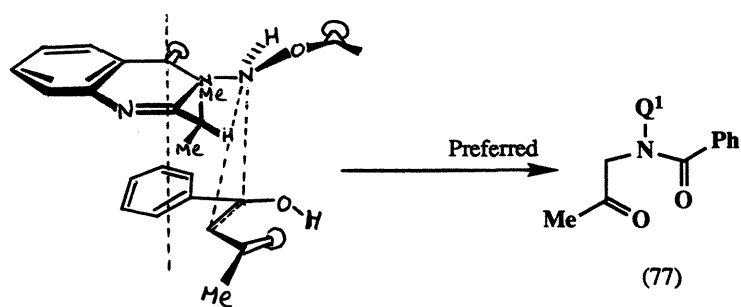
However, the phenyl-substituted enol would be expected to be more nucleophilic and therefore more reactive than the methyl-substituted one towards aziridination. The situation is complicated, however, by the influence on the transition state energies for aziridination of the two enolic double bonds of donor-acceptor interactions which are known to be important in these aziridinations (see below). Thus two transition state geometries are possible

for aziridination of both enolic double bonds (corresponding to a syn and anti disposition of enol OH and heterocycle).

Nevertheless, since the phenyl group is known to interact in this secondary sense with a phthalimido group in preference to an ester group⁴⁴ (Scheme 39) and since the phenyl-substituted enol is more nucleophilic (see above), preferential reaction via a transition state resembling that in Scheme 40 would be expected although the configuration at the exocyclic nitrogen centre is arbitrarily assigned.



SCHEME 39



SCHEME 40

In fact, after chromatography of the crude oxidation product, an inseparable mixture of (77):(78) (4.31g, 75% for both keto-amides) was obtained in a 3.32:1 ratio, (as determined by integration of appropriate resonances in the proton n.m.r. spectrum for the mixture). Keto-amides (77) and (78) were then separated by fractional crystallisation. Keto-amide (77) exists in a 1.61:1 ratio of amide rotamers (as seen from a doubling of the resonances in its proton n.m.r. spectrum), and possesses a chiral axis which can be seen from the diastereotopic nature of the isopropyl methyl groups, (δ 1.21 and 1.28, 2xd, CH_3CHCH_3 , J 6.5Hz) and methylene protons (δ 3.83 and 5.15, 2xd, CH_2N , J 17.2Hz). Keto-amide (78) exists as a 5.82:1 ratio of amide rotamers (again seen from a doubling of its resonances in the proton n.m.r. spectrum) and likewise possesses a chiral axis (δ 1.25 and 1.44, 2xd, CH_3CHCH_3 , J 6.6Hz) and (δ 4.15 and 5.88, 2xd, CH_2N , J 17.4Hz). The large difference in chemical shift for the protons in the methylene groups in both keto-amides (77) and (78) and the disparity in amide rotamer ratios in both cases is consistent with the effects in keto-amides (51) and (76) (see earlier) (see Table 2).

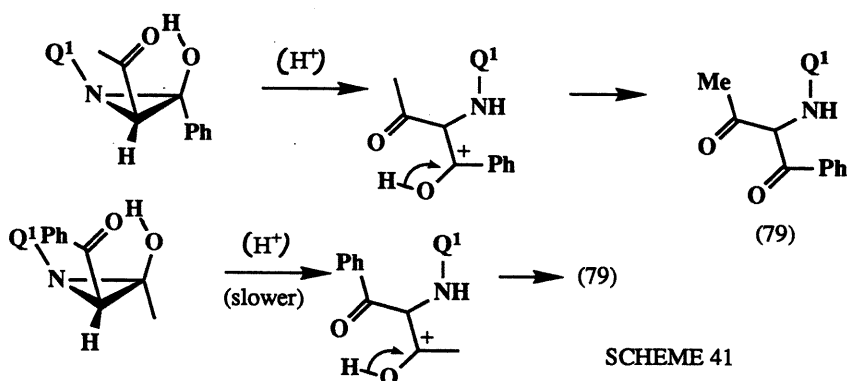
Keto-amide	δ (CH_2) (J/Hz): <u>MAJOR</u> Rotamer	δ (CH_2) (J/Hz): <u>MINOR</u> Rotamer	Ratio <u>MAJOR</u> : <u>MINOR</u> Rotamer
(51)	3.76 and 4.98 (17.3)	4.34 and 5.04 (18.7)	7.6:1
(76)	4.29 and 6.11 (17.5)	5.22 and 5.42 (19.3)	1.2:1
(77)	3.83 and 5.15 (17.2)	4.54 and 4.82 (19.6)	1.61:1
(78)	4.15 and 5.88 (17.4)	4.90 and 5.67 (19.4)	5.82:1

Table 2.

Structural assignments of keto-amide (77) and (78) were also supported by ^{13}C n.m.r. spectroscopy. Keto-amide (77) has a carbonyl group resonance at δ 200.06 which is characteristic of a ketone. Additionally, there is a benzoylamide carbonyl carbon at δ 172.52. Keto-amide (78) contains a benzoyl group at δ 191.51 (conjugation results in a shielding of the carbonyl group) and has an acetamide carbonyl carbon at δ 173.07. Infra-red spectroscopy also allowed (77) to be distinguished from (78). Keto-amide (77) has ν_{max} 1732cm^{-1} for the ketone carbonyl and 1700cm^{-1} for the benzoylamide carbonyl. Keto-amide (78) has ν_{max} 1685cm^{-1} for the benzoyl carbonyl and amide carbonyls of the

quinazolinone and exocyclic amide, which are presumably overlapping.

Another product from the reaction, apart from the deaminated quinazolinone (74) (isolated in only 9% yield), was the diketo-amine (79) isolated in 13% yield. This is assumed to result from C-N cleavage of the aziridine ring (Scheme 41), in which a hydroxybenzyl-carbocation is formed in preference to a hydroxymethyl-carbocation, the former being more stable. The aziridine ring from which the hydroxybenzyl-carbocation is derived is in turn derived from aziridination of the phenyl-bearing enol (see Scheme 38) and formation of this carbocation is competitive with formation of keto-amide (77). Thus the formation of diketo-amine (79) can be seen to be selectively detrimental to the yield of (77). This means that the ratio of attack on the two enolic forms of benzoylacetone could be as high as 4.2:1 in favour of the phenyl-substituted one.



Attempts to crystallise the keto-amine (79) from ethyl acetate resulted in a quantitative return of 2-

isopropylquinazolinone (74), presumably due to a thermal elimination of the quinazolinone moiety. The elimination of the quinazolinone ring from this compound will be discussed further in Chapter 3.

2.6 ATTEMPTED AZIRIDINATION OF BROMO-DIBENZOYLMETHANE:

FORMATION OF 3-BENZOYLAMINO-2-ISOPROPYLOUINAZOLIN-

4(3H)-ONE (81)

Alkylation on carbon α - to the N-N chiral axis could be envisaged via nucleophilic displacement of a leaving group at this position, for example (80), see Figure 11. In order to prepare a compound of this type, compound (80), the aziridination of bromo-dibenzoylmethane was undertaken.

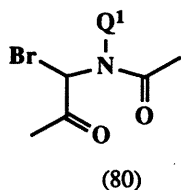
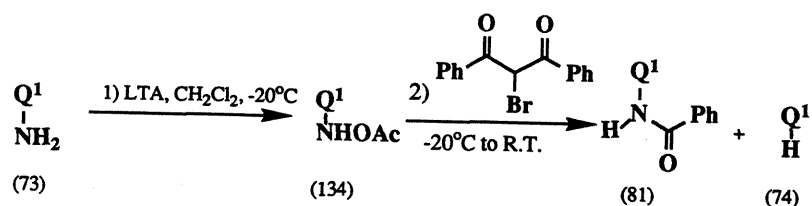


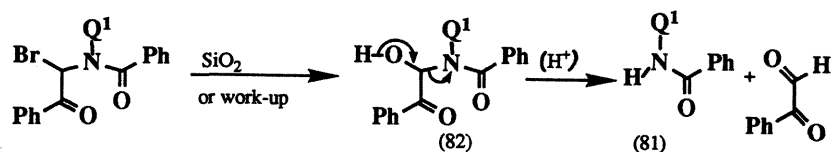
FIGURE 11

Oxidation of N-aminoquinazolinone (73) with lead tetraacetate and subsequent reaction with bromo-dibenzoylmethane gave, after chromatography of the crude oxidation product, 3-benzoylamino-2-isopropylquinazolin-4(3H)-one (81) as colourless crystals in 8% yield (Scheme 42), and the deaminated quinazolinone (74) in 62% yield.



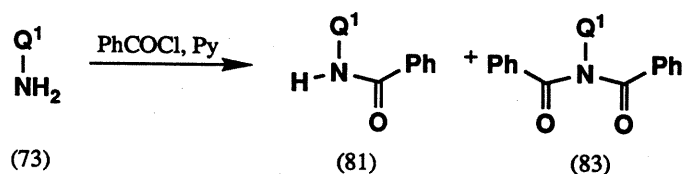
SCHEME 42

A possible mechanism for the formation of (81) is that as shown in Scheme 43. Either in the work-up or as a result of chromatography of the crude aziridination product over silica, substitution of the bromide by a hydroxy group occurred followed by breakdown of the carbinolamine (82).



SCHEME 43

An authentic sample of N-benzoylaminoquinazolinone (81) was prepared by treatment of N-aminoquinazolinone (73) with benzoyl chloride and pyridine to give (81) in 72% yield after chromatography together with the N,N-dibenzoylated quinazolinone (83) (Scheme 44).



SCHEME 44

Both the authentic sample of (81) and that isolated from attempted aziridination of bromo-dibenzoylmethane above had the same melting point of 174-174.5°C and superimposable infra-red spectra. There were, however, slight differences in the proton n.m.r spectra of these two samples. The chemical shifts of all resonances except those attributable to NH and the quinazolinone aromatic and benzoyl group were identical. These chemical shifts, however, were subsequently shown to be concentration dependent possibly resulting from reversible dimer formation as in Figure 12.

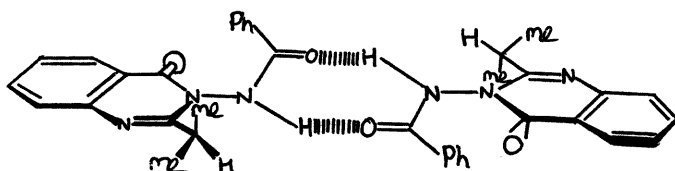
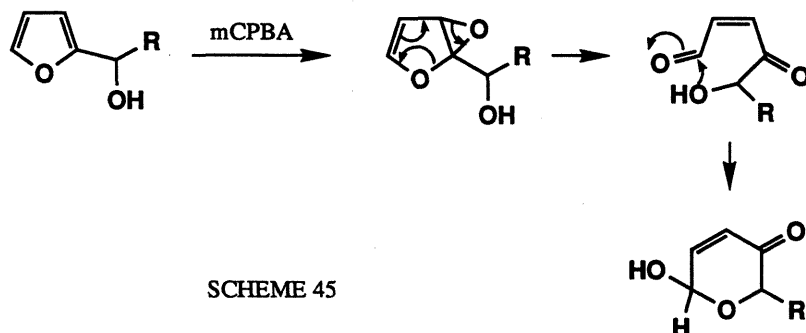


Figure (12)

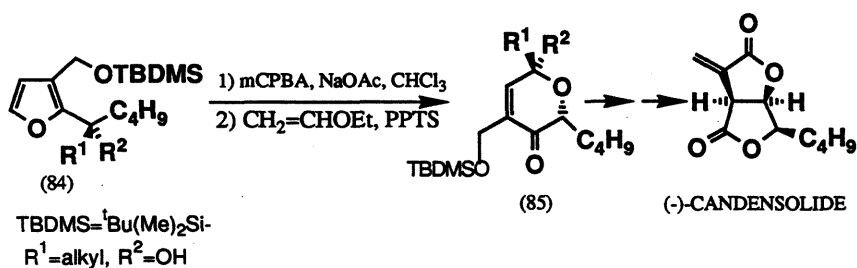
2.7 FURTHER ANALOGY BETWEEN AZIRIDINATION AND
EPOXIDATION:AZIRIDINATION OF α -HYDROXYMETHYLFURAN WITH
SUBSEQUENT REARRANGEMENT TO A PYRANONE SYSTEM

As mentioned in Chapter 1, support for analogous mechanisms in epoxidation, using peracids, and aziridination using *N*-acetoxyaminoquinazolinones comes from the epoxidation and aziridination of cyclic allylic alcohols, for example cyclohexenol^{23,39,45}. Reaction of α -hydroxymethylfurans with peracids is well known to give pyranones (Scheme 45).



SCHEME 45

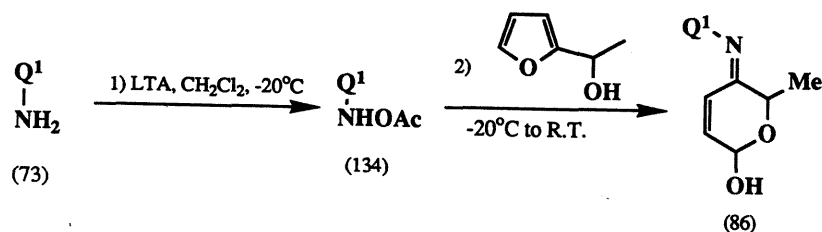
Thus oxidation of *O*-protected furan (84) with mCPBA produced the pyranone system (85). This procedure was utilised to form an intermediate pyranone by T.Honda *et al*⁴⁶ in the synthesis of (-)-candensolide⁴⁶ (Scheme 46).



SCHEME 46

In the present work, aziridination of 1-(2-furyl)ethanol was studied to examine whether the analogy between epoxidation and aziridination could be extended to the formation of α -pyranone analogues.

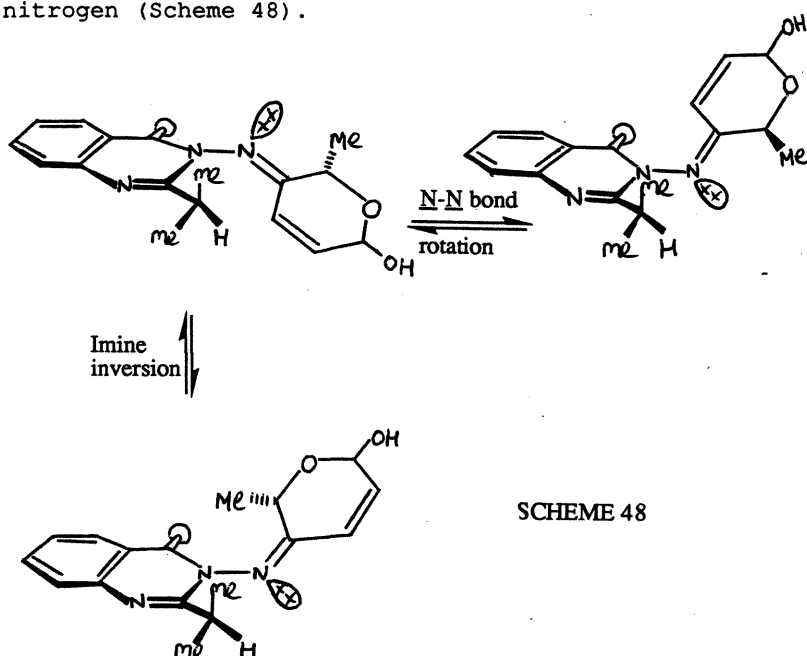
Oxidation of *N*-aminoquinazolinone (73) with lead tetraacetate at -20°C and reaction with racemic 1-(2-furyl)ethanol gave a dihydropyranone-imine (86) as a crystalline product in 76% isolated yield (Scheme 47).



SCHEME 47

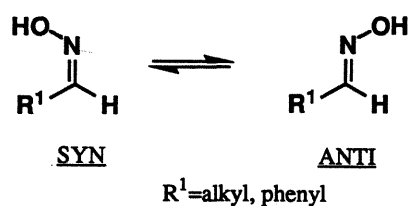
The proton n.m.r. spectrum of this compound at room temperature shows broadened signals for the quinazolinone isopropyl methyl groups and for the protons on the pyranone ring. The pyranone ring methyl doublet (δ 1.68 CH_3CH , J6.4Hz)

is, however, sharp. No other doublet for this methyl group can be seen at room temperature and so the reaction produces only one diastereoisomer. The broadening of some signals seen at room temperature in the proton n.m.r. spectrum is due to a dynamic process which is becoming fast on the n.m.r. time-scale. This process could be either N-N bond rotation or (planar) inversion at the exocyclic imine nitrogen (Scheme 48).



Note that neither of these processes interconvert the environments of the diastereotopic methyl groups.

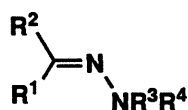
One can reasonably exclude inversion at the imine nitrogen by comparing this system to the better studied oximes (Scheme 49).



SCHEME 49

Here the oxime can exist in either syn or anti forms. However, at room temperature it is possible to isolate syn and anti forms which do not interconvert⁴⁷. Hence the dynamic process leading to broadening of signals in the n.m.r. spectrum of (86) could be expected to be due to rotation around the N-N bond.

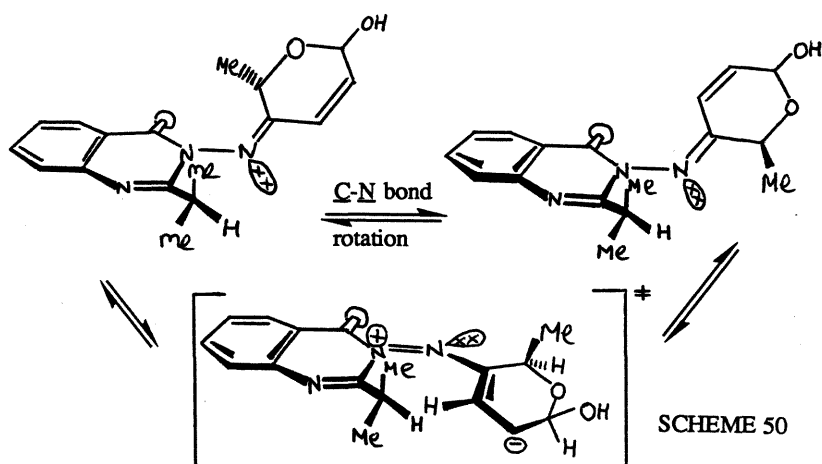
At -40°C, the above dynamic process is frozen out and a 2:1 ratio of two species is seen. The resonances for the isopropyl methyl groups and those for protons on the pyranone ring are all present in a 2:1 ratio for those belonging to their respective rotamers. From the coalescence of the pyranone ring proton (at -40°C, Major rotamer $\delta 5.40$, CH_3CHO , J6.4Hz; Minor rotamer $\delta 5.16$, CH_3CHO , J6.4Hz) at a coalescence temperature of 273K a barrier for rotation of $\Delta G^\ddagger = 13.17 \text{ K cal mol}^{-1}$ can be estimated. The literature values for planar N-inversion in hydrazones⁴⁷ of the type (87) lie in the range 18.5 to 32.1 K cal mol⁻¹ with the great majority of these in the range 23-26 K cal mol⁻¹. These barriers are too high to produce the above effects on the proton n.m.r. spectrum of (86) and so one can reasonably exclude N-inversion for the hydrazone (86).



(87)

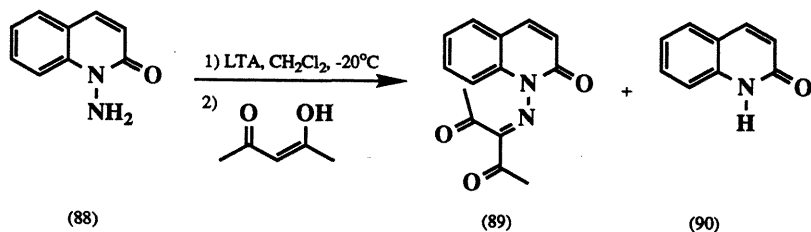
Interconversion by slow rotation around the $\text{C}=\text{N}$ bond is important in the stereomutation of some imines⁴⁷. The resonance which imparts partial single bond character to this imine bond and therefore would facilitate rotation, also requires maximal steric interaction with the quinazolinone as shown in Scheme 50. In any case, the quinazolinone nitrogen is not available for resonance donation in this sense. On the other hand, values for $\text{N}-\text{N}$ rotational barriers in hydrazines which have been reported are in the range 5.0 to 17.7 K cal mol⁻¹ which is consistent with the measured value above.⁴⁷

The imine double bond configuration which (86) assumes is not known for certain but is tentatively assigned as E as shown (Scheme 50). This assignment is based on the small chemical shift difference for the pyranone methyl and the proton on the carbon to which it is attached in the n.m.r. spectrum at -40°C (δ 1.71 and 1.73, CH_3 , d, J6.4Hz and δ 5.16 and 5.40, CH_3CHO , q, J6.4Hz). This chemical shift differences would have been expected to be considerably larger in the Z-imine. At present the relative configuration at the two chiral centres in this compound is unknown.



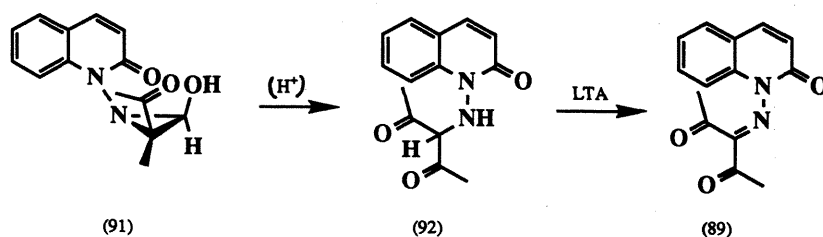
2.8 AZIRIDINATION OF PENTAN-2,4-DIONE BY OXIDATIVE ADDITION OF N-AMINOQUINOLINONE (88)

When the *N*-aminoquinolinone (88) is oxidised with lead tetra-acetate at room temperature in the presence of pentan-2,4-dione, a 10% yield of diketo-imine (89) (based on the 16% recovery of starting material) is obtained. Also isolated in 33% yield is the de-aminated quinolinone (90) (Scheme 51).



SCHEME 51

Compound (89) would result from formation of the aziridine (91) which is ring-opened via C-N cleavage. Further oxidation of the diketo-amine (92) with lead tetraacetate would give the diketo-imine (89) (Scheme 52).



SCHEME 52

As some lead tetra-acetate is consumed in this further oxidation step, there is insufficient remaining to oxidise all of the starting N-aminoquinolinone and so some is recovered.

Summary:

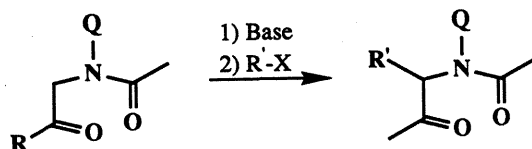
N-(Quinazolinone-N'-yl)-N-acyl- α -aminoketones (51), (54), (55), (59), (61), (63), (65), (67), (76), (77) and (78) have been prepared by reaction of N-acetoxyaminoquinazolinones (47) and (134) with β -diketones. The better yields obtained using dibenzoylmethane and benzoylacetone may be the result of a favourable donor-acceptor interaction together with a more nucleophilic enolic double bond. Aziridination of α -hydroxymethylfuran gave a pyranone-imine (86) analogous to the pyranones formed by epoxidation of α -hydroxyalkylfurans, thus strengthening the analogy between aziridination and

epoxidation.

CHAPTER THREE

3.1 INTRODUCTION

This Chapter recounts attempts made to bring about C-C bond forming reactions in N-(quinazolinone-N'-yl)-N-acyl- α -aminoketones and esters containing N-N chiral axes (Scheme 53)



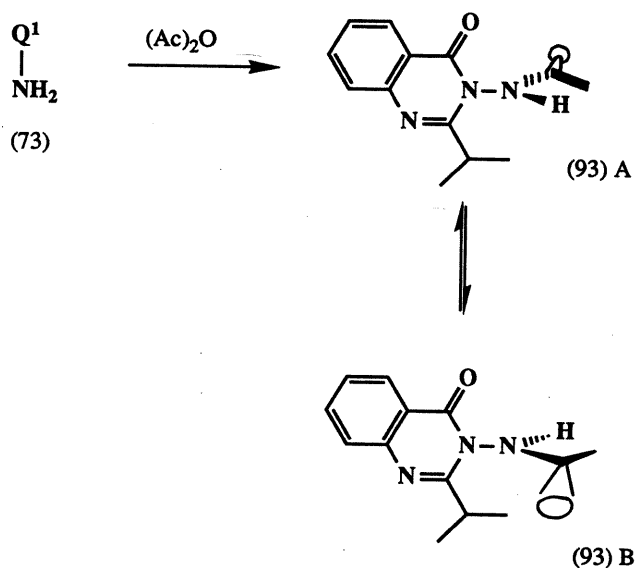
SCHEME 53

The discovery was made during this work of the good leaving group ability of the quinazolinone ring. Also revealed in the course of this work were barriers to N-N bond rotation in several compounds, including mono- and di-N-acylated-aminoquinazolinones. Barriers to N-N bond rotation in substituted hydrazines have also been studied by Verma¹⁶⁻²⁰, (see Chapter 1).

3.2 N-N ROTATIONAL BARRIERS IN N-ACYLAMINO- AND N-PYRANONE-IMINEQUINAZOLINONES

N-Aminoquinazolinone (73) was mono-acetylated by treatment with acetic anhydride in 66% yield (Scheme 54). In the n.m.r. spectrum of this compound (93), the methyl groups of the isopropyl group are non-equivalent. This diastereotopicity is the result either of retarded rotation around the N-N bond (the N-N bond constituting a chiral axis) or, less likely, the result of retarded rotation

around the amide ($\text{N}-\text{CO}$) bond.

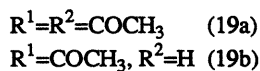
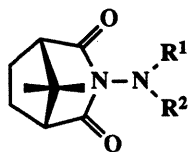


SCHEME 54

In this latter case the methyl groups within the isopropyl group of (A) are equivalent (not diastereotopic) if rotation around the $\text{N}-\text{N}$ bond is fast on the n.m.r. time-scale: likewise for the two methyl groups within the isopropyl group of (B). To account for the fact that there are two methyl groups of equal intensity within the isopropyl group in the n.m.r. spectrum of (93), both (A) and (B) would have to be present in equal concentrations which seems inherently unlikely.

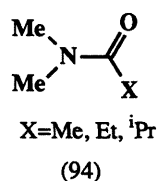
According to Verma¹⁹, when the exocyclic nitrogen of N -aminocamphorimide is mono-acylated as in (19b), the temperature-dependent phenomenon one sees in its proton n.m.r. spectrum is due, not to hindered $\text{N}-\text{N}$ bond rotation

(as he believed to be the case for (19a)) but due to hindered (N-CO) amide rotation: N-N bond rotation in this compound (19b) is assumed to be fast. The barrier to amide rotation in this compound was calculated to be 17.7 K cal mol⁻¹.

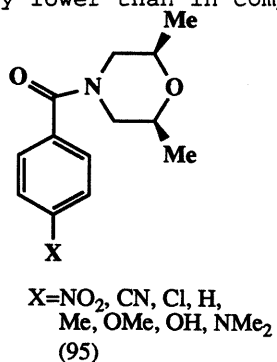


Variable-temperature n.m.r. studies were performed on compound (93) to determine the temperature at which coalescence of the diastereotopic methyl groups occurred. However, even at a temperature of 110°C complete coalescence of the isopropyl methyl groups was not observed although some broadening of the signals was apparent. This gives a minimum energy barrier for rotation around the N-N bond greater than $\Delta G^\ddagger = 20.3$ K cal mol⁻¹ which is significantly larger than the barrier in the mono-acylated aminocamphorimide (19b) measured by Verma¹⁹. Whether the barrier in (19b) measured by Verma is in fact the result of retarded amide rotation (as assigned by him) or retarded N-N bond rotation is open to question. Amide rotation can be excluded in the present case as giving rise to two methyl doublets of the isopropyl group for (93) by comparing the measured barrier with known values for amide rotation.

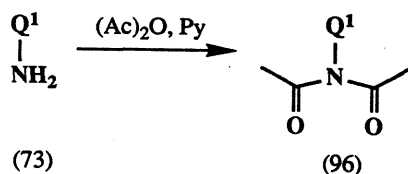
Wunderlich *et al*⁴⁸ have measured the barrier to amide ($\text{N}-\text{CO}$) rotation in N,N -diethyl amides (94). Barriers for amide rotation measured by them are in the range $\Delta G^\ddagger=16.6-17.3$ K cal mol⁻¹ which is considerably lower than the barrier measured for compound (93).



The barrier to amide ($\text{N}-\text{CO}$) rotation in compounds (95) have been measured⁴⁹ as $\Delta G^\ddagger=13.6-15.6$ K cal mol⁻¹ which is also considerably lower than in compound (93).



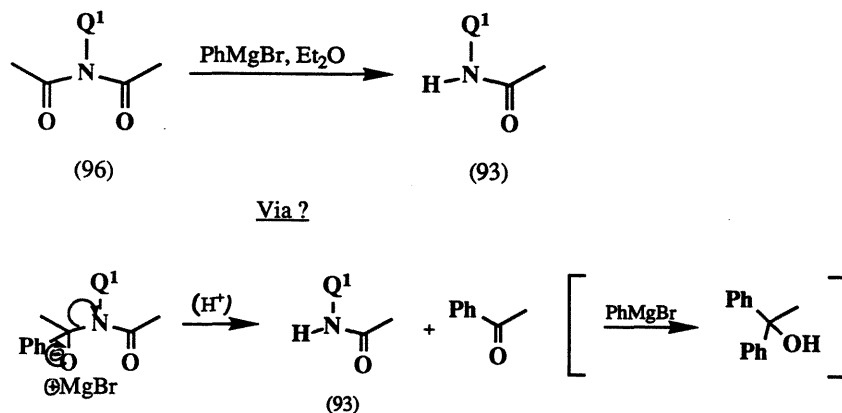
N -Aminoquinazolinone (73) can be di-acetylated on the exocyclic nitrogen by treatment with acetic anhydride and pyridine to give compound (96) in 81% yield (Scheme 55).



SCHEME 55

The proton n.m.r. spectrum of this compound shows one singlet for both acetyl methyl groups which is not unexpected since the N-N bond in this compound is not a chiral axis.

When this compound was treated with phenylmagnesium bromide, a 59% recovery of starting material was obtained along with a 95% yield (based on unreacted starting material) of mono-acetylated compound (93) after column chromatography (Scheme 56).



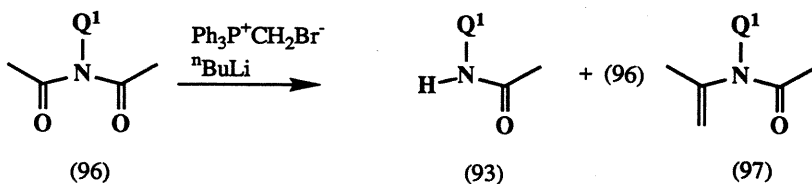
SCHEME 56

Elimination of the N-acylaminoquinazolinone moiety

presumably arises either from the magnesium alkoxide or from the derived carbinolamine (Scheme 56). Acetophenone (or diphenylmethanol) would also have been expected from this breakdown but no attempt was made to prove this.

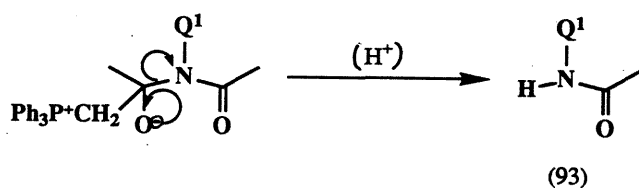
This mechanism is similar to that which would account for the formation of the N-benzoylaminoquinazolinone (81), (see Chapter 2).

Likewise, when the N-diacetylated aminoquinazolinone (96) was treated with the Wittig reagent derived from triphenylmethylphosphonium bromide and ⁿbutyllithium, in an attempt to prepare the enamine (97), a 4% recovery of unreacted starting material (96) and a 73% yield of mono-acylated quinazolinone (93) was obtained after column chromatography (Scheme 57).



SCHEME 57

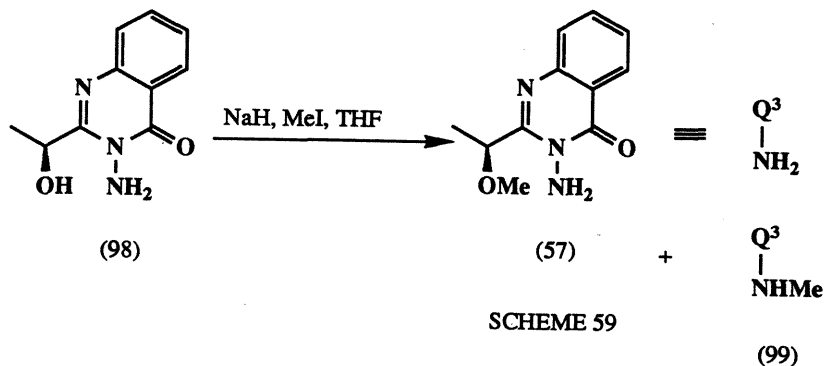
Here, the Wittig reagent adds to the carbonyl group (Scheme 58) but before elimination of triphenylphosphine oxide from a betaine takes place, the N-acylquinazolinone moiety is eliminated.



SCHEME 58

Alkylation/Acylation of Chiral N-aminoquinazolinones

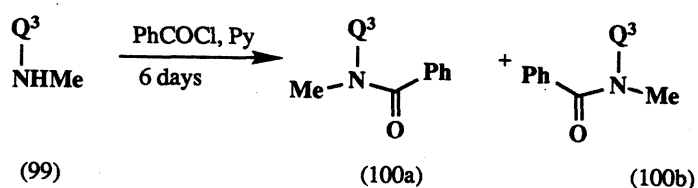
Attempted Q-methylation of (S)-(-)-3-amino-2-(1'-hydroxyethyl)quinazolin-4(3H)-one (98) using sodium hydride (greater than 1 mol equiv.) followed by methyl iodide gave a 1:1 mixture of (57) and the corresponding N-methylaminoquinazolinone (99) (Scheme 59). Use of only one mole equivalent of base ensures removal of the OH proton only and leads exclusively to the formation of (57).



SCHEME 59

Attempts to acetylate N-methylaminoquinazolinone (99) using acetic anhydride were unsuccessful. However, treating the N-methylaminoquinazolinone (99), with benzoyl chloride and pyridine and leaving the resulting solution to stand at

room temperature for 6 days, resulted in conversion to a 1.24:1 mixture of two diastereoisomers (100a) and (100b) in 40% and 37% yield respectively, see Scheme 60.



SCHEME 60

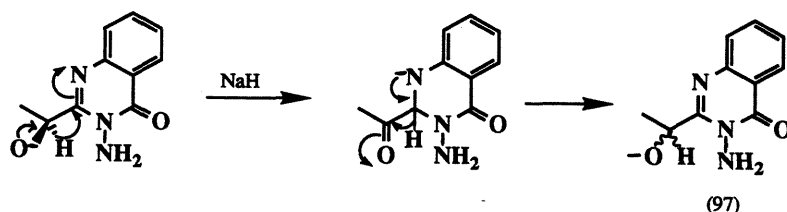
These compounds are the first to be produced by intermolecular acylation of a 3-(substituted)alkyl-aminoquinazolinone in these laboratories. A single crystal X-ray structure of one diastereoisomer (100b) has been obtained which confirms the structure as that shown in Figure 13. However, the lack of anomalous scattering in the X-ray determination is only possible if this compound is racemic in the crystal from which the structure was determined. The chiral centre at the 2-position of the quinazolinone ring may have been racemised to some extent when (S)-(-)-3-amino-2-(1'-hydroxyethyl)quinazolin-4(3H)-one (98) was treated with sodium hydride possibly by the mechanism shown in Scheme 61. However, this racemisation is incomplete as N-methylaminoquinazolinone (99) and both benzoylated diastereoisomers (100a) and (100b) are all optically active though as yet of unknown optical purity. The small number of crystals which were obtained for (100b) by setting aside a dilute solution of (100b) and which were used to obtain the X-ray structure, were subsequently found

ORTEP diagram of the molecular structure of 1,3-bis(2,4,6-trimethylphenyl)-4-methyl-5-nitro-2-imidazolidinone. The structure shows a central imidazolidone ring substituted with two 2,4,6-trimethylphenyl groups and a methyl group. The nitro group is also present. Thermal ellipsoids are drawn at the 50% probability level. Displacement ellipsoid coefficients are provided in the table below.

Atom	U ¹¹	U ²²	U ³³	U ¹²	U ¹³	U ²³
N1	0.021	0.021	0.021	0.000	0.000	0.000
N2	0.021	0.021	0.021	0.000	0.000	0.000
N3	0.021	0.021	0.021	0.000	0.000	0.000
C1	0.021	0.021	0.021	0.000	0.000	0.000
C2	0.021	0.021	0.021	0.000	0.000	0.000
C3	0.021	0.021	0.021	0.000	0.000	0.000
C4	0.021	0.021	0.021	0.000	0.000	0.000
C5	0.021	0.021	0.021	0.000	0.000	0.000
C6	0.021	0.021	0.021	0.000	0.000	0.000
C7	0.021	0.021	0.021	0.000	0.000	0.000
C8	0.021	0.021	0.021	0.000	0.000	0.000
C9	0.021	0.021	0.021	0.000	0.000	0.000
C10	0.021	0.021	0.021	0.000	0.000	0.000
C11	0.021	0.021	0.021	0.000	0.000	0.000
C12	0.021	0.021	0.021	0.000	0.000	0.000
C13	0.021	0.021	0.021	0.000	0.000	0.000
C14	0.021	0.021	0.021	0.000	0.000	0.000
C15	0.021	0.021	0.021	0.000	0.000	0.000
C16	0.021	0.021	0.021	0.000	0.000	0.000
C17	0.021	0.021	0.021	0.000	0.000	0.000
C18	0.021	0.021	0.021	0.000	0.000	0.000
C19	0.021	0.021	0.021	0.000	0.000	0.000
C20	0.021	0.021	0.021	0.000	0.000	0.000
C21	0.021	0.021	0.021	0.000	0.000	0.000
C22	0.021	0.021	0.021	0.000	0.000	0.000
C23	0.021	0.021	0.021	0.000	0.000	0.000
C24	0.021	0.021	0.021	0.000	0.000	0.000
C25	0.021	0.021	0.021	0.000	0.000	0.000
C26	0.021	0.021	0.021	0.000	0.000	0.000
C27	0.021	0.021	0.021	0.000	0.000	0.000
C28	0.021	0.021	0.021	0.000	0.000	0.000
C29	0.021	0.021	0.021	0.000	0.000	0.000
C30	0.021	0.021	0.021	0.000	0.000	0.000
C31	0.021	0.021	0.021	0.000	0.000	0.000
C32	0.021	0.021	0.021	0.000	0.000	0.000
C33	0.021	0.021	0.021	0.000	0.000	0.000
C34	0.021	0.021	0.021	0.000	0.000	0.000
C35	0.021	0.021	0.021	0.000	0.000	0.000
C36	0.021	0.021	0.021	0.000	0.000	0.000
C37	0.021	0.021	0.021	0.000	0.000	0.000
C38	0.021	0.021	0.021	0.000	0.000	0.000
C39	0.021	0.021	0.021	0.000	0.000	0.000
C40	0.021	0.021	0.021	0.000	0.000	0.000
C41	0.021	0.021	0.021	0.000	0.000	0.000
C42	0.021	0.021	0.021	0.000	0.000	0.000
C43	0.021	0.021	0.021	0.000	0.000	0.000
C44	0.021	0.021	0.021			

Figure 13

to have a melting point of 123-127°C which is considerably lower than that obtained (142-144°C) for this diastereoisomer when crystallised from ethanol in bulk at an earlier stage. This depression of melting point accords with the production of racemic (100b) in this crystallisation presumably as a result of its lesser solubility than the enantiopure material.



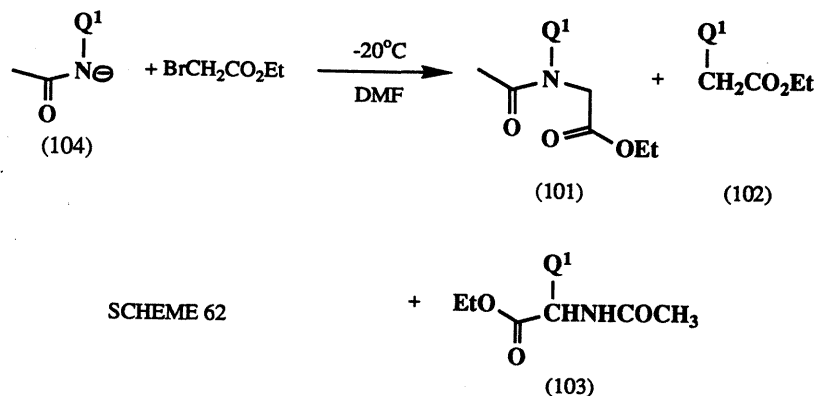
SCHEME 61

The fact that both diastereoisomers can be separated at room temperature and have an independent existence, that is they are not interconverting with one another on the real time-scale, shows that no rotation around the N-N bond is occurring. In the proton n.m.r. spectra of both diastereoisomers, a doubling of most of the signals is observed which can be ascribed to retarded amide rotation around the C-N bond; diastereoisomer (100a) exists as a 4.1:1 ratio of amide rotamers whereas (100b) exists as a 3.2:1 ratio of amide rotamers.

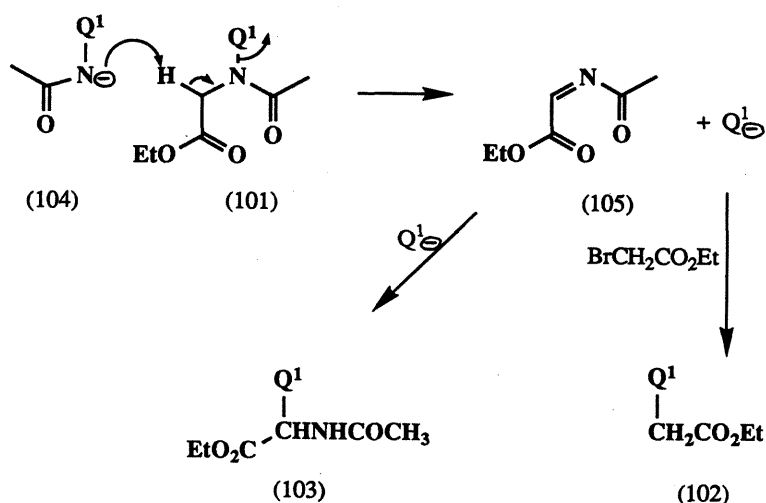
3.3 ALKYLATION OF N-ACETYLAMINOQUINAZOLINONE (93)

The N-anion of N-acetylaminoquinazolinone (93) can be alkylated by treatment with ethyl bromoacetate. When the

reaction is performed at -20°C by adding ethyl bromoacetate to the anion of N-acetylaminquinazolinone (93) then a mixture of amide-ester (101), ester (102), and N-alkyl-ester (103) was obtained in 12%, 18% and 12% isolated yields respectively (Scheme 62).



This mixture of products presumably arises from the amide-ester (101), which is formed initially from S_N2 attack of the N-acetylaminquinazolinone anion on the bromoacetate. Loss of quinazolinone anion from (101) by the action of a base, for example (104), would generate N-acylimine (105). The quinazolinone anion thereby generated is either alkylated with ethyl bromoacetate to give ester (102) or else it adds to the imine functionality of intermediate N-acylimine (105) leading to formation of rearranged N-alkyl-ester (103) (Scheme 63).



SCHEME 63

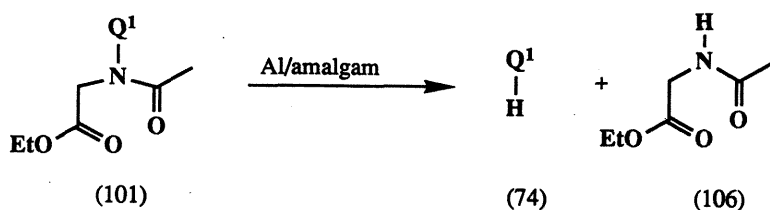
Amide-ester (101) exists as a 3.55:1 ratio of amide rotamers, as seen from a doubling of signals in its proton n.m.r. spectrum and also possesses a chiral axis which is apparent from the diastereotopic nature of both methyl groups of the isopropyl group, (CH_3CHCH_3 , δ 1.31 and 1.41, J6.6Hz for the major rotamer), and for the methylene protons α -to the exocyclic nitrogen, (δ 3.59 and 4.98 (2xd, CH_2N , J16.9Hz for the major rotamer) and δ 4.14 and 4.87 (2xd, CH_2 , J18.7Hz for the minor rotamer)). The gross difference in chemical shift for the diastereotopic methylene protons in both rotamers can be explained in terms of a preferred conformation for both rotamers as proposed previously (see Figure 7, Chapter 2).

In the rearranged ester-amide (103) the

diastereotopicity of the methyl groups of the isopropyl group, (CH_3CHCH_3 , δ 1.43, 2xd, J 6.6Hz), and the methylene protons of the ester, (CH_3CH_2 , δ 4.25, ABX₃, J 10.2, 7.1Hz) is ascribed to the presence of a chiral centre in this molecule. Proton decoupling of the doublet at δ 6.85 (CHNH) reduces the NH doublet to a singlet as expected.

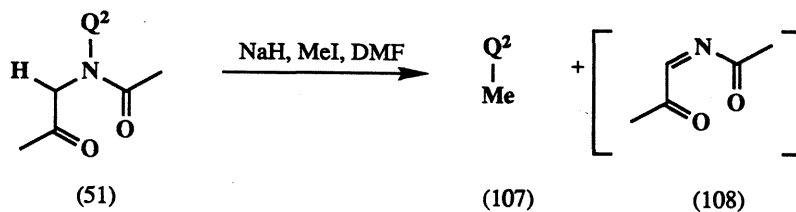
If the alkylation reaction is repeated under different conditions by adding the anion of the N-acylaminoquinazolinone (104) to a solution of ethyl bromoacetate at -20°C then one obtains exclusively the amide-ester (101) in 83% yield after chromatography. Here there is no, or very little, excess of N-acetylaminoquinazolinone anion (104) present in solution to deprotonate (101) and so the yield of this product is increased.

An aluminium amalgam reduction was performed on the amide-ester (101) which furnished ethyl N-acetylglycinate (106) (Scheme 64) in 74% yield which was identical by n.m.r. spectral comparison with a sample purchased from Aldrich. In amide-ester (101) both nitrogens are acylated which, literature precedent²² suggests 'primes' the N-N bond for reductive cleavage. This indeed turned out to be the case.



SCHEME 64

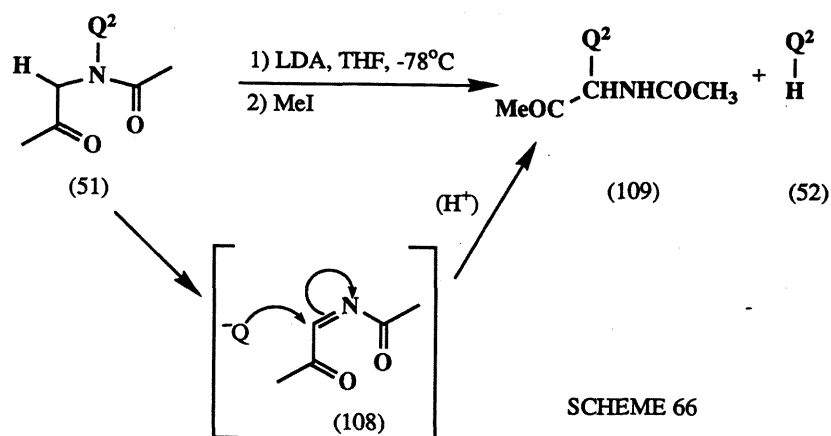
When keto-amide (51) was treated with sodium hydride and methyl iodide in DMF solution, a 66% yield of *N*-methyl-2-ethylquinazolin-4(3H)-one (107) was obtained (Scheme 65), which was identical, by proton n.m.r. and infra-red spectral comparison with a sample prepared by B. Kelly in this department. Removal of the proton α - to the ketone with concomitant loss of the quinazolinone ring followed by methylation of the latter, accounts for the formation of (107). Under these conditions, no re-addition of the quinazolinone anion to the imine moiety of the eliminated *N*-acylimine (108) apparently occurs.



SCHEME 65

However, when keto-amide (51) is treated firstly with LDA and then methyl iodide in THF, some unreacted starting material (10%) was recovered along with rearranged keto-

amide (109) (12% after an ethanol crystallisation), and 2-ethylquinazolin-4(3H)-one (12%) (52) (Scheme 66). Under these conditions, elimination of the quinazolinone anion takes place as in Scheme 65, but in this case some re-addition to the imine functionality of the *N*-acylimine (108) to give (109) does occur.



SCHEME 66

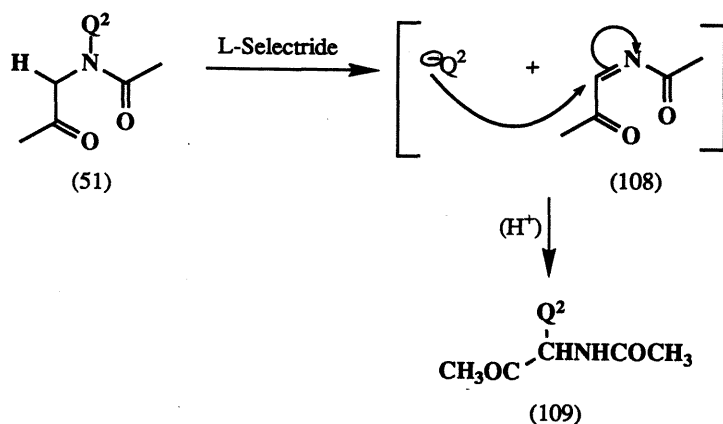
Treatment of keto-amide (51) with L-Selectride in THF gave, after chromatography, an oil. This material crystallised slowly and several crystals were obtained from ethanol which were suitable for a single crystal X-ray structure determination. The X-ray structure, see Figure 14, showed it to be the rearranged keto-amide (109). Here, the L-Selectride is functioning as a base and removing a proton α - to the ketone. The quinazolinone anion thus formed then re-adds to the imine functionality of the intermediate *N*-acylimine (108) as previously proposed, to give (109) (Scheme 67). A proton n.m.r. spectrum of the

ORTEP diagram of the molecular structure of 2,4,6-trimethyl-3,5-dinitrophenylhydrazine. The structure shows a central benzene ring with a hydrazine group (-NH-NH-) at position 1, a methyl group (-CH3) at position 2, a nitro group (-NO2) at position 3, a methyl group (-CH3) at position 4, and another nitro group (-NO2) at position 6. The atoms are labeled with their respective symbols and numbers. Thermal ellipsoids are drawn at the 50% probability level. Displacement ellipsoid coefficients are provided in the table below.

Atom	U ¹¹	U ²²	U ³³	U ¹²	U ¹³	U ²³
N1	0.026	0.026	0.026	0.000	0.000	0.000
N2	0.026	0.026	0.026	0.000	0.000	0.000
N3	0.026	0.026	0.026	0.000	0.000	0.000
N4	0.026	0.026	0.026	0.000	0.000	0.000
N5	0.026	0.026	0.026	0.000	0.000	0.000
N6	0.026	0.026	0.026	0.000	0.000	0.000
N7	0.026	0.026	0.026	0.000	0.000	0.000
N8	0.026	0.026	0.026	0.000	0.000	0.000
N9	0.026	0.026	0.026	0.000	0.000	0.000
N10	0.026	0.026	0.026	0.000	0.000	0.000
N11	0.026	0.026	0.026	0.000	0.000	0.000
N12	0.026	0.026	0.026	0.000	0.000	0.000
N13	0.026	0.026	0.026	0.000	0.000	0.000
N14	0.026	0.026	0.026	0.000	0.000	0.000
N15	0.026	0.026	0.026	0.000	0.000	0.000
N16	0.026	0.026	0.026	0.000	0.000	0.000
N17	0.026	0.026	0.026	0.000	0.000	0.000
N18	0.026	0.026	0.026	0.000	0.000	0.000
N19	0.026	0.026	0.026	0.000	0.000	0.000
N20	0.026	0.026	0.026	0.000	0.000	0.000
N21	0.026	0.026	0.026	0.000	0.000	0.000
N22	0.026	0.026	0.026	0.000	0.000	0.000
N23	0.026	0.026	0.026	0.000	0.000	0.000
N24	0.026	0.026	0.026	0.000	0.000	0.000
N25	0.026	0.026	0.026	0.000	0.000	0.000
N26	0.026	0.026	0.026	0.000	0.000	0.000
N27	0.026	0.026	0.026	0.000	0.000	0.000
N28	0.026	0.026	0.026	0.000	0.000	0.000
N29	0.026	0.026	0.026	0.000	0.000	0.000
N30	0.026	0.026	0.026	0.000	0.000	0.000
N31	0.026	0.026	0.026	0.000	0.000	0.000
N32	0.026	0.026	0.026	0.000	0.000	0.000
N33	0.026	0.026	0.026	0.000	0.000	0.000
N34	0.026	0.026	0.026	0.000	0.000	0.000
N35	0.026	0.026	0.026	0.000	0.000	0.000
N36	0.026	0.026	0.026	0.000	0.000	0.000
N37	0.026	0.026	0.026	0.000	0.000	0.000
N38	0.026	0.026	0.026	0.000	0.000	0.000
N39	0.026	0.026	0.026	0.000	0.000	0.000
N40	0.026	0.026	0.026	0.000	0.000	0.000
N41	0.026	0.026	0.026	0.000	0.000	0.000
N42	0.026	0.026	0.026	0.000	0.000	0.000
N43	0.026	0.026	0.026	0.000	0.000	0.000
N44	0.026	0.026	0.026	0.000	0.000	0.000
N45	0.026	0.026	0.026	0.000	0.000	0.000
N46	0.026	0.026	0.026	0.00		

Figure 14

crystals used for the X-ray structure determination above were shown to be identical with that from a sample isolated previously from base treatment of keto-amide (51).

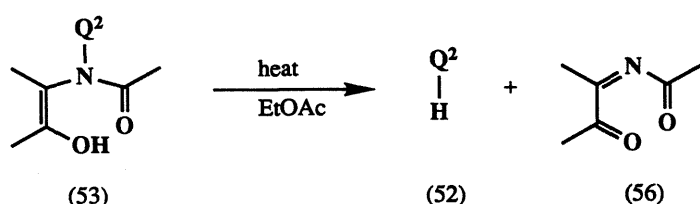


SCHEME 67

3.4 THERMAL ELIMINATION OF THE QUINAZOLINONE MOIETY:

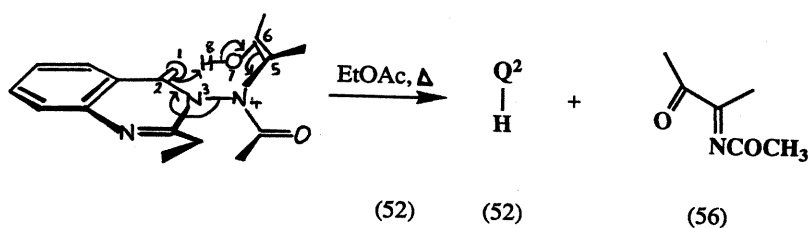
FORMATION OF N-ACYLIMINE (108)

Taking the enol-amide (53) and heating under reflux for approximately one minute in ethyl acetate resulted in an 86% yield of 2-ethylquinazolin-4(3H)-one (52) after cooling in ice and filtering. The filtrate, after evaporation, was kugelrohr-distilled to give a 95% yield of N-acylimine (56) as an unstable pale green oil (Scheme 68). The instability of this compound did not allow its full characterisation but its n.m.r. spectroscopic data (¹H: δ 1.95, 2.12, 2.27 (3xCH₃) and ¹³C: δ15.66, 24.29, 24.44 (3xCH₃), 161.10 (CN), 185.18, 198.55 (2xC=O)) agreed with the structure proposed.



SCHEME 68

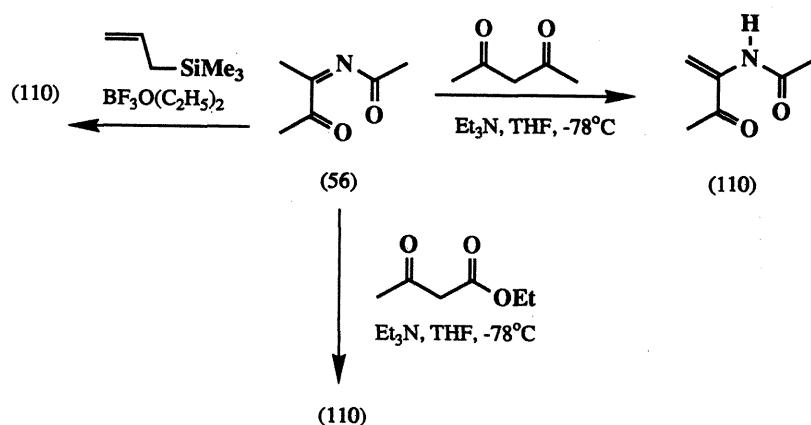
The N-acylimine was presumably formed by a thermal elimination of the quinazolinone ring by a mechanism identical with that proposed to account for the formation of 2-ethylquinazolin-4(3H)-one (52) when enol-amide (53) is heated on a Kofler hot stage, (see Chapter 2), namely elimination via an 8-membered transition state (Scheme 69).



SCHEME 69

Attempted alkylation of this N-acylimine (56) with allyltrimethylsilane and boron trifluoride etherate was unsuccessful but instead brought about tautomerisation of (56) to the α,β -unsaturated ketone (110) in 85% yield. Also, attempted stabilised anion additions using pentan-2,4-dione and triethylamine in THF at -78°C or ethyl acetoacetate and triethylamine in THF at -78°C , gave 55% and 43% yields respectively of the same α,β -unsaturated

ketone (110) (Scheme 70).



SCHEME 70

The α,β -unsaturated ketone (110) also proved to be unstable and only a melting point ($47-48^\circ\text{C}$) and a proton n.m.r. spectrum were obtained. The n.m.r. spectrum showed the disappearance of a methyl group by comparison with that of (56) and the appearance of two alkene type protons (δ 5.75, s, $\text{CH}=\text{anti}$ to NH and δ 6.87, s, $\text{CH}=\text{cis}$ to NH). The gross difference in chemical shift is due to the carbonyl group deshielding CH_B at δ 6.87, relative to CH_A at δ 5.75, see Figure 15.

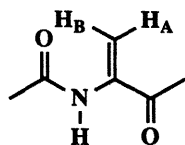
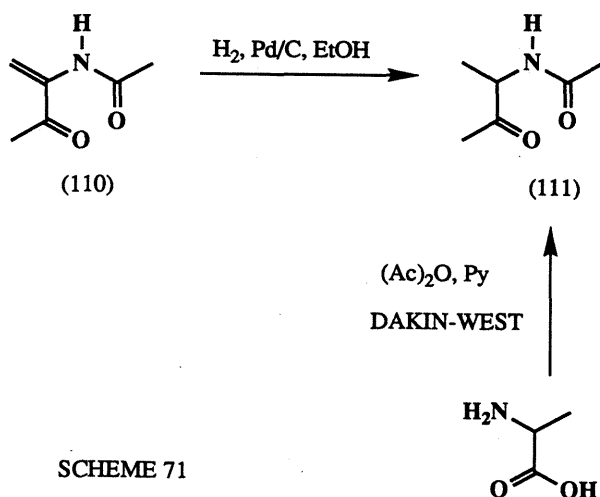


Figure 15

Immediate hydrogenation of a freshly prepared sample of the α,β -unsaturated ketone (110) using palladium on charcoal gave an 89% yield of 3-acetamido-2-butanone (111) as a colourless oil (Scheme 71). An authentic sample of 3-acetamido-2-butanone (111) was prepared from acetic anhydride and pyridine treatment of alanine by the Dakin-West reaction⁵⁰ (Scheme 71) and was identical in all respects to the sample isolated from the hydrogenation of α,β -unsaturated ketone (110).

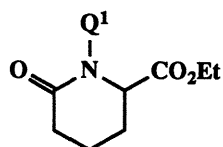


SCHEME 71

3.5 SYNTHESIS AND ATTEMPTED METHYLATION OF N-(QUINAZOLINONE-N'-YL) 6-ETHOXYCARBONYL-2-PYRIDONE (119)

Attempts to alkylate the N-acetyl-N-(quinazolinone-N'-yl)- α -aminoketones described previously were frustrated by the unsuspected facility with which the quinazolinone ring

was eliminated. If it is assumed that in this elimination there is a stereoelectronic requirement for overlap of the breaking bond and the filled carbanion p-orbital, then this elimination would be expected to be retarded in for example (119): such an overlap as in Figure 16 would require destruction of the amide resonance energy.



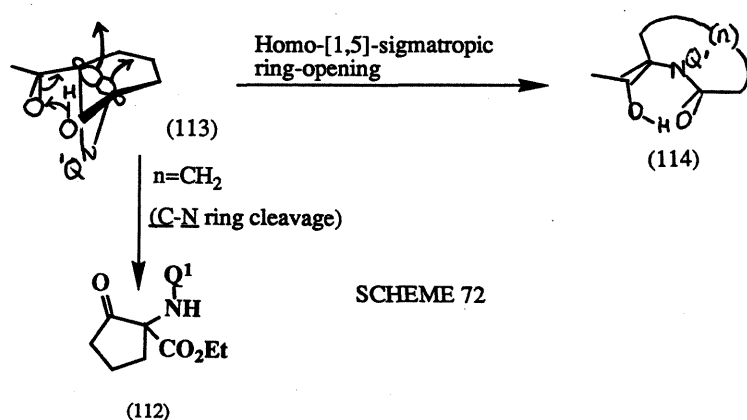
(119)

Figure 16

Thus the synthesis of (119) was attempted with the expectation that elimination of the quinazolinone ring would be slow enough to allow methylation under the influence of the N-N chiral axis.

Oxidation of N-aminoquinazolinone (73) with lead tetraacetate and subsequent reaction with ethyl 2-oxocyclopentane carboxylate gave amine-ester (112) in 77% yield after crystallisation from ethanol. This product would result from C-N ring cleavage of the intermediate aziridine (113). The absence of the desired product from C-C breaking can be rationalised in terms of stereoelectronic demands of the homo-[1,5]-sigmatropic rearrangement which makes this reaction unfavourable. As a consequence acid-catalysed aziridine ring-opening by C-N bond cleavage occurs. For C-C ring cleavage to occur in the sigmatropic rearrangement (Scheme 72), a disrotatory ring opening of

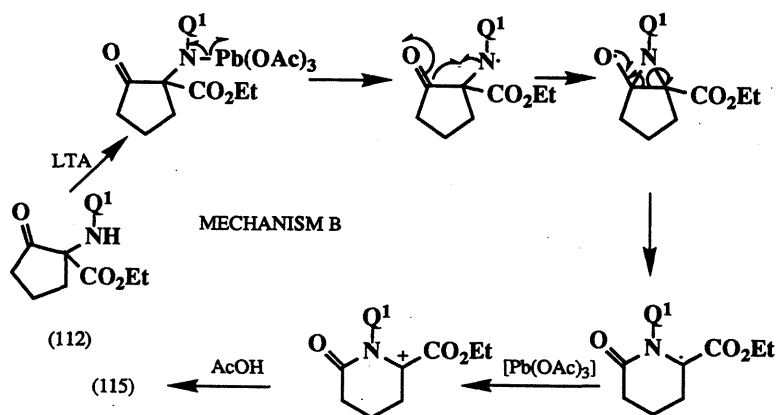
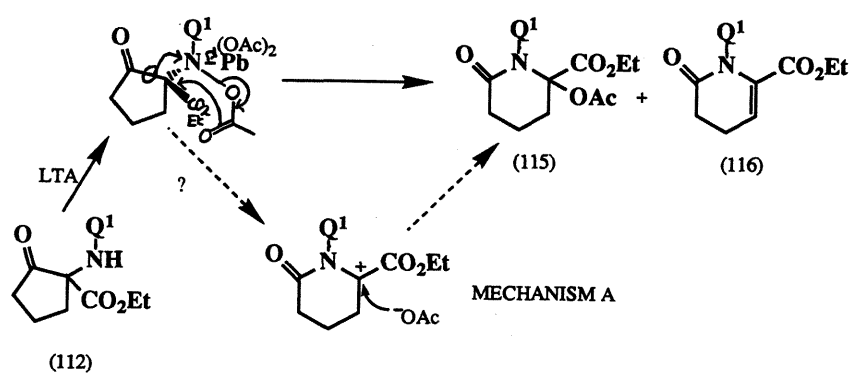
the aziridine $\underline{\text{C}}-\underline{\text{C}}$ bond is required in the direction indicated. This would give an enol-amide (114) in a highly strained conformation with too few atoms ($n=\text{CH}_2$) to span the bridge between amide and enol. As a result, this route is disfavoured and so $\underline{\text{C}}-\underline{\text{N}}$ ring cleavage occurs.



When amine-ester (112) was further treated with LTA a ring expansion occurred from a 5- to a 6-membered ring system (Scheme 73). An authoritative review by Butler⁵¹ gave no other example of this type of reaction where LTA-mediated oxidative ring expansion of a secondary amine occurs. A 46% yield of α -acetoxy ester (115) and a 22% yield of α,β -unsaturated ester (116) were isolated after column chromatography. The α -acetoxy ester (115) would be expected to possess a chiral axis as well as a chiral centre but it was apparently formed as a single diastereoisomer: only one acetate methyl singlet is visible in the n.m.r. spectrum and the presence of a single diastereoisomer can be seen from the single pair of diastereotopic methyl groups in the isopropyl group and a

single pair of diastereotopic protons in the ester methylene group. (CH_2CHCH_2 , δ 1.24 and 1.46, 2xd, $J_{6,7}\text{Hz}$ and CH_2CH_2 , δ 3.86 and 4.00, ABX₃, $J_{10,7,7.2}\text{Hz}$).

Two possible mechanisms for this oxidative ring expansion are shown in Scheme 73. In mechanism (A), a concerted ring bond migration to the exocyclic nitrogen, with cleavage of the lead-nitrogen bond and loss of lead di-acetate occurs; at the same time a stereoselective intramolecular S_N2-type attack of an acetoxy group bound to the lead occurs from the backside of the migrating ring bond to give a single diastereoisomer of α -acetoxy-ester (115). The second possible mechanism (B) involves homolysis of the lead-nitrogen bond. The radical on nitrogen then rearranges via an aziridinyloxy radical to give a more stable captodative radical. Oxidation of the radical to a carbocation followed by reaction with acetic acid gives the product (115). Formation of the α,β -unsaturated ester (116) in this reaction is suggestive of a carbocation intermediate but this does not necessarily support mechanism (B) since the timing of bond changes in mechanism (A) may also allow for carbocation formation at the position α to the ester.



SCHEME 73

The α,β -unsaturated ester (116) possesses a chiral element (a chiral axis) in the molecule which can be seen from the diastereotopic nature of the isopropyl methyl groups, (CH_3CHCH_3 , δ 1.27 and 1.43, 2xd, J 6.7Hz), and from the ester methylene protons, (CH_3CH_2 , δ 4.00 and 4.10, ABX₃, J 19.6, 7.1Hz). As mentioned above, formation of (116) could arise from a carbocation intermediate by loss of a proton

in either mechanism (A) or (B).

Treatment of amine-ester (112) with LTA in methanol gave, after chromatography, an inseparable mixture of diastereoisomeric methoxy-esters (117a/117b) in a 1.83:1 ratio. Using methanol as a solvent it appears that a carbocation is formed and quenched by methanol. This attack by methanol on the carbocation could occur, in principle, from either lobe of the vacant p-orbital. However, under the influence of the chiral axis, a 1.83:1 ratio of diastereoisomers (117a/117b) is produced, see Figure 17. Presumably as drawn, methanol would prefer to attack the top lobe of the carbocation (pathway (A)) as this is further removed from the bulky isopropyl group.

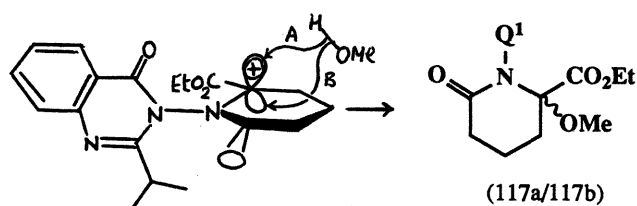
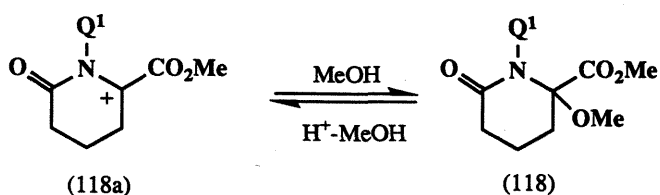


Figure (17)

This mixture of diastereoisomers was kugelrohr-distilled at 250°C and 0.1mmHg which resulted in its ratio changing from 1.83:1 to 1:1.8. Presumably, thermally-induced N-N bond rotation has occurred under these conditions.

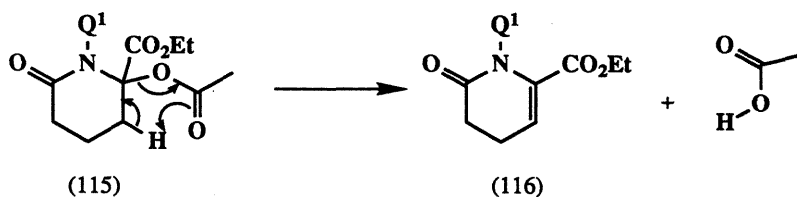
The 1.83:1 ratio of diastereoisomers (117a/117b) was treated with a catalytic amount of sulphuric acid and heated under reflux in methanol with the result that ester

exchange occurred (methyl ester for ethyl ester) to give a 77% yield of α -methoxy-methyl-ester (118) as a single diastereoisomer. Presumably, ester exchange and diastereoisomer enrichment is occurring under the influence of the chiral N-N bond resulting in the formation of only one diastereoisomer of (118) (Scheme 74). Reversible formation of the carbocation (118a) in the presence of acid could lead to a thermodynamically controlled preference for a single diastereoisomer of (118), whereas the 1.83:1 ratio of diastereoisomers (117a/117b) could result from kinetic control in the LTA oxidation in methanol.



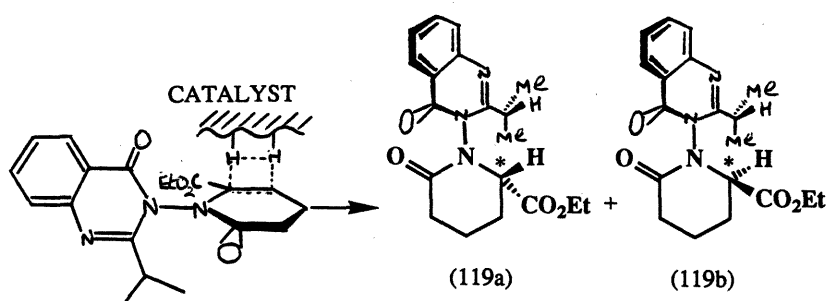
SCHEME 74

Kugelrohr-distillation of α -acetoxy-ester (115) at 250°C and 0.1mmHg resulted in elimination of acetic acid and the formation of α,β -unsaturated ester (116) in 98% yield. This presumably results from the removal of acetic acid by a six-membered transition state (Scheme 75).



SCHEME 75

α,β -Unsaturated ester (116) was hydrogenated using Adams catalyst (2 mol equiv.) in ethanol under a hydrogen atmosphere to give, after column chromatography, ester-tetrahydropyridone (119a) in 34% yield and its diastereoisomer (119b) in 16% yield. Preferential formation of isomer (119b) compared to (119a) could be rationalised by asymmetric hydrogenation under the influence of the chiral N-N axis; hydrogenation is occurring preferentially away from the bulky isopropyl group (Scheme 76) but the relative configuration in these two diastereoisomers is as yet unknown.



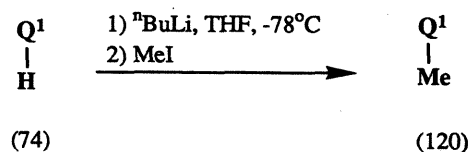
SCHEME 76

* Relative configuration arbitrarily assigned

Both diastereoisomeric ester-tetrahydropyridones (119a) and (119b) possess a chiral axis, in addition to a chiral centre and, not surprisingly, the methyl groups in each isopropyl group are diastereotopic (for (119a): CH_3CHCH_3 , 2xd, δ 1.26 and 1.32, $J_{6.7\text{Hz}}$, and for (119b): CH_3CHCH_3 , 2xd, δ 1.28 and 1.42, $J_{6.7\text{Hz}}$). Likewise, the protons in each ester methylene group are also diastereotopic (for (119a): CH_3CH_2 , ABX₃, δ 4.10, $J_{9.8,7.1\text{Hz}}$, and for (119b): CH_3CH_2 ,

ABX₃, δ 4.07, J10.8, 7.2Hz).

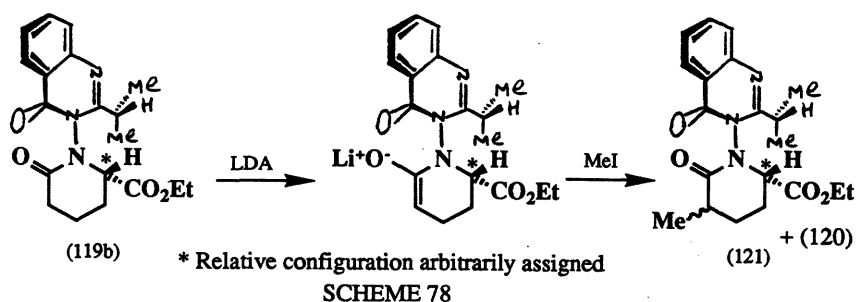
A 4:1 mixture of diastereoisomeric ester-pyridones (119b):(119a) was then treated with LDA in THF at -78°C containing 1 mol equiv. of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) and then with methyl iodide, which gave after column chromatography as an inseparable mixture: N-methyl-2-isopropylquinazolin-4(3H)-one (120) and what is believed to be methylated ester-amide (121). Also recovered in this chromatography was one of the diastereoisomers (119b) of the starting material in pure form. An authentic sample of N-methylated quinazolinone (120) was prepared by treatment of 2-isopropylquinazolin-4(3H)-one (74) with ⁿbutyllithium in THF and alkylating the anion with methyl iodide (Scheme 77).



SCHEME 77

The N-methylated quinazolinone (120) isolated in 79% yield, had peaks in its n.m.r. spectrum which were identical to those peaks which were assigned to (120) in the proton n.m.r. of the mixture of (120) and (121). An accurate mass determination on the mixture of (120) and (121) gave a mass of 371.1845 for the major highest mass peak in the mixture. This is consistent with the incorporation of a methyl group (with loss of a proton)

into diastereoisomer (119b). However, the proton α to the ester group in diastereoisomer (119b) is still present in compound (121), (δ 4.51-4.62, m, CHCOOEt) and so it is likely that methylation α to the ester group has not taken place. There was no evidence from the mass spectrum or proton n.m.r. of the mixture of (120) and (121) for the incorporation of deuterium in compound (121) when deuterium oxide was added at the end of the reaction. It is reasonable to suppose that the competitive removal of a proton by LDA will take place so that the anion formed will be stabilised by delocalisation into the carbonyl group of the amide of the lactam. Methylation would therefore occur at this position presumably non-stereoselectively to give a mixture of diastereoisomers (Scheme 78).



From the proton n.m.r. spectrum of the mixture of (120) and (121), it is possible, after subtracting the signals due to (120), to see the two methyl doublets of the isopropyl group in (121). This suggests that methylation at the 2- position of the quinazolinone ring (to give a tertiary-butyl group at this position) has not occurred.

Compound (121) still contains a chiral axis as can be seen from the diastereotopic nature of the isopropyl methyl groups, (CH_3CHCH_3 , δ -1.25, 2xd, J6.6Hz), and from the diastereotopic nature of the ester methylene protons, (CH_3CH_2 , δ 4.01-4.13, ABX₃, J14.4, 7.1Hz).

Even in a molecule like (119) in which stereoelectronic factors militate against elimination of the quinazolinone ring, this is still a major pathway on attempted alkylation via carbanion formation α - to the N-N chiral axis. The absence of incorporation of deuterium into the recovered (119a) suggests that the proton α - to the ester was never removed in the reaction except when elimination of the quinazolinone ring occurred.

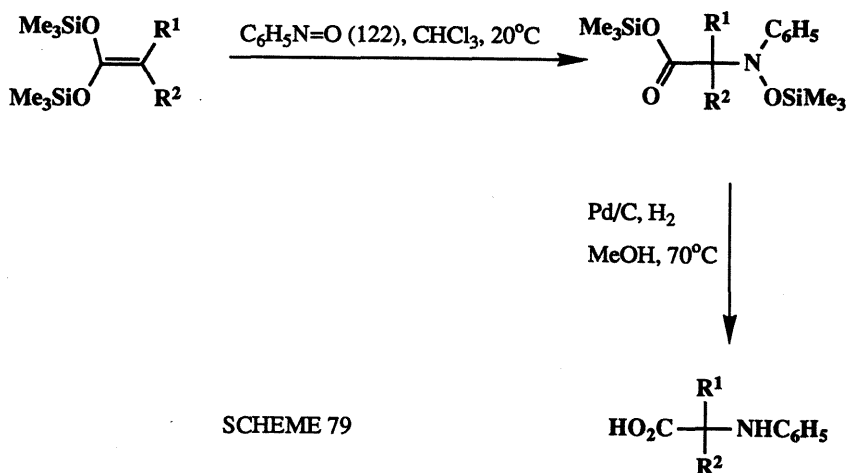
Summary:

Barriers to N-N bond rotation in N-acetylaminquinazolinone (93) and N-methylaminquinazolinone (99) were estimated by variable temperature n.m.r. spectroscopy. Attempts at C-C bond forming reactions α - to the N-N chiral axis in N-(quinazolinone-N'-yl)-N-acyl- α -aminoketones (51) proved unsuccessful with the facile elimination of the quinazolinone ring, even when the stereoelectronic factors militated against the facile elimination of the quinazolinone ring as in (119).

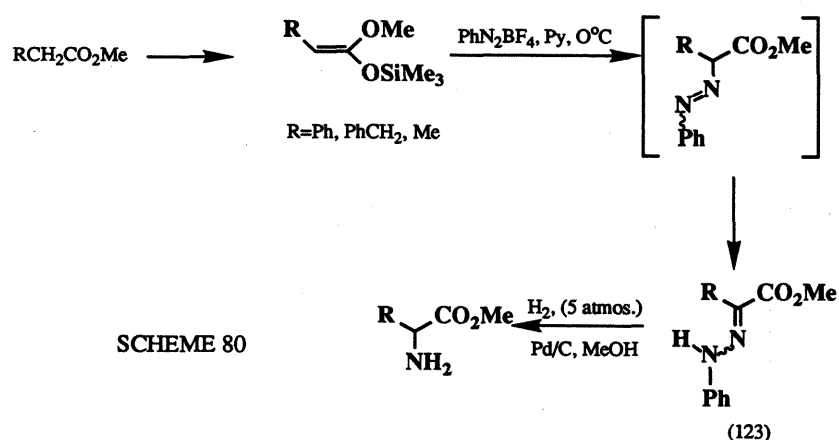
CHAPTER FOUR

4.1 INTRODUCTION

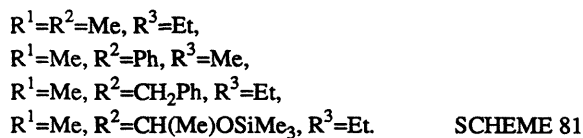
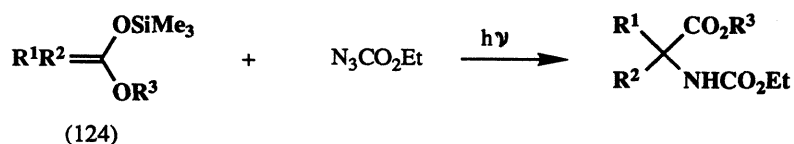
There have been a number of syntheses of amino acids which have used the reaction of electrophilic nitrogen in various forms with silyl ketene acetals. In these syntheses, the electrophilic nitrogen synthetic equivalents have been either nitroso compounds⁵², diazonium salts⁵³ or nitrenes⁵⁴. Nitroso compounds, for example (122), react with silyl ketene acetals to give *N*-phenylamino acids⁵² (Scheme 79).



Diazonium salts have been used successfully by Takana.⁵³ The products, α -hydrazono esters (123), were reduced with hydrogen and palladium on charcoal to give α -amino acid esters (Scheme 80).

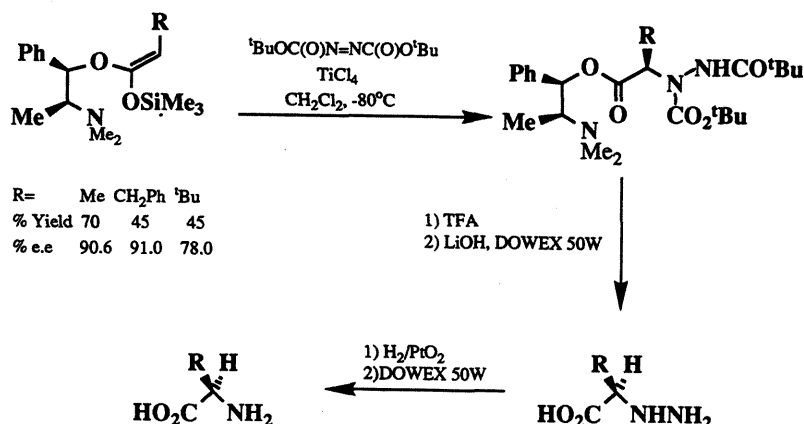


Mitani⁵⁴ has used ethyl azidoformate to generate ethoxycarbonylnitrene (EtOCON), under either photolytic or thermolytic conditions, which reacts with silyl ketene acetals (124) to give *N*-protected α -amino acid derivatives (Scheme 81).



Similarly, there have also been a number of syntheses of enantiopure aminoacids using dialkyl azodicarboxylates as NH_2^+ synthetic equivalents⁵⁵. For example, Gennari⁵⁵ has reacted *E*-silyl ketene acetals with di-*t*-butyl azodicarboxylate (Scheme 82) and obtained α -amino acids in

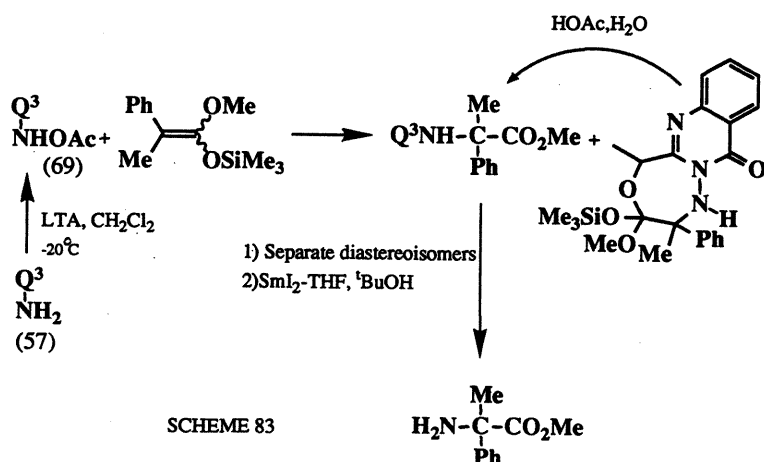
high enantiomeric excess and chemical yield.



SCHEME 82

In all of these reactions, the diastereoselectivity is substrate-controlled with the presence of a chiral auxiliary on the silyl ketene acetal directing attack on one diastereoface of the latter preferentially.

Enantiopure aminoacids have also been prepared by Atkinson *et al.*⁵⁶ They have shown that solutions of enantiopure 3-acetoxyaminoquinazolinone (69) react with silyl ketene acetals to give α -aminoacid derivatives (Scheme 83). Cleavage of the N-N bond using samarium diiodide in a single diastereoisomer gave the α -aminoacid derivative in enantiopure form. Here the diastereoselectivity is reagent-controlled with the inducing chiral centre contained in the NH₂⁺ synthon which is eventually removed as an accompaniment to the required unmasking of the amino group.



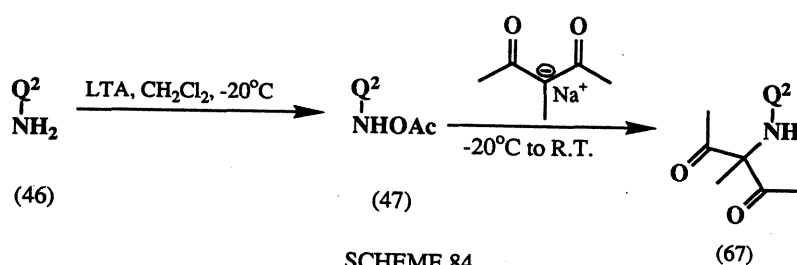
The N-acetoxyaminoquinazolinone (47) can also function as an electrophilic source of nitrogen as described below; it can function as either an NH_2^+ or an NH^+ synthetic equivalent.

4.2 THE N-ACETOXYAMINOQUINAZOLINONE (47) AS AN NH_2^+

SYNTHETIC EQUIVALENT

Treatment of the N-acetoxyaminoquinazolinone (47) at -20°C with the sodium salt of 3-methylpentan-2,4-dione resulted in the substitution of the acetoxy anion and formation of the diketo-amine (67) (27%). Compound (67) proved to be identical in all respects to that isolated previously (see Chapter 2). With the knowledge that reductive cleavage of the N-N bond in (67) is feasible, the reagent (47) is functioning as an NH_2^+ synthetic equivalent as it is in reaction with the enols in Chapter 2 to give

aziridine C-N cleavage products.



SCHEME 84

4.3 THE N-ACETOXYAMINOQUINAZOLINONE (47) AS AN NH²⁺ SYNTHETIC EQUIVALENT

In the previous chapter, formation of N-acylimines (56) and (105) arises from the fact that in N-acetoxyaminoquinazolinone (47) both the acetoxy and quinazolinone can function as leaving groups. Treatment of the N-acetoxyaminoquinazolinone (47) at -20°C with an excess of the sodium salt of ethyl acetoacetate resulted in elimination of the acetoxy and the quinazolinone ring with 2-ethylquinazolin-4(3H)-one (52) isolated in 55% yield. From the crude mixture, pyrrolinone (125) was isolated after ethanol crystallisation in 25% yield. When this reaction was repeated using a different work up procedure (see experimental relating to this chapter), a 12% yield of pyrrolinone (125) was isolated along with a 60% yield of 2-ethylquinazolin-4(3H)-one (52). Chromatography of the residue over silica gave 2-acetoxymethyl-3,5-diethoxycarbonyl-4-methylpyrrole (126) (14%) as colourless crystals which were identical in all respects with a sample prepared by the method of Clezy *et al*⁵⁷. In this reaction,

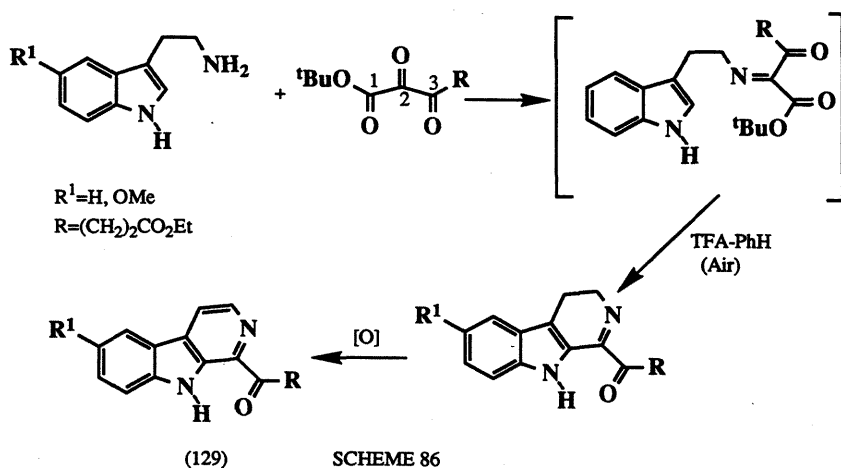
The reaction scheme illustrates the synthesis of 2-methyl-4,5-diethoxycarbonylpyrrole (125) from 2-acetyl-4,5-diethoxycarbonylpyrrole (47). The process involves several steps:

- Intermediate (47):** 2-acetyl-4,5-diethoxycarbonylpyrrole reacts with a base Q^2 to form an enolate.
- Intermediate (127):** The enolate intermediate (127) undergoes further reaction with Q^2 to form another enolate.
- Intermediate (52):** The enolate (127) reacts with Q^2 to form a diene intermediate (52) and a byproduct HN .
- Intermediate (128):** The diene intermediate (52) reacts with Q^2 to form a cyclic intermediate (128).
- Intermediate (126):** The cyclic intermediate (128) undergoes dehydration ($-H_2O$) to form a diene intermediate (126).
- Intermediate (125):** The diene intermediate (126) reacts with Q^2 to form a cyclic intermediate (125).
- Final Product (125):** The cyclic intermediate (125) undergoes further reaction with Q^2 to form the final product, 2-methyl-4,5-diethoxycarbonylpyrrole (125).

In the formation of the 1,3-dicarbonyl-2-imine (128), the N-acetoxyaminoquinazolinone is functioning as an NH^{2+} synthetic equivalent.

109

it is the central carbonyl group in a vicinal tricarbonyl system which is the most electrophilic and it is this site that is always the preferred site of attack by nucleophiles (Scheme 86).

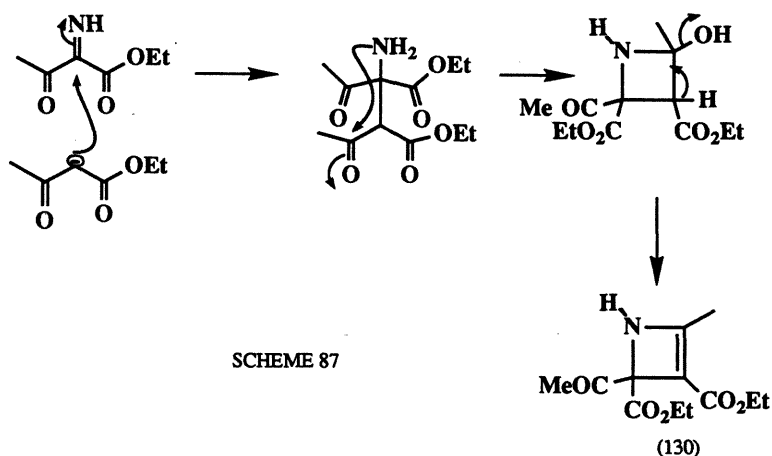


In Scheme (86), the carbonyl groups on the 1 and 3 positions serve to activate the central carbonyl group for the Pictet-Spengler condensation which is intermediate in the formation of eudistomin T (129).^{58a}

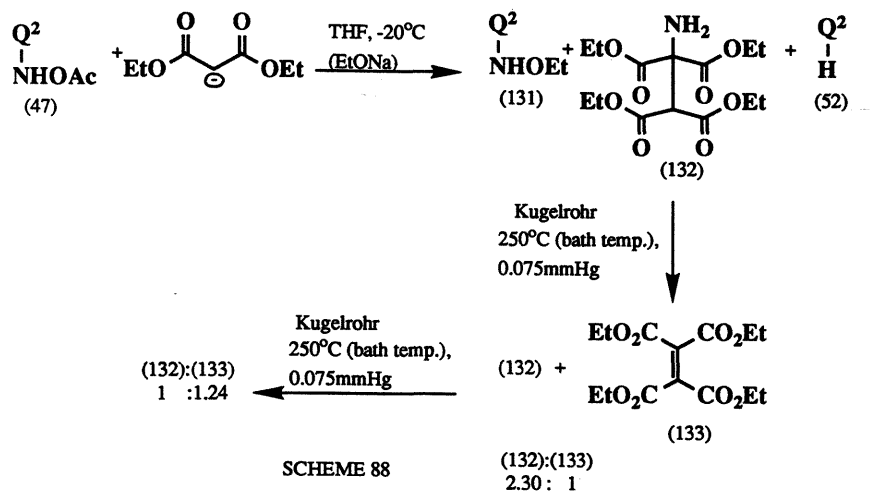
By analogy with the 1,2,3-tricarbonyl system of Wasserman, attack at the 2-imine group might have been anticipated. However, as indicated in Scheme 85, attack at the ketone carbonyl group by the second ethyl acetoacetate anion seems the most direct route to both (125) and (126) in the overall reaction.

An alternate structure for the pyrrolinone (125) which was considered was an azetine (130) which could be derived by ethyl acetoacetate anion attack on the central imine

functionality of the 1,3-dicarbonyl-2-imine system (Scheme 87). This would be the mode of reactivity anticipated from the work of Wasserman⁵⁸, see above. A distinction between (125) and (130) as the structure for the product, m.p. 126-128°C can be made on the ¹³C chemical shift of the carbonyl resonances. Pyrrolinone (125) shows no resonance in its ¹³C spectrum further downfield than $\delta 177.74$. The azetine (130) possesses a ketone carbonyl group which one would be expected to give a signal for the carbonyl group at approximately $\delta 200$. The absence of any signal further downfield than $\delta 177.74$ therefore suggests the pyrrolinone structure and not the azetine structure. Also, it seems likely that the reaction route which leads to (126) and which can also accommodate the formation (125) (Scheme 85) would support assignment of the pyrrolinone structure (125) to this product rather than the azetine (130).



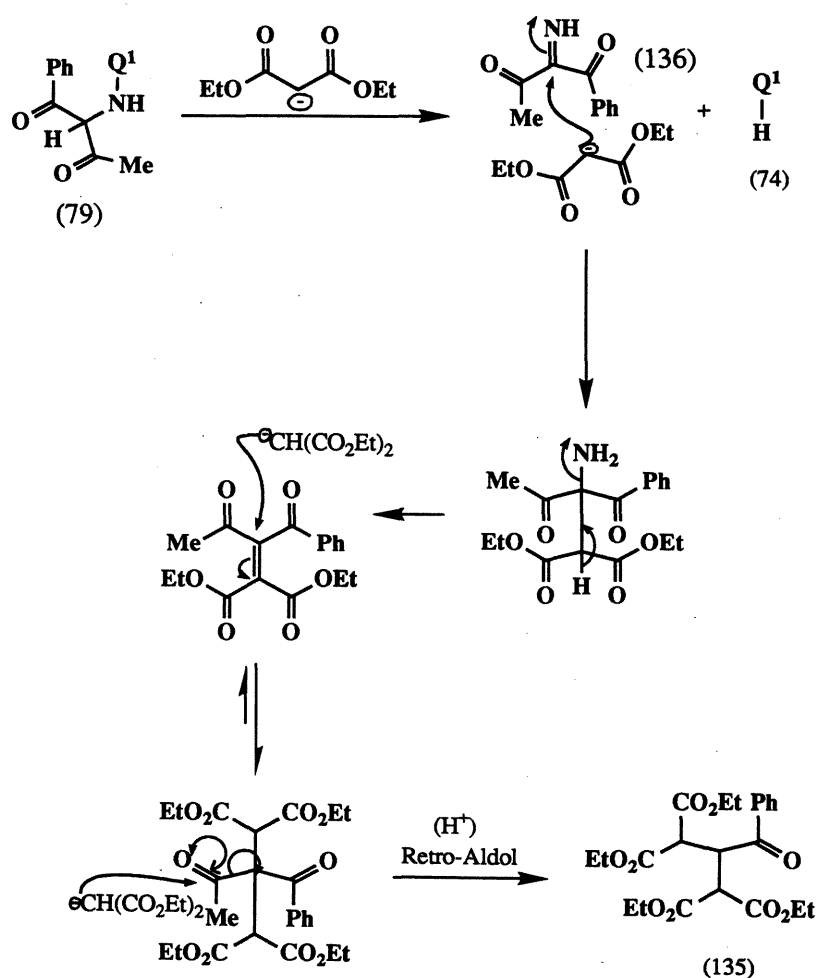
When the *N*-acetoxyaminoquinazolinone (47) was treated with an excess of the anion of diethyl malonate at -20°C , *N*-ethoxyamino-2-ethylquinazolin-4(3*H*)-one (131) was obtained in 13% yield after ethanol crystallisation. This was presumably formed from (47) by the small amount of ethanol (ethoxide) which remained after the bulk of the ethanol was removed from the sodium salt of diethyl malonate prepared in this solvent. Also isolated was amino-1,1,2,2-tetraethoxycarbonylethane (132) (9% yield) (Scheme 88) which was identical in all respects to a sample prepared by an adaptation of the method of Philipps and Uhi⁵⁹.



The proton n.m.r. spectrum of (132) shows two different multiplets (ABX_2 systems) for the two pairs of methylene protons in the two pairs of ester groups. One set is those

belonging to the two ester groups α - to the NH_2 group, the other set are those methylene protons of the two ester groups β -to the NH_2 group. Also isolated by chromatography was 2-ethylquinazolin-4(3H)-one (52) in 67% yield. In this case, attack on the central imine of the 1,3-dicarbonyl-2-imine system is occurring which is analogous to the reactivity observed by Wasserman⁵⁸ for his tricarbonyl systems. Presumably the imine site is more electrophilic than the ester carbonyl groups and so attack is directed here. Distillation of a sample of (132) produced from the reaction shown in Scheme 88 at 250°C and 0.075mmHg resulted in partial decomposition to a 2.30:1 ratio of compounds (132):(133) respectively (Scheme 88) by elimination of ammonia. Ammonia elimination at elevated temperature was also observed from (132) by Daihei and Kotaro⁶⁰. Redistillation of the 2.30:1 mixture of (132):(133) resulted in further ammonia elimination to give a 1:1.24 ratio of (132):(133). 1,1,2,2-tetraethoxycarbonylethene (133) was purchased from Lancaster Chemicals and had a proton n.m.r. spectrum identical to those resonances in the mixture of (132):(133) which did not belong to (132).

Reaction of the diketo-amine (79) with an excess of the anion of diethyl malonate results in the elimination of the quinazolinone moiety to give 2-isopropylquinazolin-4(3H)-one (74) in 34% yield after chromatography (Scheme 89).



SCHEME 89

The only other homogeneous product isolated (17%) was assigned the structure (135) (Scheme 89). The proton n.m.r. spectrum of this compound shows a doublet, which integrates for 2 protons, and a triplet which integrates for 1 proton.

In the ^{13}C n.m.r. spectrum of this compound two $\underline{\text{CH}}$ signals (δ 43.63 and 52.74) in addition to the aromatic phenyl (5x PhCH) resonances that are visible. Also seen in both the proton (and carbon) n.m.r spectra are two different sets of ester signals (^1H : δ 1.11 and 1.24 (2x $\text{CH}_3\text{CH}_2\text{CO}_2$, J 7.1Hz) and δ 3.97 and 4.16 (2x $\text{CH}_3\text{CH}_2\text{CO}_2$, ABX₃, J 14.2, 7.1 and 13.3, 7.1Hz respectively)). The two ester groups on each carbon are diastereotopic and the methylene protons within each ester group are also diastereotopic.

Formation of (135) is presumed to arise from Wasserman-type attack on the imine of (136) followed by elimination of ammonia, Michael addition of a further mole of malonate and finally loss of the acetyl group by a retro-aldol reaction.

It can be seen that the products in Schemes (85) and (88)-(89) also arise from the $\underline{\text{N}}$ -acetoxyaminoquinazolinone (47) functioning as an NH_2^+ synthetic equivalent since both the acetoxy group and the quinazolinone are able to function as leaving groups.

Summary:

The $\underline{\text{N}}$ -acetoxyaminoquinazolinone (47) has been shown to function as either an NH_2^+ or NH^{2+} synthetic equivalent by treatment with the stabilised anion of ethyl acetoacetate, diethyl malonate and acetyl acetone. In spite of the low isolated yields of products from the foregoing reactions, it can be seen there is a difference in reactivity of 1,3-dicarbonyl-2-imine systems from that of the 1,2,3-tricarbonyl systems studied by Wasserman⁵⁸. He sees

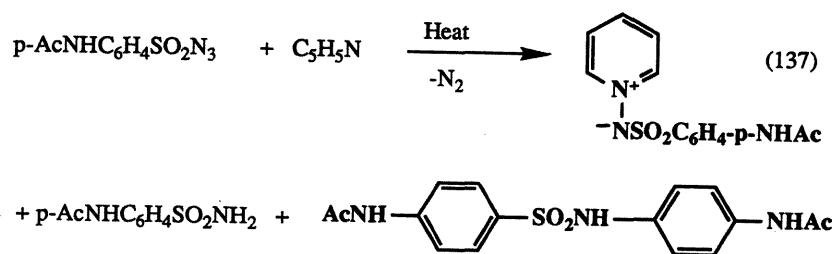
exclusive reaction with the central carbonyl group of the vicinal tricarbonyl systems. In the 1,3-dicarbonyl-2-imine system attack can occur preferentially at either the central imine functionality, analogous to the reactivity observed by Wasserman, or at the 1,(3) carbonyl depending on the nature of the latter... This difference in chemoselectivity can be explained in terms of the relative difference in electrophilicity of the possible sites of attack. In the 1,3-dicarbonyl-2-imine system, the most electrophilic site is likely to be the one to be attacked by the stabilised anion.

CHAPTER FIVE

5.1 INTRODUCTION

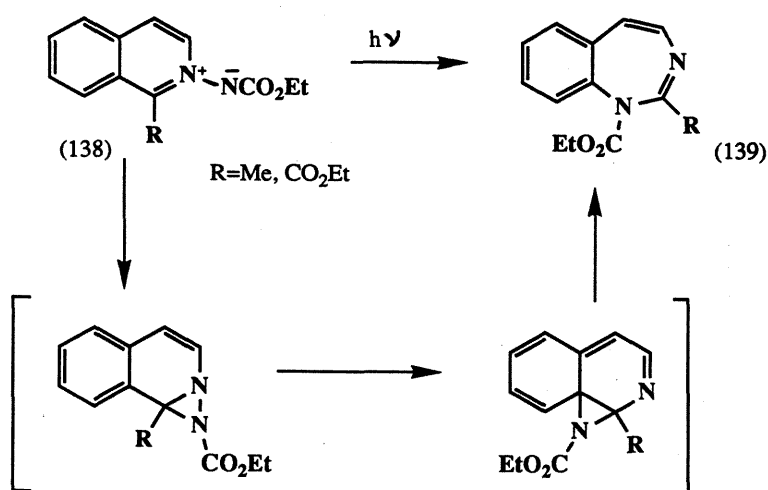
The previous chapter dealt with reaction of *N*-acetoxyaminoquinazolinone (47) with stabilised carbon anions. This chapter deals with the reaction of the *N*-acetoxyaminoquinazolinones (47) and (134) with pyridine and substituted pyridines.

There are a number of examples in the literature of the synthesis of pyridinium ylides from reaction of pyridines with nitrenes, for example 1-sulfonylimidopyridinium ylide (137), which has been synthesised from the thermolysis of benzenesulfonyl azide in pyridine⁶¹ (Scheme 90).



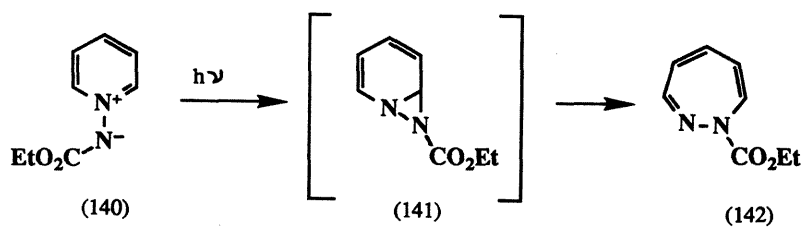
SCHEME 90

Photolysis of the 1-substituted isoquinoline *N*-ethoxycarbonylides (138) prepared by an analogous reaction of the isoquinolinone with ethoxycarbonylnitrene affords 1H-1,3-benzodiazepines (139)⁶² (Scheme 91).



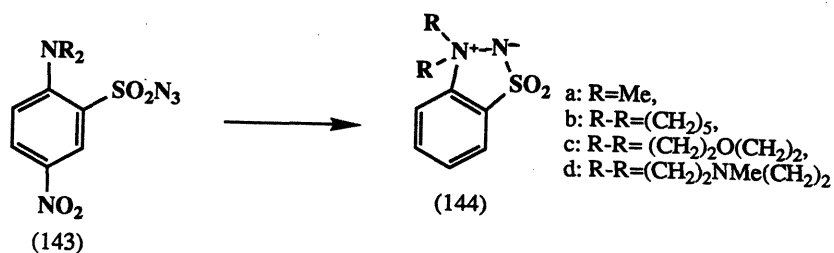
SCHEME 91

Cassel⁶³ has shown that mesoionic pyridinium derivatives, for example (140), can be considered as 1,3-dipoles. The pyridinium derivative (140) will undergo photochemically-induced ring expansion to ethyl 1H-diazepine 1-carboxylate (142) via the intermediate product from 1,3-dipolar ring closure to the diaziridine (141) followed by valence tautomerisation to (142) (Scheme 92).



SCHEME 92

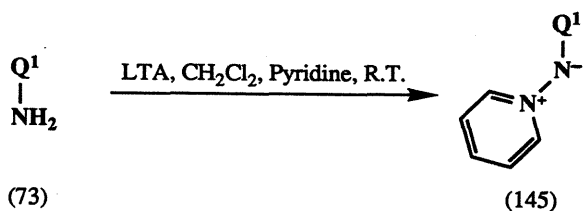
Other azaimines are also known, e.g. Suschitsky⁶⁴ has obtained mesoionic systems (144) as isolated intermediates for the cases (144b-d) from pyrolysis of the azides (143a-d), (Scheme 93).



SCHEME 93

5.2 OXIDATION OF N-AMINOQUINAZOLINONES WITH LTA IN THE PRESENCE OF PYRIDINES:FORMATION OF PYRIDINIUM YLIDES

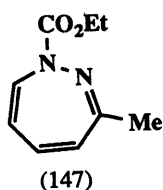
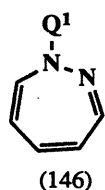
Oxidation of N-aminoquinazolinone (73) with LTA in the presence of pyridine resulted in the formation, in 36% yield, of pyridinium ylide (145) as yellow crystals (Scheme 94).



SCHEME 94

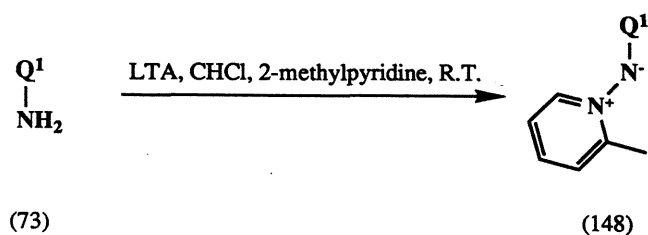
Assignment of an ylide structure to this compound (145), and those ylides described below, rather than diazepines of general structure (146) followed from the chemical shifts and coupling constants of the pyridine ring

protons in these compounds.



Thus (145) shows peaks for the pyridinium protons at δ 6.95–7.00 (CH-4), δ 7.15–7.20 (CH-3,5) and δ 7.70–7.85 (CH-2,6). By contrast, signals for the diazepine (147) has resonances for the ring protons in the range δ 5.75 to δ 6.60. This difference in chemical shifts therefore excludes the diazepine structure for the compounds isolated.

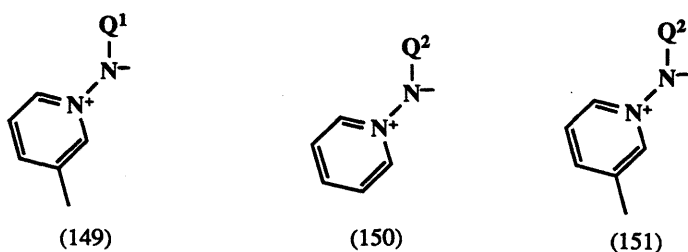
Oxidation of *N*-aminoquinazolinone (73) with LTA in the presence of 2-methylpyridine resulted in the formation of pyridinium ylide (148) in 53% yield as yellow crystals, Scheme 95.



SCHEME 95

In a similar way, oxidation of *N*-aminoquinazolinones (73) in the presence of 3-methylpyridine and (46) in the

presence of pyridine and 3-methylpyridine gave rise to the ylides (149)-(151) in the yields indicated in Table 3 (*vide infra*).



N-aminoquinazolinone (+LTA)	Pyridine type base	Ylide	Yield/ %
(73)	3-methylpyridine	149	55
(46)	pyridine	150	33
(46)	3-methylpyridine	151	31

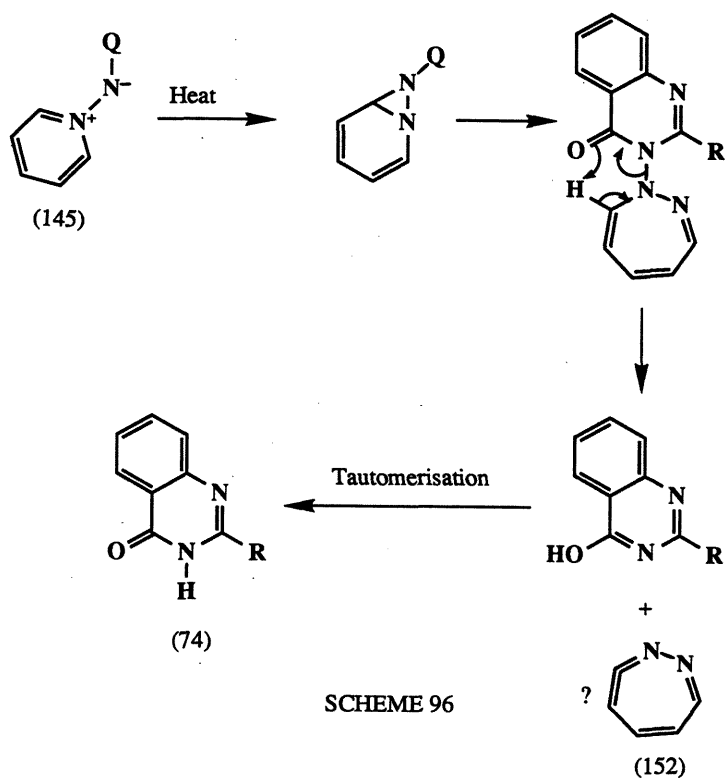
Table 3: Reaction of N-aminoquinazolinone (46) and (73) with LTA and pyridine or 3-methylpyridine.

5.3 PYROLYSIS OF PYRIDINIUM YLIDES

Taking the pyridinium ylide (145) and heating it, neat, in a round bottomed flask, to 150°C resulted in decomposition to give a 2-isopropylquinazolin-4(3H)-one (74) which was identical in all respects to that isolated previously.

Pyridinium ylides (145) and (148)-(151) all decompose between 100-142°C (within 10°C except (148)), see Table 4,

and re-solidify rapidly. The solid then re-melts in all cases at a temperature in excess of 180°C. It appears that in all cases thermal decomposition of the pyridinium ylide takes place with formation of the 3-H quinazolinone and the higher melting point corresponds to that of the latter. A possible mechanism for this elimination could be that shown in Scheme 96.



Ylide	Decomposition/ melting point Temperature/°C	Second melting point/°C.
(145)	134-136	195-197
(148)	100-102	195-198
(149)	141-142	180-182
(150)	132-135	188-190
(151)	137-140	188-190

Table 4: Decomposition temperatures for pyridinium ylides.

The pyridinium ylide could undergo a thermally induced ring closure to the diaziridine from which valence tautomerisation would lead to the diazepine. This mechanism is analogous to that proposed by Cassel⁶³ (see above). The quinazolinone could be eliminated via a 6-membered transition state in its tautomeric hydroxyquinazoline form. The fate of the diazepine moiety (152) is unknown at the present time.

5.4 N-N ROTATIONAL AND N-INVERSION BARRIERS IN PYRIDINIUM

YLIDES

There are few, if any, examples where the barrier to either N-inversion or rotation of N-N bonds has been measured in pyridinium ylides. In the carbon and proton

n.m.r. spectra of ylides (145) and (148)-(151), broadened peaks are seen for the methylene protons in the quinazolinone ethyl group of ylides (150)-(151), and broadened methyl peaks for the isopropyl group are seen in ylides (145) and (148)-(149). In all cases where there are two ortho protons present on the pyridinium ring, broadened signals from these protons are seen. These broadened signals at room temperature can be attributed to the onset of dynamic processes which are exchanging the magnetic environments of the protons in the methylene group or the two isopropyl methyl groups and similarly the magnetic environments of the pyridinium ortho protons. A 400MHz proton n.m.r. spectrum of pyridinium ylide (145), at increments down to -95°C was recorded in order to establish the barriers to these processes. In anticipation of what follows a proposed stereostructure for (145) is that shown in Figure 18.

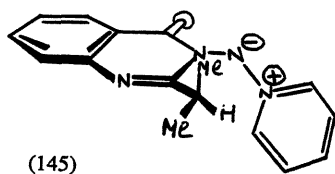


Figure 18

At -40°C the broadened isopropyl methyl signals have 'frozen' out and sharpened up fully. From the coalescence of these methyl doublet signals-the temperature of maximum broadening-a barrier of $\Delta G^{\ddagger}=14.26 \text{ K cal mol}^{-1}$ can be

calculated (see Appendix 1). By -95°C , two separated signals for the ortho protons are visible, but they have not sharpened up fully. The barrier responsible for this (second) process was calculated to be $\Delta G^{\ddagger}=11.41 \text{ K cal mol}^{-1}$ from the coalescence temperature (-17°C) of these peaks at $\delta 7.17$ and 8.26 . The process which interconverts the environments of the two methyl groups of the isopropyl group must be either rotation around the $\text{N}^1\text{-N}^2$ bond or inversion at N^2 . Since at -40°C , these signals have sharpened fully, this means that the process, whether it is N-N bond rotation or N-inversion , is completely 'frozen' on the n.m.r. time scale. At a temperature of 256K , therefore, one can exclude N-inversion at N^2 as the process leading to the exchange of the magnetic environments of the ortho protons on the pyridinium ring since this would also exchange the environments of the isopropyl methyl groups which are sharp at this temperature. Therefore one can assign the process which is frozen out at the lower temperature as being due to rotation around the $\text{N}^2\text{-N}^3$ bond.

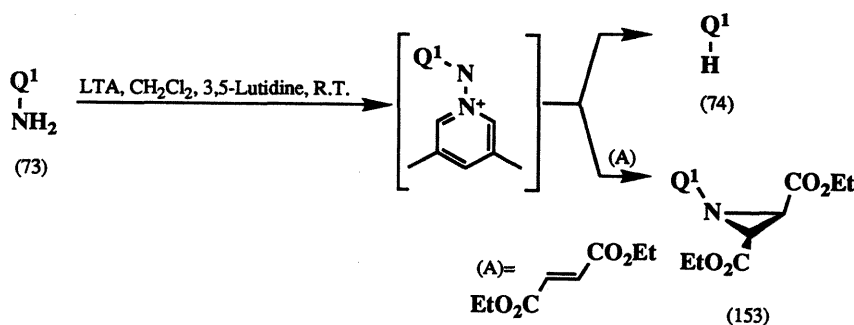
It is not possible at the present time to distinguish between N-N bond rotation or N-inversion at N^2 as the process interconverting the environments of the isopropyl methyl groups.

5.5 INTERMOLECULAR AZIRIDINATIONS USING PYRIDINIUM YLIDES

Oxidation of $\text{N-aminoquinazolinone}$ (73) with LTA in the presence of 3,5-lutidine gave an oily product.

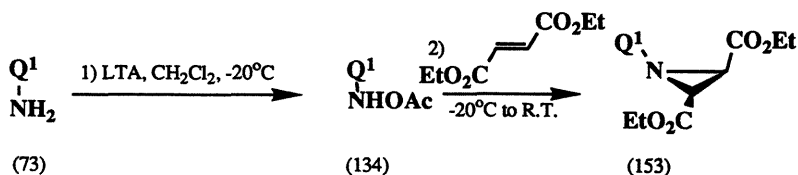
Attempts to crystallise this oil resulted in partial decomposition with the formation of 2-isopropylquinazolin-4(3H)-one (74) (Scheme 97).

When the oxidation was repeated, the oil isolated after work-up was heated immediately in the presence of diethyl fumarate at 145°C, then a 30% yield of aziridine (153) was isolated after column chromatography (Scheme 97).



SCHEME 97

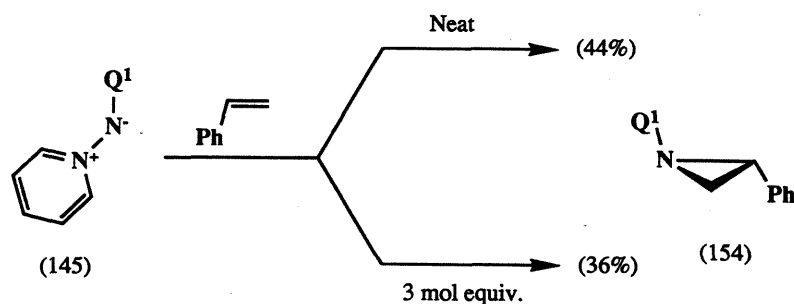
This shows that it is not necessary to isolate the pyridinium ylide in pure form as it will react *in situ* with the alkene. The identity of aziridine (153) was confirmed by its preparation from *N*-acetoxyaminoquinazolinone (134) and diethyl fumarate in 86% yield after column chromatography (Scheme 98).



SCHEME 98

The ^{13}C spectra of aziridine (153) shows different signals for the two aziridine CH carbons (δ 46.72 and 49.00). Also, the proton n.m.r. spectrum shows diastereotopic methyl groups from the isopropyl group (δ 1.15 and 1.42, $2\text{xd}, \text{CH}_3\text{CHCH}_3$, $J_{6.6\text{Hz}}$). This difference in chemical shifts of the carbon signals from the aziridine ring is due to the fact that one is attached to an ester group which is syn, and one anti, to the quinazolinone ring.

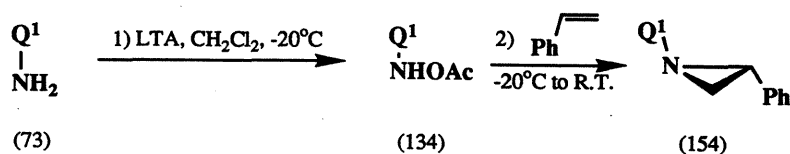
The addition of pyridinium ylide (145) to an excess of neat styrene at 135°C gave a 44% yield of aziridine (154) after column chromatography (Scheme 99). Repeating this aziridination in the presence of only 3 mol equivalents of neat styrene gave a 36% isolated yield of aziridine (154) after column chromatography.



SCHEME 99

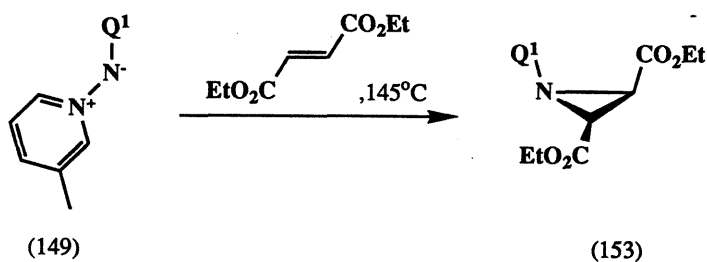
The identity of aziridine (154) was confirmed by preparation of an identical sample (Scheme 100), from N-acetoxyaminoquinazolinone (134) and styrene, to give a 75%

yield of aziridine (154) after column chromatography.



SCHEME 100

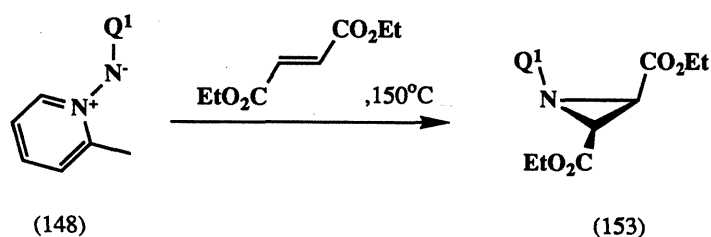
The addition of pyridinium ylide (149) to 3 mol equivalents of diethyl fumarate at 145°C gave a 33% isolated yield of aziridine (153) after column chromatography (Scheme 101).



SCHEME 101

The addition of pyridinium ylide (148) to 5 mol equivalents of diethyl fumarate at 150°C gave a 56% isolated yield of aziridine (153) after column chromatography (Scheme 102). The proton n.m.r. spectrum of the crude mixture after distillation of excess diethyl fumarate, but before chromatography, showed no polymerisation had occurred (see later): only signals from the aziridine (153) and excess diethyl fumarate were

present.

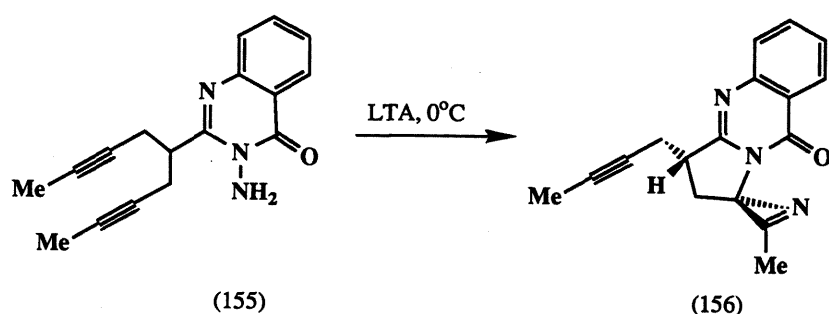


SCHEME 102

It can be seen from this series of reactions that the pyridinium ylides (145) and (148)-(151), like *N*-acetoxyaminoquinazolinones, function as aziridinating agents for both styrene and diethyl fumarate, two alkenes of very different electron availability.

5.6 INTRAMOLECULAR AZIRIDINATION OF THE PYRIDINIUM YLIDE DERIVED FROM 3-AMINO-2-(NONA-2,7-DIYN-5-YL)-QUINAZOLIN-4(3H)-ONE (159)

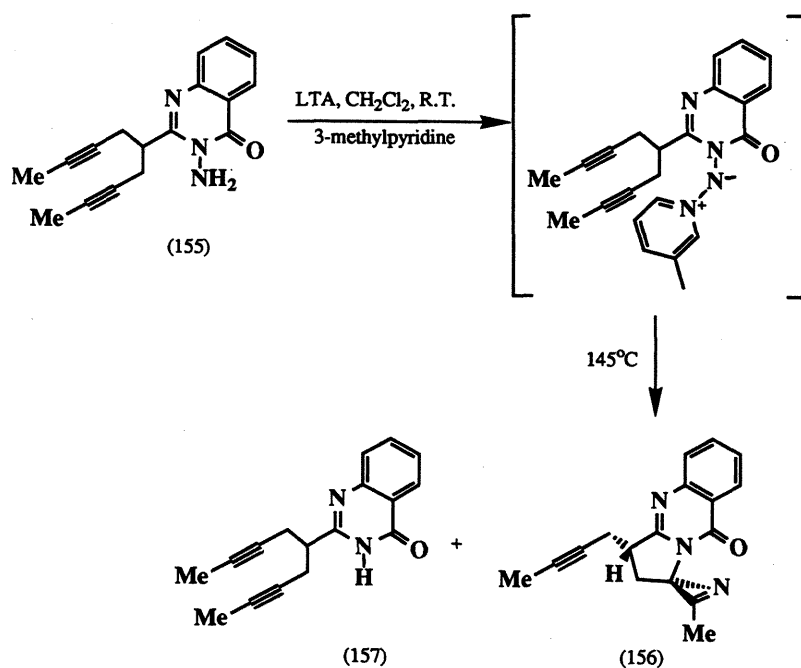
As well as the intermolecular aziridinations which the pyridinium ylides effect (shown above), it was of interest to see if intramolecular aziridinations were possible. It was shown by Grimshire⁶⁵ that when 3-amino-2-(nona-2,7-diyn-5-yl)quinazolin-4(3H)-one (155) is oxidised with LTA at 0°C, a 96% yield of azirine (156) was obtained (Scheme 103).



SCHEME 103

N-Aminoquinazolinone (155) was oxidised with LTA in the presence of 3-methylpyridine, lead diacetate removed and the reaction worked up as in procedure (4) (see experimental), and the oil which was obtained was then heated at 145°C for 10 min. After column chromatography, azirine (156) (32%) was obtained (Scheme 104) which was identical by high-field n.m.r. comparison to that isolated by Grimshire⁶⁵. A proton n.m.r. spectrum of the crude oxidation mixture before heating showed a spectrum too complex to interpret fully. However, it was clear that there was no azirine formed at this stage by the absence *inter alia* of the resonance for the 2-H, δ 1.97 (dd, J13.7 and 8.3Hz) and the ring methyl at δ 2.79 of the azirine in this spectrum. Also visible in the spectrum were signals due to the de-aminated quinazolinone (157), (δ 11.06,

bs,NH). So it could be concluded that no intramolecular cyclisation had occurred at this stage and intermolecular reaction with 3-methylpyridine was complete.



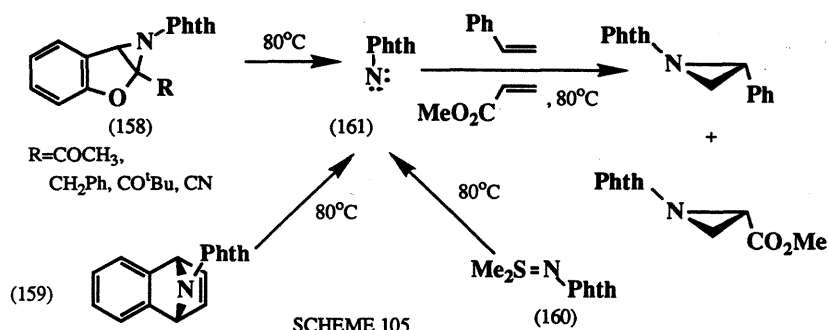
SCHEME 104

It can therefore be seen that intramolecular aziridinations are possible with pyridinium ylides as well as intermolecular aziridinations.

5.7 ATTEMPTS TO IDENTIFY THE MECHANISM OF AZIRIDINATION OF ALKENES USING PYRIDINIUM YLIDES

Atkinson, Jones, and Kelly⁶⁶ have found that thermolysis

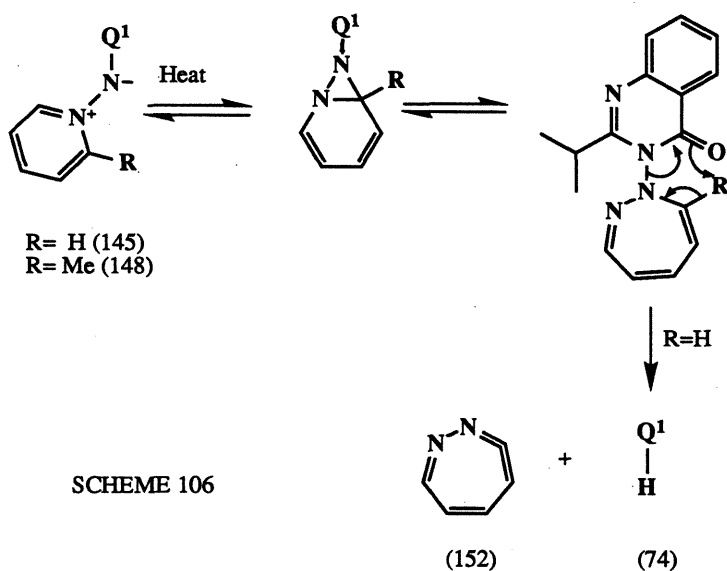
of aziridinobenzofurans (158), benzo-7-azanorbornadiene (159) and sulphimide (160) in boiling benzene in the presence of styrene and methyl acrylate (two alkenes of very different electron availability) give the same ratio of derived *N*-phthalimido aziridines. This constant ratio suggested a common intermediate in these thermolyses which is believed to be phthalimido nitrene (161) (Scheme 105). (Significantly, this ratio was different from that obtained when *N*-aminophthalimide (26) was oxidised with LTA in boiling benzene in the presence of these alkenes).



Pyridinium ylides (145) and (148) were separately heated in boiling benzene containing styrene and diethyl fumarate (10 mol equiv. each) for 195 min. After distilling off the benzene and the bulk of the unreacted alkenes, a ratio of approximately 1.2:1 of (153):(154) respectively was measured from the proton n.m.r. spectrum of the crude reaction product using pyridinium ylide (145). However with ylide (148), some polymerisation had occurred which partially obscured the resonances needed for a comparison

of the ratio of (153):(154) which could not, therefore, be determined. From the n.m.r. spectrum of the crude reaction product obtained from heating pyridinium ylide (148) with diethyl fumarate alone under the same conditions, no polymerisation was observed. The polymerisation in competition experiment above using ylide (148) may therefore involve styrene in some way.

Another difference in the above competition experiments using ylides (145) and (148) was found to be the amount of 2-isopropylquinazolin-4(3H)-one (74) produced, from examination of the proton n.m.r. spectra of the crude reaction products. With ylide (145) an approximately 1:1 ratio of 2-isopropylquinazolinone (74):aziridine (153) had formed (by comparing the isopropyl CH resonance for both compounds). With ylide (148) this ratio was determined to be approximately 1:10 for (74):(153), (again the appropriate isopropyl CH resonances were used to determine this ratio). Formation of 2-isopropylquinazolinone (74) from the ylides above is competitive with aziridination using the latter. The gross difference in yield of 2-isopropylquinazolinone (74) from these two thermolyses supports the hypothesis that elimination of the quinazolinone moiety proceeds via (reversible) conversion of the pyridinium ylide into the diazepine and irreversible elimination of 2-isopropylquinazolinone via a 6-membered transition state (see 5.3). Whereas with ylide (145) this mechanism is possible, with ylide (148) the presence of the methyl group prevents this mechanism, see Scheme 106.

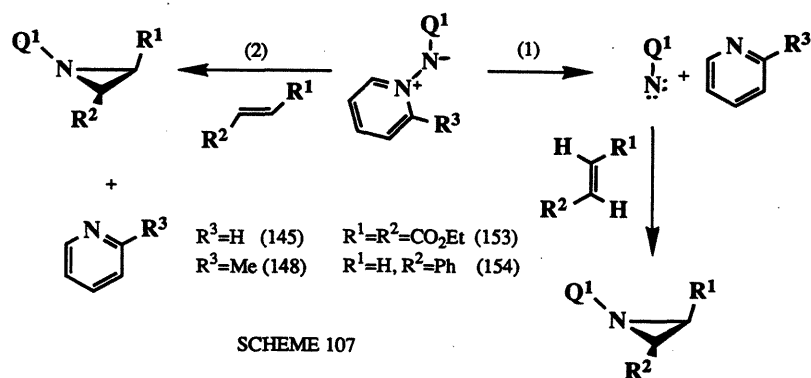


SCHEME 106

However, there must be an alternative route for the thermal elimination of 2-isopropylquinazolin-4(3H)-one (74) from (148) since this compound is obtained from (148) on heating (see above).

There are two obvious mechanisms for the aziridination of alkenes using these pyridinium ylides. The first is a two step mechanism in which the first step is loss of a quinazolinone N-nitrene and the second step is addition of this nitrene to the alkene to give the aziridine (Scheme 107). The second mechanism would be the direct

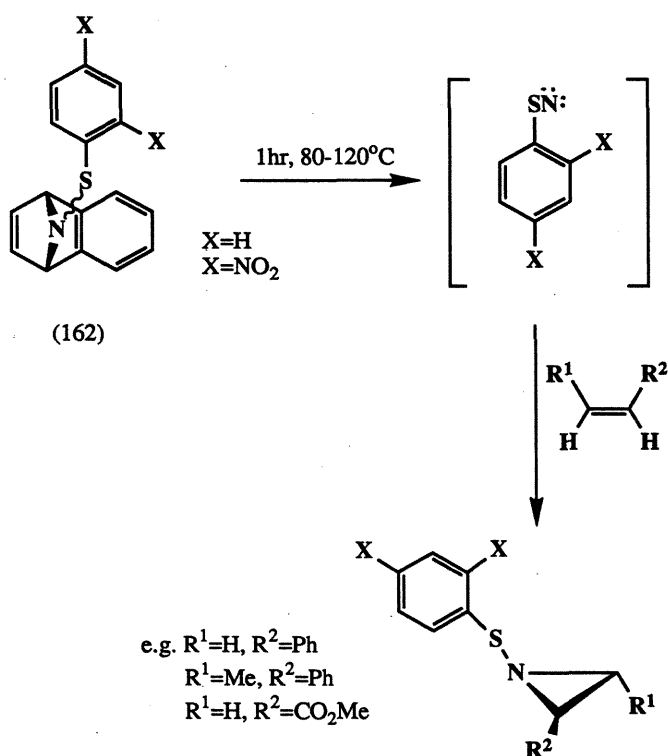
aziridination of the alkene with concomitant loss of the pyridine ring, see Scheme 107.



The competition experiments described above were performed with the intention of distinguishing between these two possible pathways. An identical aziridine ratio would have supported a nitrene mechanism whereas a significant difference would have supported a mechanism not involving a nitrene. Unfortunately the experiment described above did not allow this distinction to be made. At the present time there is no known example of aziridination of alkenes via quinazolinone N-nitrenes although a number of aziridinations in which phthalimidonitrene as an intermediate are known as described above.

Arenesulphenylnitrene has also been generated, thermally, by Atkinson et al⁶⁷ from sulphenamides (162), see

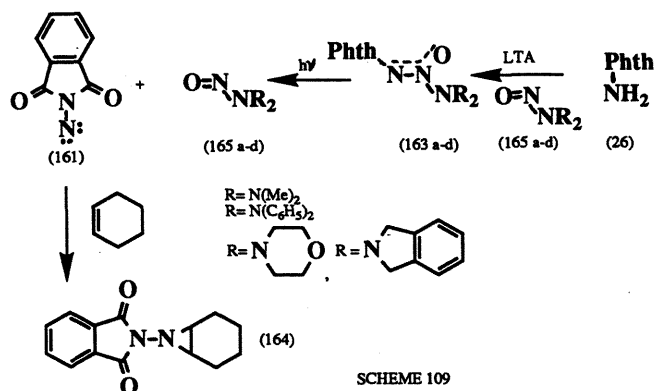
Scheme 108, and could be trapped by alkenes to give the corresponding aziridines in excellent yield.



SCHEME 108

Hoesch⁶⁸⁻⁷¹ has photochemically generated phthalimido nitrene (161) from (163): (161) reacts with cyclohexene^{68,69}

Hoesch⁶⁸⁻⁷¹ has photochemically generated phthalimido nitrene (161) from (163): (161) reacts with cyclohexene^{68,69} to form 7-phthalimido-7-azabicyclo[4.1.0]heptane (164 a-d) in 40% yield (Scheme 109). The (Z)-1-amino-2-phthalimidodiazene-1-oxide (163) was in turn formed from a lead tetraacetate oxidation of N-aminophthalimide (26) in the presence of nitrosoamine (165 a-d).



SCHEME 109

Summary:

The N-acetoxyaminoquinazolinones (47) and (134) have been shown to react with pyridine and its derivatives to give pyridinium ylides (145) and (148)-(151) which react with alkenes to give aziridines on heating. The pyridinium ylide derived from 3-amino-2-(nona-2,7-diyn-5-yl)-quinazolin-4(3H)-one (159) has been shown to aziridinate a double bond via an intramolecular reaction. An attempt was made to identify the mechanism of aziridination but no clear conclusions could be drawn. Further work in this area would be instructive. A barrier to N-N bond rotation/N-inversion about both N-N bonds in pyridinium ylide (145) was estimated from variable-temperature n.m.r. studies.

GENERAL EXPERIMENTAL

GENERAL EXPERIMENTAL

All 90MHz ^1H n.m.r. spectra were recorded on a Varian EM 390 spectrometer. High-field ^1H n.m.r. (300MHz) and ^{13}C n.m.r. (75MHz) spectra were recorded on a Bruker AM 300 spectrometer at the University of Leicester. ^1H n.m.r. (400MHz) spectra were recorded by courtesy of the high-field service [S.E.R.C.] at the University of Warwick. High-field ^{13}C n.m.r. (63MHz) spectra were recorded on a Bruker WM 250 spectrometer at I.C.I Specialties, Blackley, Manchester. All n.m.r. spectra were recorded at room temperature, unless stated otherwise. Infra-red spectra of crystalline compounds were determined using Nujol mulls and of liquids as dichloromethane solutions, using a Perkin-Elmer 298 spectrometer. Accurate mass measurements were made at either the S.E.R.C. mass spectrometry centre, University College of Swansea or at the University of Leicester. Standard mass spectra were recorded on either a Micromass 16B spectrometer or a Kratos 'concept' 1H. G.C.M.S. mass spectra were recorded at I.C.I Specialties, Blackley, Manchester. Elemental analysis was carried out by CHN Analysis, Wigston, Leicester. Melting points were determined on a Kofler hot stage and are uncorrected.

Flash chromatography was carried out according to the method of Still *et al.*⁷² using silica gel manufactured by Merck & Co., Kiesel 60 (230-400 mesh) or basic (pH 9) activated alumina UG1. Purifications by chromatotron were performed using model 7924T and Merck & Co. Kieselgel 60 (PF 254) silica plates. T.l.c. was conducted on pre-coated

alumina sheets (60-254) with a 0.2mm layer thickness, manufactured by Merck & Co.

n-Butyllithium (approximate concentration 2.5M) was used as received from Aldrich Chemical Co.

Light petroleum refers to the 40-60°C fraction unless otherwise stated and all light petroleum and ethyl acetate was distilled prior to use. Tetrahydrofuran (THF) and benzene were distilled from sodium metal in the presence of benzophenone. Ether refers to diethyl ether and was initially sodium-dried and then distilled from lithium aluminium hydride when required dry. Dichloromethane, pyridine, diisopropylamine, N,N-dimethylformamide (DMF) and triethylamine were distilled from powdered calcium hydride. Methanol and ethanol were dried by distillation from magnesium and iodine. Sodium hydride was purchased (Aldrich) as a 60% dispersion in mineral oil, and was always freed from the bulk of the mineral oil by washing several times with dry and distilled light petroleum before use.

Lead tetra-acetate was purchased as a solid under acetic acid (BDH; no longer available) and was filtered and freed from residual acetic acid under reduced pressure prior to use. Alkenes and β -diketones used in aziridination were distilled prior to use. All other reactants were reagent grade unless otherwise stated and were used as received. Saturated sodium bicarbonate solution was routinely used in basic washings during work-up.

PHYSICAL DATA

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

br-broad; s-strong; m-medium; w-weak.

In nuclear magnetic resonance (n.m.r.) spectra, chemical shifts are expressed in p.p.m. on the δ scale relative to the internal standard (TMS). The following abbreviations are used in recording n.m.r. data:

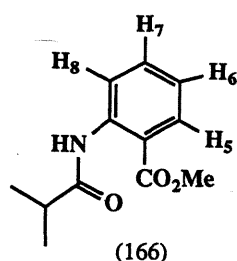
J-coupling constant (in Hz); b-broad; s-singlet; d-doublet; t-triplet; q-quartet; m-multiplet; dd-double doublet; ddd-double doublet of doublets; dq-doublet of quartets; Ar-aryl; Ph-phenyl; Pyrid-pyridine; Q¹-quinazolinone (see list of abbreviations); Q²-quinazolinone (see list of abbreviations); Q³-quinazolinone (see list of abbreviations).

Mass spectra were determined in units of mass relative to charge (M/Z) unless stated otherwise.

EXPERIMENTAL-

CHAPTER TWO

Preparation of methyl N-(isopropanoyl)anthranilate (166)



To methyl anthranilate (255.6g, 1.69mol) was added isobutyric anhydride (267.02g, 1.69mol). After the addition the stirred mixture was heated at 100°C for 2.5 hr with the exclusion of moisture. After cooling the mixture was diluted with ether (600ml) and washed with sodium bicarbonate (4x500ml) and finally with water. The ethereal layer was dried (MgSO₄) and evaporated under reduced pressure to yield crude product (166) which was crystallised from light petroleum to give methyl N-(isopropanoyl)anthranilate (166) (231.04g, 78%) as white crystals, m.p 51-2°C.

Compound (166):

C₁₂H₁₅NO₃ requires C, 65.14; H, 6.83; N, 6.33%. Found C, 65.22; H, 6.87; N, 6.34%.

δ_H (CDCl₃, 300MHz): 1.30 (d, 6H, CH₃CHCH₃, J6.9Hz), 2.62 (Heptet, 1H, CH₃CHCH₃, J6.9Hz), 3.91 (s, 3H, OCH₃) 7.04 (ddd, 1H, ArCH-2, J8.5, 7.4, 1.2Hz), 7.51 (ddd, 1H, ArCH-3, J8.0, 7.4, 1.4Hz), 8.00 (dd, 1H, ArCH-1, J8.0, 1.2Hz), 8.75 (dd, 1H, ArCH-4, J8.5, 1.4Hz), 11.13 (bs, NH).

δ_C (CDCl₃, 75MHz): 19.35 (CH₃CHCH₃), 37.34 (CH₃CHCH₃), 52.07

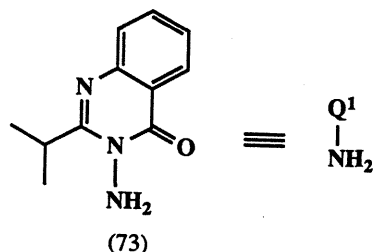
(OCH₃), 114.60 (C=CO₂Me), 120.13 (CH), 122.00 (CH), 130.59 (CH), 134.39 (CH), 141.70 (CNHCO^tPr), 168.52 (CONH), 175.79 (CO₂Me).

ν_{\max} (Nujol Mull) 3262w, 1682s, 1606m, 1590s, 1382m, 1295m, 1262s, 1242m, 1193m, 1165s, 1141m, 1092m, 1065m, 966w, 943m, 880w, 755s, 720w, 701s.

M/Z(%): 221 (M⁺, 15), 189 (21), 174 (26), 151 (31), 146 (63), 119 (24), 32 (100)

Preparation of 3-amino-2-isopropylquinazolin-4(3H)-one

(73)



Methyl N-(isopropanoyl)anthranilate (166) (231.04g, 1.04mol) and hydrazine monohydrate (325g, 6.50mol) were heated under reflux under a nitrogen atmosphere in ethanol (650ml) for 16 hr. After setting aside overnight, 3-amino-2-isopropylquinazolin-4(3H)-one (73) was filtered and the bulk of the ethanol was removed under reduced pressure from the filtrate. To the combined residues was added dichloromethane (500ml), the organic layer was washed twice with water, dried (MgSO₄) and evaporated to yield more

of the product (73). The combined product solids obtained above were recrystallised from ethanol to give 3-amino-2-isopropylquinazolin-4(3H)-one (73) (272.1g, 92%), m.p 101-2°C.

Compound (73):

C₁₁H₁₃N₃O requires C, 65.00; H, 6.45; N, 20.68%. Found C, 65.03; H, 6.50; N, 20.67%.

δ_H (CDCl₃, 300MHz): 1.35 (d, 6H, CH₃CHCH₃, J6.8Hz), 3.72 (Heptet, 1H, CH₃CHCH₃, J6.8Hz), 4.93 (s, 2H, NH₂), 7.36 (dd, 1H, ArCH Q¹H-6, J8.0, 2.2Hz), 7.64 (m, 2H, ArCH Q¹H-7/8), 8.14 (ddd, 1H, ArCH Q¹H-5, J8.0, 1.5, 0.7Hz).

δ_C (CDCl₃, 75MHz): 20.35 (CH₃CHCH₃), 30.88 (CH₃CHCH₃), 119.73 (Q¹ C=O), 125.85, 126.08, 127.17, 133.77 (4x Q¹ CH), 146.90 (Q¹ C=NC), 161.80 (Q¹ C), 161.93 (Q¹ C).

ν_{max} (Nujol Mull): 3304w, 3192m, 1666m, 1640s, 1585s, 1400m, 1378m, 1345w, 1301w, 1253w, 1174m, 1094m, 1070m, 994s, 957m, 923s, 874m, 771s, 708m, 698s, 663m.

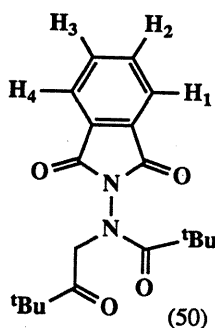
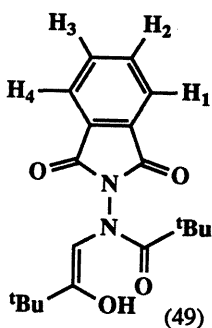
M/Z (%): 203 (M⁺, 24), 188 (44), 187 (24), 185 (11), 175 (49), 173 (47), 160 (17), 146 (19), 144 (11), 132 (16), 130 (13), 119 (20), 104 (14), 102 (13), 32 (100).

Oxidation of N-aminophthalimide Using LTA at Room

Temperature in the Presence of

2,2,6,6-tetramethylheptan-3,5-dione

Note: Compounds (49) and (50) were prepared according to the literature procedure⁴⁰.



Powdered N-aminophthalimide (26) ($0.50\text{g}, 3.10 \times 10^{-3}\text{mol}$) and acetic acid-free lead tetra-acetate (LTA) ($1.44\text{g}, 3.26 \times 10^{-3}\text{mol}$) were added alternately and continuously in very small portions over 15 min. to a vigorously stirred solution of dry dichloromethane (5ml) containing 2,2,6,6-tetramethylheptan-3,5-dione (Aldrich) ($1.71\text{g}, 9.30 \times 10^{-3}\text{mol}$). The mixture was stirred for a further 5 min. and then the insoluble lead di-acetate separated, washed with dichloromethane and the total filtrate washed successively with sodium bicarbonate solution and water. The organic layer was dried (MgSO_4) and the solvent removed under reduced pressure to yield an oil which solidified on standing. Trituration with ether gave N-phthalimido-keto-amide (50) which was recrystallised from ethanol

(120mg, 24%) m.p. 170°C (lit⁴⁰ m.p. 170°C). Evaporation of the filtrate under reduced pressure and crystallisation of the residual solid from ethanol gave N-phthalimido-enolamide (49) (86mg, 17%) m.p. 107-110°C (lit⁴⁰ m.p. 120°C).
 Compound (49): δ_H (CDCl₃, 300MHz): 1.16 (s, 9H, ((CH₃)₃C-C(OH))), 1.35 (s, 9H, (CH₃)₃C-CON), 5.80 (s, 1H, CH=), 7.78 (dd, 2H, ArH_{2/3}, J5.5, 3.2Hz), 7.87 (dd, 2H, ArH_{1/4}, J5.5, 3.1Hz), 8.06 (s, OH).

δ_C (CDCl₃, 75MHz): 27.05 ((CH₃)₃), 27.28 ((CH₃)₃), 34.65 (^tBu-C), 39.09 (^tBu-C), 100.82 (CHN), 124.11 (2xArC), 129.94 (ArC-CO), 134.79 (2xArC), 165.45 (C=O), 166.69 (COH), 177.52 (C=O).

Compound (50): δ_H (CDCl₃, 300MHz): 1.18 (s, 9H, (CH₃)₃C=O), 1.21 (s, 9H, (CH₃)₃C=O), 4.54 (s, CH₂), 7.84-7.90 (structured multiplet, 2H, ArH), 7.92-7.98 (structured multiplet, 2H, ArH).

δ_C (CDCl₃, 75MHz): 25.94 ((CH₃)₃), 28.17 ((CH₃)₃), 39.80 (C^tBu), 43.50 (C^tBu), 54.04 (CH₂), 124.07 (ArCH), 129.50 (ArCC=O), 134.99 (ArCH), 164.98 (CO), 178.61 (exocyclic NCO), 206.46 (CH₂C=O).

General procedure (1) for the aziridination of alkenes and the enolic form of β -diketones using pre-formed N-acetoxyaminoquinazolinone (at -20 to -25°C) followed by subsequent addition of the alkene/ β -diketone

Powdered N-aminoquinazolinone (1 mol equiv.) and acetic acid-free lead tetra-acetate (LTA) (1.05 mol equiv.) were added alternately and continuously in very small portions over 15 min. to a vigorously stirred solution of dry dichloromethane (1ml/100mg of N-aminoquinazolinone) cooled at -20 to -25°C with a dry ice-acetone bath. The mixture was stirred for a further five minutes at this temperature, before addition of the alkene/ β -diketone (1.5-3.5 mol equiv.) and then allowed to warm to ambient temperature. Insoluble lead di-acetate was then separated, washed with dichloromethane and the total filtrate washed successively with sodium bicarbonate solution and water. The organic layer was dried (MgSO_4) and the solvent removed by evaporation under reduced pressure.

General procedure (2) for the aziridination of alkenes and the enolic form of β -diketones using pre-formed N-acetoxyaminoquinazolinone (at -20 to -25°C) followed by subsequent addition of the alkene/ β -diketone

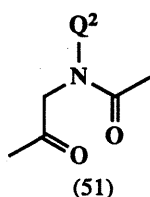
Powdered N-aminoquinazolinone (1 mol equiv.) and acetic acid-free lead tetra-acetate (1.05 mol equiv.) were added alternately and continuously in very small portions over 15 min. to a vigorously stirred solution of dry dichloromethane (1ml/100mg of N-aminoquinazolinone) containing the alkene/ β -diketone (1.5-3.5 mol equiv.) at room temperature. The mixture was stirred for 30 min. at room temperature and then insoluble lead di-acetate was separated, washed with dichloromethane and the total filtrate washed successively with sodium bicarbonate solution and water, dried with magnesium sulphate and the solvent removed by evaporation under reduced pressure.

General procedure (3) for the aziridination of alkenes and the enolic form of β -diketones using oxidative (LTA) addition of the N-aminoquinazolinones in the presence of trifluoroacetic acid

Powdered N-aminoquinazolinone (1 mol equiv.) and acetic-acid free lead tetra-acetate (1.05 mol equiv.) were added alternately and continuously in very small portions over 15 min. to a vigorously stirred solution of dry dichloromethane (1ml/100Mg of N-aminoquinazolinone),

containing the alkene/ β -diketone (1.5-3.5 mol equiv.) and trifluoroacetic acid (TFA) (3-3.4 mol equiv.) at room temperature. The mixture was then stirred for 30 min. at room temperature (lead salts remaining in solution) and then washed successively with sodium bicarbonate solution and water, dried with magnesium sulphate and the solvent removed under reduced pressure.

**Reaction of the N-acetoxyminoquinazolinone (47) with
pentan-2,4-dione**



The general procedure (1) was followed using N-aminoquinazolinone (46) (m.p. 117-118°C from ethanol), (lit.⁷³ m.p. 152-153°C) (1.03g, 5.46x10⁻³mol), LTA (2.54g, 5.75x10⁻³mol) and pentan-2,4-dione (1.64g, 16.4x10⁻³mol) in dry dichloromethane (10ml). Trituration with ice-cold ether of the solid/oil mixture obtained gave 2-ethylquinazolin-4(3H)-one (52) as colourless crystals (0.77g, 75%), m.p. 235-237°C (from ethanol) (lit⁷⁴ m.p. not quoted). The filtrate was chromatographed over silica with ethyl acetate as eluant to give keto-amide (51) (R_f0.55) as colourless crystals (0.23g, 15%), m.p. 116-118°C (from

ethanol).

Compound (51): $C_{15}H_{17}N_3O_3$ requires C, 62.70; H, 5.96; N, 14.63%. Found C, 62.71; H, 5.98; N, 14.59%. This compound exists in $CDCl_3$ solution as a 7.6:1 ratio of amide rotamers.

Major Rotamer:

δ_H ($CDCl_3$, 300MHz): 1.40 (t, 3H, $\underline{CH_3CH_2}$, J7.3Hz), 1.90 (s, 3H, $\underline{CH_2COCH_3}$), 2.24 (s, 3H, $\underline{NCOCH_3}$), 3.05 (dq, $\underline{CH_3CH_2}$, J17.5, 7.3Hz), 3.76 and 4.98 (2xd, 2H, $\underline{CH_2N}$, J17.3Hz), 7.48 (ddd, 1H, \underline{ArCH} $\underline{Q^2H-6}$, J7.9, 7.0, 1.3Hz), 7.67-7.83 (m, 2H, $2 \times \underline{ArCH}$ $\underline{Q^2H-7/8}$), 8.20 (ddd, 1H, \underline{ArCH} $\underline{Q^2H-5}$, C=O, J7.9, 1.5, 0.4Hz).

δ_C ($CDCl_3$, 75MHz): 10.43 ($\underline{CH_3CH_2}$), 19.44 ($\underline{CH_3COCH_2}$), 26.27 ($\underline{CH_2CH_3}$), 27.53 ($\underline{CH_3CON}$), 59.21 ($\underline{CH_2N}$), 120.39 ($\underline{Q^2 CCO}$), 126.74, 126.82, 127.46, 135.10 ($4 \times \underline{Q^2 CH}$), 146.58 ($\underline{Q^2 CN=C}$), 158.21 ($\underline{Q^2 C=N}$), 159.98 ($\underline{Q^2 C=O}$), 172.66 ($\underline{CH_3CON}$), 200.35 ($\underline{CH_3CO}$).

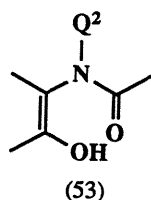
Minor Rotamer: (observable peaks): δ_H ($CDCl_3$, 300MHz): 1.31 (t, 3H, $\underline{CH_3CH_2}$, J7.3Hz), 2.20 (s, 3H, $\underline{CH_3COCH_2}$), 2.22 (s, 3H, $\underline{CH_3CON}$), 2.95 (dq, 2H, $\underline{CH_2CH_3}$, J17.2, 7.3Hz), 4.34 and 5.04 (2xd, 2H, $\underline{CH_2N}$, J18.7Hz).

δ_C ($CDCl_3$, 75MHz): 10.34 ($\underline{CH_3CH_2}$), 20.41 ($\underline{CH_3COCH_2}$), 25.48 ($\underline{CH_2CH_3}$), 27.03 ($\underline{CH_3CON}$), 61.44 ($\underline{NCH_2CO}$), 126.13, 126.47, 127.22, 134.52 ($4 \times \underline{Q^2 CH}$), 159.00 ($\underline{Q^2 C}$).

ν_{max} (Nujol Mull): 1738m, 1700s, 1603s, 1330m, 1303m, 1273m, 1235w, 1180m, 1121w, 1095w, 1071w, 1046w, 1011w, 985w, 970w, 958w, 883w, 863w, 798w, 793w, 776s, 725m, 699s, 689w, 655m.

M/Z (%): 287 (M^+), 202 (54), 175 (20), 174 (84), 173 (64), 46 (12), 130 (11), 119 (30), 43 (100).

Reaction of the N-acetoxvminoquinazolinone (47) with
3-methylpentan-2,4-dione



The general procedure (1) was followed using N-aminoquinazolinone (46) (1.0g, 5.30×10^{-3} mol), LTA (2.46g, 5.55×10^{-3} mol) and 3-methylpentan-2,4-dione (1.81g, 0.02 mol) in dry dichloromethane (10ml). NOTE: it is important to wash the organic layer with 2 equiv. of sodium bicarbonate solution and to restrict this washing (shaking in separating funnel) to as short a time as possible. After solvent removal under reduced pressure, the solid/oil mixture was triturated with ice-cold ether to yield crude product. This was crystallised with the minimum of heating from chloroform/light petroleum to give enol-amide (53) as colourless crystals (1.05g, 66%). m.p. 114°C (decomp.).

Compound (53): $C_{16}H_{19}N_3O_3$ requires C, 63.77; H, 6.36; N, 13.95%. Found C, 63.80; H, 6.33; N, 14.06%.

δ_H (CDCl₃, 300MHz): 1.38 (t, CH_3CH_2 , J7.3Hz), 1.83 (s, $CH_3C=C$), 1.91 (s, $CH_3C=C$), 2.30 (s, CH_3CON), 2.80 (dq, CH_3CH_2 , J16.8, 7.3Hz), 7.45 (ddd, ArCH Q²H-6, J8.1, 7.2, 1.3Hz), 7.70 (dd, ArCH Q²H-8, J8.2, 1.3Hz), 7.78 (ddd, ArCH Q²H-7, J8.2, 7.2, 1.5Hz), 8.23 (ddd, ArCH Q²H-5, J8.1, 1.5, 0.5Hz), 9.80 (s, OH exchangeable with D₂O).

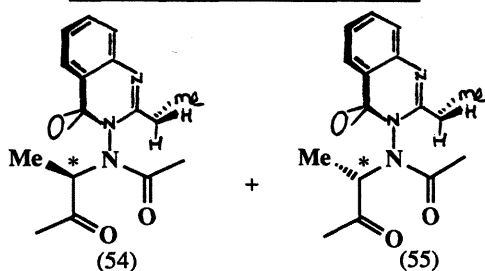
δ_c (75MHz, $CDCl_3$): 10.76 ($\underline{CH_3CH_2}$), 15.28 ($\underline{CH_3C=C}$), 17.43 ($\underline{CH_3C=C}$), 19.85 ($\underline{CH_3CON}$), 25.55 ($\underline{CH_3CH_2}$), 107.65 ($\underline{NC=C}$), 120.29 ($Q^2 \underline{CCO}$), 126.28, 127.00, 127.18, 135.14 ($4 \times Q^2 \underline{CH}$), 146.78 ($Q^2 \underline{CNC}$), 152.27 ($Q^2 \underline{C=N}$), 157.98 ($C=\underline{COH}$), 162.35 ($Q^2 \underline{C=O}$), 169.81 (\underline{CON}).

ν_{max} (Nujol Mull): 3181m, 1686m, 1661s, 1594m, 1307m, 1275m, 1246w, 1184w, 1151w, 1056w, 985w, 936w, 880w, 783m, 702m.

M/Z(%): 301 (M^+), 258 (11), 217 (16), 216 (86), 175 (26), 174 (86), 173 (88), 146 (18), 130 (18), 119 (45), 118 (14), 103 (14), 43 (100).

Reaction of the N-acetoxyaminoquinazolinone (47) with

3-methylpentan-2,4-dione



* Relative configuration arbitrarily assigned

The general procedure (1) was followed using N-aminoquinazolinone (46) (0.46g, 2.42×10^{-3} mol), LTA (1.21g, 2.74×10^{-3} mol) and 3-methylpentan-2,4-dione (1.19g, 9.68×10^{-3} mol) in dry dichloromethane (5ml). The solution was warmed to ambient temperature and stirred for 2 hr. before lead di-acetate was filtered. After the work-up as in general procedure (1), a 1:1 ratio of compounds (54) and (55) (195mg, 27%) was present in the crude product

together with 2-ethylquinazolin-4(3H)-one (52) by n.m.r. spectral analysis. Trituration of the crude mixture with ice-cold ether gave (52) (211mg, 46%). Evaporation of the ether and crystallisation of the residue from ethanol (x2) gave keto-amide (54) (84mg, 12%) m.p 162-163.5°C. Further re-crystallisation (x2) of the residue gave keto-amide (55) (76mg, 10%) m.p 127-129°C.

Compound (54): $C_{16}H_{19}N_3O_3$ requires C, 63.77; H, 6.36; N, 13.95%. Found C, 63.70; H, 6.36; N, 13.94%.

δ_H (CDCl₃, 300MHz): 1.33 (d, $\underline{CH_3}CHN$, J7.2Hz), 1.43 (t, $\underline{CH_3}CH_2$, J7.3Hz), 1.94 (s, $\underline{CH_3}CO$), 2.39 (s, $\underline{CH_3}CON$), 2.80 (ABX₃, $\underline{CH_3}CH_2$, J14.6, 7.3Hz), 4.45 (q, $\underline{CH_3}CHN$, J7.2Hz), 7.52 (dd, ArCH $\underline{Q^2H-6}$, J8.0, 1.5Hz), 7.74 (d, ArCH $\underline{Q^2H-8}$, J7.4Hz), 7.83 (ddd, ArCH $\underline{Q^2H-7}$, J8.4, 7.4, 1.3Hz), 8.26 (dd ArCH $\underline{Q^2H-5}$, J8.0, 1.3Hz).

δ_C (CDCl₃, 75MHz): 10.42 ($\underline{CH_3}CH_2$), 13.60 ($\underline{CH_3}$), 20.43 ($\underline{CH_3}$), 26.24 ($\underline{CH_3}CH_2$), 63.97 (\underline{CHN}), 120.54 ($\underline{Q^2} \underline{CO}$), 127.15, 127.17, 127.56, 135.24 (4x $\underline{Q^2} \underline{CH}$), 146.33 ($\underline{Q^2} \underline{CCN}$), 157.84 ($\underline{Q^2} \underline{CN}$), 160.72 ($\underline{Q^2} \underline{CO}$), 171.57 ($\underline{CH_3} \underline{CON}$), 203.90 ($\underline{CH_3} \underline{COCH}$).

ν_{max} (Nujol Mull): 1690s, 1606s, 1336m, 1293m, 1257m, 1236m, 1221m, 1126w, 1047w, 1011w, 953w, 881w, 806w, 781s, 698m, 658m.

M/Z (%): 301 (M⁺), 258 (14), 217 (16), 216 (90), 175 (26), 174 (97), 173 (100), 146 (17), 132 (11), 130 (17), 119 (42), 118 (11).

Compound (55): $C_{16}H_{19}N_3O_3$ requires C, 63.77; H, 6.36; N, 13.95%. Found C, 63.72; H, 6.44; N, 13.84%.

δ_H (CDCl₃, 300MHz): 0.97 (d, $\underline{CH_3}CHN$, J7.4Hz), 1.42

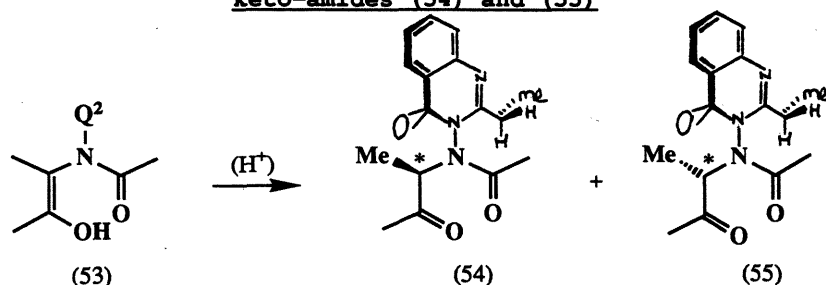
(t, CH_3CH_2 , J7.3Hz), 1.89 (s, CH_3CO), 2.38 (s, CH_3CON), 3.20 (ABX₃, CH_3CH_2 , J17.8, 7.3Hz), 4.88 (q, CH_3CHN , J7.4Hz), 7.51 (ddd, ArCH Q²H-6, J8.0, 7.1, 1.3Hz), 7.75 (dd, ArCH Q²H-8, J7.0, 1.3Hz), 7.82 (ddd, ArCH Q²H-7, J8.0, 7.0, 1.5Hz), 8.25 (ddd, ArCH Q²H-5, J8.0, 1.5, 0.4Hz).

δ_c (CDCl₃, 75MHz): 10.55 (CH_3CH_2), 13.01 (CH_3), 20.25 (CH_3), 26.56 (CH_3CH_2), 27.52 (CH_3), 61.52 (CH), 120.11 (Q² CO), 127.11, 127.14, 127.73, 135.44 (4xQ² CH), 146.99 (Q² $\text{CN}=\text{C}$), 159.54 (Q² CN), 160.95 (Q² CO), 173.14 (CH_3CON), 204.74 (CH_3CO).

ν_{max} (CH₂Cl₂): 1699s, 1606m, 1493w, 1373m, 1329m, 1293m, 1254m, 1223w, 1176w, 1123w, 1008w, 947w, 879w, 695m.

M/Z (%): 301 (M⁺, 11), 258 (18), 216 (100), 174 (24), 173 (18).

Conversion of enol-amide (53) to a mixture of keto-amides (54) and (55)

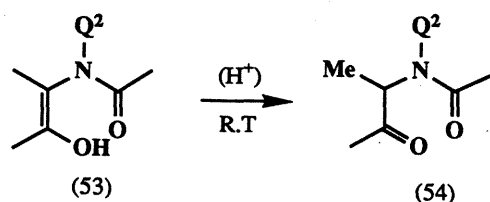


* Relative configuration arbitrarily assigned

Enol-amide (53) (0.2g, 6.64x10⁻³mol) was dissolved in boiling glacial acetic acid (2ml) and heated for approximately 1 min. After cooling, the acetic acid was

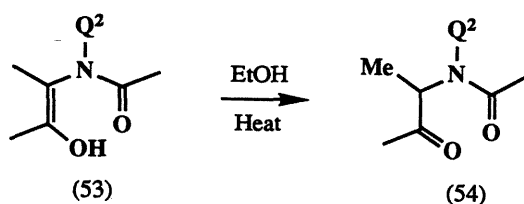
removed under reduced pressure and a proton n.m.r. spectrum of the residue indicated the presence of a 3:1 ratio of (54) : (55) .

Conversion of enol-amide (53) to keto-amide (54)



Enol-amide (53) (0.1g, 3.32×10^{-3} mol) was dissolved in the minimum quantity of glacial acetic acid (5ml) and stirred overnight at ambient temperature. Removal of the solvent under reduced pressure and examination of the residue by proton n.m.r. spectroscopy showed only keto-amide (54) to be present.

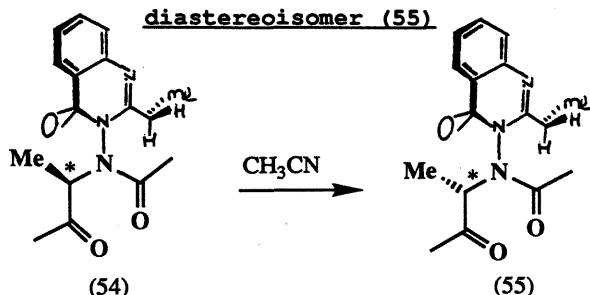
Conversion of enol-amide (53) into keto-amide (54)



Enol-amide (53) (0.25g, 8.31×10^{-3} mol) was dissolved in

boiling ethanol (3ml) and heated under reflux for approximately 1 min. After cooling and removal of solvent under reduced pressure, examination of the residue by n.m.r. spectroscopy showed only keto-amide (54) to be present.

Conversion of keto-amide (54) into its
diastereoisomer (55)

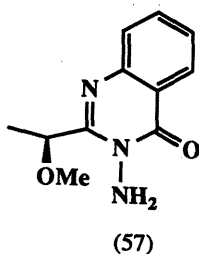


* Relative configuration arbitrarily assigned

Keto-amide (54) (0.05g, 1.59×10^{-3} mol) was dissolved in acetonitrile (1ml) and set aside for three days at ambient temperature. After this time, removal of the solvent under reduced pressure and examination of the residue by proton n.m.r. showed only keto-amide (55) to be present.

**Preparation of (S)-(-)-3-amino-2-(1'-methoxyethyl)-
quinazolin-4(3H)-one (57)**

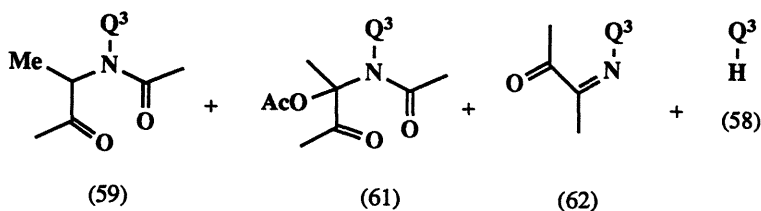
This material was prepared according to the method of Coogan⁷⁵.



To a stirred slurry of sodium hydride (1.10g, 0.027mol) in freshly distilled THF, under an argon atmosphere was added (S)-(-)-3-amino-2-(1'-hydroxyethyl)quinazolin-4(3H)-one (98) (m.p. 118-120°C from ethanol) (lit.⁵⁶ m.p. 118-120°C) (5.12g, 0.025mol). The resulting solution was stirred for 30 min. during which time a white solid formed. After this time methyl iodide (10.65g, 0.075mol) was added and the mixture stirred overnight. Sodium iodide was separated by filtration under reduced pressure and washed with THF. The filtrate was evaporated under reduced pressure and the residue dissolved in dichloromethane and washed with water (x2). The organic layer was dried (MgSO₄) and evaporated under reduced pressure to yield a solid which was crystallised from ethyl acetate/light petroleum to give (S)-(-)-3-amino-2-(1'-methoxyethyl)quinazolin-4(3H)-one (57) as colourless crystals (3.36g, 61%), m.p. 108-110°C (lit.⁷⁵. 108-110°C) (from ethyl acetate).

δ_H (CDCl₃, 300MHz): 1.67 (d, CH₃CHOMe, J6.6Hz), 3.46 (s, OCH₃), 4.96 (q, CH₃CHOMe, J6.6Hz), 5.36 (bs, NH₂), 7.49 (ddd, ArCH Q³H-6, J8.2, 6.6, 1.8Hz), 7.72-7.85 (m, 2H, ArCH Q³H-8/7), 8.27 (ddd, ArCH Q³H-5, J8.2, 1.2, 0.6Hz).

Oxidation of (S)-(-)-3-amino-2-(1'-methoxyethyl)quinazolin-4(3H)-one (57) using LTA at ambient temperature in the presence of 3-methylpentan-2,4-dione



The general procedure (2) was followed using N-aminoquinazolinone (57) (1.36g, 6.2mmol), LTA (2.89g, 6.52mmol) and 3-methylpentan-2,4-dione (2.12g, 18.6mmol) in dry dichloromethane (14ml). The solid/oil mixture obtained was triturated with ice-cold ether and (S)-(-)-2-(1'-methoxyethyl)quinazolin-4(3H)-one (58) (0.23g) separated as colourless crystals, which were identical in all respects to a sample prepared by Coogan⁷⁵. After evaporation of ether, excess 3-methylpentan-2,4-dione was removed from the residual oil by distillation at 40°C (bath temp.) and 0.02mmHg. Chromatography of the residue over silica, with ethyl acetate/light petroleum (1:4) as eluant, gave an unresolved mixture of compounds (59),

(61), and (62), unreacted starting material (57) (0.132g, 10%), R_f 0.17, and a further quantity of (S)-(-)-2-(1'-methoxyethyl)-quinazolin-4(3H)-one (58) (0.72g, total 0.95g, 75% based on unreacted starting material), R_f 0.10. The mixture of (59), (61) and (62) was then further purified by chromatotron using ethyl acetate/light petroleum (1:4) as eluant. From the chromatotron were obtained keto-amide (59) (0.048g, 2%), R_f 0.25, as a pale green oil, α -acetoxylated keto-amide (61) (0.29g, 12%), R_f 0.35, as colourless crystals m.p. 120-120.5°C (from ethanol), and keto-imine (62) (0.037g, 2%), R_f 0.25, as a pale green oil.

Compound (59): $[\alpha]_D^{25} = -83.0^\circ$, ($c=3.5$, CH_2Cl_2).

$\text{C}_{17}\text{H}_{21}\text{N}_3\text{O}_4$ requires M , 331.1532. Found; M/Z 331.1530.

δ_H (CDCl_3 , 300MHz): 0.91 (d, CH_3CHN , J 7.3Hz), 1.64 (d, $\text{CH}_3\text{CHOCH}_3$, J 6.3Hz), 2.01 (s, CH_3CO), 2.41 (s, CH_3CON), 3.49 (s, OCH_3), 4.88 (q, CH_3CHN , J 7.3Hz), 5.54 (q, $\text{CH}_3\text{CHOCH}_3$, J 6.3Hz), 7.56 (ddd, $\text{ArCH } Q^3\text{H-6}$, J 8.1, 7.9, 2.8Hz), 7.80-7.87 (m, 2H, $\text{ArCH } Q^3\text{H-7/8}$), 8.28 (ddd, $\text{ArCH } Q^3\text{H-5}$, J 7.9, 1.2, 0.8Hz).

δ_C (CDCl_3 , 75MHz): 13.33 (CH_3), 15.09 (CH_3), 20.16 (CH_3CO), 27.68 (CH_3CON), 56.46 (CH_3O), 61.55 (CH_3CHN), 72.67 ($\text{CH}_3\text{CHOCH}_3$), 120.76 ($Q^3 \text{ C=O}$), 127.11, 127.90, 128.59, 135.39 (4x $Q^3 \text{ CH}$), 146.48 ($Q^3 \text{ C=N=C}$), 156.19 ($Q^3 \text{ C=N}$), 161.04 ($Q^3 \text{ C=O}$), 174.81 (NCOCH_3), 205.15 (CH_3CO).

ν_{max} (CH_2Cl_2): 2890w, 2840w, 2740w, 1699s, 1607s, 1455s, 1380s, 1330m, 1300s, 1180m, 1125s, 1050m, 1025m, 965w, 880w, 855w, 755s, 725m, 655w.

M/Z (%): 331 (M^+), 288 (39), 247 (19), 246 (100), 214 (47),

205 (17), 203 (13), 174 (68), 173 (84), 172 (17), 146 (15),
145 (13), 130 (11), 119 (18).

Compound (61): $[\alpha]_D = -100.6^\circ$, ($c=3.5$, CH_2Cl_2).

$\text{C}_{19}\text{H}_{23}\text{N}_3\text{O}_6$ requires C, 58.60; H, 5.95; N, 10.79%. Found C, 58.73;
H, 5.96; N, 10.80%.

δ_{H} (CDCl_3 , 300MHz): 1.65 (d, $\text{CH}_3\text{CHOCH}_3$, $J_{6.3\text{Hz}}$), 1.87
(s, $\text{CH}_3\text{CNCOCCH}_3$), 2.01 (s, CH_3COC), 2.07 (s, CH_3CON), 2.61
(s, CH_3COO), 3.42 (s, OCH_3), 5.64 (q, CH_3CH , $J_{6.3\text{Hz}}$), 7.56
(ddd, ArCH $\text{Q}^3\text{H}-6$, $J_{7.9, 6.1, 2.3\text{Hz}}$), 7.80-7.87 (ArCH $\text{Q}^3\text{H}-7/8$),
8.29 (ddd, ArCH $\text{Q}^3\text{H}-5$, $J_{7.9, 1.2, 0.5\text{Hz}}$).

δ_{C} (CDCl_3 , 75MHz): 14.92 (CH_3CH), 20.35 (CH_3), 20.48 (CH_3),
20.70 (CH_3), 27.18 (CH_3), 56.31 (CH_3O), 72.84 (CH_3CH), 94.82
(CH_3CN), 121.46 ($\text{Q}^3 \text{CCO}$), 127.26, 127.81, 128.53, 135.33 (4x
 $\text{Q}^3 \text{CH}$), 146.03 ($\text{Q}^3 \text{CN}=\text{C}$), 156.87 ($\text{Q}^3 \text{CN}$), 161.13 ($\text{Q}^3 \text{CO}$),
167.22 (CH_3CON), 172.90 (CH_3COO), 200.04 (CH_3CO).

ν_{max} (CH_2Cl_2): 2980w, 2940w, 2830w, 1756s, 1704s, 1605s,
1465m, 1370s, 1333m, 1321m, 1298m, 1230s, 1155w, 1119s,
1098s, 1053m, 1030m, 1015m, 965m, 952m, 875w, 846w, 690w,
656w, 612w.

M/Z (%): 244 (11), 174 (39), 173 (27), 149 (18), 101 (27),
86 (100).

Compound (62): $[\alpha]_D = -3.7^\circ$, ($c=3$, CH_2Cl_2).

$\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_3$ requires $[\text{M}+\text{H}]$, 288.1348. Found $[\text{M}+\text{H}]$ 288.1349.

δ_{H} (CDCl_3 , 300MHz): 1.58 (d, CH_3CH , $J_{6.5\text{Hz}}$), 2.00 (s, $\text{CH}_3\text{C}=\text{N}$),
2.63 (s, CH_3CO), 3.35 (s, CH_3O), 4.58 (q, CH_3CH , $J_{6.5\text{Hz}}$), 7.53
(ddd, ArCH $\text{Q}^3\text{H}-6$, $J_{8.1, 6.7, 1.5\text{Hz}}$), 7.76-7.87 (m, ArCH $\text{Q}^3\text{H}-$
7/8), 8.29 (ddd, ArCH $\text{Q}^3\text{H}-5$, $J_{8.1, 1.3, 0.5\text{Hz}}$).

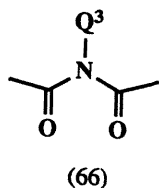
δ_{C} (CDCl_3 , 75MHz): 14.98 (CH_3CH), 17.36 (CH_3CN), 25.78

(CH_3CO), 56.94 (CH_3O), 75.98 (CH_2CH), 121.14 ($\text{Q}^3 \text{ CCO}$), 127.16, 127.32, 127.92, 134.46 (4x $\text{Q}^3 \text{ CH}$), 146.26 ($\text{Q}^3 \text{ CN=C}$), 155.34 ($\text{Q}^3 \text{ C}$), 174.30 ($\text{CH}_2\text{C=N}$), 196.94 (CH_3CO).

ν_{max} (CH_2Cl_2): 2936w, 2822w, 1710s, 1685s, 1600m, 1465m, 1348m, 1324w, 1292w, 1210w, 1122m, 1108m, 1062w, 1042w, 1020w, 980w, 936w, 909w, 877w, 685w.

M/Z (%): 245 (15), 244 (100), 187 (13), 186 (85), 173 (21).

Preparation of 3-diacetylamino-2-(1'-methoxyethyl)-quinazolin-4(3H)-one (66)



(S)-(-)-3-Amino-2-(1'-methoxyethyl)quinazolin-4(3H)-one (57) (1.55g, 7.1mmol) was dissolved in acetic anhydride (100ml). Dry pyridine (0.57g, 7.24mmol) was added and the solution stirred at room temperature for 36 hr, after which time it was heated at 100°C for 3 hr. Evaporation of the solvent under reduced pressure gave an oil which was chromatographed over silica, with ethyl acetate/light petroleum (1:2) as eluant, to give 3-diacetylamino-2-(1'-methoxyethyl)quinazolin-4(3H)-one (66), R_f 0.73, as a colourless oil (1.07g, 50%). This was triturated with light petroleum to give a solid which was crystallised from light

petroleum to give (66) as colourless crystals m.p. 58-59°C.

Compound (66): $[\alpha]_D^{25} = +47.9^\circ$, ($c=5.3$, CH_2Cl_2).

$\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_4$ requires C, 59.39; H, 5.65; N, 13.86%. Found C, 59.46; H, 5.70; N, 13.88%.

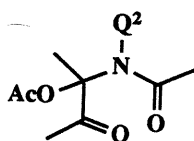
δ_{H} (CDCl_3 , 300MHz): 1.58 (d, CH_3CH , J6.3Hz), 2.25 (s, CH_3CON), 2.64 (s, CH_3CON), 3.34 (s, CH_3O), 4.17 (q, CH_3CH , J6.3Hz), 7.54 (ddd, ArCH Q^3H -6, J10.1, 6.0, 2.4Hz), 7.78-7.85 (m, 2H, ArCH Q^3H -7/8), 8.27 (ddd, ArCH Q^3H -5, J10.1, 7.7, 0.7Hz).

δ_{C} (CDCl_3 , 75MHz): 15.47 (CH_3CH), 23.56 (CH_3CON), 25.49 (CH_3CON), 56.74 (CH_3O), 75.25 (CH_2CH), 121.30 ($\text{Q}^3 \text{CCO}$), 127.26, 127.85, 128.41, 135.28 (4x $\text{Q}^3 \text{CH}$), 146.15 ($\text{Q}^3 \text{CN}=\text{C}$), 153.97 ($\text{Q}^3 \text{C}=\text{N}$), 159.53 ($\text{Q}^3 \text{C}=\text{O}$), 169.74 (CH_3CON), 171.88 (CH_3CON).

ν_{max} (Nujol Mull): 1736s, 1700s, 1610s, 1468s, 1370s, 1340w, 1320m, 1300w, 1268s, 1248s, 1220s, 1190s, 1105s, 1070w, 1050w, 1033m, 992m, 970w, 946m, 933w, 883w, 874w, 846m, 795w, 781s, 734w, 695s, 665m, 643m, 606s.

M/Z (%): 303 (M^+ , 3.7), 273 (58), 244 (33), 214 (13), 204 (26), 203 (27), 202 (100), 190 (21), 189 (16), 188 (14), 186 (13), 175 (11), 173 (25), 147 (16), 119 (15).

Preparation of α -acetoxyated keto-amide (63)



(63)

To a stirred solution of dry dichloromethane (3ml) and enol-amide (53) (0.23g, 0.77mmol) was added acetic acid-free LTA (0.75g, 1.70mmol) continuously and in very small portions over 15 min. After the addition, the solution was stirred for 10 min. before lead di-acetate was separated, washed with dichloromethane and the filtrate washed with sodium bicarbonate solution and water. The organic layer was dried (MgSO_4) and the solvent removed under reduced pressure to give a solid. Chromatography of the crude solid over silica, with ethyl acetate/light petroleum as eluant, gave α -acetoxyated keto-amide (63), R_f 0.71, as colourless crystals (0.269g, 97%), m.p. 149–149.5°C (from ethanol).

Compound (63): $\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}_5$ requires C, 60.16; H, 5.89; N, 11.69%. Found C, 60.09; H, 5.96; N, 11.66%.

δ_{H} (CDCl_3 , 300MHz): 1.41 (t, CH_3CH_2 , J7.4Hz), 1.92 (s, CH_3), 1.94 (s, CH_3), 1.99 (s, CH_3CON), 2.58 (s, CH_3COO), 3.21 (ABX₃, CH_3CH_2 , J17.5, 7.4Hz), 7.52 (ddd, ArCH Q²H-6, J8.0, 7.2, 1.2Hz), 7.76 (dd, ArCH Q²H-8, J8.1, 0.6Hz), 7.84 (ddd, ArCH Q²H-7, J8.1, 7.2, 1.1Hz), 8.27 (dd, ArCH Q²H-5, J8.0, 1.1Hz).

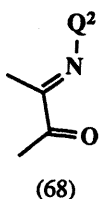
δ_{C} (CDCl_3 , 75MHz): 10.93 (CH_3CH_2), 20.35 (CH_3), 20.67 (CH_3), 20.78 (CH_3), 26.42 (CH_3CH_2), 26.99 (CH_3COO), 94.70 (AcOCON),

120.68 (Q^2 $\underline{C}CO$), 127.04, 127.29, 127.62, 135.45 ($4 \times Q^2$ $\underline{C}H$), 146.55 (Q^2 $\underline{C}N=C$), 160.31 (Q^2 $\underline{C}N$), 161.11 (Q^2 $\underline{C}O$), 167.48 ($CH_3\underline{C}ON$), 171.41 ($CH_3\underline{C}OO$), 199.63 ($CH_3\underline{C}OC$).

ν_{max} (Nujol Mull): 1760s, 1725s, 1693s, 1609s, 1572s, 1460m, 1373m, 1354m, 1328m, 1303m, 1292m, 1238s, 1218s, 1155w, 1122s, 1085w, 1048w, 1019m, 970w, 954m, 940w, 895w, 872w, 822w, 791w, 773s, 707m, 698m, 658m, 611m.

M/Z (%): 316 (11), 274 (35), 232 (63), 214 (12), 190 (100), 175 (11), 174 (77), 173 (26).

Preparation of keto-imine (68)



Keto-amine (67) (0.49g, 1.63mmol) was dissolved in dry methanol (5ml) and glacial acetic acid (2 mol equiv.) added. LTA (0.77g, 1.74mmol) was added continuously in very small portions over 15 min. to the vigorously stirred solution. The solution was stirred for 3 hr. after which time activated charcoal was added and the solution filtered. The filtrate was washed with sodium bicarbonate solution and water, dried ($MgSO_4$) and evaporated under reduced pressure to give a solid. Chromatography of the crude product, with ethyl acetate/light petroleum (1:3) as

eluant, gave a mixture of keto-imine (68) and starting material (67), R_f 0.65. The mixture was further purified by chromatotron, with ethyl acetate/light petroleum as eluant, to give keto-imine (68) as colourless crystals (0.13g, 31%), m.p. 73-75°C (from ethanol).

Compound (68): $C_{14}H_{15}N_3O_2$ requires M. 257.1164. Found: M/Z 257.1155.

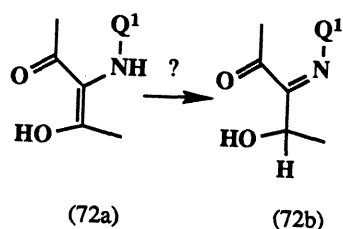
δ_H (CDCl₃, 300MHz): 1.33 (t, $\underline{CH_3CH_2}$, J7.4Hz), 2.00 (s, $\underline{CH_3C=N}$), 2.62 ($\underline{CH_3CO}$), 2.79 (q, $\underline{CH_3CH_2}$, J7.4Hz), 7.48 (ddd, ArCH $\underline{Q^2H-6}$, J8.5, 8.1, 1.7Hz), 7.71-7.80 (m, 2H, ArCH $\underline{Q^2H-7/8}$), 8.27 (ddd, ArCH $\underline{Q^2H-5}$, J8.5, 1.4, 0.6Hz).

δ_C (CDCl₃, 75MHz): 10.65 ($\underline{CH_3CH_2}$), 14.93 ($\underline{CH_3CN}$), 25.71 ($\underline{CH_3CO}$), 28.09 ($\underline{CH_3CH_2}$), 120.77 ($\underline{Q^2 CCO}$), 126.64, 127.16, 127.21, 134.38 (4x $\underline{Q^2 CH}$), 146.77 ($\underline{Q^2 CN=C}$), 155.1 ($\underline{Q^2 CN}$), 155.59 ($\underline{Q^2 CO}$), 173.43 ($\underline{CH_3C=N}$), 197.10 ($\underline{CH_3CO}$).

ν_{max} (CH₂Cl₂): 2980w, 2940w, 2880w, 1710s, 1681s, 1599s, 1570m, 1469m, 1414w, 1359m, 1215m, 1161m, 1143w, 1122m, 1085w, 1063w, 1023w, 1008w, 961w, 936w, 909w, 689w, 645w.

M/Z (%): 215 (14), 214 (100), 173 (18), 90 (16).

Oxidation of 3-amino-2-ethylquinazolin-4(3H)-one (46)
using LTA in the presence of pentan-2,4-dione and
trifluoroacetic acid (TFA)



The general procedure (3) was followed using N-aminoquinazolinone (46) (3.05g, 0.016mmol), LTA (7.49g, 0.017mmol), pentan-2,4-dione (4.84g, 0.048mmol) and TFA (5.52g, 0.048mmol) in dry dichloromethane (31ml). The solid/oil mixture which resulted was triturated with ice-cold ether to yield 2-ethylquinazolin-4(3H)-one (52) (0.58g, 19%) as colourless crystals which were identical in all respects to that isolated previously, (see above). Chromatography of the residue over alumina, with ethyl acetate as eluant, gave the enol-amine/imine-alcohol (72a/72b), R_f 0.56 as colourless crystals (0.51g, 16%), m.p. 119-121°C (from ethanol).

Compound (72a/72b):

$\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_3$ requires M . 287.1270. Found M/Z : 287.1297.

δ_{H} (CDCl_3 , 300MHz): 1.37 (t, CH_3CH_2 , J 7.4Hz), 1.77 (s, $\text{CH}_3\text{C}(\text{OH})=$), 2.15 (s, CH_3CO), 2.85 (ABX₃, CH_3CH_2 , J 16.2, 7.4Hz), 5.38 (s, NH), 7.45 (ddd, $\text{ArCH Q}^2\text{H-6}$, J 9.1, 8.0, 1.2Hz), 7.68 (dd, $\text{ArCH Q}^2\text{H-8}$, J 7.8, 0.4Hz), 7.76 (ddd, $\text{ArCH Q}^2\text{H-7}$, J 9.1, 7.8, 1.4Hz), 8.22 (ddd, $\text{ArCH Q}^2\text{H-}$

5, J8.0, 1.4, 0.4 Hz), 12.00 (bs, OH).

δ_c (CDCl₃, 75 MHz): 10.64 ($\underline{\text{CH}_3\text{CH}_2}$), 17.37 ($\underline{\text{CH}_3\text{CO}}$), 27.45 ($\underline{\text{CH}_3\text{CH}(\text{OH})}$), 29.11 ($\underline{\text{CH}_3\text{CO}}$), 99.16 ($\underline{\text{CH}}$), 120.60 ($\text{Q}^2 \underline{\text{CO}}$), 126.55, 126.87, 127.23, 134.60 (4x $\text{Q}^2 \underline{\text{CH}}$), 146.61 ($\text{Q}^2 \underline{\text{CN}=\text{C}}$), 158.82 ($\text{Q}^2 \underline{\text{C}=\text{N}}$), 160.48 ($\text{Q}^2 \underline{\text{CO}}$), 161.48 ($\underline{\text{CH}(\text{OH})\underline{\text{C}}\underline{\text{N}}}$), 197.36 ($\underline{\text{COCH}_3}$).

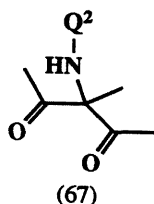
ν_{max} (CH₂Cl₂): 3153brw, 1683s, 1378s, 1333w, 1281m, 1246m, 1223w, 1195w, 1153w, 1118w, 1048w, 983w, 965w, 943w, 883m, 811w, 795w, 778s, 723w, 696w, 656w.

M/Z (%): 271 (15), 242 (10), 215 (14), 214 (100), 200 (17), 174 (10), 173 (20), 130 (12).

Oxidation of 3-amino-2-ethylquinazolin-4(3H)-one (46)

using LTA in the presence of

3-methylpentan-2,4-dione and trifluoroacetic acid (TFA)



The general procedure (3) was followed using N-aminoquinazolinone (46) (1.01g, 5.4mmol), LTA (2.49g, 5.6mmol), 3-methylpentan-2,4-dione (1.22g, 11mmol) and TFA (1.83g, 16mmol) in dry dichloromethane (10ml). The solid/oil mixture obtained was triturated with ice-cold ether to give 2-ethylquinazolin-4(3H)-one (52) (0.17g, 17%)

as colourless crystals which were identical in all respects to that isolated previously, (see above). The filtrate was concentrated under reduced pressure and left to stand at room temperature overnight. Diketo-amine (67) crystallised during this time and was recrystallised from chloroform/light petroleum to give diketo-amine (67) (1.02g, 63%), m.p. 157-160°C, as colourless crystals.

Compound (67):

$C_{16}H_{19}N_3O_3$ requires C, 63.77; H, 6.36; N, 13.95%. Found C, 63.53; H, 6.35; N, 13.94%.

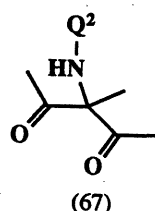
δ_H ($CDCl_3$, 300MHz): 1.24 (s, CH_3CNH), 1.37 (t, CH_3CH_2 , J7.4Hz), 2.31 (s, 2x CH_3CO), 2.80 (q, CH_3CH_2 , J7.4Hz), 7.06 (s, NH), 7.41 (ddd, $ArCH$ Q^2H -6, J8.0, 6.9, 1.3Hz), 7.65 (ddd, $ArCH$ Q^2H -8, J8.2, 1.3, 0.5Hz), 7.73 (ddd, $ArCH$ Q^2H -7, J8.2, 6.9, 1.4Hz), 8.13 (ddd, $ArCH$ Q^2H -5, J8.0, 1.4, 0.5Hz).

δ_C ($CDCl_3$, 75MHz): 10.74 (CH_3CH_2), 13.60 (CH_3CNH), 24.94 (2x CH_3CO), 27.87 (CH_3CH_2), 77.85 (CNH), 120.03 (Q^2 CCO), 126.32, 126.43, 127.05, 134.39 (4x Q^2 CH), 146.67 (Q^2 $CN=C$), 159.88 (Q^2 CN), 162.71 (Q^2 CO), 204.46 (2x CH_3CO).

ν_{max} (Nujol Mull): 3280s, 1705s, 1675s, 1595s, 1412m, 1352s, 1330w, 1292w, 1250m, 1222m, 1191m, 1161w, 1149w, 1122w, 1098w, 1050w, 1028w, 990w, 968w, 936m, 917w, 898w, 878w, 842w, 800s, 775w, 720w, 710w.

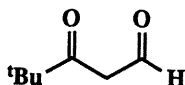
M/Z (%): 216 (11), 214 (63), 175 (41), 174 (100), 173 (100), 146 (18), 145 (11), 130 (24), 120 (14), 119 (58), 118 (15), 103 (10), 102 (11).

Methylation of enol-amine/imine-alcohol (72a/72b)



To a slurry of sodium hydride (0.044g, 1.83mmol) in dry THF (3ml) at -10°C was added enol-amine/imine-alcohol (72a/72b) (0.197g, 0.69mmol) continuously and in small portions over 10 min. The mixture was stirred at this temperature for 1 hr. before methyl iodide (0.098g, 0.69mmol) was added. The mixture was stirred for a further 1 hr. before allowing to warm to ambient temperature. Water (1ml) was added and the mixture extracted with dichloromethane (3x25ml), the organic layer was dried (MgSO_4) and evaporated under reduced pressure. The semi-solid residue was triturated with ethyl acetate, the solid separated and crystallised from ethanol to give diketo-amine (67) as colourless crystals (0.02g, 10%), identical with that isolated above. A single crystal X-ray of this diketo-amine was obtained, (see Appendix 2) which confirmed its structure as (67).

Preparation of pivaloylacetaldehyde⁷⁶



This material was prepared by the method of Levine et al⁷⁶ and gave pivaloylacetaldehyde as a colourless oil (3.42g, 25%).

δ_{H} (CDCl₃, 90MHz): 1.13 (s, (CH₃)₃C), 5.65 (d, CH=C(OH), J5.2Hz), 7.95 (d, CH=O, J5.2Hz), 14.65 (bs, OH).

Reaction of the N-acetoxyaminoquinazolinone (134) with pivaloylacetaldehyde



(74)

The general procedure (1) was followed using N-aminoquinazolinone (73) (0.51g, 2.5mmol), LTA (1.17g, 2.61mmol) and pivaloylacetaldehyde (0.97g, 7.6mmol) in dry dichloromethane (5ml). The solid/oil mixture obtained was triturated with ice-cold ether to give 2-isopropylquinazolin-4(3H)-one (74) as colourless crystals

(0.13g, 54%), m.p. 206-208°C (from ethanol). Examination of the residue from the ether solution by n.m.r. spectroscopy showed no other quinazolinone-containing species to be present.

Compound (74): $C_{11}H_{12}N_2O$ requires C, 70.18; H, 6.43; N, 14.88%. Found C, 70.12; H, 6.45; N, 14.86%.

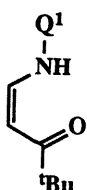
δ_H ($CDCl_3$, 300MHz): 1.46 (d, $\underline{CH_3}CHCH_3$, J7.0Hz), 3.08 (heptet, CH_3CHCH_3 , J7.0Hz), 7.46 (ddd, $ArCH$ Q^1H -6, J8.0, 6.5, 1.8Hz), 7.70-7.81 (m, $ArCH$ Q^1H -7/8), 8.31 (ddd, $ArCH$ Q^1H -5, J8.0, 1.6, 0.6Hz), 11.97 (brs, NH).

δ_C ($CDCl_3$, 75MHz): 20.40 ($\underline{CH_3}CHCH_3$), 34.93 (CH_3CHCH_3), 120.72 ($Q^1 \underline{CO}$), 126.20, 127.37, 134.58, (4x $Q^1 \underline{CH}$), 149.52 ($Q^1 \underline{CN=C}$), 160.90 ($Q^1 \underline{C=N}$), 164.36 ($Q^1 \underline{CO}$).

ν_{max} (Nujol Mull): 3174m, 3125m, 1680s, 1620s, 1608s, 1340m, 1268m, 1250m, 1237w, 1205m, 1170m, 1128w, 1096m, 1022w, 984m, 963w, 931w, 893m, 878m, 856w, 768s, 753w, 720w, 687m, 650m, 624s.

M/Z (%): 187 (46), 186 (24), 173 (15), 172 (100), 159 (18), 118 (22).

Oxidation of 3-amino-2-isopropylquinazolin-4(3H)-one (73)
using LTA in the presence of pivaloylacetaldehyde and
trifluoroacetic acid (TFA)



(75)

The general procedure (3) was followed using N-aminoquinazolinone (73) (0.75g, 3.88mmol), LTA (1.72g, 3.69mmol), pivaloylacetaldehyde (1.4g, 11mmol) and TFA (1.26g, 11mmol) in dry dichloromethane (8ml). Chromatography of the crude oxidation product over silica, with ethyl acetate/light petroleum (1:3) gave enamino-ketone (75), R_f 0.26, as colourless crystals (0.6g, 50%), m.p. 108-110°C (from ethanol). This compound exists in $CDCl_3$ solution as a 6.7:1 ratio of double bond isomers as determined from the ratio of the olefinic proton signals at δ 5.41 and 5.62 in the proton n.m.r. spectrum below.

Compound (75): $C_{17}H_{22}N_3O_2$ requires M. 313.1790. Found: M/Z 313.1787.

Major (Cis) isomer: δ_H ($CDCl_3$, 300MHz): 1.21 (s, $(CH_3)_3C$), 1.35 (d, CH_2CHCH_3 , J6.7Hz), 4.40 (heptet, CH_3CHCH_3 , J6.7Hz), 5.62 (d, $CH=CHN$ (cis), J8.4Hz), 6.68 (t, $NHCH=CH$ (cis), J9.2Hz), 7.42 (dd, ArCH Q^1H -6, J8.0, 1.2Hz), 7.64-7.76 (m, ArCH Q^1H -7/8), 8.17 (d, ArCH Q^1H -5, J8.0Hz), 10.91 (d, NH, J10.0Hz).

With proton decoupling of the doublet at 10.91 (NH) the triplet at 6.68 (CH=) collapses to a doublet. With decoupling of the triplet at 6.68 (CH=) the doublet at 10.91 (NH) collapses to a singlet. With decoupling of the doublet at 5.62 (CH=) the triplet at 6.68 (CH=) reduces to a doublet.

δ_c (CDCl₃, 75MHz): 20.74 (CH₃CHCH₃), 27.15 ((CH₃)₃C), 31.09 (CH₃CHCH₃), 94.96 (NHC=CH), 120.82 (Q¹ CCO), 126.63, 126.83, 127.53, 134.64 (4x Q¹ CH), 146.72 (Q¹ CN=C), 152.35 (CH=CNH), 161.25 (Q¹ CN), 161.89 (Q¹ CO), 207.59 (tBuCO).

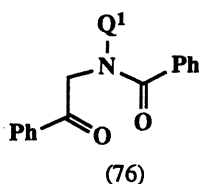
Minor (Trans) isomer (observable peaks): 1.00 (s, (CH₃)₃C), 3.27 (heptet, CH₃CHCH₃, J6.8Hz), 5.41 (d, CH=CHN (trans), J13.2Hz), 7.84 (d, ArCH Q¹H-5, J7.9Hz).

δ_c (CDCl₃, 75MHz): 25.98 (CH₃CHCH₃), 26.12 ((CH₃)₃C), 126.44, 127.11, 135.16 (3x Q¹ CH), 147.40 (Q¹ CN=C).

ν_{\max} (Nujol Mull): 3248brm, 1698s, 1678s, 1625s, 1605s, 1320w, 1298m, 1268m, 1247m, 1220w, 1170w, 1145w, 1100m, 1090m, 1070m, 1003w, 975w, 955w, 935w, 910w, 888w, 818m, 778s, 748w, 696m.

M/Z (%): 313 (M⁺, 5.5), 256 (16), 228 (33), 214 (16), 188 (61), 174 (12), 173 (100), 172 (17), 160 (22), 149 (10), 119 (23), 95 (16), 93 (36), 92 (11), 90 (12), 84 (52), 70 (20), 69 (32), 68 (10).

Reaction of the N-acetoxvminoquinazolinone (134) with
dibenzoylmethane



The general procedure (1) was followed using N-aminoquinazolinone (73) (3.45g, 17mmol), LTA (7.92g, 18mmol) and dibenzoylmethane (11.44g, 50mmol) in dry dichloromethane (35ml). The oil obtained was left at room temperature for 2 hr during which time it crystallised. The solid which crystallised was filtered and recrystallised from ethanol to give dibenzoylmethane as light yellow crystals. Chromatography of the combined residues, after removal of dibenzoylmethane, over silica with ethyl acetate/light petroleum (1:4) as eluant, gave keto-amide (76), R_f 0.21, as colourless crystals (2.97g, 48%), m.p. 154-155°C (from ethanol), and 2-isopropylquinazolin-4(3H)-one (74) (0.126g, 4%) which was identical in all respects to that isolated previously, (see above). The keto-amide (76) exists in $CDCl_3$ solution as a 1.2:1 ratio of amide rotamers. Compound (76): $C_{26}H_{23}N_3O_3$ requires C, 73.39; H, 5.45; N, 9.88%. Found C, 73.37; H, 5.51; N, 9.87%.

Major amide rotamer: δ_H ($CDCl_3$, 300MHz): 1.34 (2xd, CH_3CHCH_3 , J6.8Hz), 4.23-4.35 (m, CH_3CHCH_3), 4.29 and 6.11 (2xd, CH_2 , J17.5Hz), 7.16-7.78 (m, 11H, ArCH Q¹H-6/7/8,

8xPhH), -8.03 (dd, 2H, PhH, J4.9, 1.5Hz), 8.10 (ddd, Q¹H-5, J8.3, 1.5, 0.3Hz).

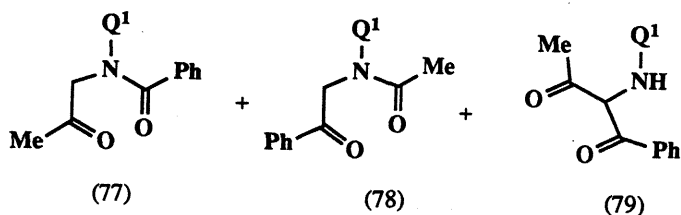
Minor rotamer (observable peaks): δ_H (CDCl₃, 300MHz): 1.18 and 1.52 (2xd, CH₃CHCH₃, J6.5Hz), 5.22 and 5.42 (2xd, CH₂, J19.3Hz), 8.24 (d, ArCH Q¹H-5, J8.1Hz).

δ_C (CDCl₃, 75MHz): (major and minor rotamers): 20.48 (CH₃), 21.89 (CH₃), 22.30 (CH₃), 23.03 (CH₃), 29.97 (CH), 30.51 (CH), 57.96 (CH₂), 58.74 (CH₂), 120.22 (Q¹ CCO), 121.08 (Q¹ CCO), 126.22 (CH), 126.70 (Q¹ CH), 126.76 (CH), 126.80 (CH), 127.39 (CH), 127.44 (CH), 127.52 (CH), 127.74 (CH), 128.04 (CH), 128.06 (CH), 128.80 (CH), 128.82 (Q¹ CH), 130.73 (CH), 131.64 (CH), 132.79 (PhC), 132.92 (PhC), 133.76 (CH), 134.12 (CH), 134.25 (CH), 134.70 (CH), 134.79 (CH), 134.97 (CH), 146.66 (Q¹ CN=C), 147.26 (Q¹ CN=C), 159.72 (Q¹ C=N), 160.83 (Q¹ C=N), 162.58 (Q¹ CO), 163.98 (Q¹ CO), 171.80 (NCOPh), 172.68 (NCOPh), 191.23 (CH₂COPh), 193.09 (CH₂COPh).

ν_{max} (Nujol Mull): 1700s, 1673s, 1598s, 1583s, 1351m, 1300w, 1259m, 1245m, 1220s, 1210m, 1168m, 1148w, 1083w, 995w, 968m, 935w, 928w, 910w, 885w, 790w, 778s, 759m, 710m, 698m, 688m, 635m.

M/Z (%): 425 (M⁺), 237 (13), 189 (26), 188 (100), 187 (94), 174 (42), 173 (100), 160 (72), 146 (21), 145 (16), 132 (15), 130 (14), 120 (25), 119 (63), 118 (17), 117 (14), 106 (93), 105 (100), 104 (21), 103 (20), 102 (11).

**Reaction of the N-acetoxyminoquinazolinone (134) with
benzoylacetone**



The general procedure (1) was followed using N-aminoquinazolinone (73) (3.2g, 15.8mmol), LTA (7.38g, 17mmol) and benzoylacetone (6.3g, 39mmol) in dry dichloromethane (32ml). The solid/oil mixture obtained was triturated with ice-cold ether to give 2-isopropylquinazolin-4(3H)-one (74) (0.26g, 9%) which was identical in all respects to that isolated previously, (see above). Chromatography of the residue over silica, with ethyl acetate/light petroleum (1:4) as eluant, gave diketo-amine (79), R_f 0.30, as colourless crystals (0.74g, 13%), m.p. 125-7°C (decomp.), (from ethanol). Further elution gave a mixture of keto-amides (77) and (78), R_f 0.21, (4.31g, 75%). The n.m.r. spectrum of the mixture of (77) and (78) shows them to be present in a 3.32:1 ratio respectively. Fractional crystallisation of this mixture with ethanol (x3) gave keto-amide (77) as colourless crystals (0.245g, 4%), m.p. 112-114°C. Further crystallisation of the residue with ethanol (x2) and then with chloroform/light petroleum gave keto-amide (78) as colourless crystals (0.148g, 2%), m.p. 115-117°C.

Compound (77): This compound exists in CDCl_3 solution as a 1.61:1 ratio of amide rotamers.

$\text{C}_{21}\text{H}_{21}\text{N}_3\text{O}_3$ requires M. 363.1583. Found: M/Z 363.1583.

Major rotamer: δ_{H} (CDCl_3 , 300MHz): 1.21 and 1.28 (2xd, CH_3CHCH_3 , J6.5Hz), 2.34 (s, CH_3CO), 3.99 (heptet, CH_3CHCH_3 , J6.5Hz), 3.83 and 5.15 (2xd, CH_2 , J17.2Hz), 7.20–7.77 (m, 8H, ArCH Q¹H-6/7/8, and 5xPhH), 8.09 (d, ArCH Q¹H-5, J8.0Hz).

Minor rotamer: (observable peaks): 1.47 (d, CH_3CHCH_3 , J6.5Hz), 1.96 (s, CH_3CO), 4.14 (heptet, CH_3CHCH_3 , J6.5Hz), 4.54 and 4.82 (2xd, CH_2 , J19.6Hz), 8.22 (d, ArCH Q¹H-5, J7.7Hz).

δ_{C} (CDCl_3 , 75MHz): Major rotamer: 20.50 (CH_3CHCH_3), 22.91 (CH_3CHCH_3), 27.62 (CH_3CO), 29.97 (CH_3CHCH_3), 60.82 (CH_2), 120.20 (Q¹ CCO), 126.29 (Ph CH), 126.68 (Q¹ CH), 126.77 (CH), 126.84 (CH), 127.36 (CH), 127.44 (Q¹ CH), 128.13 (Ph CH), 130.92 (Ph CH), 132.44 (Ph CCO), 135.02 (Q¹ CH), 146.60 (Q¹ CN=C), 160.66 (Q¹ CN), 162.24 (Q¹ CO), 172.52 (COPh), 200.06 (CH_3CO).

Minor rotamer: (observable peaks): 21.72 (CH_3CHCH_3), 22.15 (CH_3CHCH_3), 27.11 (CH_3CO), 30.36 (CH_3CHCH_3), 61.80 (CH_2), 121.05 (Q¹ CCO), 126.29 (Ph CH), 126.77 (Ph CH), 126.84 (Ph CH), 127.36 (CH), 127.44 (CH), 130.92, 131.66 (2x Q¹ CH), 132.94 (Ph CCO), 134.75 (Q¹ CH), 147.24 (Q¹ CN=C), 159.63 (Q¹ CN), 163.75 (Q¹ CO), 171.41 (COPh), 201.62 (CH_3CO).

ν_{max} (Nujol Mull): 1732s, 1700s, 1601s, 1573m, 1322s, 1310s, 1270m, 1239w, 1225m, 1205w, 1176m, 1156m, 1112w, 1096w, 1078w, 1040w, 1020w, 1008w, 980w, 935w, 912w, 886w, 874w, 850w, 795w, 790w, 770s, 725m, 716m, 696s, 670m, 652m.

M/Z (%): 188 (38), 187 (17), 173 (72), 160 (17), 105 (100.0), 77 (34).

Compound (78): This compound exists in CDCl₃ solution as a 5.82:1 ratio of amide rotamers.

C₂₁H₂₁N₃O₃ requires 363.1583. Found M/Z: 363.1583.

δ_H (CDCl₃, 300MHz): Major rotamer: 1.25 and 1.44 (2xd, CH₃CHCH₃, J6.6Hz), 1.95 (CH₃CO), 4.03 (heptet, CH₃CHCH₃, J6.6Hz), 4.15 and 5.88 (2xd, CH₂, J17.4Hz), 7.38-7.83 (m, 6H, ArCH Q¹H-6/7/8, and 3xPhH), 7.95-8.00 (m, 2H, 2xPhH), 8.25 (dd, ArCH Q¹H-5, J8.0, 1.2Hz).

Minor rotamer: (observable peaks): 1.19 and 1.37 (2xd, CH₃CHCH₃, J6.7Hz), 2.27 (s, CH₃CO), 3.76 (heptet, CH₃CHCH₃, J6.7Hz), 4.90 and 5.67 (2xd, CH₂, J19.4Hz), 8.19 (dd, ArCH Q¹H-5, J8.1, 1.1Hz).

δ_C (CDCl₃, 75MHz): Major rotamer: 19.90 (CH₃CHCH₃), 21.34 (CH₃CHCH₃), 22.25 (CH₃CO), 29.82 (CH₃CHCH₃), 57.12 (CH₂), 120.52 (Q¹ C=O), 126.94 (Q¹ CH), 127.69 (Ph CH), 128.08, 128.74 (2x Q¹ CH), 133.71 (Ph CH), 134.82 (Ph CCO), 135.28 (Q¹ CH), 147.01 (Q¹ CNC), 160.63 (Q¹ C=N), 162.76 (Q¹ CO), 173.07 (COPh), 191.51 (CH₃CO).

Minor rotamer: (observable peaks): 20.82 (CH₃CHCH₃), 29.94 (CH₃CHCH₃), 59.11 (CH₂), 126.24, 126.72, 127.44, 127.91, 129.07, 134.45, 134.72 (7x CH), 192.30 (COCH₃).

ν_{max} (Nujol Mull): 1685s, 1596s, 1582m, 1570m, 1382s, 1299m, 1262s, 1238s, 1222s, 1180m, 1148w, 1105w, 1090m, 1048w, 1038w, 1025w, 1000w, 988m, 978m, 968w, 886w, 858w, 842w, 800m, 775s, 750s, 718m, 700m, 682s, 668w, 656w, 633s, 614m.

M/Z (%): 363 (M⁺, 0.8), 189 (20), 188 (50), 187 (26), 175

(13), 174 (12), 173 (100), 160 (22), 119 (12), 105 (63), 77 (22).

Compound (79): $C_{21}H_{21}N_3O_3$ requires C, 69.40; H, 5.83; N, 11.56%. Found C, 69.32; H, 5.94; N, 11.72%.

δ_H ($CDCl_3$, 300MHz): 1.22 (2xd, CH_3CHCH_3 , J6.7Hz), 2.28 (s, CH_3CO), 3.38 (heptet, CH_3CHCH_3 , J6.7Hz), 5.02 (d, $CHNH$, J2.9Hz), 6.71 (d, NH , J2.9Hz), 7.37 (ddd, $ArCH$ Q^1H -6, J8.1, 6.7, 1.6Hz), 7.46 (dd, 2H, 2xPhH, J7.4, 1.6Hz), 7.65 (m, 2H, $ArCH$ Q^1H -7/8), 8.00 (dd, 3xPhH, J3.2, 1.4Hz), 8.11 (dd, $ArCH$ Q^1H -5, J8.1, 1.1Hz).

δ_C ($CDCl_3$, 75MHz): 20.68 (CH_3CHCH_3), 20.92 (CH_3CHCH_3), 26.19 (CH_3CO), 30.81 (CH_3CHCH_3), 77.80 ($CHNH$), 120.56 (Q^1 CCO), 126.29 (CH), 126.39 (CH), 127.42 (Ph CH), 128.89, 129.34 (Q^1 2x CH), 134.06 (Ph CCO), 134.39 (CH), 134.45 (CH), 147.00 (Q^1 $CN=C$), 162.06 (Q^1 CN), 162.95 (Q^1 CO), 193.11 (Ph CCO), 201.42 (CH_2CO).

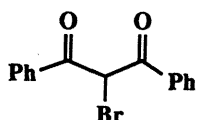
ν_{max} (Nujol Mull): 3174brm, 1700s, 1620s, 1600s, 1271m, 1253m, 1206w, 1174m, 1099w, 1073w, 1026w, 989m, 966w, 934w, 897m, 879m, 775s, 761m, 717m, 709m, 690m, 629m.

M/Z (%): 188 (24), 187 (16), 174 (11), 173 (68), 160 (13), 119 (15), 105 (39), 32 (100).

When this diketo-amide was heated briefly (approximately 2 min.) in ethyl acetate, decomposition occurred. A quantitative yield of 2-isopropylquinazolin-4(3H)-one (74) was recovered by cooling the solution in ice and filtering the solid (74) which crystallised.

Preparation of bromo-dibenzoyl methane⁷⁷

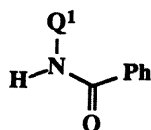
This material was prepared by an adaptation of the method by Shoppee and Stevenson.⁷⁷



Dibenzoylmethane (11.23g, 0.05mol) was dissolved in dry, stirred, carbon tetrachloride (50ml) which was then treated, dropwise, with a solution of bromine (6.32g, 79mmol) in dry carbon tetrachloride (5ml) over 5 min. The mixture was allowed to stand overnight, during which time a solid crystallised out. This was separated, washed with a small amount of carbon tetrachloride and water and recrystallised from ethanol to give bromo-dibenzoylmethane (11.81g, 78%) as colourless crystals.

δ_{H} (CDCl₃, 90MHz): 6.55 (s, CH), 7.23-7.70 (m, 3xPhH), 7.90-8.17 (m, 2xPhH).

Reaction of the N-acetoxyminoquinazolinone (134) with
bromo-dibenzoylmethane



(81)

The general procedure (1) was followed using the N-aminoquinazolinone (73) (1.14g, 5.6mmol), LTA (2.62g, 5.9mmol) and bromo-dibenzoylmethane (5.06g, 17mmol) in dry dichloromethane (11ml). The solid obtained was recrystallised from ethanol to give bromo-dibenzoylmethane (1.77g, 35% recovery). Chromatography of the residue over silica, with ethyl acetate/light petroleum (1:4) as eluant, gave 3-benzoylamino-2-isopropylquinazolin-4(3H)-one (81), R_f 0.56, as colourless crystals (0.13g, 8%), m.p. 174–174.5°C (from ethanol). Further elution gave 2-isopropylquinazolin-4(3H)-one (74) (0.65g, 62%) which was identical in all respects to that isolated previously.

Compound (81): $C_{18}H_{17}N_3O_2$ requires C, 70.34; H, 5.58; N, 13.67%. Found C, 70.32; H, 5.67; N, 13.66%.

δ_H ($CDCl_3$, 300MHz) (c~10mg/0.5ml): 1.35 (dd, CH_3CHCH_3 , J6.7Hz), 3.25 (heptet, CH_3CHCH_3 , J6.7Hz), 7.30–7.50 (m, ArCH Q^1H -6, and 3xPhH), 7.66–7.76 (m, ArCH Q^1H -7/8), 7.90–7.93 (dd, 2xPhH, J6.3, 1.2Hz), 8.15 (ddd, ArCH Q^1H -5, J8.0, 1.5, 0.4Hz), 9.85 (s, NH).

δ_H (c~60mg/0.5ml) (7.00–11.00 region only): 7.16–7.21 (m, 2H,

2xPhH), 7.32-7.38 (m, 2H, ArCH Q¹H-6, and 1xPhCH), 7.62-7.72 (m, ArCH Q¹H-7/8), 7.84-7.87 (m, 2H, 2xPhH), 8.08 (dd, ArCH Q¹H-5, J8.0, 1.1Hz), 10.52 (s, NH). The positions of all other resonances were unchanged at this higher concentration.

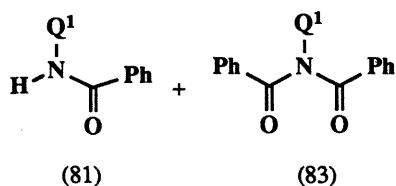
δ_c (CDCl₃, 75MHz): 19.85 (CH₃CHCH₃), 21.22 (CH₃CHCH₃), 31.04 (CH₃CHCH₃), 120.23 (Q¹ CCO), 126.35 (Ph CH), 126.51 (Ph CH), 127.49, 127.53, 128.41 (3x Q¹ CH), 130.20 (PhCCO), 132.44 (CH), 134.72 (CH), 147.12 (Q¹ CN=C), 161.55 (Q¹ CN), 161.90 (Q¹ CO), 166.77 (PhCON).

ν_{max} (Nujol Mull): 3299brm, 1678s, 1670s, 1607s, 1513m, 1345m, 1300m, 1272s, 1255m, 1225m, 1188w, 1173w, 1160w, 1113w, 1090w, 1070w, 1025w, 1000w, 953w, 920w, 895w, 885w, 845w, 795w, 772s, 715m, 703m, 690s, 682m, 660w, 640m.

M/Z (%): 307 (M⁺, 6.7), 173 (21), 105 (59), 86 (64), 84 (100), 77 (17).

Benzoylation of 3-amino-2-isopropylquinazolin-4(3H)-one

(73)



N-Aminoquinazolinone (73) (1.12g, 5.53mmol) was dissolved in dry dichloromethane (5ml). To this stirred solution was added dry pyridine (0.46g, 5.8mmol) followed

by benzoyl chloride (1.64g, 11.6mmol) dropwise. The solution was stirred overnight. Dry ether was added, pyridinium hydrochloride separated and washed with dry ether. The filtrate was concentrated under reduced pressure and chromatography of the residue over silica, with ethyl acetate/light petroleum (1:4) as eluant, gave a fraction R_f 0.30, as colourless crystals (1.21g, 72%), whose proton n.m.r. and m.p. were identical to those given above for (81). Further elution gave 3-dibenzoylamino-2-isopropylquinazolin-4(3H)-one (83), R_f 0.25, as colourless crystals (0.23g, 10%), m.p. 195-197°C (from ethanol).

Compound (83): $C_{25}H_{21}N_3O_3$ requires C, 72.98; H, 5.14; N, 10.21%. Found C, 73.07; H, 5.24; N, 10.22%.

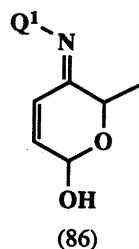
δ_H ($CDCl_3$, 300MHz): 1.39 (d, CH_3CHCH_3 , J6.7Hz), 3.27 (heptet, CH_3CHCH_3 , J6.7Hz), 7.18-7.32 (m, 6H, 6xPhCH), 7.45 (ddd, ArCH Q^1H -6, J7.7, 3.5, 1.6Hz), 7.71-7.79 (m, 6H, ArCH Q^1H -7/8, and 4xPhH), 8.27 (d, ArCH Q^1H -5, J7.7Hz).

δ_C ($CDCl_3$, 75MHz): 21.37 (CH_3CHCH_3), 31.36 (CH_3CHCH_3), 121.07 ($Q^1 CCO$), 126.72 (PhCH), 127.09 (PhCH), 127.57 (PhCH), 128.41, 129.31, 132.76, 133.85 (4x $Q^1 CH$), 134.94 (Ph $CCON$), 147.11 ($Q^1 CN=C$), 160.07 ($Q^1 CN$), 161.39 ($Q^1 CO$), 170.16 (NCOPh).

ν_{max} (Nujol Mull): 1695s, 1683s, 1600s, 1583w, 1570w, 1320m, 1303m, 1289m, 1230m, 1180w, 1135m, 1080w, 1025w, 1003w, 938w, 925w, 902s, 885w, 850w, 804m, 788w, 770m, 713s, 695m, 660m, 645m.

M/Z (%): 411 (M^+ , 2.2), 290 (38), 188 (11), 173 (25), 149 (11), 105 (100), 84 (13), 77 (34).

Reaction of the N-acetoxyaminoquinazolinone (134) with
1-(2-furyl)ethanol



The general procedure (1) was followed using N-aminoquinazolinone (73) (1.02g, 5.1mmol), LTA (2.35g, 5.31mmol) and 1-(2-furyl)ethanol (1.70g, 15mmol) in dry dichloromethane (10ml). Chromatography of the crude oxidation product over silica, with ethyl acetate/light petroleum (1:3) as eluant, gave dihydropyranone-imine (86), R_f 0.21, as colourless crystals (1.20g, 76%), m.p. 78-80°C (from ethanol).

Compound (86):

$C_{17}H_{19}N_3O_3$ requires C, 65.16; H, 6.11; N, 13.41%. Found C, 65.03; H, 6.20; N, 13.36%.

δ_H ($CDCl_3$, 300MHz, room temperature): 1.28 (bm, CH_3CHCH_3), 1.68 (d, CH_3 , J6.4Hz), 3.20 (heptet, CH_3CHCH_3 , J6.7Hz), 5.12-5.21 (bm, $OCHCH_3$ and OH, (the latter exchangeable with D_2O)), 5.58 (bm, $CHOH$), 6.07 (d, $N=CCH=CH$, J10.3Hz), 6.51-6.54 (bd, $CH=CHC=N$), 7.46 (dd, ArCH Q^1H -6, J8.2, 4.1Hz), 7.67-7.74 (m, ArCH Q^1H -7/8), 8.23 (d, ArCH Q^1H -5, J8.2Hz).

δ_H ($CDCl_3$, 300MHz, -40°C): This compound exists as a 2:1 ratio of N-N bond rotamers: Major rotamer: 1.19 and 1.42 (2xd, CH_3CHCH_3 , J6.7Hz), 1.73 (d, CH_3CHO , J6.4Hz), 3.27 (heptet,

CH₃CHCH₃, J6.7Hz), 5.40 (q, CH₃CHO, J6.4Hz), 5.53-5.56 (m, HOCHO), 6.11 (d, N=CCH=CH, J10.2Hz), 6.28 (bm, OH), 6.68 (dd, CH=CHC=N, J10.2, 3.6Hz), 7.48-7.54 (m, ArCH Q¹H-6), 7.74-7.84 (m, ArCH Q¹H-7/8), 8.23-8.26 (d, ArCH Q¹H-5, J7.9Hz).

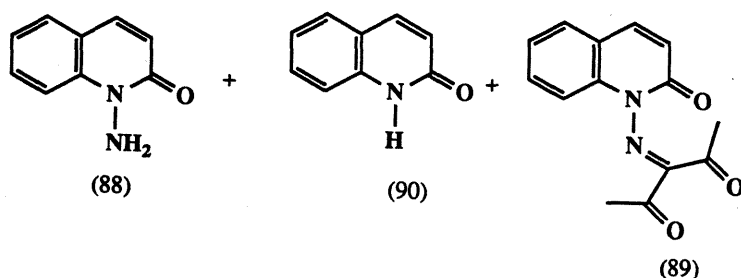
Minor rotamer (observable peaks): 1.12 and 1.39 (2xd, CH₃CHCH₃, J6.7Hz), 1.71 (d, CH₃CHO, J6.4Hz), 3.22 (heptet, CH₃CHCH₃, J6.7Hz), 5.16 (q, CH₃CHO, J6.4Hz), 5.71 (brm, OH), 6.13 (d, N=CCH=CH, J10.1Hz), 6.51 (dd, CH=CHC=N, J10.1, 3.6Hz).

δ_c (CDCl₃, 75MHz): 16.98 (CH₃CHO), 20.08 (CH₃CHCH₃), 31.60 (CH₃CHCH₃), 66.45 (CH₃CHO), 87.82 (CH(OH)), 118.16 (CH=CHC=N), 120.48 (Q¹ CCO), 126.40, 126.96, 127.29, 134.13 (4x Q¹ CH), 140.46 (N=CCH=CH), 146.88 (Q¹ CNC), 157.10 (Q¹ CN), 159.61 (Q¹ CO), 171.11 (N=CCH=CH).

ν_{max} (Nujol Mull): 3355brm, 1650s, 1592m, 1342w, 1287w, 1230w, 1213m, 1179m, 1132w, 1110w, 1076m, 1043s, 943w, 920w, 889w, 848w, 792w, 773s, 687m, 660w, 643w.

M/Z (%): 188 (45), 187 (26), 174 (24), 173 (100), 160 (20), 149 (28), 119 (21), 93 (15), 69 (11).

Oxidation of 1-aminoquinolin-2(1H)-one (88) using LTA
in the presence of pentan-2,4-dione at
room temperature



Powdered N-aminoquinolinone (88) (1.10g, 6.86mmol) and LTA (3.19g, 7.2mmol) were added alternately and continuously in very small portions over 15 min. to a vigorously stirred solution of dry dichloromethane (11ml) and pentan-2,4-dione (2.06g, 7.2mmol) at room temperature. The mixture was then stirred for 5 min. at room temperature. The insoluble lead di-acetate was separated and washed with dichloromethane and the total filtrate washed successively with sodium bicarbonate solution and water, dried with magnesium sulphate and the solvent removed by evaporation under reduced pressure. The solid/oil mixture obtained was triturated with ice-cold ether to yield quinolin-2(1H)-one (90) (0.325g, 33%) as colourless crystals, m.p. 198–200°C (from ethanol) (lit⁷⁸. m.p. 199–200°C). Chromatography of the residue over silica, with ethyl acetate/light petroleum (1:3) as eluant, gave diketo-imine (89), *R_f* 0.19, as bright yellow crystals (0.146g, 10% based on unreacted starting material), m.p. 157–158°C (from ethanol). Also obtained on

further elution was unreacted starting material (88)
(0.173mg, 16% recovery), m.p. 128–130°C (lit.⁷⁹ m.p. 130°C).

Compound (89): $C_{14}H_{12}N_2O_3$ requires C, 65.62; H, 4.72; N, 10.93%.
Found C, 65.58; H, 4.79; N, 10.96%.

δ_H ($CDCl_3$, 300MHz): 2.54 (s, CH_3CO), 2.69 (s, $COCH_3$), 6.64
(d, $CH=CHCO$, J9.5Hz), 7.33 (dd, 1xArCH, J8.0, 1.4Hz), 7.57–7.66
(m, 3H, 3xArCH), 7.70 (d, $CH=CHCO$, J9.5Hz).

δ_C ($CDCl_3$, 75MHz): 26.23 (CH_3CO), 28.34 ($COCH_3$), 115.94
($CH=CHCO$), 120.31 (Ar $CCH=CH$), 120.57, 124.09, 128.45,
131.15 (4x ArCH), 138.36 (Ar CN), 140.02 ($CH=CHCO$), 156.20
($C=N$), 162.12 (Ar NCO), 192.76 (CH_3CO), 197.32 ($COCH_3$).

ν_{max} (Nujol Mull): 1693s, 1650s, 1622m, 1590s, 1562m, 1488w,
1452m, 1415w, 1402w, 1377w, 1357m, 1346w, 1289w, 1260m,
1237w, 1225w, 1190m, 1130m, 1068m, 1047w, 1036w, 1020w,
979w, 947w, 916w, 860w, 822m, 758s, 745w, 720w, 704w, 682w,
635m, 608m.

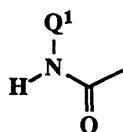
M/Z (%): 256 (M^+ , 0.6), 214 (14), 213 (100), 172 (10), 171
(92), 148 (15), 147 (10), 145 (26), 128 (22), 117 (21), 116
(17), 90 (11), 89 (18), 71 (12), 69 (15).

EXPERIMENTAL

CHAPTER THREE

Acetylation of 3-amino-2-isopropylquinazolin-4(3H)-one

(73)



(93)

3-Amino-2-isopropylquinazolin-4(3H)-one (73) (20.82g, 0.1mol) was dissolved in acetic anhydride (100ml) and stirred for 48hr. After this time the solution was poured into water (1l) and the solid which crystallised was separated and dried in air. It was then recrystallised from chloroform/light petroleum to give 3-acetylamino-2-isopropylquinazolin-4(3H)-one (93) (16.57g, 66%), m.p. 74-76°C.

Compound (93):

C₁₃H₁₅N₃O₂·H₂O requires C, 59.30; H, 6.51; N, 15.96%. Found C, 59.07; H, 6.49; N, 15.89%.

δ_H (d₆-DMSO, 300MHz, room temperature): 1.22 (2xd, CH₃CHCH₃, J_{6.7}Hz), 2.12 (s, CH₃CON), 3.13 (heptet, CH₃CHCH₃, J_{6.7}Hz), 3.32 (bs, H₂O of crystallisation), 7.53 (dd, ArCH Q¹H-6, J_{8.0}, 1.0Hz), 7.67 (d, ArCH Q¹H-8, J_{8.1}Hz), 7.85 (ddd, ArCH Q¹H-7, J_{8.1}, 7.3, 1.6Hz), 8.10 (dd, ArCH Q¹H-5, J_{8.0}, 1.6Hz), 10.95 (bs, NH, D₂O exchangeable).

δ_H (d₆-DMSO, 300MHz, 383K): identifiable signals for CH₃CHCH₃ have not coalesced at this temperature and thus for N-N bond rotation ΔG[‡] > 20 K cal mol⁻¹.

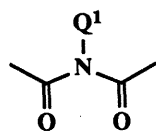
δ_c (d_6 -DMSO, 75MHz): 24.02 ($\underline{CH_3CHCH_3}$), 24.54 ($CH_3CH\underline{CH_3}$), 25.04 ($\underline{CH_3CON}$), 34.38 ($CH_3\underline{CHCH_3}$), 124.46 ($Q^1 \underline{CCO}$), 130.28, 130.59, 131.13, 138.80 (4x $Q^1 \underline{CH}$), 150.42 ($Q^1 \underline{CN=C}$), 162.97 ($Q^1 \underline{CN}$), 166.53 ($Q^1 \underline{CO}$), 173.51 ($CH_3\underline{CON}$).

ν_{max} (Nujol Mull): 3420bs (H_2O), 3180m, 1700s, 1677s, 1570m, 1340w, 1315m, 1298m, 1281m, 1250w, 1224w, 1195w, 1172w, 1145w, 1107w, 1092w, 1045w, 1029w, 1002w, 973m, 935w, 887w, 849w, 767s, 688s, 662m.

M/Z (%): 245 (M^+ , 63), 203 (45), 202 (22), 188 (50), 187 (61), 186 (31), 185 (18), 176 (10), 175 (100), 173 (12), 160 (11), 146 (11), 130 (11), 119 (18).

Di-acetylation of 3-amino-2-isopropylquinazolin-4(3H)-one

(73)



(96)

3-Amino-2-isopropylquinazolin-4(3H)-one (73) (2.88g, 14mmol) was dissolved in acetic anhydride (8.69g, 80mmol) and dry pyridine (3.36g, 40mmol) added. The stirred solution was heated at 50°C for 48hr. After this time water (30ml) was added and the solution extracted with dichloromethane and washed successively with sodium bicarbonate solution and water, dried ($MgSO_4$) and the

solvent, including pyridine, removed under reduced pressure to yield an oil. After setting aside overnight, the oil solidified and was crystallised from ethanol to give 3-diacetylamino-2-isopropylquinazolin-4(3H)-one (96) (3.32g, 81%) as colourless crystals, m.p. 71.5-72°C as the hemihydrate.

Compound (96):

$C_{15}H_{17}N_3O_3 \cdot H_2O$ requires C, 60.80; H, 6.15; N, 14.18%. Found C, 60.86; H, 6.15; N, 14.18%.

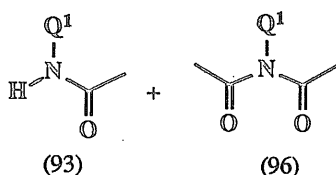
δ_H ($CDCl_3$, 300MHz): 1.32 (d, CH_3CHCH_3 , J6.7Hz), 2.20 (brs, H_2O), 2.42 (s, $2 \times CH_3CON$), 2.86 (heptet, CH_3CHCH_3 , J6.7Hz), 7.47 (ddd, ArCH Q^1H-6 , J7.9, 6.9, 1.4Hz), 7.72 (dd, ArCH Q^1H-8 , J7.8, 1.4Hz), 7.79 (ddd, ArCH Q^1H-7 , J7.8, 6.9, 1.5Hz), 8.23 (ddd, ArCH Q^1H-5 , J7.9, 1.5, 0.5Hz).

δ_C ($CDCl_3$, 75MHz): 21.54 (CH_3CHCH_3), 24.66 ($CH_3CONCOCH_3$), 30.76 (CH_3CHCH_3), 120.62 ($Q^1 CCO$), 126.98, 127.20, 127.70, 135.27 ($4 \times Q^1 CH$), 146.98 ($Q^1 CN=C$), 159.56 ($Q^1 CN$), 161.14 ($Q^1 CO$), 170.41 ($CH_3CONCOCH_3$).

ν_{max} (Nujol Mull): 3543s (H_2O), 3383s, 1731s, 1675s, 1561m, 1425m, 1412m, 1333m, 1300m, 1263s, 1239s, 1223s, 1186s, 1159w, 1128w, 1112w, 1097m, 1073w, 1040w, 1032w, 1008m, 948m, 933w, 888w, 860w, 800w, 780s, 719w, 700s, 680w, 665w, 640m, 609s.

M/Z (%): 287 (M^+ , 47), 245 (34), 244 (23), 230 (14), 229 (13), 228 (84), 203 (57), 202 (100), 188 (32), 187 (50), 186 (32), 185 (15), 176 (12), 175 (74), 173 (10), 160 (13), 130 (16), 119 (14), 103 (10), 76 (15).

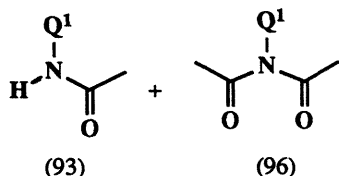
Grignard reaction of phenyl magnesium bromide with
3-diacetylamino-2-isopropylquinazolin-4(3H)-one (96)



Magnesium turnings (0.038g, 1.59mmol) were placed in a two-necked flask, under a dry nitrogen atmosphere, and were covered with dry ether. Then bromobenzene (0.21g, 1.35mmol) was added along with a crystal of iodine. The mixture was stirred until the colour had discharged and then the mixture was heated under reflux for 15 min. In a separate flask, under a dry nitrogen atmosphere, was placed 3-diacetylamino-2-isopropylquinazolin-4(3H)-one (96) (0.388g, 1.35mmol) as a solution in dry ether (5ml). The Grignard reagent was then cannulated into this flask, dropwise, the flask containing the Grignard reagent rinsed with more dry ether (2x10ml) and cannulated into the reaction flask, and the resulting mixture stirred for one hour. The resulting mixture was quenched with saturated ammonium chloride solution and extracted with ether (3x25ml), the organic layer was dried (MgSO_4) and evaporated under reduced pressure. Chromatography of the residue over silica, with ethyl acetate/light petroleum (1:4) as eluant, gave unreacted starting material (96), R_f 0.53, (0.23g, 59% recovery) and N-acetylaminquinazolinone (93), R_f 0.01,

(0.13g, 95% based on unreacted starting material; 39% absolute yield), which was identical in all respects to that isolated previously, (see above).

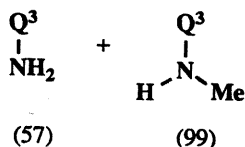
Attempted Wittig methylenation of
3-diacetylamino-2-isopropylquinazolin-4(3H)-one
(96)



Methyltriphenylphosphonium bromide (0.55g, 1.55mmol) was stirred in freshly distilled THF (5ml) at 0°C under an argon atmosphere. n-Butyl lithium was added slowly at this temperature and the mixture allowed to stir at this temperature for twenty minutes, during which time an intense orange colour formed. This was then cannulated, dropwise, into a flask containing 3-diacetylamino-2-isopropylquinazolin-4(3H)-one (96) (0.425g, 1.48mmol) in freshly distilled THF (8ml) under reflux and an argon atmosphere. The flask was rinsed out with more THF (2x10ml) and the reaction was left heating under reflux for two hours and then cooled and quenched with water (20ml). Evaporation of the bulk of the THF under reduced pressure and extraction of the residue with ethyl acetate (3x25ml),

drying (MgSO₄) and evaporation of the solvent under reduced pressure gave an oil. Chromatography of the residue, with ethyl acetate/light petroleum (1:4) as eluant, gave unreacted starting material (96), R_f0.53, (0.0168g, 4% recovery) and N-acetylaminoquinazolinone (93), R_f0.01, (0.2533g, 75% yield based on recovered starting material; 70% absolute yield).

N,O-Dimethylation of (S)-(-)-3-amino-2-(1'-hydroxyethyl)-quinazolin-4(3H)-one (98)



To a stirred solution of sodium hydride (3.00g, 125mmol) in freshly distilled THF (50ml) under an argon atmosphere, was added (S)-(-)-3-amino-2-(1'-hydroxyethyl)quinazolin-4(3H)-one (98) (5.13g, 25mmol). The solution was stirred for thirty minutes during which time a white solid formed. To this slurry was added methyl iodide (17.78g, 125mmol) and the solution stirred overnight. Dry ether was added and the sodium iodide thus formed was separated and washed with ether. The total filtrate was evaporated under reduced pressure and the residue dissolved in dichloromethane and washed with water (x2). The organic layer was dried (MgSO₄)

and evaporated under reduced pressure to give a solid which crystallised from ethyl acetate/light petroleum to give a 1:1 mixture of (S)-(-)-3-amino-2-(1'-methoxyethyl)quinazolin-4(3H)-one (57), (identical in all respects to that isolated previously, see Experimental relating to Chapter one), and (S)-(-)-3-methylamino-2-(1'-methoxyethyl)quinazolin-4(3H)-one (99) as colourless crystals (3.02g, 55% [total]).

Compound (99): $[\alpha]_D^{25} = -22.9^\circ$, (c=2.4, CH₂Cl₂).

C₁₂H₁₅N₃O₂ requires C, 61.79; H, 6.48; N, 18.01%. Found C, 61.80; H, 6.57; N, 17.85%.

δ_H (CDCl₃, 300MHz, room temperature): 1.57 (d, CH₃CHOCH₃, J6.4Hz), 2.79 (bs, CH₃NH), 3.43 (s, OCH₃), 4.94 (q, CH₃CH₂CHOCH₃, J6.4Hz), 5.54 (brs, NH, exchangeable with D₂O), 7.42 (ddd, ArCH Q³H-6, J8.1, 7.1, 1.3Hz), 7.70 (ddd, ArCH Q³H-7, J8.2, 7.1, 1.5), 7.78 (dd, ArCH Q³H-8, J8.2, 1.3Hz), 8.21 (dd, ArCH Q³H-5, J8.1, 1.1Hz).

δ_H (d₆-Acetone, 300MHz, -20°C): 1.23 (d, CH₃CHOME, J6.4Hz), 2.83 (d, CH₃N, J5.7Hz), 3.49 (s, OCH₃), 4.96 (bs, CH₃CHOME), 5.57 (bq, NH, exchangeable with D₂O), 7.51 (ddd, ArCH Q³H-6, J8.1, 7.1, 1.3Hz), 7.79 (ddd, ArCH Q³H-7, J8.2, 7.1, 1.5Hz), 7.87 (dd, ArCH Q³H-8, J8.2, 1.3Hz), 8.27 (ddd, ArCH Q³H-5, J8.1, 1.5, 1.1Hz).

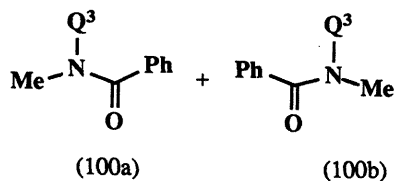
δ_C (CDCl₃, 75MHz): 19.17 (CH₃CHOME), 38.24 (CH₃NH), 56.95 (CH₃O), 74.51 (CH₃CHOME), 120.79 (Q³ CCO), 126.11, 126.51, 127.72, 134.11 (4x Q³ CH), 146.75 (Q³ CN=C), 157.28 (Q³ CN), 161.08 (Q³ CO).

ν_{max} (CH₂Cl₂): 3317w, 2978w, 2935w, 2900w, 2824w, 1675s,

1597s, 1568w, 1510w, 1467m, 1372w, 1330w, 1294w, 1235w, 1210w, 1182w, 1168w, 1146w, 1108m, 1068w, 1022w, 979w, 900w, 878w, 845w, 825w.

M/Z (%): 233 (M⁺, 5.6), 203 (15), 175 (19), 174 (100), 173 (42), 146 (20), 130 (13), 119 (13), 69 (11.7).

Benzoylation of compound (97)



Compound (99) (0.19g, 0.86mmol) was dissolved in benzoyl chloride (10ml) and dry pyridine (0.11g, 1.44mmol) was added. The mixture was left at room temperature for 6 days. After which time the bulk of the pyridine and benzoyl chloride was removed by distillation at 0.2mmHg and 90°C (bath temp.). The residue was dissolved in dichloromethane and washed with sodium bicarbonate solution and water, dried (MgSO₄) and the solvent removed under reduced pressure. Chromatography of the residue over silica, with ethyl acetate/light petroleum (1:2) as eluant, gave 3-(N-benzoyl-N-methylamino-2-(1'-methoxyethyl)quinazolin-4(3H)-one as a single diastereoisomer (100a), R_f 0.41, as colourless crystals (0.11g, 40%), m.p. 119-121°C (from ethyl acetate/light petroleum), followed by a diastereoisomer of

(100a), namely (100b), R_f 0.32, as colourless crystals (0.089g, 37%), m.p. 142–144°C (from ethanol). The ratio of these diastereoisomers (100a):(100b) was estimated to be 1.24:1 respectively from n.m.r spectroscopy of the mixture prior to chromatography.

Compound (100b) was crystallised from ethanol and a single crystal X-ray structure determination obtained (see Appendix 2).

Compound (100a): $[\alpha]_D = -146.3^\circ$, ($c=10.4$, CH_2Cl_2).

$\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}_3$ requires C, 67.64; H, 5.68; N, 12.45%. Found C, 67.49; H, 5.76; N, 12.44%.

This compound exists in CDCl_3 solution as a 4.1:1 ratio of amide rotamers.

δ_h (CDCl_3 , 300MHz): Major rotamer: 1.64 (d, $\text{CH}_3\text{CHOCH}_3$, J6.7Hz), 3.42 (s, CH_3N), 3.46 (CH_3O), 4.63 (q, $\text{CH}_3\text{CHOCH}_3$, J6.7Hz), 7.43–7.58 (m, 4H, ArCH Q^3H -6, and 3xPhH), 7.69–7.85 (m, 4H, ArCH Q^3H -7/8, and 2xPhH), 8.32 (ddd, ArCH Q^3H -5, J7.9, 1.3, 0.7Hz).

Minor rotamer (observable peaks): 1.63 (d, $\text{CH}_3\text{CHOCH}_3$, J6.4Hz), 3.25 (s, CH_3N), 3.50 (s, CH_3O), 4.72 (q, $\text{CH}_3\text{CHOCH}_3$, J6.4Hz), 7.15–7.28 (m, 4H, 4xPhCH), 8.16 (dd, ArCH Q^3H -5, J7.9, 1.3Hz).

δ_c (CDCl_3 , 75MHz): Major rotamer: 17.16 (CH_3CHOME), 40.62 (CH_3N), 56.24 (CH_3O), 75.12 (CHOME), 121.89 ($\text{Q}^3 \text{CCO}$), 126.23, 126.93 (2x PhCH), 127.36 ($\text{Q}^3 \text{CH}$), 128.13 (PhCH), 128.69, 131.06 (2x $\text{Q}^3 \text{CH}$), 133.48 (PhCCO), 134.79 ($\text{Q}^3 \text{CH}$), 146.42 ($\text{Q}^3 \text{CN}=\text{C}$), 155.62 ($\text{Q}^3 \text{CN}$), 159.02 ($\text{Q}^3 \text{CO}$), 170.81 (PhCON).

Minor rotamer (observable peaks): 37.00 (CH_3N), 56.16 (CH_3O), 73.85 (CHOME), 121.18 ($\text{Q}^3 \text{CCO}$), 130.55, 134.93 (2x $\text{Q}^3 \text{CH}$), 145.72 ($\text{Q}^3 \text{CN}=\text{C}$), 154.58 ($\text{Q}^3 \text{CN}$), 160.00 ($\text{Q}^3 \text{CO}$),

172.70 (PhCNO).

ν_{\max} (CH₂Cl₂ solution): 2935m, 2815w, 1700s, 1606s, 1467m, 1372m, 1327m, 1210w, 1188w, 1108m, 1047m, 1018m, 908w, 878w, 843w, 635w.

M/Z (%): 337 (M⁺, 2.6), 307 (24), 203 (16), 175 (10), 174 (38), 173 (13), 118 (10), 105 (100), 77 (33).

Compound (100b): $[\alpha]_D = +59.5^\circ$, (c=8.6, CH₂Cl₂).

C₁₉H₁₉N₃O₃ requires M.337.1426. Found: M/Z 337.1431.

This compound exists in CDCl₃ solution as a 3.2:1 ratio of amide rotamers.

δ_H (CDCl₃, 300MHz): Major rotamer: 1.65 (d, CH₃CHOCH₃, J6.4Hz), 3.45 (s, CH₃N), 3.47 (s, CH₃O), 4.64 (q, CH₃CHOCH₃, J6.4Hz), 7.45-7.57 (m, 4H, ArCH Q³H-6, and 3xPhH), 7.65-7.73 (m, ArCH Q³H-7/8), 7.74-7.85 (m, 2xPhH), 8.31 (ddd, ArCH Q³H-5, J8.6, 2.1, 0.9Hz).

Minor rotamer: (observable peaks): 1.54 (d, CH₃CHOCH₃, J6.4Hz), 3.46 (s, CH₃N), 3.56 (s, CH₃O), 4.81 (q, CH₃CHOCH₃, J6.4Hz), 7.14-7.24 (m, 2H, 2x PhCH), 7.37-7.35 (m, 1H, 1xPhH), 8.18 (ddd, ArCH Q³H-5, J8.6, 2.1, 0.9Hz).

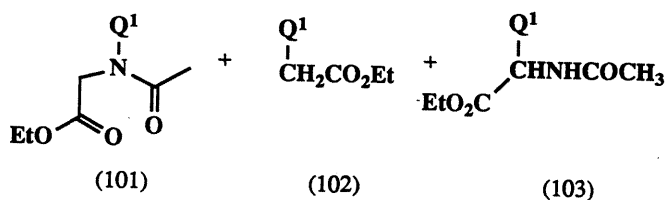
δ_C (CDCl₃, 75MHz): Major rotamer: 19.74 (CH₃CHOCH₃), 41.06 (CH₃N), 57.41 (CH₃O), 77.07 (CHOCH₃), 121.78 (Q³ CCO), 127.05 (CH), 127.27 (CH), 127.60 (Q³ CH), 127.89 (CH), 128.70, 131.21 (2x Q³ CH), 133.30 (Ph CCON), 135.10 (Q³ CH), 146.56 (Q³ CN=C), 156.82 (Q³ CN), 159.15 (Q³ CO), 170.92 (PhCON).

Minor rotamer (observable peaks): 18.71 (CH₃CHOCH₃), 38.24 (CH₃N), 56.67 (CH₃O), 73.84 (CHOCH₃), 126.97 (CH), 127.21 (CH), 128.04 (CH), 128.14 (CH), 130.76, 133.20, 134.91 (3x Q³ CH), 156.00 (Q³ CN).

ν_{\max} (CH_2Cl_2): 3150w, 2992w, 2940w, 2830w, 1700s, 1680s, 1600s, 1572w, 1465m, 1337s, 1210m, 1110s, 1042m, 1018s, 905w, 878w, 850w, 636w.

M/Z (%): 337 (M^+ , 2.2), 307 (17), 204 (10), 203 (18), 175 (12), 174 (40), 173 (14), 118 (10), 105 (100), 77 (33).

Alkylation of N-acetylaminoquinazolinone (93) using ethyl bromoacetate



To sodium hydride (0.21g, 8.9mmol) was added dry DMF (15ml) and N-acetylaminoquinazolinone (93) (1.14g, 4.7mmol) sequentially. The solution was stirred at room temperature until no more effervescence was observed and then the solution was cooled to -20°C . Freshly distilled ethyl bromoacetate (2.34g, 14mmol) was added in one portion and the solution stirred at this temperature for three hours before allowing to warm to room temperature and then setting aside overnight. Addition of approximately equal volumes of dry ether and dry ethyl acetate precipitated sodium bromide which was separated, washed with ether, and the total filtrate evaporated under reduced pressure. Chromatography of the residue over silica, with ethyl

acetate/light petroleum (1:1) as eluant, gave amide-ester (101), R_f 0.68, as colourless crystals (0.2g, 12%), m.p. 102-103°C (from ethanol). Further elution gave ester (102), R_f 0.60, as colourless crystals (0.225g, 18%), m.p. 81-82°C (from ethyl acetate/light petroleum), followed by rearranged ester-amide (103), R_f 0.39, as colourless crystals (0.193g, 12%), m.p. 160-162°C (from ethanol).

Compound (101): $C_{17}H_{21}N_3O_4$ requires C, 61.62; H, 6.39; N, 12.68%. Found C, 61.58; H, 6.40; N, 12.72%.

This compound exists in $CDCl_3$ solution as a 3.55:1 ratio of amide rotamers.

δ_H ($CDCl_3$, 300MHz): Major rotamer: 1.308 (t, $\underline{CH_3CH_2}$, J7.1Hz), 1.31 and 1.41 (2xd, $\underline{CH_3CHCH_3}$, J6.6Hz), 1.91 (s, $\underline{CH_3CON}$), 3.89 (heptet, $\underline{CH_3CHCH_3}$, J6.6Hz), 3.59 and 4.98 (2xd, $\underline{CH_2N}$, J16.9Hz), 4.26 (ABX₃, $\underline{CH_3CH_2}$, J7.1, 1.5Hz), 7.48 (ddd, \underline{ArCH} $\underline{Q^1H-6}$, J8.0, 7.0, 1.3Hz), 7.71 (dd, \underline{ArCH} $\underline{Q^1H-8}$, J7.6, 0.7Hz), 7.80 (ddd, \underline{ArCH} $\underline{Q^1H-7}$, J7.6, 7.0, 1.5Hz), 8.23 (ddd, \underline{ArCH} $\underline{Q^1H-5}$, J8.0, 1.5, 0.7).

Minor rotamer (observable peaks): 2.35 (s, $\underline{CH_3CON}$), 4.14 and 4.87 (2xd, $\underline{CH_2N}$, J18.7Hz), 7.41 (ddd, \underline{ArCH} $\underline{Q^1H-6}$, J8.0, 7.0, 1.3Hz), 7.65 (dd, \underline{ArCH} $\underline{Q^1H-8}$, J7.6, 0.7Hz), 8.18 (dd, \underline{ArCH} $\underline{Q^1-5}$, J8.0, 0.7Hz).

δ_C ($CDCl_3$, 75MHz): Major rotamer: 14.09 ($\underline{CH_3CHCH_3}$), 19.83 ($\underline{CH_3CHCH_3}$), 21.34 ($\underline{CH_3CH_2}$), 22.22 ($\underline{CH_3CON}$), 29.94 ($\underline{CH_3CHCH_3}$), 52.99 ($\underline{CH_2N}$), 61.45 ($\underline{CH_3CH_2O}$), 120.55 ($\underline{Q^1 CCO}$), 126.97, 127.03, 127.70, 135.27 (4x $\underline{Q^1 CH}$), 146.95 ($\underline{Q^1 CN=C}$), 160.31 ($\underline{Q^1 CN}$), 162.45 ($\underline{Q^1 CO}$), 167.35 ($\underline{CH_3CON}$), 173.16 ($\underline{OCOCH_2}$).

Minor rotamer (observable peaks): 20.90 ($\underline{CH_3CHCH_3}$), 21.50

(CH_3CH_2), 22.05 (CH_3CON), 30.07 (CH_3CHCH_3), 54.23 ($\text{CH}_3\text{CH}_2\text{O}$), 62.03 (CH_2N), 126.27, 126.82, 127.42, 134.70 ($4\times\text{Q}^1\text{CH}$), 147.30 ($\text{Q}^1\text{CN}=\text{C}$).

ν_{max} (Nujol Mull): 1739s, 1698s, 1600s, 1330w, 1295m, 1282m, 1230w, 1205w, 1093w, 1035w, 1005w, 953w, 887w, 860w, 785m, 746w, 700m, 656m.

M/Z (%): 331 (M^+ , 20), 216 (24), 189 (18), 188 (19), 187 (27), 174 (13), 173 (100), 160 (38).

Compound (102): $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_3$ requires C, 65.67; H, 6.61; N, 10.21%.

Found C, 65.69; H, 6.72; N, 9.95%.

δ_{H} (CDCl_3 , 300MHz): 1.29 (t, CH_3CH_2 , J7.2Hz), 1.37 (d, CH_3CHCH_3 , J6.6Hz), 2.91 (heptet, CH_3CHCH_3 , J6.6Hz), 4.25 (q, CH_3CH_2 , J7.2Hz), 4.92 (s, NCH_2), 7.42 (ddd, $\text{ArCH Q}^1\text{H}-6$, J7.9, 6.9, 1.5Hz), 7.66 (ddd, $\text{ArCH Q}^1\text{H}-8$, J7.6, 1.5, 0.4Hz), 7.72 (ddd, $\text{ArCH Q}^1\text{H}-7$, J7.6, 6.9, 1.5Hz), 8.23 (ddd, $\text{ArCH Q}^1\text{H}-5$, J7.9, 1.5, 0.4Hz).

δ_{C} (CDCl_3 , 75MHz): 14.12 (CH_3CHCH_3), 21.07 (CH_3CH_2), 32.26 (CH_3CHCH_3), 44.36 (CH_2N), 61.93 ($\text{CH}_3\text{CH}_2\text{O}$), 120.00 (Q^1CCO), 126.36, 126.75, 127.21, 134.27 ($4\times\text{Q}^1\text{CH}$), 147.35 ($\text{Q}^1\text{CN}=\text{C}$), 160.32 (Q^1CN), 162.32 (Q^1CO), 167.86 (OCO).

ν_{max} (Nujol Mull): 1736s, 1678s, 1612m, 1588s, 1572m, 1422m, 1337w, 1303w, 1233s, 1203s, 1184m, 1160m, 1106w, 1083w, 1043w, 1023w, 980m, 885w, 860w, 838w, 800w, 773s, 736w, 708m, 692w, 636m.

M/Z (%): 274 (M^+ , 77), 260 (12), 259 (100), 246 (23), 231 (18), 201 (26), 187 (17), 175 (11), 174 (40), 130 (11).

Compound (103): $\text{C}_{17}\text{H}_{21}\text{N}_3\text{O}_4$ requires C, 61.62; H, 6.39; N, 12.68%.

Found C, 61.51; H, 6.37; N, 12.57%.

δ_H (CDCl₃, 300MHz): 1.21 (t, CH₃CH₂, J7.1Hz), 1.43 (2xd, CH₃CHCH₃, J6.6Hz), 2.08 (s, CH₃CON), 3.75 (heptet, CH₃CHCH₃, J6.6Hz), 4.25 (ABX₃, CH₃CH₂, J10.2, 7.1Hz), 6.85 (d, CHNH, J9.1Hz), 7.43 (ddd, ArCH Q¹H-6, J8.0, 6.8, 1.6Hz), 7.63 (d, CHNH, J9.1Hz), 7.67-7.77 (m, ArCH Q¹H-7/8), 8.15 (ddd, ArCH Q¹H-5, J8.0, 1.3, 0.5Hz).

Proton decoupling of the doublet at 6.85 (CHNH) collapses the NH doublet to a singlet.

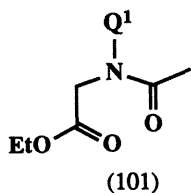
δ_C (CDCl₃, 75MHz): 13.95 (CH₃CHCH₃), 20.71 (CH₃CHCH₃), 21.70 (CH₃CH₂O), 22.89 (CH₃CON), 31.49 (CH₃CHCH₃), 60.72 (CHNH), 62.78 (CH₃CH₂O), 120.09 (Q¹ CCO), 126.22, 126.53, 127.50, 134.76 (4xQ¹ CH), 147.58 (Q¹ CN=C), 160.07 (Q¹ CN), 163.22 (Q¹ CO), 166.66 (CH₃CON), 170.29 (OCO).

ν_{max} (Nujol Mull): 3311brm, 1755s, 1690s, 1658s, 1611m, 1592m, 1510m, 1305m, 1238m, 1218m, 1164m, 1145m, 1090m, 1030m, 955w, 887w, 862w, 850w, 810w, 770w, 732m, 703m, 652w, 639m.

M/Z (%): 188 (18), 173 (34), 149 (100), 111 (15), 94 (36), 93 (52), 83 (26), 69 (34).

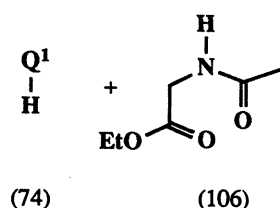
A single crystal X-ray structure determination confirmed that assigned above (see Appendix 2).

Alkylation of N-acetylaminoquinazolinone (93) using ethyl
bromoacetate



To sodium hydride (0.126g, 5.24mmol) was added dry DMF (15ml) and N-acetylaminoquinazolinone (93) (1.16g, 4.76mmol) and the solution stirred at room temperature until no more effervescence was observed. This solution was then added dropwise over 30 min. to a vigorously stirred solution of ethyl bromoacetate (2.38g, 14mmol) in dry DMF (5ml) at -20°C. The resulting mixture was stirred for a further 2.5hr. at this temperature, allowed to warm to room temperature and then set aside overnight. Addition of approximately equal volumes of dry ether and dry ethyl acetate precipitated out sodium bromide which was separated, washed with dry ether, and the total filtrate evaporated under reduced pressure. Chromatography of the residue over silica, with ethyl acetate/light petroleum (1:2) as eluant, gave amide-ester (101), R_f 0.31, as colourless crystals (1.49g, 83%), m.p. 102-103°C (from ethanol), identical in all respects with the material isolated previously (see above).

Aluminium amalgam reduction of ester amide (101)



Ester-amide (101) (0.296g, 0.90mmol) was dissolved in dry methanol (50ml), aluminium amalgam (prepared from aluminium turnings (2g)) was added and the solution stirred under a nitrogen atmosphere in a flask immersed in water at ambient temperature for 48hr. The solution was centrifuged, the methanol decanted, the solid re-suspended in methanol (approximately 20ml) and again centrifuged and the methanol separated. Evaporation of the combined methanol extracts under reduced pressure and chromatography of the residue over silica, eluting with ethyl acetate, gave impure 2-isopropylquinazolin-4(3H)-one (74). Further elution with methanol/ethyl acetate (1:1) gave ethyl *N*-acetylglycinate (106) (0.096g, 74%), after combination of those fractions R_f 0.16 (methanol/ethyl acetate (1:1)), evaporation and kugelrohr-distillation of the residue. The n.m.r. spectrum of this material was identical with that of an authentic sample (Aldrich).

Compound (106):

δ_{H} (CDCl₃, 90MHz): 1.25 (t, CH₃CH₂, J7.5Hz), 2.00 (s, CH₃CON), 3.97 (d, CH₂NH, J5.4Hz), 4.21 (q, CH₃CH₂, J7.5Hz), 6.29 (brs, NH).

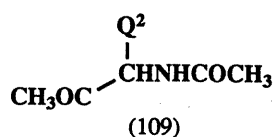
Attempted alkylation of keto-amide (51)



(107)

To sodium hydride (0.041g, 1.69mmol) was added dry DMF (2ml) and the slurry stirred for 5 min. at room temperature. Keto-amide (51) (0.235g, 0.82mmol) was then added continuously in very small portions over 15 min. The solution was stirred for a further 5 min. before methyl iodide (0.23g, 1.64mmol) was added. The resulting mixture was stirred for 30 min. and water (5ml) and ether (3x10ml) were then added. The organic layer was dried (MgSO₄) and evaporated under reduced pressure to give N-methyl-2-ethylquinazolin-4(3H)-one (107) as colourless crystals (0.102g, 66%) which was identical by melting point and infra red spectral comparison with an authentic sample prepared and characterised previously by B. Kelly³⁴. No additional products were isolated from this reaction.

Further attempted alkylation of keto-amide (51)



Diisopropylamine (72.2mg, 0.71mmol) was added to stirred, dry, THF (3.3ml) under a nitrogen atmosphere at 0 to -5°C. n-Butyllithium (46mg, 0.71mmol) was added dropwise and the solution left at this temperature for 20 min. It was then cooled to -78°C and keto-amide (51) (0.15g, 0.52mmol) in dry THF (3.2ml) was added dropwise. After 2 min. methyl iodide (0.44g, 3.14mmol) was added and the reaction mixture was stirred at this temperature for 2 hr. before being quenched with saturated ammonium chloride solution (10ml). The solution was extracted with dichloromethane (3x25ml) and the organic layer dried (MgSO₄) and evaporated under reduced pressure. Chromatography of the residue over silica, with ethyl acetate as eluant, gave unreacted keto-amide (51), R_f0.55, (15mg, 10% recovery), followed by rearranged keto-amide (109), R_f0.41 as colourless crystals (16mg, 12% based on unreacted starting material), m.p. 192-195°C (from ethanol), and 2-ethylquinazolin-4(3H)-one (52), R_f0.38, (10mg, 12% based on unreacted starting material) identical with an authentic sample.

Compound (109): C₁₅H₁₇N₃O₃ requires M. 287.1266. Found: M/Z

287.1270.

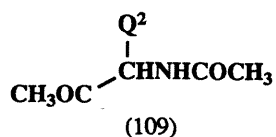
δ_H (CDCl₃, 400MHz): 1.42 (t, CH₃CH₂, J7.3Hz), 2.08 (s, CH₃COC), 2.29 (s, CH₃CON), 3.36 (ABX₃, CH₃CH₂, J16.3, 7.3Hz), 6.56 (d, CHNH, J9.3Hz), 7.44 (dd, ArCH Q²H-6, J8.1, 1.2Hz), 7.48 (bs, NH), 7.70 (d, ArCH Q²H8, J7.6Hz), 7.76 (ddd, ArCH Q²H-7, J8.5, 1.4Hz), 8.12 (dd, ArCH Q²H-5, J8.1, 1.4Hz).

With proton decoupling of the broad singlet at 7.48 (NH) the doublet at 6.56 (CH) collapses to a singlet.

δ_C (CDCl₃, 100MHz): 10.99 (CH₃CH₂), 22.86 (CH₃CO), 25.61 (CH₃CON), 28.05 (CH₃CH₂), 66.54 (CHNH), 120.06 (Q² CCO), 126.23, 126.72, 127.41, 134.97 (4x Q² CH), 147.64 (Q² CN=C), 156.59 (Q² CN), 163.01 (Q² CO), 170.32 (CH₃CON), 199.10 (CH₃COCH).

M/Z (%): 287 (M⁺), 244 (11), 175 (29), 174 (39), 173 (45), 119 (20), 113 (11), 43 (100).

Further attempted alkylation of keto-amide (51)

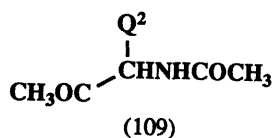


To sodium hydride (60mg, 2.5mmol) was added dry THF (2ml) and the slurry cooled to -10°C. To this stirred

solution was added keto-amide (51) (0.373g, 1.3mmol) continuously in very small portions over 15 min. Methyl iodide (0.18g, 1.3mmol) was then added and the solution stirred at -10°C for a further 30 min. Water (2ml) and dichloromethane (10ml) were added subsequently and the organic layer separated, dried (MgSO₄), and evaporated under reduced pressure. From the residue, 2-ethylquinazolin-4(3H)-one (52) (0.03g, 8%) was obtained by crystallisation from ethanol. Further crystallisation from ethanol after removal of (52) gave rearranged keto-amide (109) (0.014g, 4%), which was identical in all respects to that isolated previously, (see above).

Attempted reduction of keto-amide (51) using

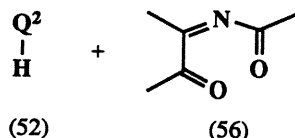
L-Selectride



To a stirred solution of freshly distilled THF (5ml)

and keto-amide (51) (0.26g, 0.91mmol) under an argon atmosphere was added L-Selectride (0.18g, 0.95mmol) and the resulting mixture was stirred overnight. After quenching with water (5ml), the bulk of the THF was removed under reduced pressure and the bulk of the residue dissolved in dichloromethane. The solution was made acidic by washing with dilute hydrochloric acid and the organic layer dried (MgSO₄), and evaporated under reduced pressure. Chromatography of the residue over silica, with 1% methanol in ethyl acetate as eluant, gave a colourless oil (0.251g) which solidified on standing. This material was recrystallised from ethanol to give a product whose proton n.m.r. spectrum was identical in all respects to that obtained for the rearranged keto-amide (109), (see experiment above). A single crystal X-ray structure of this compound was obtained (from ethanol) which confirmed the structure (109) assigned (see Appendix 2).

Decomposition of enol-amide (53) in boiling ethyl acetate



Enol-amide (53) (0.1g, 0.33mmol) was heated under reflux

in ethyl acetate (2ml) for approximately 1 min. Cooling the solution in ice and filtering the crystalline solid which formed resulted in the isolation of 2-ethylquinazolin-4(3H)-one (52) (0.05g,86%). The residue was evaporated under reduced pressure and the residue kugelrohr-distilled at 0.1mmHg and 50°C (bath temp.) to give N-acetylimine (56) (0.04g,95%) as an unstable pale green oil.

Compound (56):

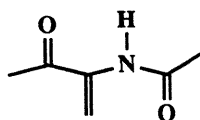
δ_H (CDCl₃, 300MHz): 1.95 (s,CH₃CN), 2.12 (CH₃CO), 2.27 (CH₃CON).

δ_C (CDCl₃, 75MHz): 15.66 (CH₃CN), 24.29 (CH₃), 24.44 (CH₃), 161.10 (CN), 185.18 (CH₃CON), 198.55 (CH₃CO).

ν_{max} (CH₂Cl₂): 1706s, 1673s, 1650s, 1304w, 1223s, 1123s, 995m, 969m, 934w, 835m, 638s, 618s.

G.C.M.S. M/Z: 127 (M⁺), 99, 86, 85, 84, 49, 44, 43, 42, 41, 40, 32, 28, 27, 18, 17.

Attempted allylation of N-acetylimine (56)



(110)

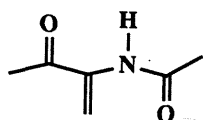
N-Acetylimine (56) (0.147g,1.16mmol) (prepared by the method given above) was added to freshly distilled THF and

the solution stirred at -78°C under an argon atmosphere. Allyltrimethylsilane (0.132g, 1.16mmol) was added dropwise and then boron trifluoride etherate (0.16g, 1.16mmol) was added dropwise to the mixture which was then stirred for 2 hr. at this temperature before allowing to warm to room temperature and then setting aside overnight. THF was removed under reduced pressure and the residue dissolved in ethyl acetate and washed with sodium bicarbonate solution then water, dried (MgSO_4), and evaporated under reduced pressure. The residue was crystallised from ethyl acetate/light petroleum to give the unstable α, β -unsaturated ketone (110) (0.125g, 85%) as colourless crystals, m.p. $47-48^{\circ}\text{C}$.

Compound (110):

δ_{H} (CDCl_3 , 90MHz): 2.13 (s, $\text{CH}_3\text{COC}=\text{C}$), 2.41 (CH_3CON), 5.75 (s, $\text{CH}=\text{anti}$ to NH), 6.87 (s, $\text{HC}=\text{cis}$ to NH), 7.70-8.52 (brs, NH). This compound was characterised as its reduction product as described below.

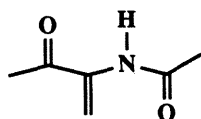
Attempted reaction of N-acetylimine (56) with
pentan-2,4-dione and triethylamine



(110)

Pentan-2,4-dione (0.13g, 1.35mmol) and triethylamine (0.136g, 1.35mmol) were stirred in dry THF (0.5ml) for 30 min. at room temperature before being added, dropwise, to a stirred solution of N-acetylimine (56) (prepared as above) (0.163g, 1.28mmol) in dry THF at -78°C under a dry nitrogen atmosphere. The solution was stirred for a further 2 hr. at this temperature before being allowed to warm to room temperature and then set aside overnight. Addition of aqueous citric acid to acidify and then sodium bicarbonate solution to neutralise gave a solution which was extracted with ethyl acetate (x3). The organic layer was dried (MgSO_4) and evaporated under reduced pressure to give the unstable α, β -unsaturated ketone (110) (0.072g, 55%) which was identical in all respects to that isolated above.

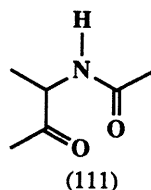
Attempted reaction of N-acetylimine (56) with
ethyl acetoacetate and triethylamine



(110)

Ethyl acetoacetate (0.3g, 2.2mmol) and triethylamine (0.23g, 2.31mmol) were stirred in dry THF (0.5ml) for 30 min. at room temperature before being added, dropwise, to a stirred solution of N-acetylimine (56) (prepared as above) (0.28g, 2.2mmol) in dry THF (0.5ml) at -78°C under a dry nitrogen atmosphere. The solution was stirred for a further 3 hr. at this temperature before being allowed to warm to room temperature and then set aside overnight. Addition of aqueous citric acid to acidify and sodium bicarbonate solution to neutralise gave a solution which was extracted with ethyl acetate (x3). The organic layer was dried (MgSO₄), evaporated under reduced pressure, and the residue rapidly chromatographed over silica, with ethyl acetate/light petroleum (1:4) as eluant, to give the unstable α,β -unsaturated ketone (110), R_f 0.32, as colourless crystals (0.12g, 43%) which was identical in all respects with that isolated above.

Hydrogenation of the α,β -unsaturated ketone (110)



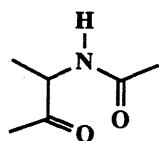
The α,β -unsaturated ketone (110) (0.11g, 0.87mmol) (prepared as above using allyl trimethylsilane and boron trifluoride etherate), was dissolved in dry ethanol (10ml) and palladium on charcoal (0.11g) was added. After flushing the flask with hydrogen, a positive pressure of hydrogen was maintained by means of a balloon filled with hydrogen attached to the flask. The flask was shaken for 6.5 hr. after which time the catalyst was then filtered under gravity, the filtrate evaporated under reduced pressure and the residue kugelrohr-distilled at 0.15mmHg and 150°C (bath temp.) to give 3-acetamido-2-butanone (111) as a colourless oil, (0.10g, 89%) (lit.⁸⁰ b.p. 0.4mmHg and 107°C).

Compound (111):

δ_H (CDCl₃, 300MHz): 1.35 (d, CH_3CHN , J7.2Hz), 2.02 (CH_3CO), 2.22 (CH_3CO), 4.55 (dq, CHN , J14.2, 7.2Hz), 7.00 (bs, NH , exchangeable with D₂O).

δ_C (CDCl₃, 75MHz): 17.00 (CH_3CHN), 22.92 (CH_3CO), 26.48 (CH_3CO), 54.64 (CHN), 169.95 (CH_3CON), 207.32 (CH_2COC).

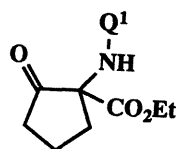
Preparation of an authentic sample of
3-acetamido-2-butanone (111)⁸⁰



(111)

This material was prepared according to the literature procedure of Wiley and Borum⁸⁰ as a colourless oil (3.32g, 35%) which was identical in all respects with that isolated above.

Reaction of N-acetoxyminoquinazolinone (134) with
ethyl 2-oxocyclopentane carboxylate



(112)

The general procedure (1) was followed using the N-aminoquinazolinone (73) (3.99g, 19.7mmol), LTA (9.15g, 21mmol) and ethyl 2-oxocyclopentane carboxylate (9.21g, 59mmol) (Aldrich) in dry dichloromethane (40ml). The solid/oil mixture obtained was triturated with ice-cold ether and the insoluble 2-isopropylquinazolin-4(3H)-one

(74) (0.428g, 12%) separated as colourless crystals, identical in all respects to that isolated previously, (see experimental relating to Chapter 1). Evaporation of the ether and kugelrohr-distillation at 60°C (bath temp.) and 0.02mmHg removed excess ethyl 2-oxocyclopentane carboxylate and the residue was chromatographed over silica with ethyl acetate/light petroleum (1:2) as eluant, to give aminoacid-ester (112), R_f 0.57, as colourless crystals (5.42g, 77%), m.p. 87-88°C (from ethanol).

Compound (112): $C_{19}H_{23}N_3O_4$ requires C, 63.85; H, 6.48; N, 11.76%. Found C, 63.74; H, 6.50; N, 11.76%.

δ_H ($CDCl_3$, 300MHz): 1.29-1.35 (m, 9H, $\underline{CH_3}CHCH_3$ and $\underline{CH_2}CH_2$), 1.67 (ddd, $\underline{HCHC}(CO_2Et)$, J 13.4, 9.6, 7.6Hz), 1.85-2.06 (m, 2H, $\underline{CH_2}CH_2CO$), 2.40 (ddd, $\underline{HCHC}(CO_2Et)$, J 13.4, 6.9, 4.0Hz), 2.51 (m, $\underline{CH_2}CO$), 3.72 (heptet, $\underline{CH_3}CHCH_3$, J 6.8Hz), 4.29 (ABX₃, $\underline{CH_3}CH_2$, J 13.2, 7.1Hz), 6.06 (s, \underline{NH}), 7.41 (ddd, $\underline{ArCH} \text{ } Q^1H-6$, J 8.2, 6.7, 1.5Hz), 7.67 (ddd, $\underline{ArCH} \text{ } Q^1H-8$, J 8.2, 1.5, 0.5Hz), 7.73 (ddd, $\underline{ArCH} \text{ } Q^1H-7$, J 8.2, 6.7, 1.5Hz), 8.16 (ddd, $\underline{ArCH} \text{ } Q^1H-5$, J 8.2, 1.5, 0.5Hz).

δ_C ($CDCl_3$, 75MHz): 14.00 ($\underline{CH_3}CH_2$), 18.64 ($\underline{CH_2}$), 20.73 ($\underline{CH_3}CHCH_3$), 21.03 ($\underline{CH_3}CHCH_3$), 29.56 ($\underline{CH_2}$), 30.78 ($\underline{CH_3}CHCH_3$), 35.90 ($\underline{CH_2}$), 62.33 ($\underline{CH_3}CH_2$), 71.99 (\underline{CNH}), 120.23 ($Q^1 \underline{CCO}$), 126.29, 126.54, 127.37, 134.48 (4x $Q^1 \underline{CH}$), 147.02 ($Q^1 \underline{CN=C}$), 163.32 ($Q^1 \underline{CN}$), 163.98 ($Q^1 \underline{CO}$), 169.22 (\underline{COO}), 211.19 (\underline{COCNH}).

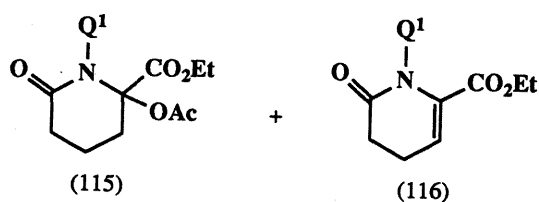
ν_{max} (Nujol Mull): 3275m, 1750s, 1730s, 1682m, 1373s, 1290w, 1255m, 1230m, 1164m, 1125w, 1110w, 1090w, 1015m, 930w, 775s, 720w, 703m.

M/Z (%): 286 (13), 284 (17), 256 (28), 228 (12), 189 (52),

188 (78), 187 (31), 173 (100), 160 (39).

Oxidative ring expansion of aminoacid-ester (112) using

LTA



Aminoacid-ester (112) (5.42g, 15mmol) was dissolved in dry dichloromethane (40ml) and LTA (7.06g, 16mmol) was added and the solution stirred overnight. Insoluble lead diacetate was then filtered and washed with dichloromethane. The total filtrate was washed with sodium bicarbonate solution then water, dried (MgSO₄) and evaporated under reduced pressure. Chromatography of the crude oxidation products over silica, with ethyl acetate/light petroleum (1:2) as eluant, gave α -acetoxy ester (115), R_f 0.31 as a colourless oil (2.89g, 46%), and α,β -unsaturated ester (116), R_f 0.51 as colourless crystals (1.19g, 22%), m.p. 139–140.5°C (from ethanol).

Examination of the proton n.m.r. spectrum of the crude oxidation products before chromatography showed the presence of a 2.42:1 ratio of compounds (115):(116).

Compound (115): C₂₁H₂₅N₃O₆ requires M. 415.1743. Found M/Z: 415.1726.

δ_H (CDCl₃, 300MHz): 0.96 (t, CH₃CH₂, J7.2Hz), 1.24 and 1.46 (2xd, CH₃CHCH₃, J6.7Hz), 1.96–2.09 (m, 1H), 2.11 (s, CH₃COO), 2.23–2.36 (m, 1H), 2.51–2.59 (m, 1H), 2.72–2.88 (m, 2H), 3.17 (ddd, 1H, J13.8, 10.1, 3.5Hz), 3.38 (heptet, CH₃CHCH₃, J6.7Hz), 3.86 and 4.00 (ABX₃, CH₃CH₂, J10.7, 7.2Hz), 7.38 (ddd, ArCH Q¹H-6, J8.0, 6.9, 1.4Hz), 7.66 (ddd, ArCH Q¹H-8, J8.2, 1.4, 0.5Hz), 7.72 (ddd, ArCH Q¹H-7, J8.2, 6.9, 1.5Hz), 8.13 (ddd, ArCH Q¹H-5, J8.0, 1.5, 0.5Hz).

δ_C (CDCl₃, 63MHz): 12.29 (CH₃CH₂), 15.22 (CH₂CH₂CH₂), 20.23 (CH₃CHCH₃), 20.48 (CH₃CHCH₃), 21.53 (CH₃CO), 29.46 (CH₂), 30.03 (CH₃CHCH₃), 31.48 (CH₂), 61.83 (CH₃CH₂), 92.17 (COAc), 119.97 (Q¹ CCO), 125.33, 125.95, 126.28, 133.73 (4x Q¹ CH), 146.00 (Q¹ CN=C), 158.96 (CH₂CON), 162.67 (Q¹ CN), 162.94 (Q¹ CO), 167.33 (C=O), 168.06 (C=O).

M/Z (%): 415 (M⁺, 16), 301 (17), 300 (89), 282 (33), 188 (48), 187 (40), 174 (13), 173 (100), 160 (21), 119 (15), 92 (10), 90 (14).

Compound (116): C₁₉H₂₁N₃O₄ requires C, 64.21; H, 5.96; N, 11.83%. Found C, 64.27; H, 6.03; N, 11.77%.

δ_H (CDCl₃, 300MHz): 1.09 (t, CH₃CH₂, J7.1Hz), 1.27 and 1.43 (2xd, CH₃CHCH₃, J6.7Hz), 2.50–2.65 (m, 1H), 2.77–2.90 (m, 3H), 3.19 (heptet, CH₃CHCH₃, J6.7Hz), 4.05 (ABX₃, CH₃CH₂, J19.6, 7.1Hz), 6.75 (m, CH=CN), 7.39 (ddd, ArCH Q¹H-6, J8.1, 6.1, 2.2Hz), 7.67–7.75 (m, ArCH Q¹H-7/8), 8.16 (ddd, ArCH Q¹H-5, J8.1, 1.4, 0.6Hz).

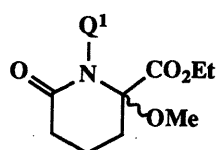
δ_C (CDCl₃, 75MHz): 13.82 (CH₃CH₂), 20.37 (CH₂), 21.01 (CH₃CHCH₃), 22.19 (CH₃CHCH₃), 31.10 (CH₂), 31.29 (CH₃CHCH₃), 61.55 (CH₃CH₂OCO), 120.83 (Q¹ CCO), 123.00 (CCOOCH₂CH₃),

126.14, 126.76, 127.45 (3x Q¹ CH), 133.05 (CH=COOCH₂CH₃), 134.55 (Q¹ CH), 147.19 (Q¹ CN=C), 159.35 (Q¹ CN), 160.07 (Q¹ CO), 163.62 (C=O), 168.43 (C=O).

ν_{\max} (Nujol Mull): 1723s, 1693s, 1595s, 1568w, 1338w, 1325w, 1312w, 1295w, 1250s, 1220w, 1212w, 1185w, 1154m, 1091w, 1068w, 1026m, 992w, 958w, 928w, 880w, 865w, 842w, 770s, 740s, 715w, 696m, 678w, 668w, 620m.

M/Z (%): 355 (M⁺, 14), 283 (17), 282 (100), 240 (16), 187 (28), 173 (31).

Ring expansion of aminoacid-ester (112) using LTA in methanol



(117a/117b)

Aminoacid-ester (112) (0.381g, 1.06mmol) was dissolved in dry methanol and LTA (0.50g, 1.12mmol) added. The solution was stirred overnight before lead di-acetate was filtered and the solvent removed under reduced pressure. The residue was dissolved in dichloromethane and washed successively with sodium bicarbonate solution and water, the solvent dried (MgSO₄) and evaporated under reduced pressure. Chromatography of the residue over silica, with ethyl acetate/light petroleum (1:3) as eluant, gave an

inseparable 1.83:1 mixture of diastereoisomers of α -methoxy ester (117a) and (117b), R_f 0.65, as a colourless oil (0.391g, 95%). Further elution gave 2-isopropylquinazolin-4(3H)-one (74), R_f 0.45, as colourless crystals (0.006g, 3%), identical in all respects to that isolated previously, (see experimental relating to Chapter 1).

Compound (117):

Diastereoisomer (117a): δ_H ($CDCl_3$, 300MHz): 1.32 (d, CH_3CHCH_3 , J6.7Hz), 1.44 (t, CH_3CH_2 , J7.1Hz), 1.88-1.98 (m, 2H, $CH_2CH_2CH_2$), 2.28-2.33 (m, 2H, CH_2), 2.46-2.55 (m, 2H), 3.21 (heptet, CH_3CHCH_3 , J6.7Hz), 3.55 (s, OMe), 4.46 (q, CH_3CH_2 , J7.1Hz), 7.38-7.48 (m, ArCH Q^1H -6), 7.67-7.78 (m, ArCH Q^1H -7/8), 8.25 (dd, ArCH Q^1H -5, J7.5, 0.6Hz).

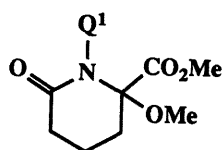
Diastereoisomer (117b): δ_H : (observable peaks): 1.11 (t, CH_3CH_2 , J7.1Hz), 1.36 (d, CH_3CHCH_3 , J6.7Hz), 2.10-2.20 (m, 2H, $CH_2CH_2CH_2$), 2.93-2.98 (m, 2H), 3.38 (heptet, CH_3CHCH_3 , J6.7Hz), 3.70 (s, OCH₃), 4.15 (q, CH_3CH_2 , J7.1Hz), 8.18 (dd, ArCH Q^1H -5, J7.5, 0.6Hz).

The mixture of diastereoisomers (117a)/(117b) was kugelrohr distilled at 250°C (bath temp.) and 0.1mmHg which resulted in their ratio changing to 1:1.8. In the n.m.r. spectrum of this mixture, resonances for diastereoisomer (117b) were now visible at

δ_H ($CDCl_3$, 300MHz): 1.11 (t, CH_3CH_2 , J7.1Hz), 1.36 (d, CH_3CHCH_3 , J6.7Hz), 2.10-2.20 (m, 2H, $CH_2CH_2CH_2$), 2.45-2.55 (m, 2H), 2.93-2.98 (m, 2H), 3.38 (heptet, CH_3CHCH_3 , J6.7Hz), 3.70 (s, OCH₃), 4.15 (q, CH_3CH_2 , J7.1Hz), 7.38-7.48 (m, ArCH Q^1H -6), 7.67-7.78 (m, ArCH Q^1H -7/8), 8.18 (ddd, ArCH Q^1H -

5, J7.5, 1.3, 0.6 Hz) in addition to those resonances for (117a) as described above.

Ester exchange on diastereoisomers (117a) and (117b)



(118)

The mixture of diastereoisomers (117a):(117b) (ratio 1.83:1 respectively) (0.21g, 0.54mmol) was dissolved in methanol and two drops of concentrated sulphuric acid added. The resulting solution was heated under reflux for 2 hr. before removing the bulk of the solvent under reduced pressure. The residue was dissolved in dichloromethane and then washed successively with sodium bicarbonate solution and water, dried (MgSO₄) and evaporated under reduced pressure. Chromatography of the residue over silica, with ethyl acetate/light petroleum (1:4) as eluant, gave α -methoxy-methyl ester (118), R_f 0.29, as a colourless oil (0.159g, 77%) apparently as a single diastereoisomer.

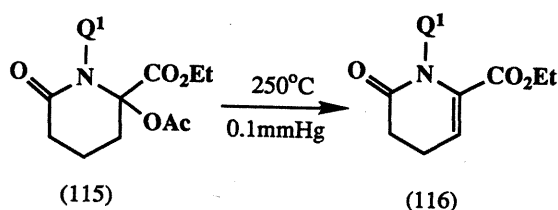
Compound (118): C₂₀H₂₅N₃O₅ requires [M+H].388.1872. Found: [M+H] 388.1873.

δ_H (CDCl₃, 300MHz): 1.36 (d, CH₃CHCH₃, J6.8Hz), 1.86-2.00 (m, 2H, (CH₂CH₂CH₂), 2.38 (m, 2H), 2.90-2.96 (m, 2H), 3.66 (OCH₃) 3.76 (heptet, CH₃CHCH₃, J6.8Hz), 3.85 (s, COOCH₃), 7.40 (ddd,

ArCH Q¹H-6, J8.0, 4.6, 1.8Hz), 7.63-7.74 (m, ArCH Q¹H-7/8), 8.18 (ddd, ArCH Q¹H-5, J8.0, 1.4, 0.5Hz).

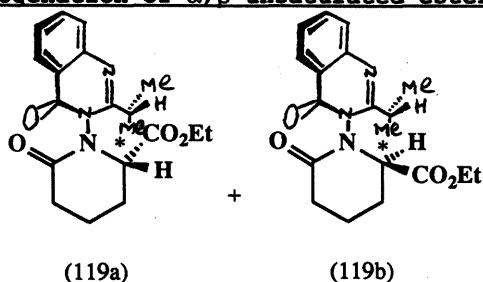
δ_c (CDCl₃, 300MHz): 18.12 (CH₂CH₂CH₂), 20.47 (CH₃CHCH₃), 31.01 (CH₃CHCH₃), 32.60 (CH₂), 38.32 (CH₂), 51.61 (CH₃O), 52.93 (CH₃O), 102.27 (COMe), 119.90 (Q¹ CCO), 126.03, 126.27, 127.33, 133.96 (4x Q¹ CH), 147.06 (Q¹ CN=C), 161.13 (Q¹ CN), 161.96 (Q¹ CO), 173.17 (CH₂CON), 193.22 (COOMe).

Distillation of α -acetoxy ester (115)



α -Acetoxy ester (115) (0.095g, 0.24mmol) was kugelrohr distilled at 250°C (bath temp.) and 0.1mmHg to give α,β -unsaturated ester (116) (0.08g, 98%) as an oil which remained in the distillation bulb and crystallised on standing. This was identical in all respects to that isolated previously (see above).

Hydrogenation of α,β -unsaturated ester (116)



* Relative configuration arbitrarily assigned

α,β -Unsaturated ester (116) (1.00g, 2.82mmol) was dissolved in dry ethanol (17ml) and platinum (IV) oxide (1.29g, 5.68mmol) added. The stirred solution was hydrogenated under a positive pressure (balloon) of hydrogen for 100 min. After this time, the catalyst was filtered under gravity, and the solvent removed under reduced pressure. Chromatography of the residue over silica, with ethyl acetate/light petroleum (1:2) as eluant gave N-(2-isopropylquinazolin-4(3H)-one-3-yl)-6-ethoxycarbonyl-2-tetrahydropyridone (119a), R_f 0.15 as a colourless oil (0.341g, 34%). Further elution gave a diastereoisomer of (119a), namely (119b), R_f 0.03 as a colourless oil (0.161g, 16%).

Compound (119a): $C_{19}H_{23}N_3O_4$ requires M. 357.1688. Found M/Z: 357.1696.

δ_H (CDCl₃, 300MHz): 1.14 (t, CH₃CH₂, J7.1Hz), 1.26 and 1.32 (2xd, CH₃CHCH₃, J6.7Hz), 1.98-2.27 (m, 3H), 2.45-2.55 (m, 1H), 2.71-2.75 (m, 2H), 3.53 (heptet, CH₃CHCH₃, J6.7Hz), 4.10 (ABX₃, CH₃CH₂, J9.8, 7.1Hz), 4.67 (dd, CHCOOEt, J7.0, 5.4Hz), 7.42 (ddd, ArCH Q¹H-6, J8.0, 4.5, 1.5Hz), 7.68 (ddd, ArCH Q¹H-7, J8.2, 4.5, 1.5Hz), 7.74 (ddd, ArCH Q¹H-8, J8.2, 1.5, 0.6Hz),

8.20 (ddd, ArCH Q¹H-5, J8.0, 1.5, 0.6 Hz).

δ_c (CDCl₃, 75 MHz): 13.48 ($\underline{\text{CH}_3\text{CH}_2}$), 17.42 ($\underline{\text{CH}_2}$), 21.32 ($\underline{\text{CH}_3\text{CHCH}_3}$), 21.59 ($\text{CH}_3\text{CH}\underline{\text{CH}_3}$), 25.83 ($\underline{\text{CH}_2}$), 30.60 ($\text{CH}_3\text{CH}\underline{\text{CH}_3}$), 31.98 ($\underline{\text{CH}_2}$), 61.80 ($\underline{\text{CH}_2\text{OCO}}$), 62.56 ($\underline{\text{CHCOO}}$), 121.00 (Q¹ $\underline{\text{CCO}}$), 126.30, 126.86, 127.12, 134.40 (4x Q¹ $\underline{\text{CH}}$), 146.66 (Q¹ $\underline{\text{CN}=\text{C}}$), 159.26 (Q¹ $\underline{\text{CN}}$), 161.31 (Q¹ $\underline{\text{CO}}$), 167.95 ($\underline{\text{C}=\text{O}}$), 168.26 ($\underline{\text{C}=\text{O}}$).

ν_{max} (CH₂Cl₂): 2965m, 2938m, 2868w, 1732s, 1680s, 1600s, 1572m, 1463m, 1382m, 1328m, 1280m, 1200s, 1180m, 1092m, 1058w, 1043w, 1020m, 980w, 932w, 903w, 875w, 842w, 650w, 625w.

M/Z (%): 357 (M⁺, 7), 284 (10), 189 (23), 188 (96), 187 (31), 174 (11), 173 (100), 160 (40).

Compound (119b): C₁₉H₂₃N₃O₄ requires M. 357.1688. Found M/Z: 357.1693.

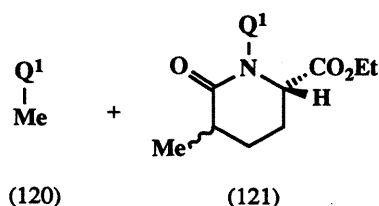
δ_H (CDCl₃, 300 MHz): 1.04 (t, $\underline{\text{CH}_3\text{CH}_2}$, J7.1 Hz), 1.28 and 1.42 (2xd, $\underline{\text{CH}_3\text{CHCH}_3}$, J6.7 Hz), 1.90-1.97 (m, 1H), 2.19-2.40 (m, 2H), 2.51-2.68 (m, 2H), 2.83-2.95 (m, 2H), 4.07 (ABX₃, $\underline{\text{CH}_3\text{CH}_2}$, J10.8, 7.1 Hz), 4.18 (dd, $\underline{\text{CHCOOEt}}$, J5.8, 3.3 Hz), 7.40 (ddd, ArCH Q¹H-6, J8.1, 7.0, 1.4 Hz), 7.64-7.75 (m, ArCH Q¹H-7/8), 8.18 (ddd, ArCH Q¹H-5, J8.1, 1.9, 0.4 Hz).

δ_c (CDCl₃, 75 MHz): 13.77 ($\underline{\text{CH}_3\text{CH}_2}$), 18.67 ($\underline{\text{CH}_2\text{CH}_2\text{CH}_2}$), 21.72 ($\underline{\text{CH}_3\text{CHCH}_3}$), 22.31 ($\text{CH}_3\text{CH}\underline{\text{CH}_3}$), 27.35 ($\underline{\text{CH}_2}$), 30.24 ($\text{CH}_3\text{CH}\underline{\text{CH}_3}$), 32.26 ($\underline{\text{CH}_2}$), 61.58 ($\underline{\text{CH}_3\text{CH}_2}$), 63.41 ($\underline{\text{CHCOO}}$), 120.90 (Q¹ $\underline{\text{CCO}}$), 126.07, 126.62, 127.18, 134.54 (4x Q¹ $\underline{\text{CH}}$), 147.07 (Q¹ $\underline{\text{CN}=\text{C}}$), 159.22 (Q¹ $\underline{\text{CN}}$), 163.71 (Q¹ $\underline{\text{CO}}$), 169.81 ($\underline{\text{C}=\text{O}}$), 170.20 ($\underline{\text{C}=\text{O}}$).

ν_{max} (CH₂Cl₂): 2970m, 2940m, 1745s, 1700s, 1600s, 1572w, 1462m, 1383s, 1369m, 1327m, 1265m, 1242m, 1195s, 1170s, 1090m, 1062w, 1023m, 982m, 920m, 870w, 807w, 650w, 618w.

M/Z (%): 357 (M⁺, 41), 314 (13), 285 (11), 284 (75), 189 (51), 188 (96), 187 (31), 174 (10), 173 (100), 160 (48).

Attempted alkylation of ester-pyridones (119a) and (119b)



Freshly distilled diisopropylamine (0.088g, 0.87mmol) and freshly distilled THF (5ml) were stirred under a dry nitrogen atmosphere at -5°C. n-Butyllithium (0.067g, 1.04mmol) was added dropwise to this solution and the resulting mixture stirred for 20 min. The solution was cooled to -78°C and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) (0.086g, 0.67mmol) was added. A 4:1 mixture of ester-pyridones (119a):(119b) (0.24g, 0.67mmol total) was then added as a solution in dry THF (3.5ml) and the total solution stirred at this temperature for 90 min., after which time it was allowed to warm to ambient and set aside overnight. Deuterium oxide (1ml) was added and the bulk of the THF evaporated under reduced pressure. The residue was dissolved in dichloromethane and the organic layer dried (MgSO₄), and evaporated under reduced pressure. Chromatography of the residue over silica, with ethyl acetate/light petroleum (1:4) as eluant, gave an

inseparable mixture of N-methyl-2-isopropylquinazolin-4(3H)-one (120) and methylated ester-pyridone (121), R_f 0.39, as a colourless oil (0.127g total), and unreacted starting material (119a only), R_f 0.27, as a colourless oil (0.05g, 21% recovery).

Compound (120): $C_{12}H_{14}N_2O$ requires M.202.1106. Found M/Z: 202.1100.

The proton n.m.r. spectrum of the mixture contained peaks which corresponded exactly with that of an authentic sample of compound (120) prepared as described below.

M/Z (%): (spectrum of mixture of (120) and (121)): 371 (M^+ , (121)), 299 (18), 285 (10), 189 (45), 188 (100), 187 (53), 186 (10), 184 (16), 174 (21), 173 (100), 160 (53), 145 (10), 130 (20), 119 (15), 103 (14).

Compound (121): $C_{20}H_{25}N_3O_4$ requires M.371.1845. Found M/Z: 371.1840.

δ_H ($CDCl_3$, 300MHz): (observable peaks from the n.m.r. of the mixture with (120)): 1.14 (t, CH_3CH_2 , J7.1Hz), 1.25 (2xd, CH_3CHCH_3 , J6.6Hz), 1.98-2.14 (m, 1H), 2.14-2.56 (m, 3H), 2.63-2.80 (m, 1H, (MeCHCON?)), 3.53 (heptet, CH_3CHCH_3 , J6.6Hz), 4.01-4.13 (ABX₃, CH_2CH_2 , J14.1, 7.1Hz), 4.57-4.62 (m, 1H, $CHCOOEt$), 8.15 (m, ArCH Q¹H-5). There was no evidence from the proton n.m.r. or mass spectrum of the mixture of compounds (120) and (121) for the incorporation of deuterium in compound (121).

N-Methylation of 2-isopropylquinazolin-4(3H)-one (74)



To a stirred slurry of 2-isopropylquinazolin-4(3H)-one (74) (0.422g, 2.24mmol) in freshly distilled THF (5ml) under an argon atmosphere at -78°C was added, dropwise, n -butyllithium (0.15g, 2.36mmol). After 2 min. methyl iodide (0.96g, 6.73mmol) was added and the solution stirred at this temperature for 3 hr. before being warmed to ambient temperature slowly. The mixture was stirred at room temperature for a further 90 min. before addition of water (6ml) and evaporation of the solvent under reduced pressure. Chromatography of the residue over silica, with ethyl acetate/light petroleum (1:2) as eluant, gave N-methyl-2-isopropylquinazolin-4(3H)-one (120), R_f 0.55, as colourless crystals (0.16g, 79% based on recovered starting material), m.p. $77-78^{\circ}\text{C}$ (from ethanol). Further elution gave unreacted starting material (74), R_f 0.35, (0.233g, 55% recovery).

Compound (120):

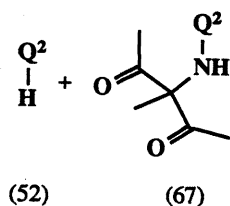
δ_{H} (CDCl_3 , 300MHz): 1.37 (d, CH_3CHCH_3 , J6.7Hz), 3.18 (heptet, CH_3CHCH_3 , J6.7Hz), 3.65 (s, NCH_3), 7.39 (ddd, $\text{ArCH Q}^1\text{H-6}$, J8.1, 6.6, 1.6Hz), 7.61-7.71 (m, $\text{ArCH Q}^1\text{H-7/8}$), 8.23 (ddd, $\text{ArCH Q}^1\text{H-5}$, J8.1, 1.4, 0.6Hz).

δ_c (CDCl₃, 75MHz): 20.82 (CH₃CHCH₃), 30.00 (NCH₃), 32.10
 (CH₃CHCH₃), 120.14 (Q¹ CCO), 126.09, 126.54, 127.02, 133.82
 (4x Q¹ CH), 147.25 (Q¹ CN=C), 160.97 (Q¹ CN), 162.68 (Q¹ CO).
 ν_{\max} (CH₂Cl₂): 2975m, 2939m, 2880w, 1730s, 1612s, 1595s,
 1572m, 1473m, 1426m, 1363w, 1336m, 1300m, 1230w, 1176w,
 1143m, 1118m, 1093m, 1073s, 1027w, 1006m, 962w, 940w, 878w,
 839w, 654w, 632m.

EXPERIMENTAL

CHAPTER FOUR

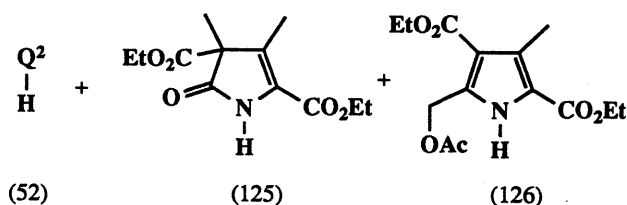
Preparation of diketo-amine (67)



Powdered 3-amino-2-ethylquinazolin-4(3H)-one (46) (0.99g, 5.23mmol) and acetic acid-free lead tetra-acetate (LTA) (2.43g, 5.49mmol) were added alternately and continuously in very small portions over 15 min. to a vigorously stirred solution of dry tetrahydrofuran (10ml) cooled at -20 to -25°C with a dry ice-acetone bath. The mixture was then stirred for a further 5 min. at low temperature before addition of the sodium salt of 3-methylpentan-2,4-dione (1.78g, 15.7mmol) as a slurry in dry THF (10ml). [The sodium salt was made by dissolving sodium metal (0.36g, 15.7mmol) in dry ethanol (20ml), adding 3-methylpentan-2,4-dione (1.78g, 15.7mmol) and then removing the ethanol under reduced pressure]. After allowing to warm to ambient temperature the insoluble lead di-acetate was separated, washed with dichloromethane and the total filtrate washed successively with sodium bicarbonate solution and water, dried (MgSO_4) and the solvent removed under reduced pressure. Ice-cold ether trituration of the solid/oil mixture obtained gave 2-ethylquinazolin-4(3H)-one (52) as colourless crystals (0.32g, 33%) which were identical in all respects to that isolated previously, (see

experimental relating to Chapter 1). Chromatography of the residue with ethyl acetate as eluant, gave diketo-amine (67), R_f 0.65, as colourless crystals (0.26g, 27%), m.p. 157-160°C, identical in all respects to that isolated previously, (see experimental relating to Chapter 1).

Reaction of N-acetoxyaminoquinazolinone (47)
with the sodium salt of ethyl acetoacetate



Powdered 3-amino-2-ethylquinazolin-4(3H)-one (46) (2.06g, 10mmol) and LTA (5.07g, 10mmol) were added alternately and continuously in very small portions over 15 min. to a vigorously stirred solution of dry tetrahydrofuran (21ml) cooled at -20 to -25°C with a dry ice-acetone bath. The mixture was then stirred for a further 5 min. at low temperature before addition of the sodium salt of ethyl acetoacetate (4.25g, 32.7mmol) as a slurry in dry THF (20ml) in one portion at this temperature. [This sodium salt was made by dissolving sodium metal (0.76g, 33mmol) in dry ethanol (20ml), adding ethyl acetoacetate (4.25g, 32.7mmol) and then removing the ethanol under reduced pressure]. After allowing to warm to

ethanol under reduced pressure]. After allowing to warm to ambient temperature, glacial acetic acid was added to dissolve the solid and the bulk of the solvent was then removed under reduced pressure. The bulk of the residue was dissolved in dichloromethane and the insoluble lead diacetate was separated, washed with dichloromethane and the total filtrate washed successively with sodium bicarbonate solution and water, dried (MgSO_4) and the solvent removed under reduced pressure. Ice-cold ether trituration of the solid/oil mixture obtained gave 2-ethylquinazolin-4(3H)-one (52) as colourless crystals (1.53g, 55%) which were identical in all respects to that isolated previously, (see experimental relating to Chapter 1). After removal of ether by evaporation under reduced pressure, the residue was crystallised from ethanol to give pyrrolinone (125) as colourless crystals (0.88g, 25%), m.p. 126-128°C (from ethanol).

Compound (125): $\text{C}_{12}\text{H}_{17}\text{NO}_5$ requires C, 56.46; H, 6.71; N, 5.49%. Found C, 56.41; H, 6.70; N, 5.47%.

δ_{H} (CDCl_3 , 300MHz): 1.22 (t, $\text{CH}_3\text{CH}_2\text{OCO}$, J7.1Hz), 1.27 (t, $\text{CH}_3\text{CH}_2\text{OCO}$, J7.1Hz), 1.60 (s, $\text{CH}_3\text{CCO}_2\text{Et}$), 2.44 ($\text{CH}_3=$), 4.08-4.26 (m, 4H, 2x $\text{CH}_3\text{CH}_2\text{OCO}$), 9.32 (bs, NH).

δ_{C} (CDCl_3 , 75MHz): 13.18 ($\text{CH}_3\text{CCO}_2\text{Et}$), 13.77 ($\text{CH}_3\text{CH}_2\text{OCO}$), 13.99 ($\text{CH}_3\text{CH}_2\text{OCO}$), 18.94 ($\text{CH}_3\text{C}=\text{C}$), 57.13 (CCO_2Et), 59.65 ($\text{CH}_3\text{CH}_2\text{OCO}$), 61.55 ($\text{CH}_3\text{CH}_2\text{OCO}$), 111.29 ($\text{CH}_3\text{C}=\text{C}$), 152.86 ($\text{C}=\text{CCO}_2\text{Et}$), 163.07 (CO), 168.19 (CO), 177.74 (CO).

ν_{max} (Nujol Mull): 3208brs, 1747s, 1704s, 1643m, 1417m, 1312m, 1250m, 1214m, 1108s, 1086s, 1073w, 1044w, 1015w,

M/Z (%): 256 (11), 183 (19), 182 (70), 154 (54), 137 (16), 136 (81), 32 (100).

A repeat of this experiment using N-aminoquinazolinone (46) (1.14g, 6.0mmol), LTA (2.81g, 6.35mmol), THF (11ml) with addition of the sodium salt of ethyl acetoacetate (3.14g, 24mmol) in THF (20ml) gave, after the same work up, 2-ethylquinazolin-4(3H)-one (52) (0.63g, 60%) after trituration with ether. After evaporation of ether, excess ethyl acetoacetate was removed using a kugelrohr at 50°C (bath temp.) and 0.2mmHg and the residue crystallised from ethanol to give the foregoing pyrrolinone (125) (0.19g, 12%) as colourless crystals which were identical in all respects with that isolated previously. Chromatography of the residue after removal of ethanol over silica, with ethyl acetate/light petroleum (1:4) as eluant, gave 2-acetoxymethyl-3,5-diethoxycarbonyl-4-methylpyrrole (126), R_f 0.20, as colourless crystals (0.253g, 14%), m.p. 113-113.5°C (from ethanol), (lit⁸¹. 114°C).

Compound (126): $C_{14}H_{19}NO_6$ requires C, 56.56; H, 6.44; N, 4.71%. Found C, 56.57; H, 6.43; N, 4.67%.

δ_H ($CDCl_3$, 300MHz): 1.34-1.40 (m, 6H, $2 \times CH_3CH_2OCO$), 1.37 (s, CH_3COO), 1.38 (s, $CH_3C=C$), 4.28-4.38 (m, 4H, $2 \times CH_3CH_2OCO$), 5.42 (s, CH_2OAc), 9.62 (brs, NH).

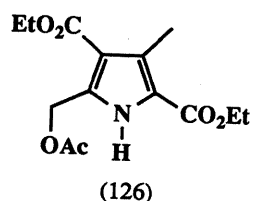
δ_C ($CDCl_3$, 75MHz): 11.61 (CH_3), 14.27 (CH_3), 14.31 (CH_3), 20.75 (CH_3), 58.46 ($CO_2CH_2CH_3$), 59.85 ($CO_2CH_2CH_3$), 60.49 (CH_2OAc), 114.26, 119.56, 130.27, 134.90 ($4 \times C=C$), 161.28 ($C=O$), 164.48 ($C=O$), 170.93 ($C=O$).

ν_{max} (Nujol Mull): 3270s, 1738s, 1710s, 1673s, 1576w, 1486s,

1295s, 1253s, 1237s, 1213m, 1173w, 1128w, 1113w, 1096s, 1057w, 1026m, 968m, 956w, 927w, 888w, 868w, 857w, 793m, 783m, 775m, 757m, 748w, 739w, 729w, 697w, 642m.

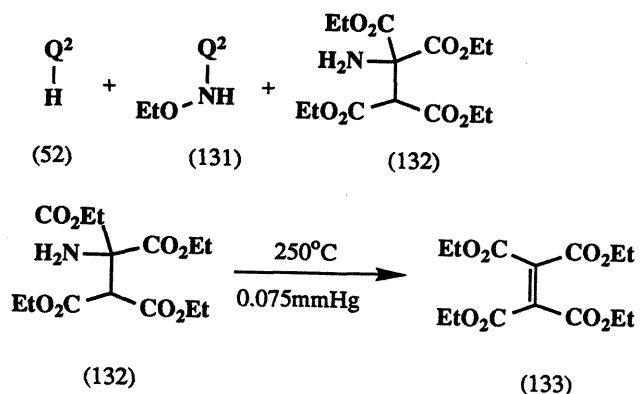
M/Z (%): 297 (M⁺, 22), 255 (16), 254 (34), 240 (13), 239 (37), 238 (17), 237 (16), 211 (12), 210 (37), 209 (48), 208 (100), 194 (22), 193 (19), 192 (11), 182 (16), 180 (12), 166 (14), 165 (18), 164 (45), 163 (14), 162 (61), 148 (29), 147 (15), 135 (11).

Preparation of 2-acetoxymethyl-3,5-diethoxycarbonyl-4-methyl-pyrrole (126)⁵⁷



This material was prepared by an adaptation of the procedure by Clezy *et al.*⁵⁷ Chromatography of the crude product over silica, with ethyl acetate/light petroleum (1:4) as eluant, gave 2-acetoxymethyl-3,5-diethoxycarbonyl-4-methylpyrrole (126), R_f 0.20, as colourless crystals (0.235g, 15%) which was identical in all respects to that isolated in the preceding experiment.

Reaction of N-acetoxyaminoquinazolinone (47)
with the sodium salt of diethyl malonate



Powdered 3-amino-2-ethylquinazolin-4(3H)-one (46) (2.78g, 14.7mmol) and LTA (6.86g, 15.5mmol) were added alternately and continuously in very small portions over 15 min. to a vigorously stirred solution of dry tetrahydrofuran (28ml) cooled at -20 to -25°C with a dry ice-acetone bath. The mixture was then stirred for a further 5 min. at low temperature, before addition of the sodium salt of diethyl malonate (9.43g, 59mmol) as a solution in dry THF (25ml) and then allowing to warm to ambient temperature. [The sodium salt was made by dissolving sodium metal (1.36g, 59mmol) in dry ethanol (50ml) adding diethyl malonate (9.43g, 59mmol) and removing the bulk of the ethanol under reduced pressure]. Glacial acetic acid was added to dissolve the bulk of the solid and the bulk of the solvent was then removed under reduced pressure. The residue was dissolved in dichloromethane and

the insoluble lead di-acetate was then separated, washed with dichloromethane and the total filtrate washed successively with sodium bicarbonate solution and water, dried (MgSO_4) and the solvent removed under reduced pressure. Ice-cold ether trituration of the solid/oil mixture obtained gave 2-ethylquinazolin-4(3H)-one (52) as colourless crystals (1.72g, 67%) which were identical to that isolated previously, (see experimental relating to Chapter 1). After evaporation of ether, excess diethyl malonate was removed using a kugelrohr at 50°C (bath temp.) and 0.2mmHg. Chromatography of the residue over silica, with ethyl acetate/light petroleum (1:5) as eluant, gave N-ethoxyamino-2-ethylquinazolin-4(3H)-one (131), R_f 0.56, as colourless crystals (0.46g, 13%), m.p. 55-56.5°C (from ethanol). Further elution with methanol gave amino-1,1,2,2-tetraethoxycarbonylethane (132) as a colourless oil (0.425g, 9%).

Kugelrohr-distillation of this material at 250°C (bath temp.) and 0.075mmHg resulted in partial elimination of ammonia from (132) to give tetraethoxycarbonylethene (133) (ratio of (132):(133) was 2.30:1 respectively). Redistillation at this same temperature and pressure gave a ratio for (132):(133) of 1:1.24.

Compound (131): $\text{C}_{12}\text{H}_{15}\text{N}_3\text{O}_2$ requires C, 61.79; H, 6.48; N, 18.01%. Found C, 61.77; H, 6.49; N, 18.11%.

δ_{H} (CDCl_3 , 300MHz): 1.24 (t, Q^2 CH_3CH_2 , J7.0Hz), 1.40 (t, $\text{CH}_3\text{CH}_2\text{O}$, J7.4Hz), 2.90-3.13 (bm, Q^2 CH_3CH_2), 3.99 (q, $\text{CH}_3\text{CH}_2\text{O}$, J7.4Hz), 7.43 (ddd, ArCH Q^2H -6, J8.0, 7.0, 1.3Hz),

7.66 (ddd, ArCH $\underline{Q^2H}$ -8, J8.3, 1.3, 0.4Hz), 7.74 (ddd, ArCH $\underline{Q^2H}$ -7, J8.3, 7.0, 1.5Hz), 8.24 (ddd, ArCH $\underline{Q^2H}$ -5, J8.0, 1.5, 0.4Hz), 9.27 (s, NH).

δ_c (CDCl₃, 75MHz): 11.13 ($\underline{Q^2 CH_3CH_2}$), 14.00 ($\underline{CH_3CH_2O}$), 26.85 ($\underline{Q^2 CH_3CH_2}$), 68.07 ($\underline{CH_3CH_2O}$), 120.18 ($\underline{Q^2 CCO}$), 126.47, 127.04, 127.35, 134.80 (4x $\underline{Q^2 CH}$), 147.07 ($\underline{Q^2 CN=C}$), 158.36 ($\underline{Q^2 CN}$), 160.79 ($\underline{Q^2 CO}$).

ν_{max} (Nujol Mull): 3207w, 2973m, 2924m, 2878m, 1677s, 1602s, 1572m, 1541w, 1500m, 1468m, 1373m, 1334m, 1302m, 1239m, 1183m, 1127m, 1089w, 1067m, 1037s, 965w, 921m, 902m, 850w, 650w, 615w.

M/Z (%): 233 ($\underline{M^+}$, 14), 189 (33), 175 (43), 174 (100), 173 (95), 160 (15), 146 (13), 132 (16), 131 (30), 130 (34), 119 (49), 103 (12), 92 (10), 90 (18), 77 (19), 76 (27).

Compounds (132) and (133): The spectroscopic data below relates to a 2.30:1 mixture of (132) and (133).

δ_H (CDCl₃, 300MHz): 1.28 (t, $\underline{CH_3CH_2}$ of (132), J7.1Hz), 1.32 (t, $\underline{CH_3CH_2}$ of (133), J7.1Hz), 2.56 (brs, $\underline{NH_2}$ of (132)), 4.23 and 4.24 (structured multiplet, $\underline{CH_3CH_2}$ of (132), J7.1Hz), 4.32 (q, $\underline{CH_3CH_2}$ of (133), J7.1Hz), 4.52 (s, \underline{CH} of (132)).

δ_c (CDCl₃, 75MHz): 13.65 ($\underline{CH_3CH_2}$ of (133)), 13.75 ($\underline{CH_3CH_2}$ of (132)), 56.65 (\underline{CH} of (132)), 61.63 ($\underline{CHCO_2CH_2CH_3}$ of (132)), 62.38 ($\underline{CH_3CH_2}$ of (133)), 62.44 ($\underline{C(NH_2)CO_2CH_2CH_3}$ of (132)), 66.94 ($\underline{CNH_2}$ of (132)), 135.18 ($\underline{C=C}$ of (133)), 162.13 ($\underline{C=O}$), 167.23 ($\underline{C=O}$), 168.90 ($\underline{C=O}$).

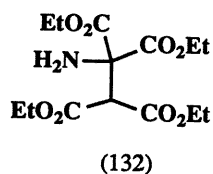
ν_{max} (CH₂Cl₂): 3407w, 3327w, 2977m, 2930w, 2897w, 2867w, 1735s, 1577w, 1457w, 1370m, 1302m, 1235s, 1156m, 1098w, 1045s, 1027s, 907w, 861w, 807w.

M/Z (%): 334 (24), 333 (M⁺ of (132), 0.4), 316 (M⁺ of (133), 0.6), 261 (13), 260 (100), 243 (14), 187 (14), 174 (11), 142 (47), 114 (29).

A sample of tetraethoxycarbonylethene (133) (Lancaster) showed peaks in its proton n.m.r. spectrum which were identical to those present in the spectrum of a 2.30:1 mixture of (132):(133) after subtracting those peaks assigned to (132).

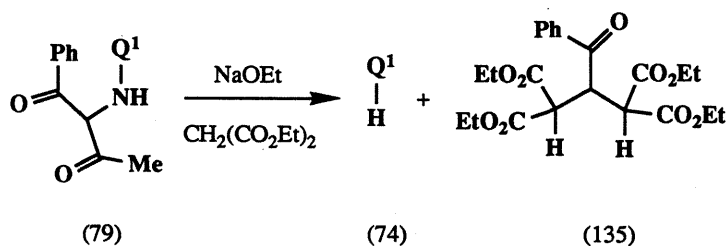
Preparation of amino-1,1,2,2-tetraethoxy-
carbonylethane (132)⁵⁹

This material was prepared by an adaptation of the method of Philippi and Uhl⁵⁹.



Tetraethoxycarbonylethene (0.358g, 1.13mmol) was dissolved in dry ethanol (20ml). Ammonia was bubbled through for 4.5hr. After this time, the solution was filtered through celite and evaporated under reduced pressure to give amino-1,1,2,2-tetraethoxycarbonylethane (132) as a colourless oil (0.36g, 95%) which was identical in all respects with that isolated previously, (see previous experiment).

Treatment of diketo-amine (79) with the sodium salt of diethyl malonate



Sodium metal (37.1mg, 1.61mmol) was dissolved in dry ethanol (4ml) and diethyl malonate (0.215g, 1.34mmol) added. The resulting suspension was stirred for 30 min. before diketo-amine (79) (0.215g, 0.61mmol) was added continuously and in very small portions over 5 min. The resulting mixture was stirred under an argon atmosphere overnight before sufficient dilute hydrochloric acid was added to dissolve the solid formed. The mixture was extracted with dichloromethane (3x20ml) and the organic layer washed with water, dried (MgSO₄) and evaporated under reduced pressure. Chromatography of the residue over silica, with ethyl acetate/light petroleum (1:4) as eluant, gave keto-diester (135), R_f 0.68, as a colourless oil (0.045g, 17%). Further elution gave 2-isopropylquinazolin-4(3H)-one (74) as colourless crystals (0.039g, 34%) which were identical to that isolated previously, (see experimental relating to Chapter 1).

Compound (135): C₂₂H₂₈O₆, requires M.436.1733. Found: M/Z 436.1725.

δ_H (CDCl₃, 300MHz): 1.11 (t, 3H, CH₃CH₂COO, J7.1Hz), 1.24 (t,

3H, $\text{CH}_3\text{CH}_2\text{COO}$, J7.1Hz), 3.97 (ABX₃, 2H, $\text{CH}_3\text{CH}_2\text{COO}$, J14.2, 7.1Hz), 4.08 (d, 2H, $\text{HC}(\text{CO}_2\text{Et})_2$, J8.0Hz), 4.16 (ABX₃, 2H, $\text{CH}_3\text{CH}_2\text{OCO}$, J13.3, 7.1Hz), 4.86 (t, 1H, HCCOPh , J8.0Hz), 7.40–7.60 (m, 3xPhH), 8.01–8.03 (m, 2xPhH).
 δ_c (CDCl₃, 75MHz): 13.72 (CH_3CH_2), 13.90 (CH_3CH_2), 43.63 (PhCOCH), 52.74 (OCOCH), 61.91 ($\text{CH}_2\text{CH}_2\text{O}$), 128.39, 128.91, 130.09, 133.26 (4x PhCH), 136.65 (PhCCO), 167.54 (OCO), 167.75 (OCO), 198.78 (PhCO).
 ν_{max} (CH₂Cl₂): 2993w, 2943w, 2913w, 1735s, 1688m, 1600w, 1583w, 1468w, 1449w, 1371m, 1250m, 1178m, 1095w, 1026m, 960w, 933w, 859w.
 M/Z (%): 105 (100), 77 (12).

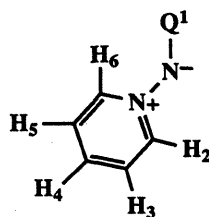
EXPERIMENTAL

CHAPTER FIVE

General procedure (4) for the oxidation of
N-aminoquinazolinones using ITA in the presence of
pyridine derivatives at room temperature:
N-(quinazolin-4(3H)-one-3-yl)-N-(pyridinium-1-yl) ylides

Powdered N-aminoquinazolinone (1 mol equiv.) and acetic acid free lead tetra-acetate (1.05mol equiv.) were added alternately and continuously in very small portions over 15 min. to a vigorously stirred solution of dry dichloromethane (1ml/100mg of N-aminoquinazolinone) containing the freshly distilled pyridine derivative (10-50 mol equiv.) at room temperature. The mixture was stirred for 5 min. at room temperature before dichloromethane was removed at 30°C (bath temp.) and water pump pressure. Most of the excess pyridine derivative was then removed under reduced pressure at 60°C (bath temp.) and 0.1mmHg and the bulk of the residue dissolved in dichloromethane (100ml) and magnesium sulphate and activated charcoal added. The solution was filtered and the solvent removed under reduced pressure.

Preparation of N-(quinazolin-4(3H)-one-3-yl)-
N-(pyridinium-1-yl) ylide (145)



(145)

The general procedure (4) was followed using N-aminoquinazolinone (73) (3.39g, 16.7mmol), LTA (7.78g, 17.6mmol) and pyridine (39.61g, 0.5mol) in dry dichloromethane (34ml). Addition of dry ether to the residue precipitated the crude ylide which was filtered. Crystallisation from chloroform/light petroleum removed 2-isopropylquinazolin-4(3H)-one (74) identical to that isolated previously (see experimental relating to Chapter 1). Evaporation of the chloroform/light petroleum and crystallisation of the residue from ethanol (x2) gave pure N-(2-isopropylquinazolin-4(3H)-one-3-yl)-N-(pyridinium-1-yl) ylide (145) as bright yellow crystals (0.78g, 36%), m.p. 134-136°C (decomp.).

Compound (145): C₁₆H₁₆N₄O requires M. 280.1324. Found M/Z: 280.1324.

δ_H (CDCl₃, 300MHz): 1.29 (broadened m, 6H, CH₃CHCH₃), 3.39 (heptet, CH₃CHCH₃, J_{6.8}Hz), 6.95-7.00 (m, 1H, pyrid. CH-4), 7.15-7.20 (m, 2H, pyrid. CH-3,5), 7.42 (ddd, ArCH Q¹H-6, J_{8.0}, 5.3, 3.0Hz), 7.70-7.85 (m, 4H, ArCH Q¹H-7/8, and 2x pyrid. CH-2,6), 8.26 (dd, ArCH Q¹H-5, J_{8.0}, 1.2, 0.8Hz).

δ_c (CDCl₃, 75MHz): 20.80 (CH₃CHCH₃), 31.02 (CH₃CHCH₃), 120.97 (Q¹ CO), 122.43 (pyrid. CH), 125.33 (pyrid. CH, broadened), 125.55 (pyrid. CH), 125.60 (CH), 126.42, 126.99, 133.58 (3x Q¹ CH), 147.03 (Q¹ CN=C), 160.24 (Q¹ CN), 163.81 (Q¹ CO).

ν_{max} (Nujol Mull): 3108w, 3082w, 1667m, 1610m, 1582s, 1565m, 1543w, 1458s, 1379m, 1350w, 1298w, 1275w, 1250w, 1230w, 1208w, 1170m, 1152m, 1140m, 1105w, 1085w, 1040w, 1018w, 995s, 958w, 937m, 888w, 838m, 793w, 768s, 753m, 746w, 737w, 720w, 693m, 672m, 661m, 640m.

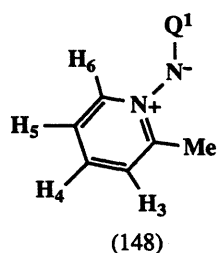
M/Z (%): 280 (M⁺, 0.5), 188 (25), 187 (12), 175 (10), 173 (43), 160 (10), 93 (16), 84 (20), 79 (100).

The barriers to N-N bond rotation for the bonds N¹-N² and N²-N³ were measured from the n.m.r. spectra at 400MHz at various low temperatures (see Appendix 1), and were determined to be $\Delta G^\ddagger=14$ and 11 K cal mol⁻¹ respectively.

Preparation of

N-(2-isopropylquinazolin-4(3H)-one-3-yl)-2-methyl-

N-(pyridinium-1-yl) ylide (148)



The general procedure (4) was followed using N-

aminoquinazolinone (73) (1.07g, 5.29mmol), LTA (2.46g, 5.55mmol) and 2-methylpyridine (4.92g, 0.05mol) in dry dichloromethane (11ml). Trituration of the residue with light petroleum gave a solid which was crystallised from ethanol to give pure N-(2-isopropylquinazolin-4(3H)-one-3-yl)-N-(2-methylpyridinium-1-yl) ylide (148) as bright yellow crystals (0.83g, 53%), m.p. 100-102°C (decomp.).

Compound (148): $C_{17}H_{18}N_4O$ requires M. 294.1480. Found M/Z: 294.1481.

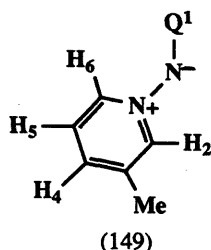
δ_H ($CDCl_3$, 300MHz): 1.19 and 1.29 (2xd, CH_3CHCH_3 , J6.5Hz), 2.66 (s, CH_3CN), 3.29 (heptet, CH_3CHCH_3 , J6.5Hz), 6.88-6.93 (m, 1H, pyrid. CH), 6.99-7.03 (m, 1H, pyrid. CH), 7.17-7.20 (m, 1H, pyrid. CH), 7.23-7.28 (m, 1H, pyrid. CH), 7.39-7.42 (m, Ar CH Q^1H -6), 7.71-7.72 (m, Ar CH Q^1H -7/8), 8.26 (d, Ar CH Q^1H -5, J7.8Hz).

δ_C ($CDCl_3$, 75MHz): 19.65 (CH_3), 20.86 (CH_3), 21.18 (CH_3), 31.36 (CH_3CHCH_3), 121.24 ($Q^1 CCO$), 121.88 (pyrid. CH), 123.18 (CH), 123.38 (CH), 125.75 (CH), 126.33 (CH), 126.61 (CH), 127.16 (CH), 133.69 ($Q^1 CH$), 137.74 (pyrid. $CCCH_3$), 147.22 ($Q^1 CN=C$), 160.59 ($Q^1 CN$), 163.98 ($Q^1 CO$).

ν_{max} (Nujol Mull): 1674m, 1609m, 1583s, 1561m, 1490w, 1468s, 1452s, 1376m, 1352w, 1298m, 1272w, 1247w, 1229w, 1220m, 1165m, 1150s, 1100w, 1087w, 1068w, 1052w, 1026w, 1014w, 979w, 965w, 939m, 823m, 776s, 742s, 694s, 684m, 662m, 643m.

M/Z (%): 294 (M^+ , 6.7), 201 (18), 200 (14), 188 (45), 187 (24), 174 (13), 173 (100), 160 (20), 145 (18), 130 (22), 119 (16), 93 (81), 92 (26), 78 (13).

Preparation of
N-(2-isopropylquinazolin-4(3H)-one-3-yl)-N-(3-methyl
pyridinium-1-yl) ylide (149)



The general procedure (4) was followed using N-aminoquinazolinone (73) (1.59g, 7.82mmol), LTA (3.64g, 8.22mmol) and 3-methylpyridine (21.82g, 0.23mol) in dry dichloromethane (16ml). Addition of dry ether precipitated the crude ylide which was filtered, and crystallised twice from ethanol gave pure N-(2-isopropylquinazolin-4(3H)-one-3-yl)-N-(3-methylpyridinium-1-yl) ylide (149) as bright yellow crystals (1.27g, 55%), m.p. 141-142°C (decomp.).

Compound (149): $C_{17}H_{18}N_4O$ requires M. 294.1481. Found M/Z: 294.1480.

δ_H ($CDCl_3$, 300MHz): 1.19-1.22 and 1.36-1.38 (2x broadened d, CH_3CHCH_3 , J 6.8 Hz), 2.25 (s, CH_3), 3.36 (heptet, CH_3CHCH_3 , J 6.8 Hz), 6.80 (d, 1H, pyrid. CH , J 7.7 Hz), 7.05 (dd, 1H, pyrid. CH , J 7.1, 7.1 Hz), 7.42 (ddd, Ar CH Q^1H -6, J 8.0, 5.1, 3.3 Hz), 7.53 (broadened s, 1H, pyrid. CH -2), 7.64 (broadened m, 1H, pyrid. CH -6), 7.70-7.76 (m, Ar CH Q^1H -7/8), 8.27 (ddd, Ar CH Q^1H -5, J 8.0, 1.2, 0.8 Hz).

δ_C ($CDCl_3$, 75MHz): 18.80 (CH_3), 21.01 (CH_3), 21.08 (CH_3),

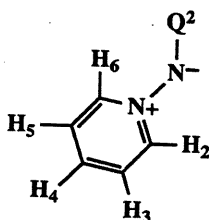
31.23 (CH_2CHCH_3), 121.26 ($\text{Q}^1 \text{ CCO}$), 123.16 (pyrid. CH broadened), 124.31, 125.16 (2x pyrid. CH), 125.53 ($\text{Q}^1 \text{ CH}$), 125.78 (pyrid. CH , broadened), 126.75, 127.18, 133.78 (3x $\text{Q}^1 \text{ CH}$), 136.26 (pyrid. CCH_3), 147.29 ($\text{Q}^1 \text{ CN=C}$), 160.68 ($\text{Q}^1 \text{ CN}$), 164.25 ($\text{Q}^1 \text{ CO}$).

ν_{max} (Nujol Mull): 3110w, 1665s, 1610m, 1582s, 1566m, 1420m, 1350w, 1332w, 1299w, 1262w, 1228w, 1208w, 1170w, 1129m, 1100w, 1085w, 1040w, 1021w, 995m, 954w, 912w, 887w, 876w, 850w, 782m, 763m, 692m, 677w, 661w, 640m.

M/Z (%): 294 (M^+ , 0.3), 203 (10), 188 (35), 187 (17), 175 (15), 173 (52), 160 (12), 119 (11), 93 (100), 92 (33).

Preparation of

N-(2-ethylquinazolin-4(3H)-one-3-yl)-N-(pyridinium-1-yl) ylide (150)



(150)

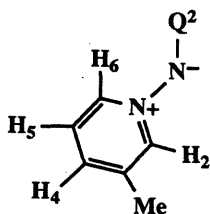
The general procedure (4) was followed using N-aminoquinazolinone (46) (1.78g, 9.4mmol), LTA (4.37g, 9.88mmol) and pyridine (26.22g, 0.28mol) in dry dichloromethane (18ml). Addition of dry ether to the residue precipitated the crude ylide which was filtered and crystallised from chloroform/light petroleum twice to

remove 2-ethylquinazolin-4(3H)-one (52) as colourless crystals which were identical to that isolated previously, (see experimental relating to Chapter 1). Evaporation of chloroform/light petroleum and crystallisation of the residue from ethanol (x2) gave pure N-(2-ethylquinazolin-4(3H)-one-3-yl)-N-(pyridinium-1-yl) ylide (150) as bright orange crystals (0.815g, 33%), m.p. 132-135°C (decomp.).

Compound (150): δ_H (CDCl₃, 300MHz): 1.29 (t, CH₃CH₂, J7.4Hz), 2.82-2.89 (bq, CH₃CH₂), 6.97-7.02 (m, 1H, pyrid. CH-4), 7.16-7.21 (m, 2H, pyrid. CH-3/5), 7.43 (ddd, ArCH Q²H-6, J8.0, 6.3, 2.1Hz), 7.69-7.77 (m, 4H, ArCH Q²H-7/8, and pyrid. 2x CH-2/6), 8.27 (ddd, ArCH Q²H-5, J8.0, 1.4, 0.6Hz).

Preparation of

N-(2-ethylquinazolin-4(3H)-one-3-yl)-N-(3-methylpyridinium-1-yl) ylide (151)



(151)

The general procedure (4) was followed using N-aminoquinazolinone (46) (1.77g, 9.36mmol), LTA (4.36g, 9.85mmol) and 3-methylpyridine (26.11g, 0.28mol) in dry dichloromethane (18ml). Addition of dry ether to the residue precipitated the crude ylide which was filtered and

crystallised from ethanol twice to give pure N-(2-ethylquinazolin-4(3H)-one-3-yl)-N-(3-methyl pyridinium-1-yl) ylide (151) as bright yellow crystals (0.811g, 31%), m.p. 137-140°C (decomp.).

Compound (151): $C_{16}H_{16}N_4O$ requires C, 68.55; H, 5.75; N, 19.99%. Found C, 68.51; H, 5.95; N, 19.81%.

δ_H ($CDCl_3$, 300MHz): 1.29 (t, CH_3CH_2 , J7.4Hz), 2.24 (s, pyrid. CH_3), 2.84 (bm, CH_3CH_2), 6.79-6.82 (m, 1H, pyrid. $CH-4$), 7.03-7.08 (m, 1H, pyrid. $CH-5$), 7.41 (ddd, ArCH Q^2H-6 , J7.9, 6.1, 2.2Hz), 7.57 (bs, 1H, pyrid. $CH-2$), 7.63 (bm, 1H, pyrid. $CH-6$), 7.69-7.76 (m, ArCH $Q^2H-7/8$), 8.27 (ddd, ArCH Q^2H-5 , J7.9, 1.2, 0.5Hz).

δ_C ($CDCl_3$, 75MHz): 11.37 (CH_3), 18.79 (CH_3), 27.42 (CH_3CH_2), 121.41 ($Q^2 CCO$), 123.06 (pyrid. $CH-2$), 124.47, 124.55 (2x CH), 125.24 (pyrid. $CH-6$), 125.86, 126.80, 126.95 (3x CH), 133.89 ($Q^2 CH$), 136.35 (pyrid. CCH_3), 147.22 ($Q^2 CN=C$), 160.60 ($Q^2 CN$), 161.79 ($Q^2 CO$).

ν_{max} (Nujol Mull): 3095w, 1662s, 1611m, 1566m, 1422m, 1376m, 1364m, 1342m, 1300w, 1280w, 1265w, 1226w, 1215w, 1173w, 1150w, 1127s, 1101m, 1064w, 1056w, 1022w, 994m, 964m, 944w, 910m, 786m, 767s, 721w, 694m, 678w, 646m.

M/Z (%): 280 (M^+ , 2.1), 189 (18), 175 (17), 174 (78), 173 (85), 146 (21), 130 (10), 120 (10), 119 (49), 94 (28), 93 (100), 92 (71), 90 (18), 78 (14), 67 (33).

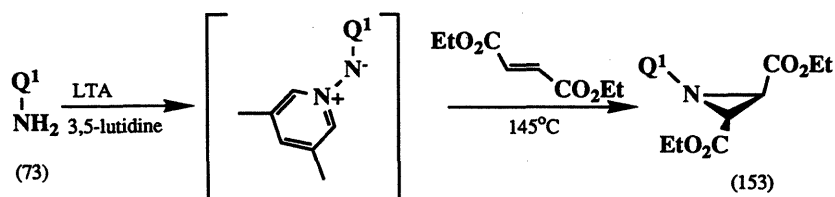
Attempted preparation of
N-(2-ethylquinazolin-4(3H)-one-3-yl)-N-(3,5-dimethyl
pyridinium-1-yl) ylide



(74)

The general procedure (4) was followed using N-aminoquinazolinone (73) (2.98g, 15mmol), LTA (7.04g, 16mmol) and 3,5-lutidine (47.20g, 0.44mol) in dry dichloromethane (30ml). Attempts to crystallise the residue from ether were unsuccessful and resulted in partial decomposition with formation of small quantities of 2-isopropylquinazolin-4(3H)-one (74).

Preparation of
N (2-ethylquinazolin-4(3H)-one-3-yl)-N-(3,5-dimethyl
pyridinium-1-yl) ylide in situ and subsequent
aziridination of diethyl fumarate



The general procedure (4) was followed using the N-aminoquinazolinone (73), LTA (2.27g, 5.1mmol) and 3,5-lutidine (26.04g, 0.24mol) in dry dichloromethane (10ml). Freshly distilled diethyl fumarate (8.73g, 48.7mmol) was added immediately to the oil thus obtained and the mixture heated at 145°C for 10 min. The bulk of the diethyl fumarate was removed by distillation at 65°C (bath temp.) and 0.5mmHg. Chromatography of the solid/oil residue over silica, with ethyl acetate/light petroleum (1:4) as eluant, gave diethyl 1-(2-isopropylquinazolin-4(3H)one-3-yl)aziridine 2,3-dicarboxylate (153), R_f 0.23, as a colourless oil (0.55g, 30%).

Compound (153): $\text{C}_{19}\text{H}_{23}\text{N}_3\text{O}_5$ requires M. 373.1637. Found M/Z: 373.1644.

δ_{H} (CDCl_3 , 300MHz): 1.15 (t, $\text{CH}_3\text{CH}_2\text{O}$, J7.2Hz), 1.38 (t, $\text{CH}_3\text{CH}_2\text{O}$, J7.2Hz), 1.15 and 1.42 (2xd, CH_3CHCH_3 , J6.6Hz), 3.39 (heptet, CH_3CHCH_3 , J6.6Hz), 3.80 (d, aziridine CH anti to

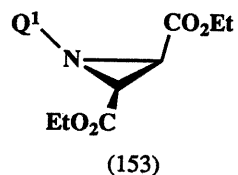
Q^1 , J4.6Hz), 4.08 (d, aziridine \underline{CH} syn to Q^1 , J4.6Hz), 4.10 (q, $\underline{CH_3CH_2O}$, J7.2Hz), 4.35 (dq, $\underline{CH_3CH_2O}$, J7.2Hz), 7.40 (ddd, Ar \underline{CH} Q^1H -6, J7.9, 6.8, 1.5Hz), 7.61-7.71 (m, Ar \underline{CH} Q^1H -7/8), 8.16 (ddd, Ar \underline{CH} Q^1H -5, J7.9, 1.4, 0.5Hz).

δ_c (CDCl₃, 75MHz): 13.62 ($\underline{CH_3CH_2O}$), 13.88 ($\underline{CH_3CH_2O}$), 19.95 ($\underline{CH_3CHCH_3}$), 21.14 ($\underline{CH_3CHCH_3}$), 30.73 ($\underline{CH_3CHCH_3}$), 46.72 (aziridine \underline{CH}), 49.00 (aziridine \underline{CH}), 62.29 ($\underline{CH_3CH_2O}$), 62.38 ($\underline{CH_3CH_2O}$), 120.70 ($Q^1 \underline{CO}$), 126.08, 126.21, 127.00, 133.64 (4x $Q^1 \underline{CH}$), 145.91 ($Q^1 \underline{CN=C}$), 158.77 ($Q^1 \underline{CN}$), 159.59 ($Q^1 \underline{CO}$), 164.35 ($\underline{CO_2Et}$), 166.08 ($\underline{CO_2Et}$).

ν_{max} (CH₂Cl₂): 3065w, 2978m, 2938m, 2910w, 2876w, 1735s, 1675s, 1571m, 1383m, 1370s, 1323s, 1218s, 1195s, 1092m, 1026s, 962w, 937w, 849w.

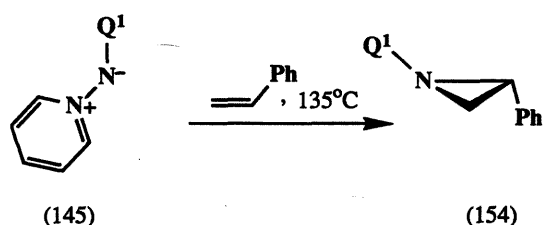
M/Z (%): 373 (M⁺, 38), 301 (18), 300 (98), 214 (10), 188 (47), 187 (31), 174 (14), 173 (100), 160 (19), 146 (17), 145 (72), 144 (11), 130 (41), 127 (59), 126 (21), 119 (16), 99 (41), 93 (30), 90 (13), 86 (18), 85 (14), 84 (24), 77 (11), 76 (17), 71 (15), 69 (12).

Aziridination of diethyl fumarate using
3-amino-2-isopropylquinazolin-4(3H)-one (73)



The general procedure (1) (see Chapter 1) was followed using N-aminoquinazolinone (73) (1.2g, 5.9mmol), LTA (2.77g, 6.26mmol) and diethyl fumarate (3.05g, 18mmol) in dry dichloromethane (12ml). Most of the excess diethyl fumarate was removed by kugelrohr-distillation at 70°C (bath temp.) and 0.2mmHg. Chromatography of the residue over silica, with ethyl acetate/light petroleum (1:4) as eluant, gave diethyl 1-(2-isopropylquinazolin-4(3H)-one-3-yl) aziridine 2,3-dicarboxylate (153), R_f 0.23, as a colourless oil (1.79g, 81%) which was identical in all respects to that isolated above.

Reaction of pyridinium ylide (145) with styrene



Freshly distilled styrene (5.45g, 47mmol) was heated to 135°C and pyridinium ylide (145) (0.31g, 1.11mmol) added continuously and in very small portions over 10 min. The mixture was heated at this temperature for a further 1 min. and then cooled. The bulk of the styrene was removed by kugelrohr-distillation at 57°C (bath temp.) and 0.1mmHg. Chromatography of the residue over silica, with ethyl acetate/light petroleum (1:4) as eluant, gave 1-(2-isopropylquinazolin-4(3H)-one-3-yl)-2-phenylaziridine (154), R_f 0.25, as colourless crystals (0.15g, 44%), m.p. 108-109°C (from ethanol).

A repetition of this experiment with styrene (0.11g, 1.02mmol) and pyridinium ylide (145) (0.096g, 0.34mmol) gave aziridine (154) as colourless crystals (0.038g, 36%) after the same work up.

Compound (154): $C_{19}H_{19}N_3O$ requires C, 74.73; H, 6.27; N, 13.76%. Found C, 74.60; H, 6.39; N, 13.72%.

δ_H ($CDCl_3$, 300MHz): 1.34 (2xd, CH_3CHCH_3 , J6.7Hz), 2.85 (dd, aziridine CH anti to Q^1 , J5.4, 2.1Hz), 3.21 (dd, aziridine CH syn to Q^1 , J7.9, 2.1Hz), 3.64 (heptet, CH_3CHCH_3 , J6.7Hz), 3.80 (dd, aziridine CH syn to Q^1 , gem to Ph, J5.4, 7.9Hz), 7.31-7.43

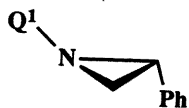
(m, 6H, ArCH Q¹H-6, and 5xPhCH), 7.62-7.71 (m, ArCH Q¹H-7/8), 8.20 (ddd, ArCH Q¹H-5, J8.0, 1.5, 0.5Hz).

δ_c (CDCl₃, 75MHz): 20.90 (CH₃CHCH₃), 20.94 (CH₃CHCH₃), 30.97 (CH₃CHCH₃), 42.96 (aziridine CH₂), 46.97 (aziridine CH), 121.26 (Q¹ CCO), 126.06, 126.34, 126.91, 127.99, 128.53 (5x CH), 133.55 (Q¹ CH), 136.56 (PhCCHCH₂), 146.13 (Q¹ CN=C), 160.10 (Q¹ CN), 161.35 (Q¹ CO).

ν_{max} (Nujol Mull): 3084w, 1667s, 1610m, 1570m, 1384m, 1375m, 1343w, 1335w, 1300w, 1287m, 1230w, 1223w, 1175w, 1161w, 1102w, 1090w, 1082w, 1068w, 1025w, 1013w, 935m, 890w, 878w, 860w, 780s, 758s, 695s, 655m.

M/Z (%): 305 (M⁺, 16), 214 (37), 188 (52), 173 (100), 160 (18), 149 (31), 137 (19), 117 (82), 111 (41), 104 (61), 97 (64), 95 (55), 83 (62), 81 (63), 71 (52), 69 (94).

Aziridination of styrene using
3-amino-2-isopropylquinazolin-4(3H)-one (73)

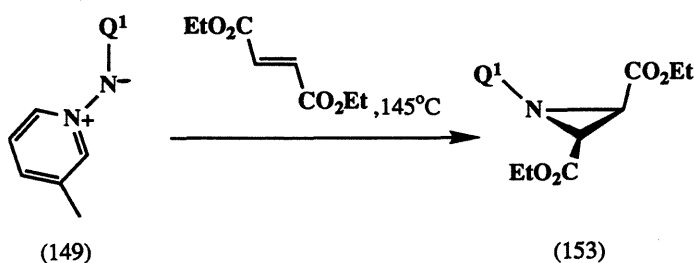


(154)

The general procedure (1) (see Chapter 1) was followed using N-aminoquinazolinone (73) (1.54g, 7.60mmol), LTA (3.57g, 8.07mmol) and styrene (2.37g, 23mmol) in dry dichloromethane (16ml). Trituration of the solid/oil

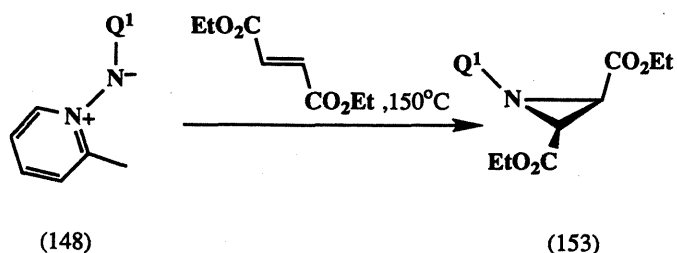
mixture obtained gave a solid which was filtered and crystallised from ethanol to give aziridine (154) as colourless crystals (1.74g, 75%), which were identical in all respects to that isolated previously (see above).

Reaction of pyridinium ylide (149) with diethyl fumarate



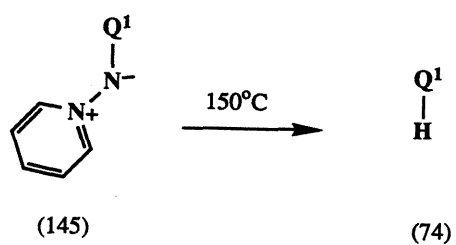
Freshly distilled diethyl fumarate (0.39g, 2.29mmol) was heated to $145^\circ C$ and pyridinium ylide (149) (0.22g, 0.76mmol) added continuously and in very small portions over 10 min. The mixture was heated at this temperature for a further 2 min. and then cooled. The bulk of the excess diethyl fumarate was removed by kugelrohr-distillation at $80^\circ C$ (bath temp.) and 0.1mmHg. Chromatography of the residue over silica, with ethyl acetate/light petroleum (1:4) as eluant, gave diethyl 1-(2-isopropylquinazolin-4(3H)-one-3-yl) aziridine 2,3-dicarboxylate (153), $R_f 0.23$, as a colourless oil (0.047g, 33%) which was identical to that isolated above.

Reaction of pyridinium ylide (148) with diethyl fumarate



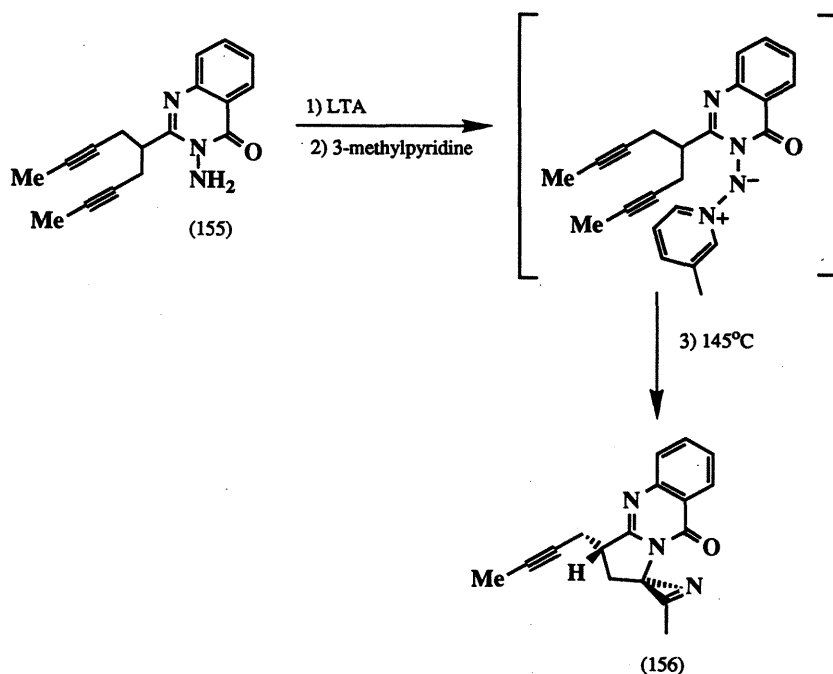
Freshly distilled diethyl fumarate (0.13g, 0.8mmol) was heated to 150°C and pyridinium ylide (148) (0.046g, 0.16mmol) added continuously and in very small portions over 10 min. The mixture was heated at this temperature for a further 2 min. and then cooled. Chromatography of the residue over silica, with ethyl acetate/light petroleum (1:4) as eluant, gave diethyl-1-(2-isopropylquinazolin-4(3H)-one-3-yl) aziridine-2,3-dicarboxylate (153), R_f 0.23, as a colourless oil (0.032g, 56%) identical to that isolated above. The proton n.m.r spectrum of the crude material before chromatography showed only the presence of aziridine (153) and residual diethyl fumarate; there was no evidence for polymerisation of diethyl fumarate.

Pyrolysis of pyridinium ylide (145)



Pyridinium ylide (145) (0.137g, 0.49mmol) was heated neat, in a round bottomed flask, to 150°C for approximately 20 seconds. After cooling, chromatography of the residue with ethyl acetate/light petroleum (1:2) as eluant, gave 2-isopropylquinazolin-4(3H)-one (74), R_f 0.21, as colourless crystals (0.058g, 63%) identical to that isolated previously, (see experimental relating to Chapter 1).

Intramolecular aziridination of
3-amino-2-(nona-2,7-diyn-5-yl)quinazolin-4(3H)-one (155)
mediated by ylide formation with 3-methylpyridine



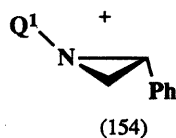
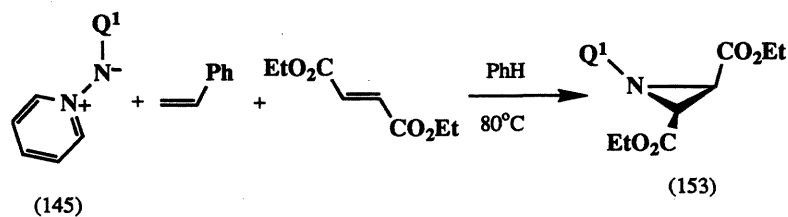
Powdered 3-amino-2-(nona-2,7-diyn-5-yl)quinazolin-4(3H)-one (155) (0.736g, 2.64mmol) (prepared by M. Grimshire⁶⁵) and LTA (1.24g, 2.81mmol) were added alternately and continuously in very small portions over 15 min. to a vigorously stirred solution of dry dichloromethane (10ml) and freshly distilled 3-methylpyridine (12.16g, 0.13mol) at room temperature. The mixture was then stirred for 5 min. before dichloromethane was removed at 30°C (bath temp.) and water pump pressure. The bulk of residual 3-methylpyridine

was then removed under reduced pressure at 60°C (bath temp.) and 0.1mmHg and the residue dissolved in dichloromethane (100ml), magnesium sulphate and activated charcoal added, the solution filtered and the solvent removed under reduced pressure to give an oil. A proton n.m.r. spectrum was obtained on this material (see below). The remaining oil was then heated directly at 145°C for 20 min. Chromatography of the solid/oil residue over silica, with ethyl acetate/light petroleum (1:4) as eluant, gave azirine (156), R_f 0.45, as colourless crystals (0.233g, 32%) which was identical with a sample previously prepared by M. J. Grimshire⁶⁵ from comparison of their high field n.m.r. spectra.

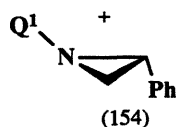
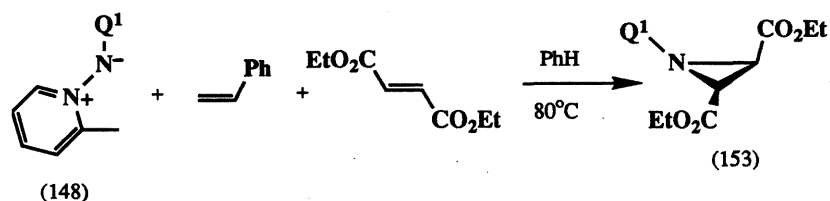
The proton n.m.r. spectrum of the crude intermediate pyridinium ylide showed no resonances due to the 2-H (δ 1.97, dd, J 13.7, 8.3Hz) or the azirine ring methyl (δ 2.79, s, CH_3) of azirine (156), so it could be concluded that intramolecular cyclisation had not occurred at this stage.

Competition experiments of pyridinium ylides (145)
and (148) with styrene and diethyl fumarate

REACTION 1



REACTION 2



Reaction 1: Pyridinium ylide (145) (0.041g, 0.15mmol), freshly distilled styrene (0.15g, 1.5mmol) and diethyl fumarate (0.25g, 1.5mmol) in benzene (3ml), were boiled under reflux under an argon atmosphere for 195 min. The solvent and the bulk of the olefins were removed by kugelrohr-distillation at 0.1mmHg and 70°C (bath temp.) and

a 300MHz proton n.m.r. spectrum of the crude mixture indicated an approximately 1.2:1 ratio of aziridines (153):(154) to be present using integration of the CH_3CHCH_3 heptet (δ 3.39) for aziridine (153) and the aziridine CH_{syn} to the quinazolinone (δ 3.21) in (154) for comparison. Also produced was 2-isopropylquinazolin-4(3H)-one (74) in an approximately 1:1 ratio of (74):(153), from integration of the CH_3CHCH_3 heptets from both (74) and (153).

Reaction 2: Pyridinium ylide (148) (0.065g, 0.22mmol), freshly distilled styrene (0.23g, 2.2mmol) and diethyl fumarate (0.38g, 2.2mmol) in benzene (3ml), were boiled under reflux under an argon atmosphere for 195 min. The solvent and the bulk of the olefins were removed by kugelrohr-distillation at 0.1mmHg and 70°C (bath temp.). A 300MHz proton n.m.r. spectrum of the crude mixture taken showed some polymerisation had taken place, partially obscuring the resonances which could have been used to determine the ratio of aziridines (153):(154). However, from integration of the CH_3CHCH_3 heptets as described above in this spectrum, the ratio of (74):(153) was approximately 1:10, that is, considerably less (74) was produced than in the reaction above.

APPENDICES

APPENDIX 1

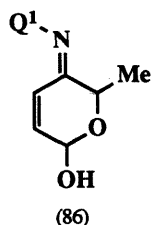
Determination of the Energy Barriers Separating Stereoisomers of (86), (93), (99) and (145)

Compounds (86), (93), (99) and (145) were found to exhibit variable temperature n.m.r. spectral behaviour. Using the expression

$$\Delta G^\ddagger = \frac{4.574 T_c}{1000} \times (9.9722 + \log_{10} T_c / \Delta \nu)$$

With ΔG^\ddagger in K cal mol⁻¹, where $\Delta \nu$ = frequency separation of coalescing signals (in Hz, measured at a temperature lower than T_c), and T_c = coalescence temperature (in degrees Kelvin) the above equation is valid for uncoupled signals.

Compound (86)

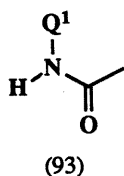


$$\Delta \nu = 73 \text{ Hz} \pm 5 \text{ Hz},$$

$$T_c = 273 \text{ K} \pm 2 \text{ K}.$$

At room temperature and 300MHz in the proton n.m.r. spectrum, broad signals are apparent for the dihydropyranone imine ring protons (CH_3CHO δ 5.12-5.21, J6.4Hz) and for the two methyl groups of the isopropyl group. At 233K and 300MHz one sees signals for the two rotamers of the dihydropyranone imine ring proton (CH_3CHO : Major rotamer δ 5.40, J6.4Hz; Minor rotamer δ 5.16, J6.4Hz) (Minor:Major rotamer ratio 1:2). These signals have coalesced at 273K. These values enable a free energy of activation $\Delta G^\ddagger = 14$ K cal mol⁻¹ to be estimated.

Compound (93)



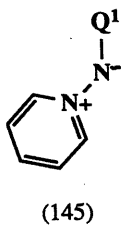
$$\Delta\nu=9.11\pm5\text{Hz},$$

$$T_c=256\pm2\text{K}.$$

At room temperature and 300MHz, the proton n.m.r. spectrum of compound (93) shows diastereotopic methyl groups of the isopropyl group (δ 1.22, 2xd, CH_3CHCH_3 , J6.7Hz).

These signals have not coalesced at 383K, although some broadening is apparent. Thus for N-N bond rotation $\Delta G^\ddagger > 20$ K cal mol⁻¹.

Compound (145)



$$\Delta\nu=68.50\pm5\text{Hz}, T_c=294\pm2\text{K for } \text{CH}_3\text{CHCH}_3$$

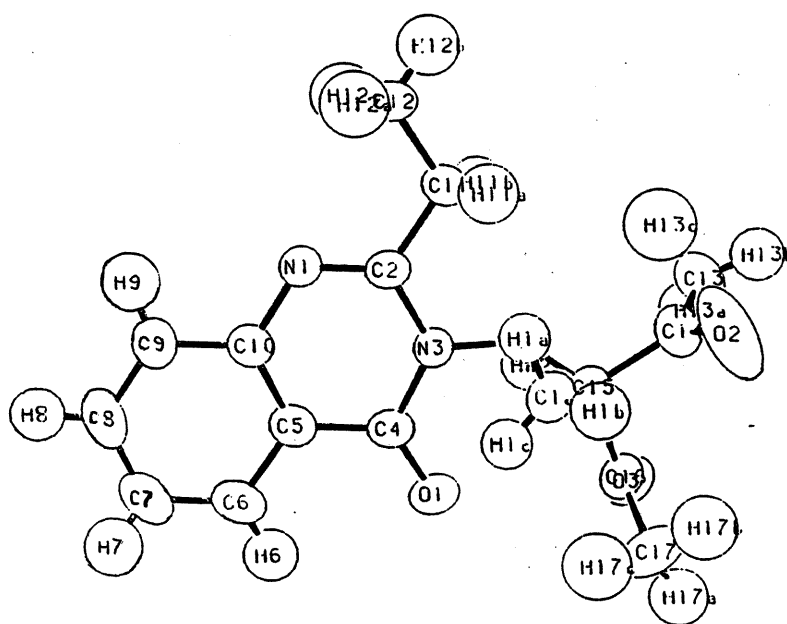
$$\Delta\nu=435.58\pm5\text{Hz}, T_c=256\pm2\text{K for pyrid. CH-2,6}.$$

At room temperature and 400MHz broad signals are apparent for the two ortho protons of the pyridinium ring (δ 7.70-7.75, pyrid. CH-2,6) and broad signals are evident

for the two methyl groups of the isopropyl group (δ 1.29, CH_3CHCH_3). At 236K and 400MHz, signals for the two methyl groups of the isopropyl group are visible (δ 1.20 and 1.37, CH_3CHCH_3). These signals coalesce at 294K and 400MHz. At 181K and 400MHz, signals for the two ortho protons of the pyridinium ring (pyrid CH -2,6) have separated (δ 7.17 and 8.26) but are still not sharp. Coalescence of these signals was seen at 256K and 400MHz. These values enable an approximate free energy of activation of $\Delta G^\ddagger=11$ K cal mol⁻¹ to be estimated for the $\text{N}-\text{N}$ bond rotation around the N^2-N^3 bond and $\Delta G^\ddagger=14$ K cal mol⁻¹ to be estimated for the process (either N^1-N^2 bond rotation or N^2 inversion) which exchanges the environments of the two methyl groups of the isopropyl group.

APPENDIX 2

Diketo-amine (67) X-Ray Crystal Structure Determination



Bond Angles (°) with Estimated Standard Deviations
in Parentheses

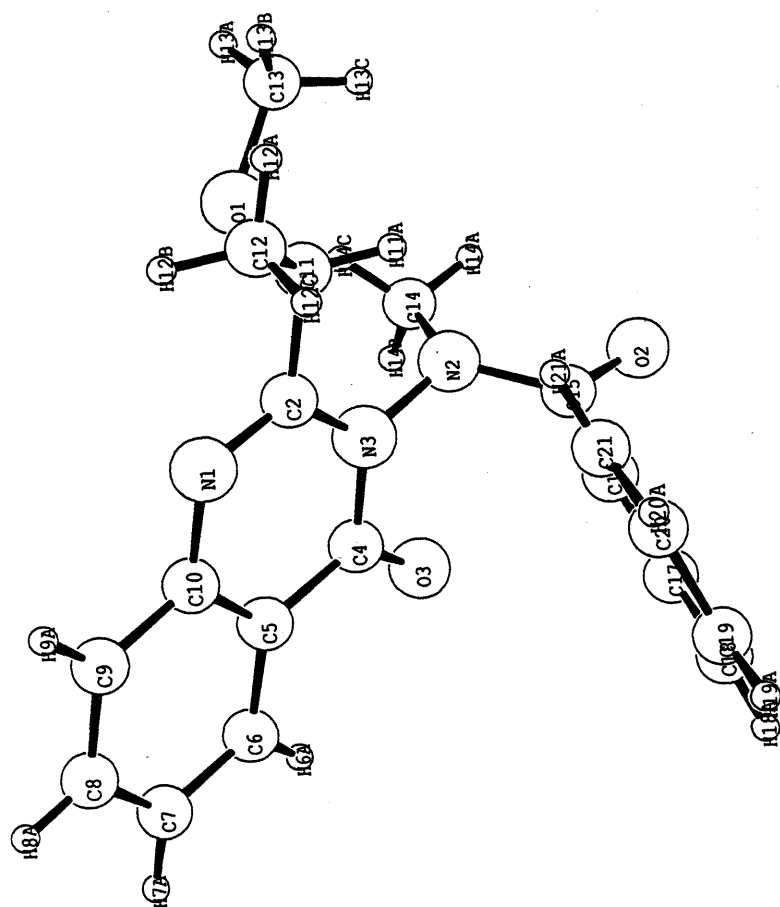
C(10)-N(1)-C(2)	117.9(2)
C(15)-N(2)-Hn(2)	112.2(15)
C(2)-N(3)-N(2)	117.9(1)
C(4)-N(3)-C(2)	123.2(2)
H(1)c-C(1)-H(1)a	111.9(20)
C(15)-C(1)-H(1)a	110.2(13)
C(15)-C(1)-H(1)c	111.3(14)
C(11)-C(2)-N(1)	120.4(2)
O(1)-C(4)-N(3)	120.3(2)
C(5)-C(4)-O(1)	125.7(2)
C(10)-C(5)-C(4)	119.2(2)
H(6)-C(6)-C(5)	117.1(15)
C(7)-C(6)-H(6)	123.2(15)
C(8)-C(7)-C(6)	120.4(2)
H(8)-C(8)-C(7)	120.7(14)
C(9)-C(8)-H(8)	118.4(14)
C(10)-C(9)-C(8)	120.1(2)
C(5)-C(10)-N(1)	122.6(2)
C(9)-C(10)-C(5)	119.0(2)
H(11)b-C(11)-C(2)	107.0(15)
C(12)-C(11)-C(2)	113.8(2)
C(12)-C(11)-H(11)b	112.2(15)
H(12)b-C(12)-C(11)	112.0(17)
H(12)c-C(12)-C(11)	108.8(20)
H(12)c-C(12)-H(12)b	99.6(25)
H(13)c-C(13)-H(13)a	111(3)
C(14)-C(13)-H(13)a	111.7(20)
C(14)-C(13)-H(13)c	107.1(21)
C(15)-C(14)-O(2)	119.0(2)
C(1)-C(15)-N(2)	113.2(2)
C(14)-C(15)-C(1)	110.1(2)
C(16)-C(15)-C(1)	113.1(2)
C(15)-C(16)-O(3)	119.2(2)
C(17)-C(16)-C(15)	118.5(2)
H(17)b-C(17)-C(16)	106.8(18)
H(17)c-C(17)-C(16)	104.7(22)
H(17)c-C(17)-H(17)b	111.2(27)

N(3)-N(2)-Hn(2)	103.1(16)
C(15)-N(2)-N(3)	114.8(1)
C(4)-N(3)-N(2)	118.8(1)
H(1)b-C(1)-H(1)a	102.9(21)
H(1)c-C(1)-H(1)b	107.5(22)
C(15)-C(1)-H(1)b	112.7(16)
N(3)-C(2)-N(1)	123.1(2)
C(11)-C(2)-N(3)	116.6(2)
C(5)-C(4)-N(3)	114.0(2)
C(6)-C(5)-C(4)	120.9(2)
C(10)-C(5)-C(6)	119.9(2)
C(7)-C(6)-C(5)	119.7(2)
H(7)-C(7)-C(6)	119.8(19)
C(8)-C(7)-H(7)	119.6(19)
C(9)-C(8)-C(7)	120.8(2)
H(9)-C(9)-C(8)	126.8(16)
C(10)-C(9)-H(9)	113.1(16)
C(9)-C(10)-N(1)	118.4(2)
H(11)a-C(11)-C(2)	106.8(18)
H(11)b-C(11)-H(11)a	106.9(23)
C(12)-C(11)-H(11)a	109.7(17)
H(12)a-C(12)-C(11)	110.8(19)
H(12)b-C(12)-H(12)a	116.4(23)
H(12)c-C(12)-H(12)a	108.5(27)
H(13)b-C(13)-H(13)a	112.0(25)
H(13)c-C(13)-H(13)b	102.5(26)
C(14)-C(13)-H(13)b	112.3(16)
C(13)-C(14)-O(2)	121.5(2)
C(15)-C(14)-C(13)	119.5(2)
C(14)-C(15)-N(2)	106.4(2)
C(16)-C(15)-N(2)	110.4(1)
C(16)-C(15)-C(14)	102.9(2)
C(17)-C(16)-O(3)	122.1(2)
H(17)a-C(17)-C(16)	106.9(16)
H(17)b-C(17)-H(17)a	107.9(23)
H(17)c-C(17)-H(17)a	118.6(26)

Bond Lengths (Å) with Estimated Standard Deviations
in Parentheses

C(2)-N(1)	1.286(2)
Hn(2)-N(2)	0.894(24)
C(15)-N(2)	1.492(2)
C(4)-N(3)	1.398(2)
C(14)-O(2)	1.199(3)
H(1)a-C(1)	0.978(24)
H(1)c-C(1)	0.936(23)
C(11)-C(2)	1.507(3)
C(6)-C(5)	1.411(3)
H(6)-C(6)	0.986(26)
C(7)-H(7)	0.891(29)
H(8)-C(8)	0.987(27)
H(9)-C(9)	0.990(29)
H(11)a-C(11)	0.94(3)
C(12)-C(11)	1.516(3)
H(12)b-C(12)	1.04(3)
H(13)a-C(13)	0.92(3)
H(13)c-C(13)	1.00(4)
C(15)-C(14)	1.553(3)
C(17)-C(16)	1.495(3)
H(17)b-C(17)	1.05(3)
C(10)-N(1)	1.398(2)
N(3)-N(2)	1.404(2)
C(2)-N(3)	1.392(2)
C(4)-O(1)	1.224(2)
C(16)-O(3)	1.210(2)
H(1)b-C(1)	0.97(3)
C(15)-C(1)	1.518(3)
C(5)-C(4)	1.449(3)
C(10)-C(5)	1.400(3)
C(7)-C(6)	1.367(4)
C(8)-C(7)	1.386(4)
C(9)-C(8)	1.375(3)
C(10)-C(9)	1.397(3)
H(11)b-C(11)	0.979(26)
H(12)a-C(12)	1.04(3)
H(12)c-C(12)	1.00(4)
H(13)b-C(13)	0.935(28)
C(14)-C(13)	1.491(4)
C(16)-C(15)	1.551(3)
H(17)a-C(17)	0.986(28)
H(17)c-C(17)	0.96(4)

X-Ray Crystal Data



Bond Angles (°) with Estimated Standard Deviations
in Parentheses

C(10)-N(1)-C(2)	119.1(2)
C(14)-N(2)-N(3)	115.4(1)
C(15)-N(2)-N(3)	116.8(1)
C(15)-N(2)-C(14)	119.3(2)
C(2)-N(3)-N(2)	120.0(1)
C(4)-N(3)-N(2)	116.6(1)
C(4)-N(3)-C(2)	123.4(1)
N(3)-C(2)-N(1)	122.3(2)
C(11)-C(2)-N(1)	119.6(2)
C(11)-C(2)-N(3)	118.1(1)
C(5)-C(4)-N(3)	114.0(2)
C(6)-C(5)-C(4)	120.7(2)
C(10)-C(5)-C(4)	119.0(2)
C(10)-C(5)-C(6)	120.3(2)
H(6)A-C(6)-C(5)	119.6(1)
C(7)-C(6)-C(5)	119.6(2)
C(7)-C(6)-H(6)A	120.9(1)
H(7)A-C(7)-C(6)	119.6(1)
C(8)-C(7)-C(6)	120.4(2)
C(8)-C(7)-H(7)A	120.0(1)
H(8)A-C(8)-C(7)	119.4(1)
C(9)-C(8)-C(7)	121.1(2)
C(9)-C(8)-H(8)A	119.4(1)
H(9)A-C(9)-C(8)	120.6(1)
C(10)-C(9)-C(8)	119.8(2)
C(10)-C(9)-H(9)A	119.6(1)
C(5)-C(10)-N(1)	122.4(2)
C(9)-C(10)-N(1)	118.9(2)
C(9)-C(10)-C(5)	118.8(2)
H(11)A-C(11)-C(2)	108.8(1)
C(12)-C(11)-C(2)	112.7(2)
C(12)-C(11)-H(11)A	109.2(1)
H(12)A-C(12)-C(11)	110.3(1)
H(12)B-C(12)-C(11)	109.2(1)
H(12)B-C(12)-H(12)A	109.5(0)
H(12)C-C(12)-C(11)	108.9(1)
H(12)C-C(12)-H(12)A	109.5(0)
H(12)C-C(12)-H(12)B	109.5(0)
H(13)B-C(13)-H(13)A	109.5(0)

H(13)C-C(13)-H(13)A 109.5(0)
 H(13)C-C(13)-H(13)B 109.5(0)
 H(14)A-C(14)-N(2) 109.6(1)
 H(14)B-C(14)-N(2) 109.3(1)
 H(14)B-C(14)-H(14)A 109.5(0)
 H(14)C-C(14)-N(2) 109.5(1)
 H(14)C-C(14)-H(14)A 109.5(0)
 H(14)C-C(14)-H(14)B 109.5(0)
 C(16)-C(15)-N(2) 119.0(2)
 C(17)-C(16)-C(15) 118.0(2)
 C(21)-C(16)-C(15) 122.0(2)
 C(21)-C(16)-C(17) 119.7(2)
 H(17)A-C(17)-C(16) 119.9(1)
 C(18)-C(17)-C(16) 120.1(3)
 C(18)-C(17)-H(17)A 120.0(2)
 H(18)A-C(18)-C(17) 120.8(2)
 C(19)-C(18)-C(17) 120.6(3)
 C(19)-C(18)-H(18)A 118.6(2)
 H(19)A-C(19)-C(18) 119.9(2)
 C(20)-C(19)-C(18) 120.2(3)
 C(20)-C(19)-H(19)A 119.9(2)
 H(20)A-C(20)-C(19) 119.5(2)
 C(21)-C(20)-C(19) 119.5(3)
 C(21)-C(20)-H(20)A 120.9(2)
 C(20)-C(21)-C(16) 119.8(2)
 H(21)A-C(21)-C(16) 119.8(1)
 H(21)A-C(21)-C(20) 120.4(2)
 C(13)-O(1)-C(11) 113.3(2)
 O(3)-C(4)-N(3) 120.0(2)
 C(5)-C(4)-O(3) 126.1(2)
 C(2)-C(11)-O(1) 104.6(1)
 H(11)A-C(11)-O(1) 108.6(1)
 C(12)-C(11)-O(1) 112.8(2)
 H(13)A-C(13)-O(1) 109.9(1)
 H(13)B-C(13)-O(1) 109.3(1)
 H(13)C-C(13)-O(1) 109.3(1)
 O(2)-C(15)-N(2) 119.5(2)
 C(16)-C(15)-O(2) 121.5(2)

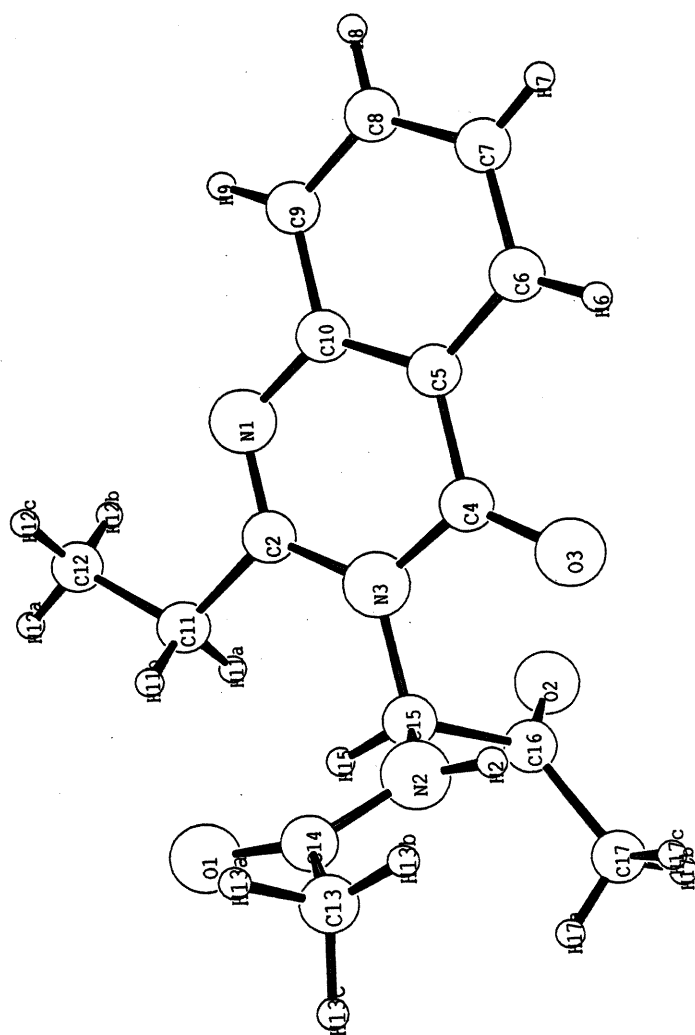
Bond Lengths (Å) with Estimated Standard Deviations
in Parentheses

C(2)-N(1)	1.272(2)
C(10)-N(1)	1.380(2)
N(3)-N(2)	1.394(2)
C(14)-N(2)	1.452(2)
C(15)-N(2)	1.370(2)
C(2)-N(3)	1.379(2)
C(4)-N(3)	1.393(2)
C(11)-C(2)	1.509(2)
C(5)-C(4)	1.440(3)
C(6)-C(5)	1.391(3)
C(10)-C(5)	1.387(3)
C(7)-C(6)	1.358(3)
C(8)-C(7)	1.360(3)
C(9)-C(8)	1.370(3)
C(10)-C(9)	1.384(3)
C(12)-C(11)	1.481(3)
C(16)-C(15)	1.476(3)
C(17)-C(16)	1.381(3)
C(21)-C(16)	1.380(3)
C(18)-C(17)	1.349(4)
C(19)-C(18)	1.364(4)
CC(21)-C(20)	1.371(3)
C(11)-O(1)	1.415(2)
C(13)-O(1)	1.406(2)
C(15)-O(2)	1.203(2)
C(4)-O(3)	1.215(2)

All hydrogen atoms were included in calculated positions with C-H = 0.96Å

Rearranged Keto-amide (109) - X-Ray Crystal Structure

Data



Bond Angles (°) with Estimated Standard Deviations
in Parentheses

C(10)-N(1)-C(2)	118.0(3)
C(15)-N(2)-C(14)	121.0(3)
C(4)-N(3)-C(2)	121.2(3)
C(15)-N(3)-C(2)	124.6(2)
C(15)-N(3)-C(4)	114.2(2)
N(3)-C(2)-N(1)	124.4(3)
C(11)-C(2)-N(1)	118.3(3)
C(11)-C(2)-N(3)	117.3(3)
O(3)-C(4)-N(3)	119.1(3)
C(5)-C(4)-N(3)	114.9(3)
C(5)-C(4)-O(3)	126.1(3)
C(6)-C(5)-C(4)	120.5(3)
C(10)-C(5)-C(4)	119.5(3)
C(10)-C(5)-C(6)	120.0(3)
C(7)-C(6)-C(5)	118.9(3)
C(8)-C(7)-C(6)	121.1(3)
C(9)-C(8)-C(7)	121.4(3)
C(10)-C(9)-C(8)	118.7(3)
C(5)-C(10)-N(1)	122.0(3)
C(9)-C(10)-N(1)	118.1(3)
C(9)-C(10)-C(5)	119.9(3)
C(12)-C(11)-C(2)	112.8(3)
O(1)-C(14)-N(2)	122.4(3)
C(13)-C(14)-N(2)	114.8(3)
C(13)-C(14)-O(1)	122.9(3)
N(3)-C(15)-N(2)	113.5(3)
C(16)-C(15)-N(2)	113.6(3)
C(16)-C(15)-N(3)	110.1(2)
C(15)-C(16)-O(2)	118.3(3)
C(17)-C(16)-O(2)	122.4(3)
C(17)-C(16)-C(15)	119.2(3)
C(14)-N(2)-H(2)	116.9(22)
C(15)-N(2)-H(2)	122.1(22)
H(6)-C(6)-C(5)	120.5(2)

C(7)-C(6)-H(6)	120.5(2)
H(7)-C(7)-C(6)	119.4(2)
C(8)-C(7)-H(7)	119.4(2)
H(8)-C(8)-C(7)	119.3(2)
C(9)-C(8)-H(8)	119.3(2)
H(9)-C(9)-C(8)	120.7(2)
C(10)-C(9)-H(9)	120.7(2)
H(11)a-C(11)-C(2)	108.6(2)
H(11)b-C(11)-C(2)	108.6(2)
H(11)b-C(11)-H(11)a	109.5(0)
C(12)-C(11)-H(11)a	108.6(2)
C(12)-C(11)-H(11)b	108.6(2)
H(12)a-C(12)-C(11)	109.5(2)
H(12)b-C(12)-C(11)	109.5(2)
H(12)b-C(12)-H(12)a	109.5(0)
H(12)c-C(12)-C(11)	109.5(2)
H(12)c-C(12)-H(12)a	109.5(0)
H(12)c-C(12)-H(12)b	109.5(0)
H(13)b-C(13)-H(13)a	111(5)
H(13)c-C(13)-H(13)a	111(4)
H(13)c-C(13)-H(13)b	115(4)
C(14)-C(13)-H(13)a	100.8(29)
C(14)-C(13)-H(13)b	113(3)
C(14)-C(13)-H(13)c	105.6(26)
H(15)-C(15)-N(2)	109.4(18)
H(15)-C(15)-N(3)	105.5(18)
C(16)-C(15)-H(15)	104.1(18)
H(17)a-C(17)-C(16)	111(3)
H(17)b-C(17)-C(16)	114(3)
H(17)b-C(17)-H(17)a	111(4)
H(17)c-C(17)-C(16)	114(3)
H(17)c-C(17)-H(17)a	97(4)
H(17)c-C(17)-H(17)b	109(4)

Bond Lengths (Å) with Estimated Standard Deviations
in Parentheses

C(2)-N(1)	1.301(5)
C(10)-N(1)	1.382(4)
C(14)-N(2)	1.354(4)
C(15)-N(2)	1.440(4)
C(2)-N(3)	1.416(4)
C(4)-N(3)	1.391(4)
C(15)-N(3)	1.500(4)
C(14)-O(1)	1.230(4)
C(16)-O(2)	1.204(4)
C(4)-O(3)	1.264(4)
C(11)-C(2)	1.515(4)
C(5)-C(4)	1.466(5)
C(6)-C(5)	1.417(4)
C(10)-C(5)	1.417(5)
C(7)-C(6)	1.403(5)
C(8)-C(7)	1.391(6)
C(9)-C(8)	1.390(5)
C(10)-C(9)	1.434(5)
C(12)-C(11)	1.536(5)
C(14)-C(13)	1.523(5)
C(16)-C(15)	1.555(5)
C(17)-C(16)	1.522(5)
H(2)-N(2)	1.01(4)
H(13)a-C(13)	0.97(6)
H(13)b-C(13)	0.93(5)
H(13)c-C(13)	1.11(5)
H(15)-C(15)	0.96(3)
H(17)a-C(17)	1.01(6)
H(17)b-C(17)	1.04(6)
H(17)c-C(17)	1.01(5)

REFERENCES

(1) For excellent reviews of the stereostructure and chirality of allenes see: Runge, in Landor, "The Chemistry of the Allenes," vol.3, pp579-678, Academic Press, New York, 1982, and in Patai, "The Chemistry of Ketones, Allenes, and Related Compounds," pt.1, pp99-154, Wiley, New York, 1980.

(2) M. Nakagawa, K. Shingu, and K. Naemura, Tetrahedron Letters., 1961, 802.

(3) For pertinent reviews see (a) R. Noyori and H. Takaya, Acc. Chem. Res., 1990, 23, 345; (b) R. Noyori, Chem. Soc. Rev., 1989, 18, 187; (c) T. Ohta, H. Takaya, M. Kitamura, K. Nagai and R. Noyori, J. Org. Chem., 1987, 52, 3174.

(4) For a review, see M. Oki, Top. Stereochem, 1983, 14, 1-81.

(5) R. W. Stoughton and R. Adams, J. Am. Chem. Soc., 1932, 54, 4426.

(6) R. S. Atkinson and B. D. Judkins, J. Chem. Soc. Perkin Trans 1., 1981, 1309.

(7) M. Raban and D. Kost, Tetrahedron, 1984, 40, 3345-3381.

(8) F.A.L. Anet, R. D. Trepka and D. J. Cram, J. Am. Chem. Soc., 1967, 89, 357.

(9) (a) D. Kost,, W. A. Stacer and M. Raban, J. Am. Chem. Soc., 1972, 94, 3233, (b) M. Raban and D. Kost, J. Am. Chem. Soc., 1972, 94, 3234, (c) M. Raban and D. Kost, J. Am. Chem. Soc., 1976, 98, 8333.

(10) J.M. Lehn and J. Wagner, J. Chem. Soc. Chem. Commun., 1968, 1298.

(11) M. Raban and G. Yamamoto, J. Am. Chem. Soc., 1979,

101, 5890.

(12) M. Raban, E. H. Carlson, S. K. Lauderbach, J. M. Moldowan and F. B. Jones, J. Am. Chem. Soc., 1972, 94, 2738.

(13) (a) F. Montenari, I. Moretti and G. Torre, Chem. Commun., 1969, 1086, (b) A. Mannschreck, Liebigs Ann., 1969, 727, 224.

(14) J. Lee and K. G. Orrell, Trans. Faraday Soc., 1964, 61, 2342.

(15) Y. Shvo in 'The Chemistry of the Hydrazo, Azo and Azoxy groups'. ed. S. Patai, Inter-science, New York, 1974, part 2.

(16) S. M. Verma and C. K. Rao Tetrahedron, 1972, 28, 5029.

(17) S. M. Verma and R. M. Sing, J. Org. Chem., 1975, 40, 897.

(18) S. M. Verma and O. S. Rao, Aust. J. Chem., 1963, 26, 1973.

(19) S. M. Verma and R. Prasad, J. Org. Chem., 1973, 38, 1004.

(20) S. M. Verma and R. Prasad, J. Org. Chem., 1973, 38, 3745.

(21) C. Roussel, M. Adjimi, A. Chemlal and A. Djafri, J. Org. Chem., 1988, 53, 5076.

(22) J. M. Mellor and N. M. Smith, J. Chem. Soc. Perkin Trans 1., 1984, 2927.

(23) H. B. Henbest and R. A. L. Wilson, J. Chem. Soc., 1957, 1958.

(24) K. B. Sharpless and T. R. Verhoeven, Aldrich Chim.

Acta., 1979, 12, 63; K. B. Sharpless et al, Pure Appl. Chem., 1983, 55, 589; S. S. Woodward, M. G. Finn, and K. B. Sharpless, J. Amer. Chem. Soc., 1991, 113, 106, and refs. therein.

(25) K. B. Sharpless and T. Katsuki, J. Am. Chem. Soc., 1980, 102, 5974 and refs. therein.

(26) D. A. Evans, M. M. Faul, and M. T. Bilodeau, J. Org. Chem., 1991, 56, 6744; J-P. Mahy, G. Bedi, P. Battioni, and D. Mansuy, J. Chem. Soc. Perkin Trans. 2., 1988, 1517; R. S. Atkinson, M. Lee, and J. R. Malpass, J. Chem. Soc. Chem Commun., 1984, 919; R. S. Atkinson and B. D. Judkins, J. Chem Soc. Perkin Trans 1., 1981, 2615; J. C. Bottaro, J. Chem Soc. Chem Commun., 1980, 560; W. Lwowski and O. Subba Rao, Tetrahedron Letters, 1980, 727; N. Furukawa, T. Yoshimura, M. Ohtsu, T. Akasaka, and S. Oae, Tetrahedron, 1980, 36, 73.

(27) D. J. Anderson, T. L. Gilchrst, D. C. Horwell and C. W. Rees, J. Chem. Soc (C), 1970, 576.

(28) R. S. Atkinson and C. W. Rees, J. Chem. Soc (C), 1969, 772.

(29) R. S. Atkinson in 'Azides and Nitrenes', ed E. F. V. Scriven, Academic Press, Orlando, Florida, 1984.

(30) R. S. Atkinson and R. Martin, J. Chem. Soc., Chem. Commun., 1974, 386.

(31) R. S. Atkinson and J. R. Malpass, J. Chem. Soc. Perkin Trans. 1., 1977, 2242.

(32) G. Tughan, Ph.D. Thesis, Leicester University, 1987.

(33) M. J. Grimshire, Ph.D. Thesis, Leicester University,

1986.

(34) B. J. Kelly, Ph.D. Thesis, Leicester University, 1989.

(35) R. S. Atkinson and G. Tughan, J. Chem. Soc. Perkin Trans 1., 1987, 8303.

(36) R. S. Atkinson and G. Tughan, J. Chem. Soc. Perkin Trans 1., 1987, 2797.

(37) R. S. Atkinson and B. J. Kelly, J. Chem. Soc. Perkin Trans. 1., 1989, 1627.

(38) P. D. Bartlett, Rec. Chem. Progr., 1950, 11, 47; G. Berti in 'Topics in Stereochemistry,' eds. N. L. Allinger and E. L. Eliel, Wiley-Interscience, New York, Vol 7, 1973.

(39) P. Chamberlain, M. L. Roberts and G. H. Whitham, J. Chem. Soc. (b)., 1970, 1374.

(40) H. Person, K. Luanglath and A. Foucaud, Tetrahedron Letters, 1977, 221-224.

(41) D. Enders in 'Asymmetric Synthesis'.ed. J. D. Morrison, Academic Press, New York, 1984, vol. 3.

(42) E. J. Corey, R. J. McCaully and H. S. Sachdev, J. Am. Chem. Soc., 92, 1970, 2476.

(43) M. Bassetti, G. Cerichelli and B. Floris, Tetrahedron, 1988, 44, 2997.

(44) J. R. Malpass and R. S. Atkinson, unpublished results, Leicester University.

(45) R. S. Atkinson and B. J. Kelly J. Chem. Soc. Perkin Trans. 1., 1989, 1515.

(46) T. Honda, Y. Kobayashi and M. Tsubuki, Tetrahedron Letters, 1990, 4891.

(47) W. B. Jennings and V. E. Wilson in 'Acyclic

Organonitrogen Stereodynamics,' eds. J. B. Lambert and Y. Takeuchi, VCH Publishers, New York, 1992, pp. 177-223.

(48) M. D. Wunderlich, L. K. Leung, J. A. Sandberg, K. D. Meyer and C. H. Yoder, J. Amer. Chem. Soc., 1978, 100, 1500.

(49) W. B. Jennings and B. M. Saket, J. Chem. Soc. Perkin Trans. 2, 1985, 1005.

(50) N. L. Allinger, G. L. Wang and B. D. Dewhurst, J. Org. Chem., 39, 1974, 1730.

(51) R. N. Butler, Chem. Rev., 1984, 84, 249.

(52) T. Sasaki, K. Mori and M. Ohno, Synthesis, 1985, 280.

(53) T. Sakahuru and M. Takana, J. Chem. Soc. Chem. Commun., 1985, 1309.

(54) M. A. Loreto, L. Pellacani and P. A. Tardella, J. Chem. Res. (S), 1988, 304; M. Mitani, O. Tachizawa, H. Takeuchi and K. Koyama, Chem. Lett., 1987, 1029; S. Fioravanti, M. A. Loreto, L. Pellacani and P. A. Tardella, Tetrahedron Asymm., 1990, 931.

(55) C. Gerrari, L. Colombo and G. Bertolini, J. Am. Chem. Soc., 1986, 108, 6394; D. A. Evans, T. C. Britton, R. L. Dorow and J. F. Dellaria, ibid., 1986, 108, 6395; L. A. Trimble and J. C. Vederas, ibid., 1986, 108, 6397; W. Oppolzer and R. Moretti, Helv. Chim. Acta., 1986, 69, 1923.

(56) R. S. Atkinson, B. J. Kelly and J. A. Williams, Tetrahedron., 1992, 48, 7713.

(57) P. S. Clezy, A. J. Liepa, A. W. Nichol and G. A. Smythe, Aust. J. Chem., 1970, 23, 589.

(58) (a) H. H. Wasserman and T. A. Kelly, Tetrahedron

Letters, 1989, 7117; (b) H. H. Wasserman and L. J. Lombardo, Tetrahedron Letters, 1989, 1725; (c) H. H. Wasserman, R. Frechette, T. Oida and J. H. van Duzer, J. Org. Chem., 1989, 54, 6012; (d) H. H. Wasserman, M. Thyse, S. Wolff and V. Rusiecki, Tetrahedron Letters, 1988, 4973; (e) H. H. Wasserman and R. M. Amici, J. Org. Chem., 1989, 54, 5843; (f) H. H. Wasserman, S. L. Henke, P. Luce and E. Nakanishi, J. Org. Chem., 1990, 55, 5821; (g) H. H. Wasserman, J. D. Cook and C. B. Vu, J. Org. Chem., 1990, 55, 1701; (h) H. H. Wasserman and Gee-Hong Kuo, Tetrahedron Letters, 1989, 873; (i) H. H. Wasserman, R. Amici, R. Frechette and J. H. van Duzer, Tetrahedron Letters, 1989, 869.

(59) E. Philipps and A. Uhi, Monatshefte, 1910, 34, 721, 725.

(60) O. Daihei and S. Kotaro, Chem. Abs., 59, 5016d.

(61) R. A. Abramovitch and T. Takaya, J. Org. Chem., 1972, 37, 2022.

(62) T. Tsuchiga, M. Enkaku, J. Kurita and H. Sawanishi, J. Chem. Soc. Chem. Commun., 1979, 534.

(63) J. M. Cassel and J. Streith, Angew. Chem. Internat. Ed., 1968, 7, 129.

(64) J. Martin, O. Meth-Cohn and H. Suschitzky, J. Chem. Soc. Perkin Trans 1., 1974, 2451.

(65) R. S. Atkinson and M. J. Grimshire, J. Chem. Soc. Perkin Trans. 1., 1986, 1215.

(66) R. S. Atkinson, D. W. Jones and B. J. Kelly J. Chem. Soc. Perkin Trans 1., 1991, 1344.

- (67) R. S. Atkinson, M. Lee and J. R. Malpass, J. Chem. Soc. Chem. Commun., 1984, 919.
- (68) L. Hoesch, Helv. Chim. Acta., 1981, 64, 890.
- (69) L. Hoesch and T. H. Briers, Helv. Chim. Acta., 1981, 64, 905.
- (70) L. Hoesch, Helv. Chim. Acta., 1981, 64, 38.
- (71) L. Hoesch and B. Kopple, Helv. Chim. Acta., 1981, 64, 864.
- (72) W. C. Still, M. Kahn and A. Mitra, J. Org. Chem., 1978, 43, 2923.
- (73) R. Soliman and F. S. G. Soliman, Synthesis, 1979, 803.
- (74) R. F. Smith and R. A. Kent, J. Org. Chem., 1965, 30, 1312.
- (75) M. P. Coogan, unpublished results, Leicester University.
- (76) R. Levine, J. A. Conroy, J. T. Adams and C. R. Hauser, J. Am. Chem. Soc., 1945, 67, 1510.
- (77) C. W. Shoppee and D. Stevenson, J. Chem. Soc. Perkin Trans 1., 1972, 3015 and references therein.
- (78) Dictionary of Organic Compounds, 5, 4889.
- (79) C. Ainsworth, J. Am. Chem. Soc., 1958, 80, 967.
- (80) R. H. Wiley and O. Borum, Org. Synthesis, 1953, 33, 5.
- (81) H. Fischer and P. Halbig, Liebigs Ann., 1926, 447, 123.