University of Leicester

Intramolecular Reactions of 3-Acetoxy-aminoquinazolin-4(3*H*)-ones with Aromatic Rings

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by

Rawdah Q. Lamphon M.Sc.

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789 East Eisenhower Parkway
P.O. Box 1346
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ABSTRACT

The intramolecular reactions of 3-acetoxyaminoquinazolin-4(3*H*)-ones (QNHOAc) with aromatic rings linked to the 2-position of the quinazolinone (Q) ring have been studied.

It has been shown previously that the reactivity of QNHOAc compounds as aziridinating agents for less reactive double bonds is increased in the presence of trifluoracetic acid (TFA). Similarly (Chapter 2), reaction of the tethered aromatic ring with the acetoxyamino nitrogen occurred only in the presence of TFA in QNHOAc compounds with 4-methoxy-phenyl-ethyl or -propyl and phenoxy-methyl or -ethyl as the (Q)2-substituent. The major product in each case was that from *ortho*-substitution, formally by $Q\overset{+}{N}H$, on the aromatic ring. In the absence of TFA only the corresponding 3*H*-quinazolinone (QH) was obtained.

In three cases, with 2-chloro-, 2-bromo or 2,4-dibromophenoxymethyl as the QNHOAc 2-substituent, no reaction products resulting from attack on the aromatic ring were obtained even in the presence of TFA. It was surprising, therefore, that attack on the aromatic ring took place with 2,4-dichlorophenoxyethyl or 1-(2,4-dichlorophenoxy)ethyl as the (Q)2-substituent (in QNHOAcs **190** and **212**, respectively) in the presence or absence of TFA. In the absence of TFA, the major products from **190** and **212** were analogous 4,6-dichloroazepines believed to arise by aziridination of the 1,6-double bond of the aromatic ring. In the presence of TFA, the major products are related but not analogous azepinones and either 2-(2-nitroso-4-chlorophenoxymethyl-3*H*-quinazolin-4(3*H*)-one (from **190** or the product from formal insertion into the *ortho*-carbon chlorine bond (from **212**) all of which, it is suggested, are derived by aziridination of the 1,2-double bond of the 2,4-dichlorophenyl ring. Thus addition of TFA to the reaction medium brings about a change in the regioselectivity of the intramolecular aziridination.

In Chapter 3, the synthesis and intramolecular reactions of a further seven QNHOAc compounds with α- or β-naphthylalkyl or α- or β-naphthoxymethyl as 2-substituents were examined as model compounds for the synthesis of enantiopure 1,2,3,4-substituted naphthalenes.

In three cases the intermediate aziridines were isolated and in one of these cases the unreacted (styrenoid) double bond was further aziridinated intermolecularly. The QNHOAc compound having a 2-[1-(6-methoxy-α-naphthyl)ethyl] substituent, derived from (*S*)-Naproxen, underwent aziridination of the naphthalene 1,2-bond highly diastereoselectively.

In the reactions of the QNHOAc compounds containing at least three atoms in the tether with the aromatic ring, the double bond that is attacked is often a more distant one which allows a precedented attractive interaction between the Q ring and a non-reacting double bond of the aromatic ring in the reaction transition state.

Finally in Chapter 4, the reaction conditions using TFA giving rise to the highest yields in the intramolecular reaction in Chapter 2 were applied to the intermolecular reaction of xylenes and toluene with 3-acetoxyamino-2-ethylquinazolin-4(3*H*)-one. In the case of *p*-xylene, one of the products was identical with that obtained from *m*-xylene *i.e.* a methyl migration is involved.

STATEMENT

The accompanying thesis submitted for the degree of Doctor of Philosophy entitled 'Intramolecular Reactions of 3-Acetoxyaminoquinazolin-4(3*H*)-ones with Aromatic Rings' is based on work conducted by the author in the Department of Chemistry of the University of Leicester (United Kingdom) and in the Department of Education, King Abdulaziz University, Medina (Saudi Arabia) in the period 1990-2002.

All the work in this thesis is original unless otherwise acknowledged by references. None of the work has been submitted for any other degree.

Signed: Rawdah ..... Date: November 2002

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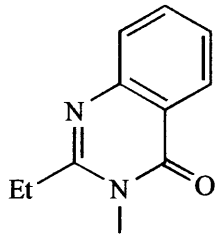
I feel especially indebted to my mother, my brother Mohamed Lemfon, my brother Ali Lemfon who cheerfully accompanied me all over my scientific journey, also to my husband, El sayed Mahmoud Abdul Hai, for his patience, may Allah safe them all.

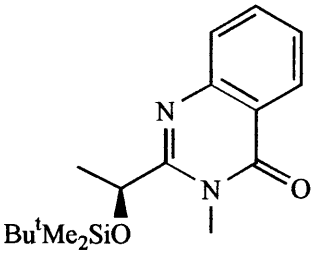
ABBREVIATIONS

bicarbonate	=	saturated aqueous sodium hydrogen carbonate
eq.	=	equivalent
ether	=	diethyl ether
HMDS	=	hexamethyldisilazane
LDA	=	lead di-acetate
LTA	=	lead tetra-acetate
mp	=	melting point
Q	=	quinazolin-4(3*H*)-one
TFA	=	trifluoroacetic acid
Ph	=	phenyl

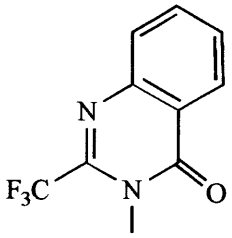
Throughout this thesis



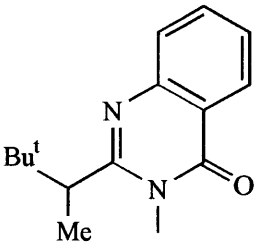
≡ Q^1



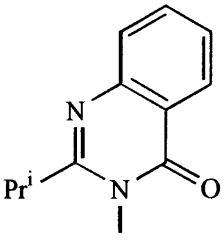
≡ Q^2



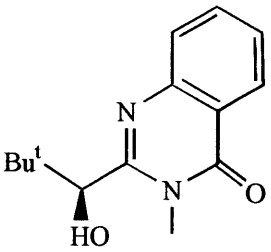
≡ Q^3



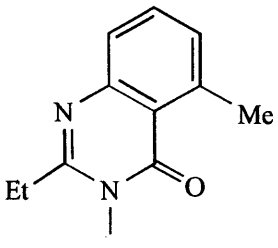
≡ Q^4



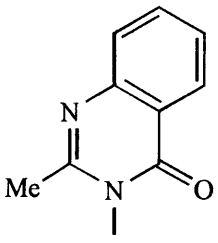
≡ Q^5



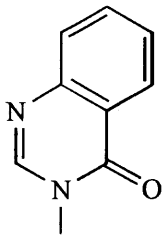
≡ Q^6



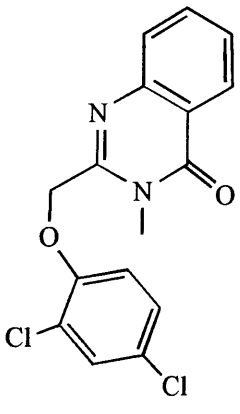
≡ Q^7



≡ Q^8



≡ Q^9



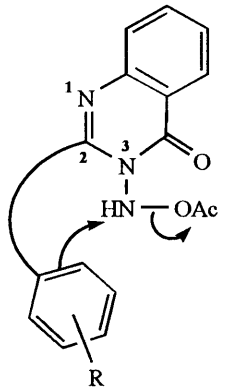
≡ Q^{10}

CONTENTS

CHAPTER 1

Introduction

Most of the research described in this thesis examines the reactions of an electrophilic nitrogen bearing a leaving group (acetoxy) at the 3-position of a quinazolinone (Q) ring with various benzenoid aromatic rings tethered to the 2-position of the Q-ring by alkyl or oxyalkyl chains **1**.

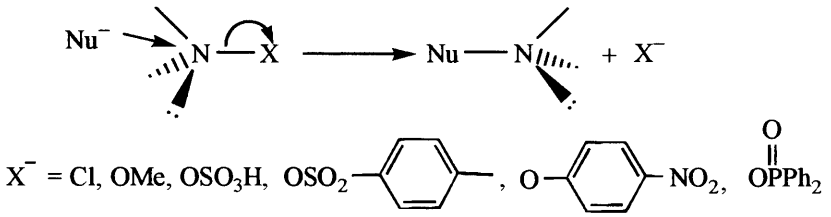


1

This Introduction will, therefore, have three major themes: i) a consideration of various electrophilic nitrogen species and, in particular, their reactions with aromatic rings; ii) the presently known chemistry of 3-acetoxyaminoqunazolinones (QNHOAc) and iii) the advantages of intramolecular reactions and design of the tether.

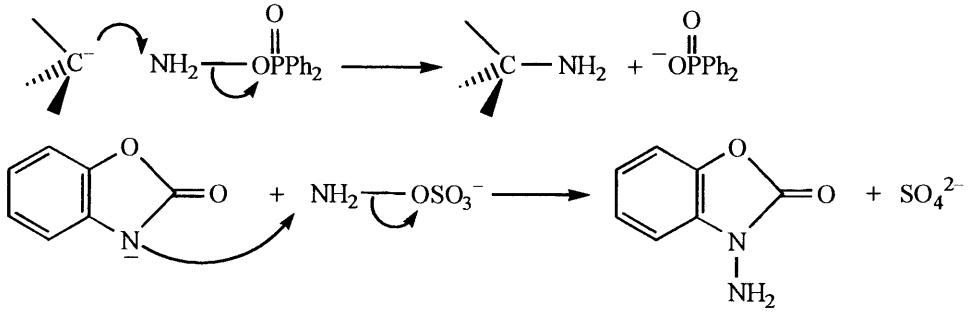
1.1 Electrophilic nitrogen: reactions with benzenoid aromatic rings

The presence of a substituent on sp^3-hybridised nitrogen more electronegative than nitrogen – usually oxygen or halogen – makes the nitrogen susceptible to nucleophilic attack.[1,2]



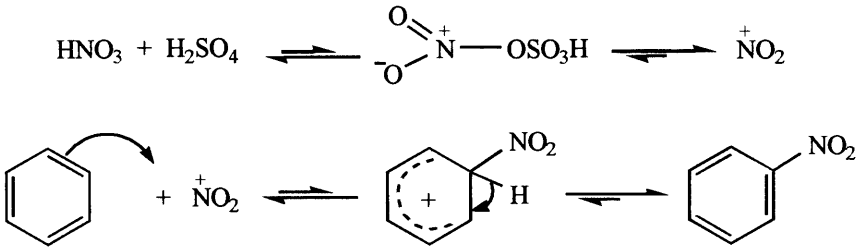
Scheme 1

As indicated in Scheme 1, nucleophilic attack appears to take place with inversion of configuration. However, whereas in S_N2 reactions at sp^3-hybridised carbon, the configurations of starting material and product can be determined, this is not at present possible for the reaction in Scheme 1 because of the low barrier to *N*-inversion in the starting material and product; inversion of configuration in the reaction can only be shown indirectly.[3] The nucleophilic component may be a carbanion or a (anionic) heteroatom including nitrogen, *i.e.* this is a means by which *N–N* bonds can be made[4,5] (Scheme 2).



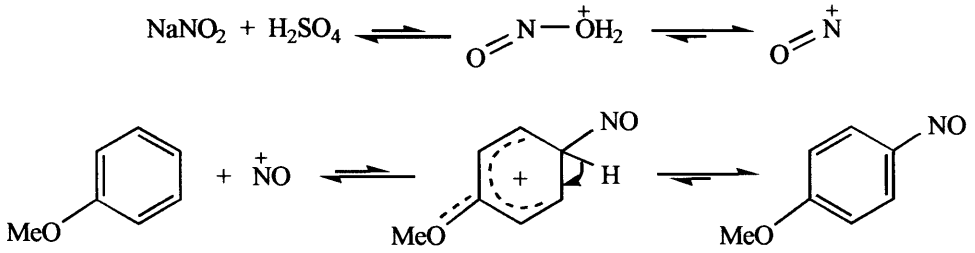
Scheme 2

The most familiar source of sp^2-hybridised electrophilic nitrogen is the nitronium ion NO_2^+, produced by dehydration of nitric acid, *in situ*, by the action of concentrated sulphuric acid; it is the nitronium ion that is the reactive species in the familiar electrophilic aromatic substitution of benzene (Scheme 3).



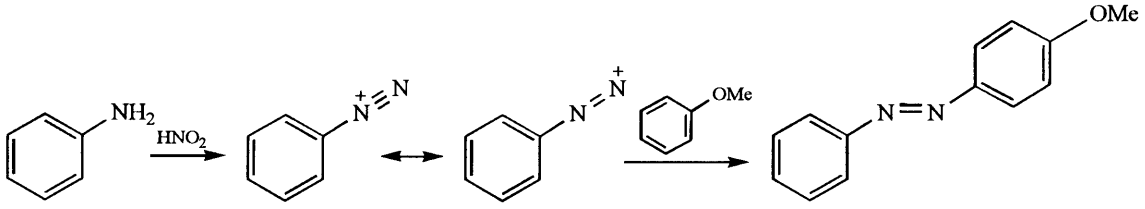
Scheme 3

Similarly, dehydration of nitrous acid generates the nitrosonium ion although a much weaker acid is required than for generation of the nitronium ion above; the nitrosonium ion is correspondingly less reactive and only activated aromatic rings – those bearing electron-donating groups – react in acceptable yields (Scheme 4).



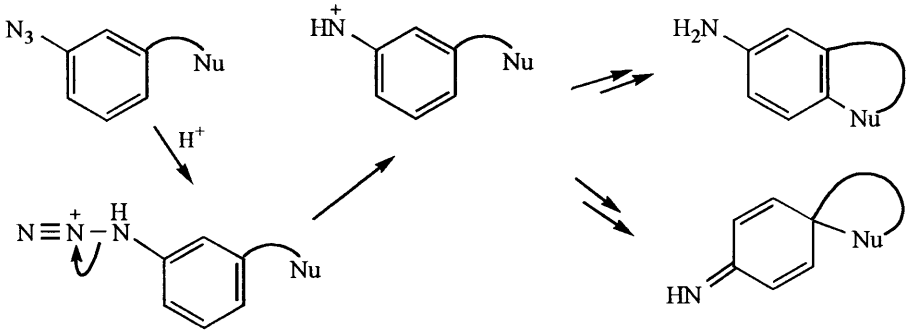
Scheme 4

Diazonium salts contain a more resonance-stabilised and therefore less reactive positively-charged nitrogen and also react only with activated aromatic rings to give azo-compounds (Scheme 5).



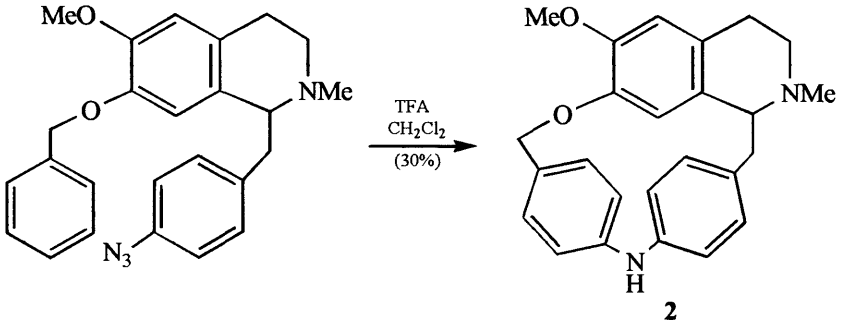
Scheme 5

Arylnitrenium ions $ArN\overset{+}{H}$ have received much attention mainly as a result of their possible intermediacy as reactive metabolites of mutagenic and carcinogenic amines and nitro-aromatics. They are readily obtained by reaction of azides or hydroxylamines with acids and it is attack on them, intramolecular or otherwise, by nucleophiles (including nitrogen in DNA) (Scheme 6) that is of greatest interest.[6-10]



Scheme 6

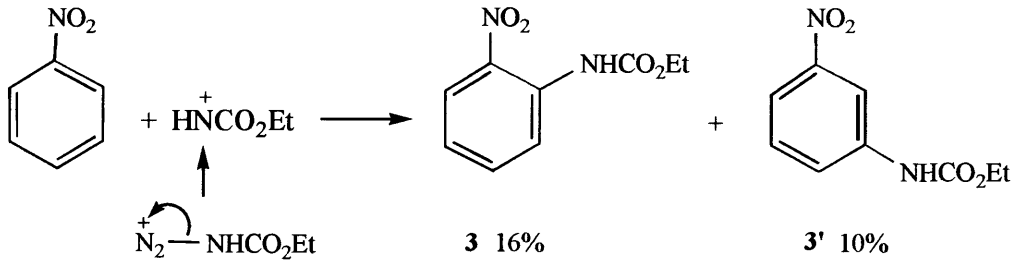
Of interest and relevance to the present work was the finding by Abramovitch *et al.*[11] that intramolecular attack of an arylnitrenium ion on an aromatic ring can occur giving a strained 16-membered ring product **2** (Scheme 7).



Scheme 7

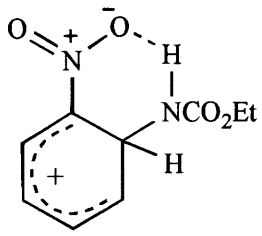
An attractive interaction between the highly electron-deficient arylnitrenium ion (or its protonated azide precursor) and the electron-rich benzyloxy group was postulated, resulting in a lower activation energy and favourable entropy for intramolecular cyclisation compared with other intermolecular pathways.[12]

Azides bearing electron-withdrawing substituents will generate corresponding more reactive nitrenium cations. Takeuchi and Koyama have shown that the decomposition of ethoxycarbonyl azide in the presence of TFA generates the protonated nitrenium ion whose reactivity is different from the nitrene generated in its absence. This nitrenium ion will even attack nitrobenzene[13] (no attack takes place in the absence of TFA).



Scheme 8

As expected for an electrophilic substitution, attack on the *m*-position occurs. The formation of larger than expected amounts of *o*-substitution product is accounted for by stabilisation of the σ-complex **4**.



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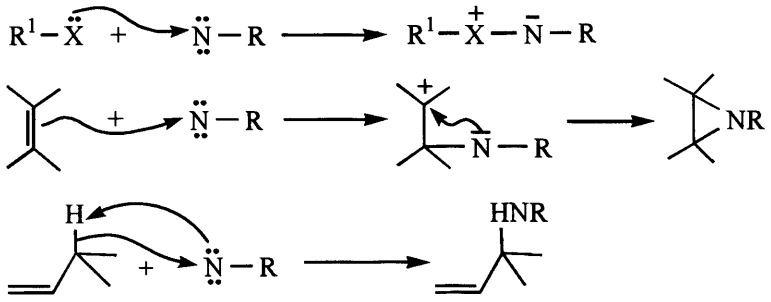
1.1.1 Nitrenes

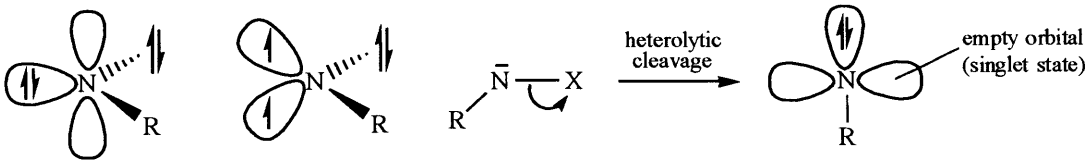
Nitrenes $R-\ddot{N}:$ are inherently electrophilic by virtue of the sextet of electrons in their outer shell and readily accept a pair of electrons to attain the desired octet. These electrons may be supplied by a non-bonded lone pair, by a pair of electrons in a π-bond or by those in a σ-bond.[14,15]



Scheme 9

Because π-bonds are always weaker than σ-bonds, attack of the nitrene on an aromatic ring will preferentially occur on the aromatic π-system and because the nitrene is inherently electrophilic, attack on the more electron-available aromatic rings bearing electron-donating substituents will be favoured.

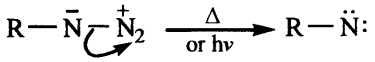
The behaviour above refers to the singlet state of the nitrene where both pairs of electrons are contained in two separate orbitals and have paired spins **5**. Electrophilic attack by the nitrene is dependent on the presence of a vacant orbital, *e.g.* a p-orbital in **5**, which can accept the electron pair of the nucleophilic substrate. However, there is another electron configuration for the nitrene, the triplet **5'** which is often lower in energy than the singlet. Here, one pair of electrons with opposite spins is contained in one orbital but the other two electrons are each contained in different orbitals with parallel spins. The presence of two unpaired electrons in the triplet state gives rise to its free radical-like chemistry.



5 5'

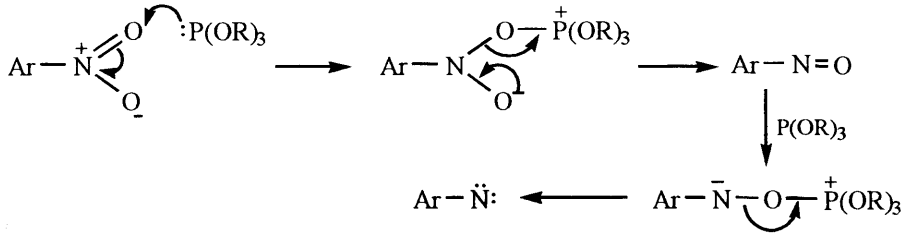
Scheme 10

Although the triplet state may be the ground state, in practice most methods of generating nitrenes give the singlet state initially because most of these methods involve heterolytic cleavage of a bond rather than homolytic cleavage which would be required for direct formation of the triplet (Scheme 10 above). Azides are much used precursors for nitrenes because they readily lose nitrogen by heating at moderately high temperatures (> ~150 °C) or by photolysis.[16]



Scheme 11

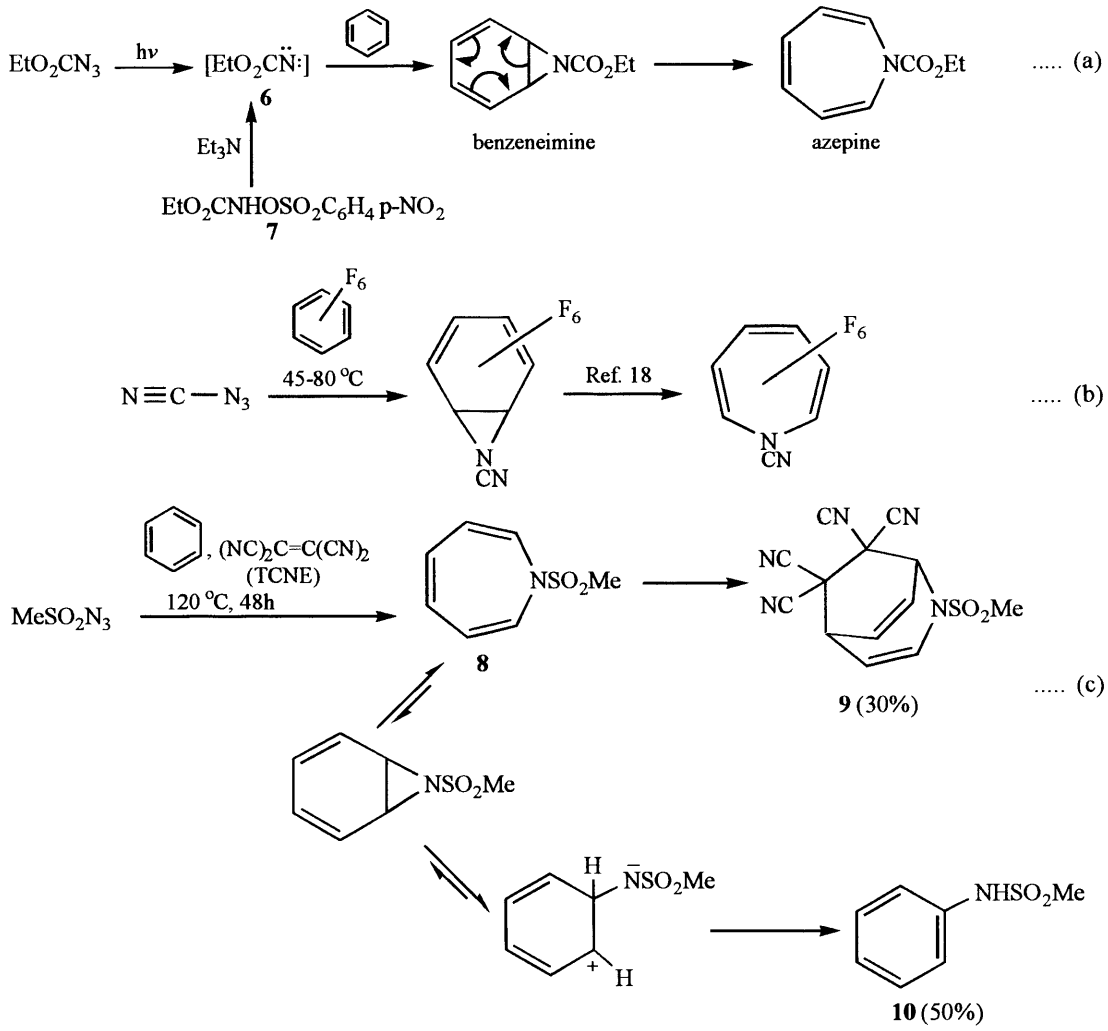
Deoxygenation of arylnitroso or arylnitro compounds, usually by trivalent phosphorus, has been widely used for generating arylnitrenes (Scheme 12).



Scheme 12

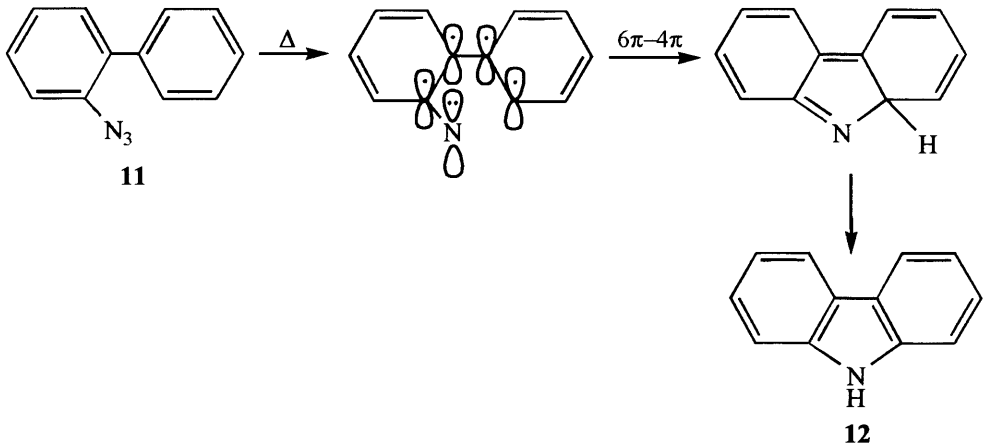
Only a few nitrenes are stable enough to undergo intermolecular reactions because of the faster intramolecular reactions that many undergo. Even in these cases, the substrate (*e.g.* an aromatic ring) must be present in large excess or even used as the solvent. Commonly observed products are azepines, formed by electrocyclic ring-opening of the initially formed benzeneimines (Scheme 13a–c). The same ethoxycarbonylnitrene species **6** formed on photolysis of the azide is obtained by α-elimination from the *N*-(p-nitrobenzenesulphonyl-oxy)urethane **7** (Scheme 13a).[17]

In Scheme 13c the azepine **8** is detected as an intermediate only by trapping it as the Diels-Alder adduct **9** with tetracyanoethylene; the product otherwise was the *N*-methanesulphonylaniline **10**. Substitution products such as **10** are also commonly observed from reactions with aromatic rings and, although formally the result of insertion into the aromatic C–H bond, in practice are invariably formed *via* the route shown in Scheme 13c (see also below).[19]



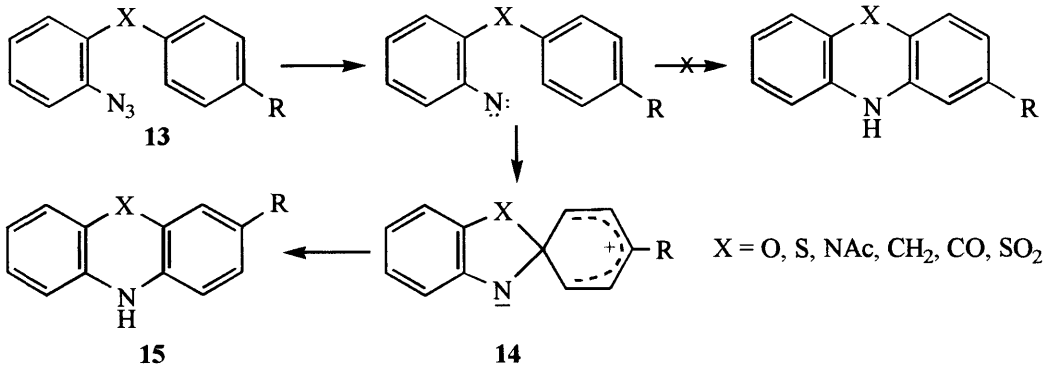
Scheme 13

Intramolecular reactions of arylnitrenes with a variety of appended heteroaromatic rings have been studied[20-22] but this discussion will focus on the intramolecular reactions of singlet nitrenes with benzenoid rings.



Scheme 14

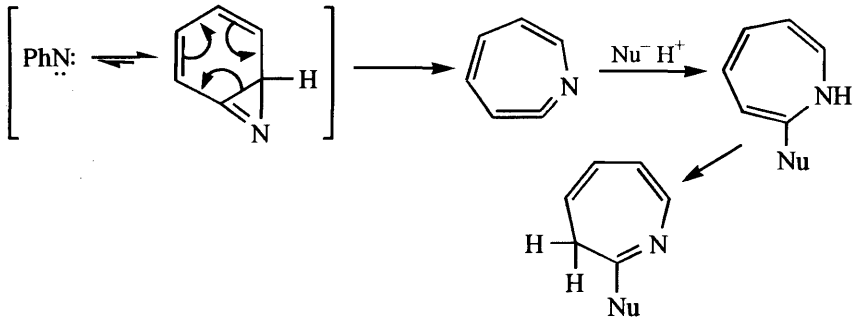
The conversion of *o*-diphenylazide **11** into carbazole **12** (Scheme 14) is probably best interpreted as involving a $6\pi \rightarrow 4\pi$ concerted electrocyclic ring closure (assuming that a pair of electrons on the nitrene nitrogen is utilised in the cyclisation). A preference for intramolecular reaction *via* a 5- rather than a 6-membered ring is exemplified in the conversion of **13** → **15** which is presumed to pass through the dipolar *spiro*-diene intermediate **14** (Scheme 15).



Scheme 15

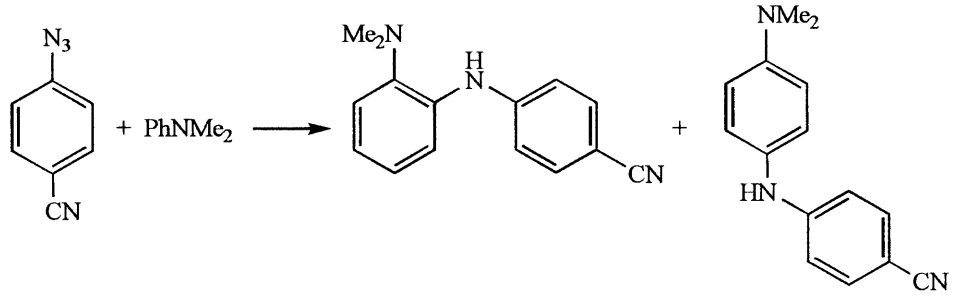
The site of the substituent R in the product reveals that a rearrangement is involved and that the product is not formed by attack of the nitrene on the R-substituted ring *via* a 6-membered TS$^{\#}$.[20]

An important competitive intramolecular reaction of arylnitrenes is (reversible) benzazirine formation leading to azepine derivatives (Scheme 16).



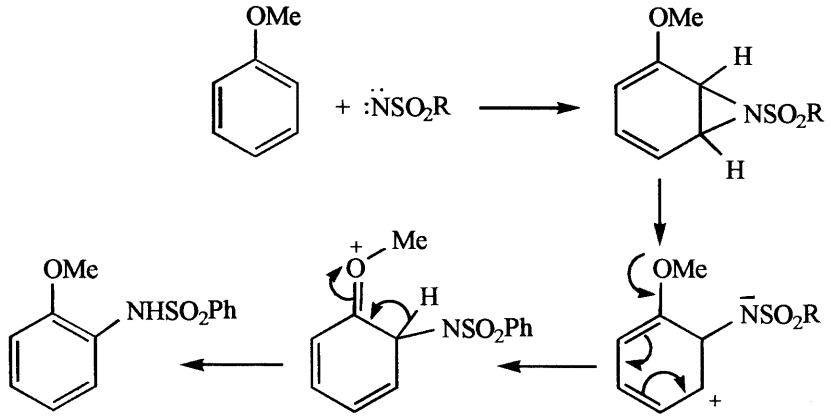
Scheme 16

This reaction is sufficiently fast to prevent the interception of arylnitrenes by intermolecular reactions and to compete with reactions of appended aromatic rings as above. One way in which this intramolecular reaction of the arylnitrene can be suppressed, and intermolecular reactions of arylnitrenes encouraged, is by the substitution of a strongly electron-withdrawing group into the ring bearing the azide precursor of the nitrene[23] (Scheme 17).



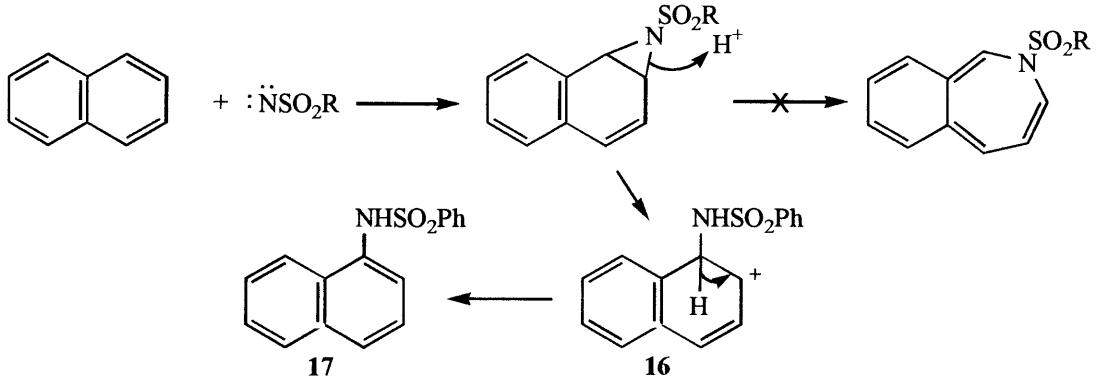
Scheme 17

The isolation of substitution products from these reactions occurs where $4\pi \rightarrow 6\pi$ electrocyclic ring-opening of the benzeneimine species, formed by aziridination of one double bond of the aromatic ring, is slower than aziridine ring-opening to regenerate the aromatic system (Scheme 18). Substitution products may also arise where benzeneimine $\rightarrow$ azepine conversion is reversible as in Scheme 13c above.



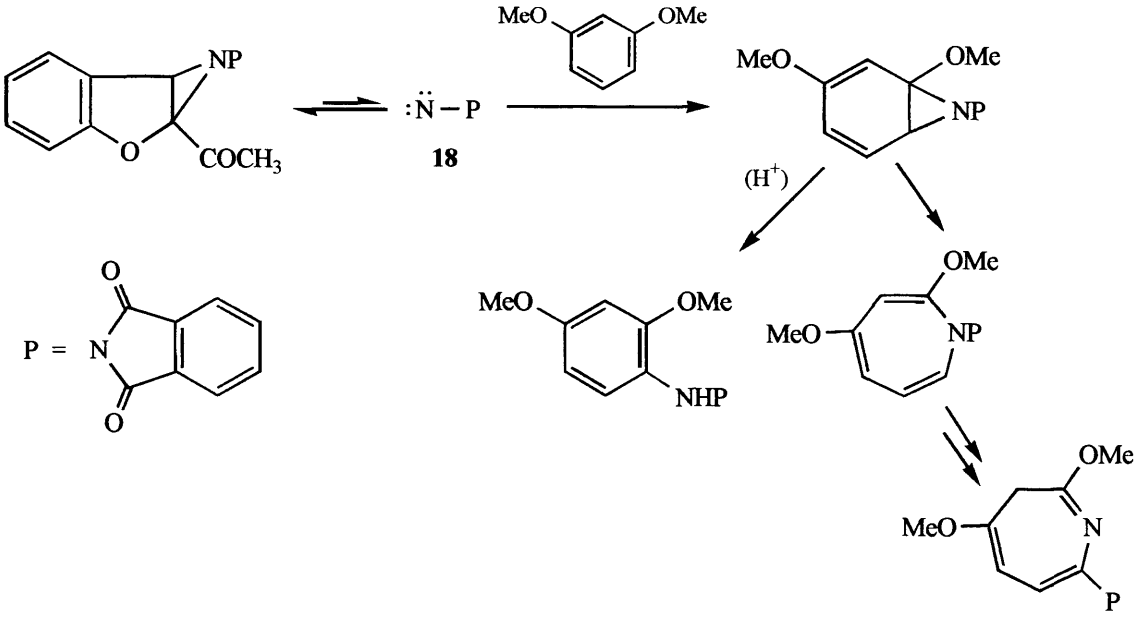
Scheme 18

Azepine formation is particularly discouraged from the aziridination product of naphthalene. Attack of sulphonylnitrene occurs at the 1,2-position, this being the most double bond-like in character, but azepine formation would require desaromatisation of the unreacting benzene ring. Regiospecific aziridine ring-opening occurs *via* the more stable carbocation **16** to give **17** (Scheme 19).



Scheme 19

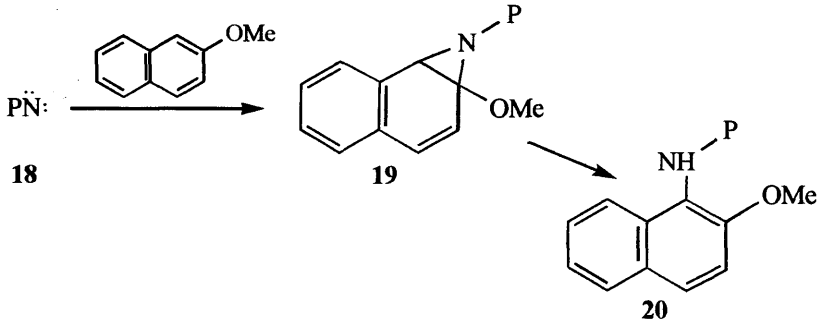
Reactions of phthalimidonitrene **18** (see later for a discussion of this and related reagents) with 1,3-dimethoxybenzene (Scheme 20) illustrates the competition between azepine formation and formal insertion into one of the C–H bonds of the aromatic ring.[24,25]



Scheme 20

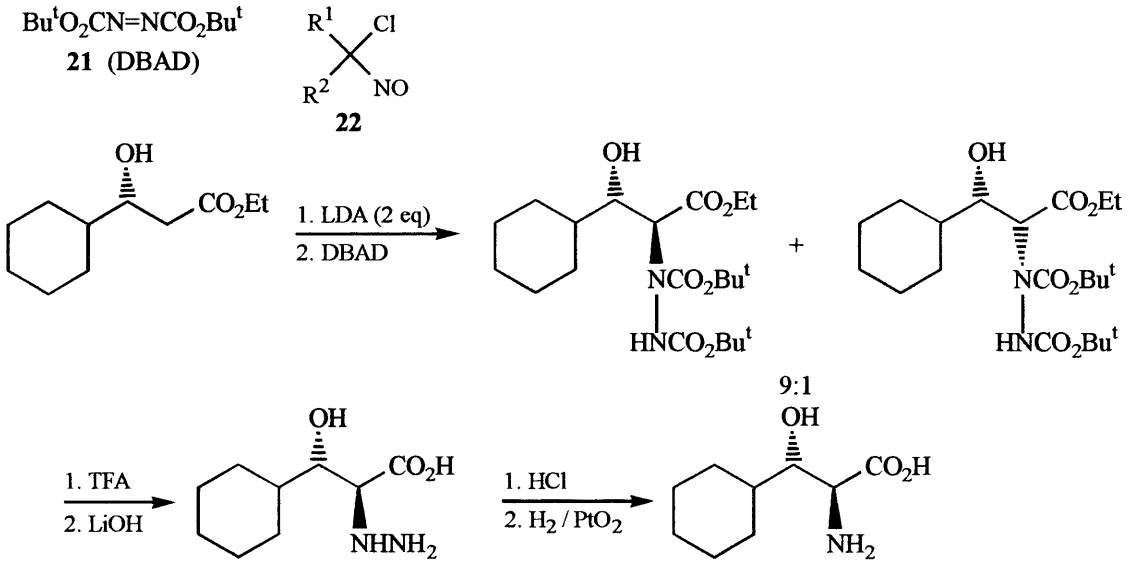
A detailed discussion of intramolecular 3-acetoxyaminoquinazolinones with appended aromatic rings is given in part 1.3.

Jones and Thornton-Pett also found that in the reaction of PN̈: **18** with 2-methoxy-naphthalene, only the insertion product **20** was produced *via* the intermediate **19** (Scheme 21).[24]



Scheme 21

Other sources of electrophilic nitrogen are known including **21** and **22** but it is their (stereoselective) reactions with enolates (Scheme 22) which have been most widely studied.[26]

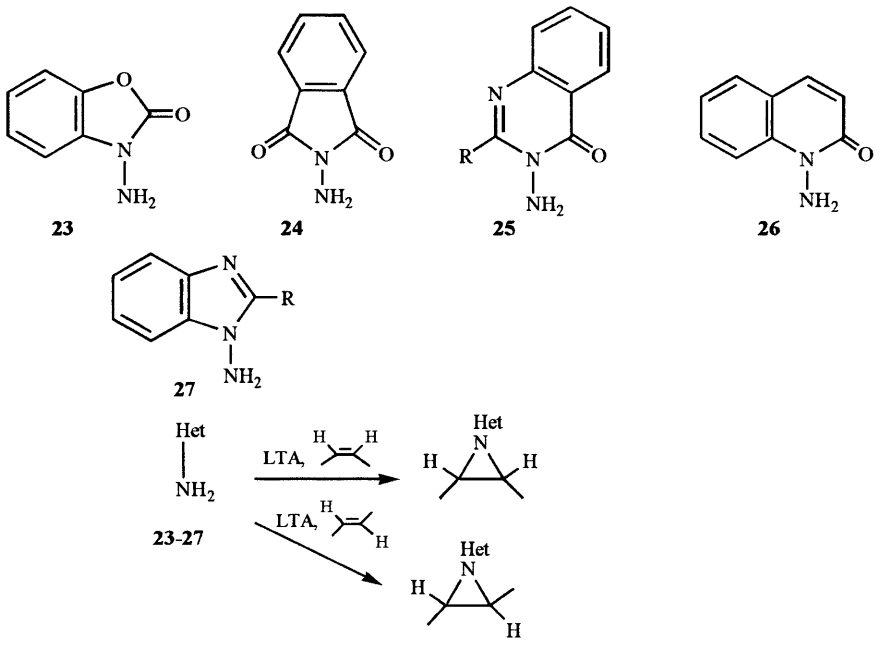

Bu^{t}O$_2$CN=NCO$_2$Bu^t
21 (DBAD)
R^1 Cl
R^2 NO
22
OH
CO$_2$Et
1. LDA (2 eq)
2. DBAD
NCO$_2$Bu^t
HNCO$_2$Bu^t
+
9:1
1. TFA
2. LiOH
CO$_2$H
NHNH$_2$
1. HCl
2. H$_2$ / PtO$_2$
NH$_2$

Scheme 22

1.2 The Chemistry of 3-Acetoxyaminoquinazolinones

1.2.1 Background

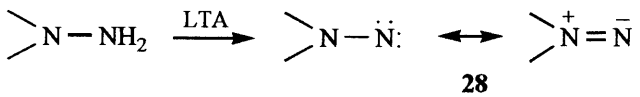
It was shown first by Rees *et al.*[27,28] in the late 1960s that oxidation of a family of *N*-aminoheterocyclic compounds, including **23**–**27**, by lead tetra-acetate (LTA) in the presence of alkenes gave aziridines, often in high yields. When applied to *cis*- and *trans*-alkenes, this aziridination was stereospecific with retention of configuration of the alkene in the product (Scheme 23).



Scheme 23

The reactive intermediates in these heterocyclic *N*-amino compound oxidations were presumed to be *N*-nitrenes[28] although, at least for the cases of **24** and **25**, this presumption was eventually shown to be in error. With hindsight, it is of interest that, of oxidizing agents tried, the only one – other than LTA – which was successfully used to accomplish the aziridination in Scheme 23 was iodobenzene diacetate $PhI(OAc)_2$; it required nearly twenty years before the significance of the acetoxy group, common to both $Pb(OAc)_4$ and $PhI(OAc)_2$, became apparent.

Common to all the family members **23**–**27** is the presence of features which would reduce the double bond character in the N–N bond in the corresponding *N*-nitrene intermediates (Scheme 24). Thus the heterocycle-contained nitrogen is either part of an amine N–C=O or an amide, N–C=N (or both) or else has its lone pair involved as part of an aromatic ring.



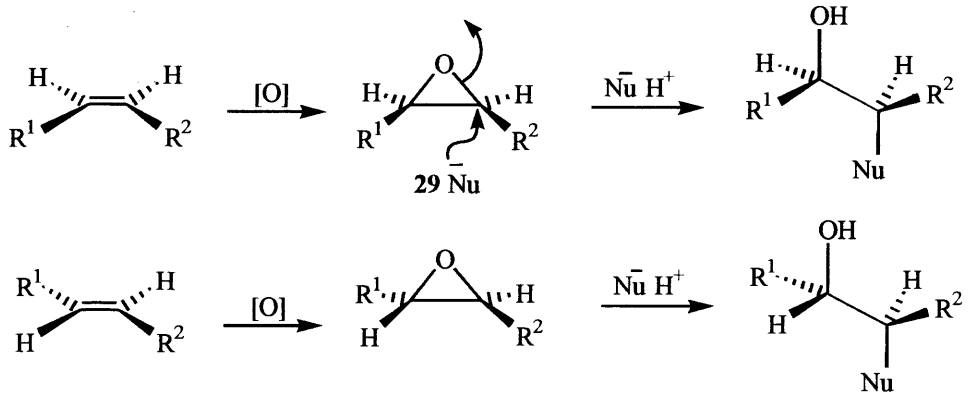
Scheme 24

Rees *et al.* also identified another family of heterocyclic *N*-amino compounds whose LTA oxidation products resulted from loss of nitrogen.[29-31] The features referred to above, by reducing the contribution from the double bond resonance structure **28** in Scheme 24 were thought to raise the barrier to intramolecular reaction by elimination of nitrogen.[32]

Oxidation of *N*-amino compounds **23–27** using LTA has been routinely used for aziridinations of alkenes carried out since the pioneering work of C. W. Rees *et al.* When aziridination is carried out in dichloromethane at –20 °C, more than 95% of the lead is recovered as its di-acetate which could, in principle, be reconverted into lead tetra-acetate.

1.2.2 Epoxides and aziridines as synthetic relay intermediates[33]

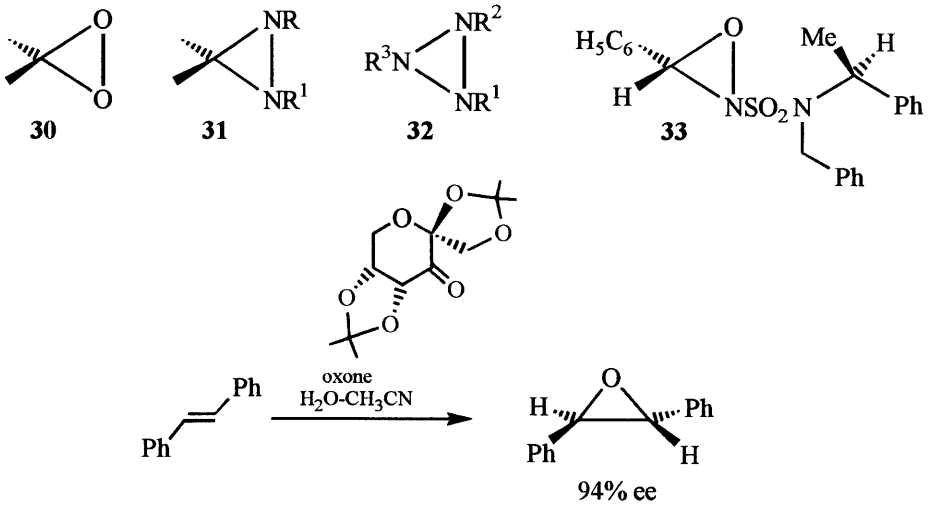
Epoxides are particularly useful as relay intermediates in synthesis. The sequence *E* or *Z*-alkene → epoxide → ring-opened product is a much used route to chiral alcohols as single diastereoisomers since the epoxidation and epoxide ring-opening are almost always stereospecific (Scheme 25). A number of methods for (stereospecific) epoxidation[34-35] are available and the ring strain present in epoxides facilitates the ring-opening by nucleophiles. The widened angle to the exocyclic bonds facilitates the nucleophilic attack in an S_N2 sense in **29**. By contrast, the analogous sequence, alkene → aziridine → ring-opened (amine) product is nothing like so widely used in synthesis in spite of the fact that aziridines have a similar ring strain to epoxides and are stereospecifically ring-opened by nucleophiles to provide access to α- and β-amino acids, 1,2-diamines, 1,2-aminoalcohols and other useful products.[35,36] It is the dearth of methods, and particularly stereoselective ones, for synthesis of aziridines which is the major reason for the disparity in use made of these two types of 3-membered ring as synthetic relay compounds.



Scheme 25

A common method for epoxidation uses commercially available peroxyacids and, in particular, *m*-chloroperoxybenzoic acid or monoperoxyphthalic acid. Another widely-used method employs *tert*-butylhydroperoxide in the presence of a metal catalyst [titanium(IV), vanadium(V)].[37] By contrast, neither the nitrogen analogues of peroxyacids (NH_2OCOR) nor of *tert*-butylhydroperoxide (Bu^tONHR) are useful aziridination agents. Dioxiranes **30**

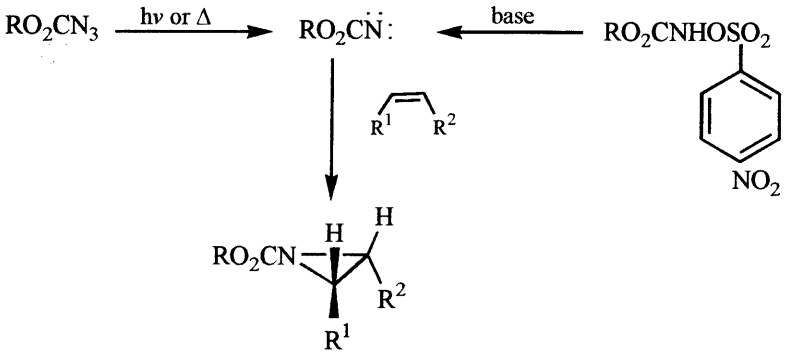
are increasingly finding use as epoxidising agents particularly for the less reactive alkenes: the dioxirane intermediate in Scheme 26 brings about the epoxidation highly enantioselectively.[38] Diaziridines **31**[39] (or triaziridines **32**)[40] are not used as aziridinating agents. The work of Davis *et al.*[41] has shown that oxaziridines, *e.g.* **33**, behave as epoxidizing agents rather than aziridinating agents. At least some of these differences can be attributed to the weakness of the *O–O* bond relative to the *N–N* bond.



Scheme 26

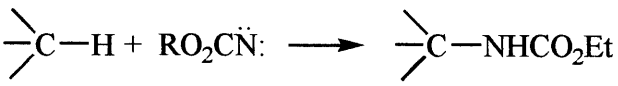
1.2.3 (i) Aziridination via nitrene addition

Direct aziridination of alkenes by alkoxycarbonylnitrenes has been well-studied by Lwowski *et al.*[42,43] (Scheme 27 - *cf.* Scheme 13a in Part 1). However, this is not a good synthetic method for aziridination because:

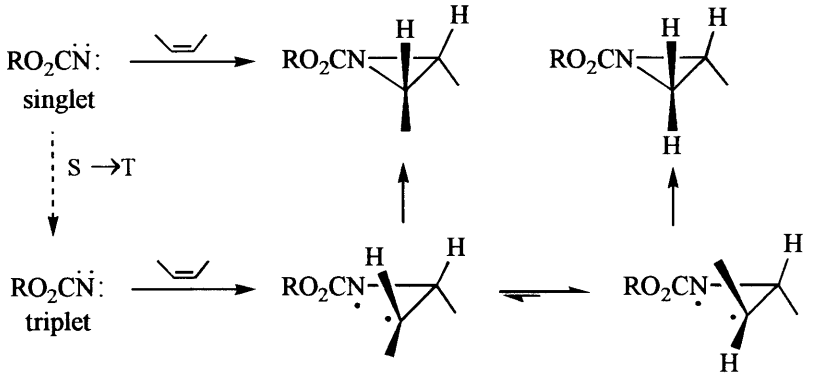


Scheme 27

(i) competitive insertion into C–H bonds occurs, particularly allylic ones, *i.e.*



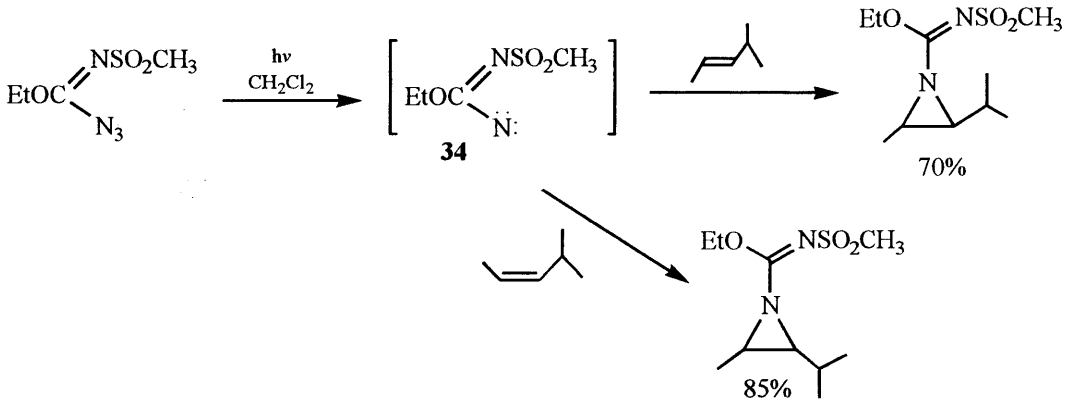
(ii) conversion of the initially formed singlet state (S) of the nitrene to the triplet ground state (T) can occur before aziridination takes place: whereas the singlet state reacts stereospecifically, the triplet reacts non-stereospecifically (Scheme 28). To avoid S → T transformation it is usually necessary to use the alkene in large excess, preferably as the solvent.



Scheme 28

(iii) the chemoselectivity of the nitrene is low; there is little selectivity between different types of double bond or tolerance of other functional groups, particularly those containing available lone pairs.

However, Lwowski has shown that *N*-(methanesulfonyl)ethoxycarbimidoylnitrene **34** has a singlet ground state and reacts stereospecifically with *cis*- and with *trans*-4-methylpent-2-ene[44] (Scheme 29).

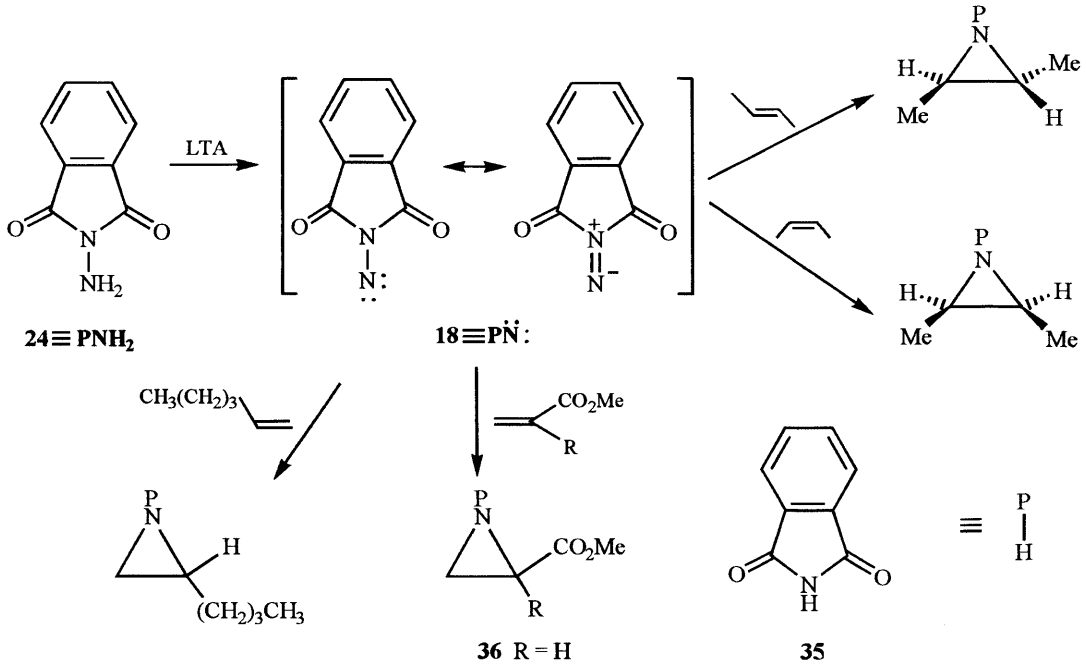


Scheme 29

(ii) Intermolecular aziridination of alkenes via N-nitrenes

Most of the aziridination studies carried out by Rees *et al.*[28] used the oxidative addition of *N*-aminophthalimide **24** to alkenes. The presumed *N*-nitrene intermediate derived from LTA oxidation of **24** was shown to add stereospecifically and often in good yields to a range of substituted alkenes including α,β-unsaturated esters and α,β-unsaturated ketones (Scheme 30).

The epoxidation methods described in the earlier section are almost all electrophilic and proceed in low yields, if at all, with electron-deficient alkenes and so the high yields which resulted from oxidative addition of *N*-aminophthalimide **24** to, for example, α,β-unsaturated carbonyl compounds were unexpected. They were rationalised by assuming some nucleophilic character for the nitrene as expressed by the 1,1-diazine-containing resonance hybrid in **18**. The poorest yields of aziridines were obtained by using monoalkyl-substituted alkenes such as propene or hex-1-ene as traps: the major product in these cases was phthalimide **35** (Scheme 30), *i.e.* formally the result of deamination of *N*-aminophthalimide.



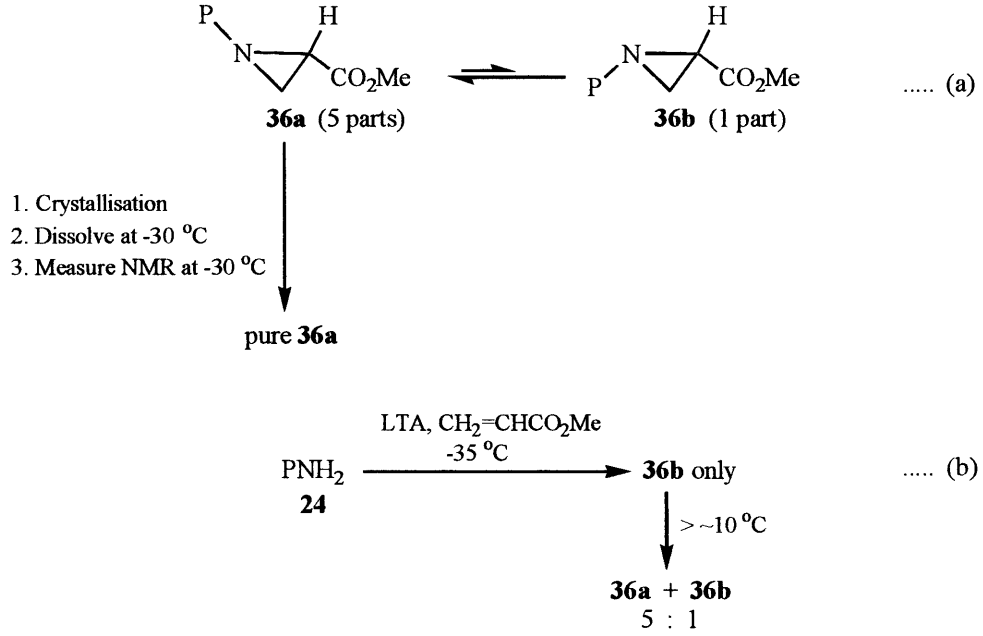
Scheme 30

1.2.4 Aziridination by oxidative addition of N-aminophthalimide to alkenes; configuration at nitrogen in the first-formed aziridines

The barrier to *N*-inversion in aziridines is raised by comparison with acyclic amine analogues and, moreover, the phthalimido group as an electron-withdrawing substituent on the aziridine ring nitrogen raises the barrier to *N*-inversion even more (see later). For the methyl acrylate-derived aziridine **36a,b** the NMR spectrum at room temperature shows a 5:1 ratio of *N*-invertomers with the major one having the phthalimido and methoxycarbonyl groups *trans* (Scheme 31a), *i.e.* *N*-inversion in this aziridine is slow on the NMR timescale. When a crystalline sample of aziridine **36** is dissolved in deuterochloroform at –30 °C and the NMR spectrum measured at this temperature without any intermediate warming of the solution, only signals from **36a** are visible, *i.e.* at –30 °C *N*-inversion of this aziridine is slow on the real timescale.[45]

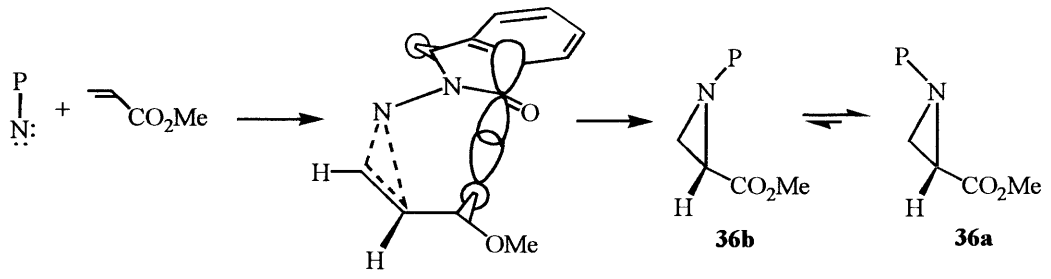
In this *second order asymmetric transformation*, crystallisation of the major *N*-invertomer **36a** present in Scheme 31 disturbs the equilibrium between **36a** and **36b** eventually leading

to only **36a** in the crystal. Re-establishment of the **36a** ⇌ **36b** equilibrium takes place at >5 °C which means that the *N*-inversion barrier interconverting **36a** and **36b** is ~20 kcal/mol.



Scheme 31

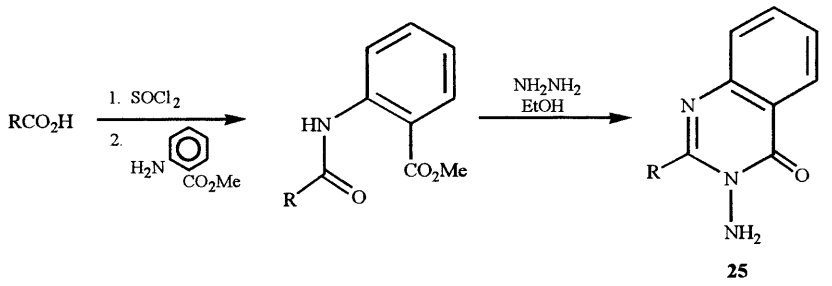
When oxidation of *N*-aminophthalimide with LTA was carried out at –35 °C in deutero-chloroform solution and the reaction mixture examined by NMR spectroscopy without any intermediate warming of the solution, only signals from the *cis-N*-invertomer **36b** were visible (Scheme 31b). On raising the temperature of the solution, signals from the *trans-N*-invertomer appeared with the eventual establishment of the 5:1 ratio of **36a**:**36b** as above. The faster formation of *N*-invertomer **36b** over **36a** clearly arises from a kinetic control in the aziridination and it was suggested that there was interaction (Scheme 32) between the phthalimido and ester groups in the transition state for the aziridination which was less important, or absent, in the product aziridine. With a face-to-face approach of phthalimido-nitrene and α,β-unsaturated ester and with an s-*cis*-conformation for the α,β-unsaturated ester as in Scheme 32, an attractive p-orbital overlap of the ester carbonyl oxygen and phthalimido carbonyl carbon can occur leading to the observed aziridine **36b** as the first-formed product.[47]



Scheme 32

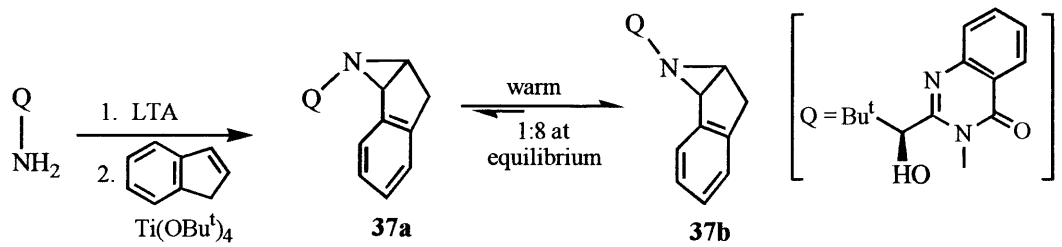
Analogous results were obtained by oxidative addition of *N*-aminophthalimide to styrene and to butadiene with the kinetically-formed *N*-invertomer in each case being that having the π-electron containing substituent (Ph, $CH{=}CH_2$) *cis* to the *N*-phthalimido group.[46] Analogous transition state geometries to those in Scheme 32 were suggested.

3-Aminoquinazolinones **25** are readily available members of the family of *N*-amino-heterocyclic compounds in Scheme 23 and are prepared in good overall yield from the corresponding acids as in Scheme 33.



Scheme 33

The barrier to *N*-inversion in these N-(Q)-substituted aziridines is sufficiently lower than the corresponding N-(P) analogues that the rate of *N*-inversion becomes comparable to or faster than the rate of aziridination. Consequently, it is not routinely possible to show by NMR spectroscopy that the kinetically-formed product is exclusively that having the Q and π-electron containing substituent (Ph, $CH{=}CH_2$, CO_2R) *cis* although this is believed to be the case. Exceptionally, the kinetically-formed *N*-invertomers of some of these *N*-(Q)-aziridines are stable in solution even at 0 °C. Thus the *cis*-aziridine **37a** is the only *N*-invertomer (produced as a single diastereoisomer) obtained in aziridination of indene when the work-up was carried out at ~0 °C (Scheme 34). At room temperature, conversion for the most part to the *trans*-*N*-invertomer **37b** took place confirming, at least in this case, that the aziridination mechanism using 3-aminoquinazolinone resembles that using *N*-aminophthalimide.[48]



Scheme 34

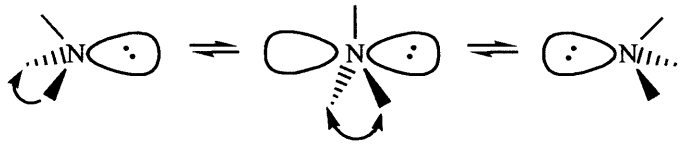
A pure sample of aziridine **37b** was obtained by crystallisation (dissolving the crystalline material at –40 °C: see second order asymmetric transformation previously).

Gattrell *et al.*[48] have shown that **37a** and **37b** show very different stereochemistry in their ring-opening reactions (see later). It is unfortunate that the barrier to *N*-inversion in N(Q)-aziridines is not quite high enough to routinely allow isolation of *N*-invertomers because this

would allow a wider exploration of the stereo- and regiochemistry of ring-opening for these two diastereoisomers (*N*-invertomers) of the three-membered ring.

1.2.5 Nitrogen inversion in aziridines: effect of changes in the N-substituent

Inversion in an acyclic amine having an sp^3-hybridised nitrogen is very rapid (2×10^{11} s^{-1} for ammonia). The constriction of the C–N–C angle as in a three-membered aziridine ring slows the nitrogen inversion rate to the point where it can be measured by nuclear magnetic resonance (NMR) techniques. The barrier to *N*-inversion is raised because inversion occurs *via* a planar (N, sp^2-hybridised) transition state **(B)** (Scheme 35) in which the strained C–N–C bond angle **(A)** (formally ~109°) must become even more strained to accommodate the increase in bond angle (formally 120°).



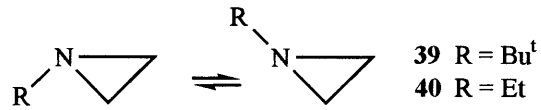
ϕ ~109° **(A)** **(B)** ϕ ~120°

Scheme 35

Several factors affect the rate of inversion at the aziridine nitrogen atom but the major ones are (i) steric effects, (ii) conjugative effects and (iii) σ-electronegativity effects.

(i) Steric effects

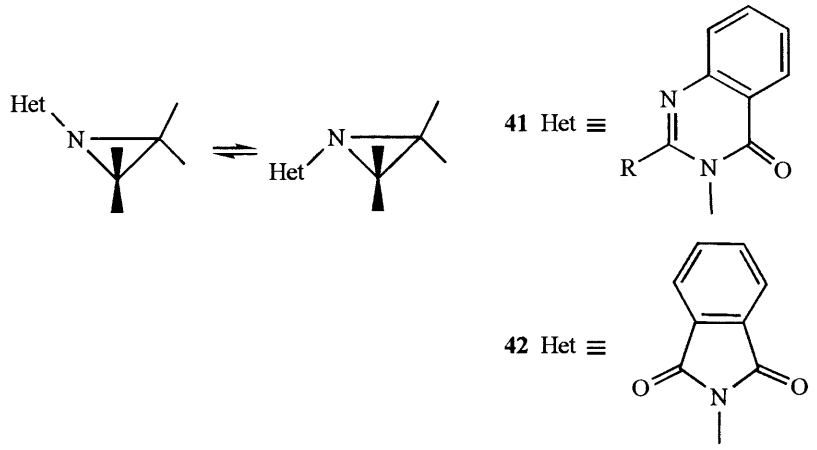
Brois[49] and Bottini *et al.*[50] found that as the size of the aziridine *N*-substituent increases, the inversion barrier decreases, *e.g.* *t*-butylaziridine **39** has a lower inversion barrier than 1-ethylaziridine **40** (Scheme 36) due to steric repulsion of the *t*-butyl group and the ring hydrogen atoms. This steric repulsion raises the ground state energy of the aziridine with respect to the transition state energy (assumed to be approximately the same for both aziridines) and thus lowers the barrier for *N*-inversion.



39 R = Bu^t
40 R = Et

Scheme 36

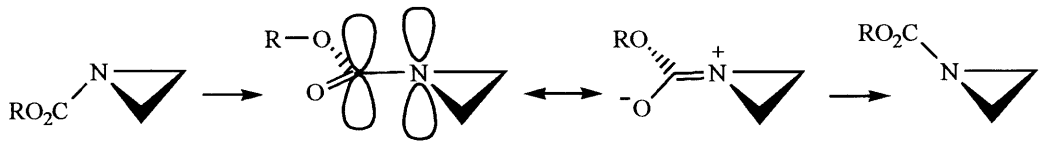
Similarly, the barrier to *N*-inversion in *N*-(3,4-dihydro-4-oxoquinazolin-3-yl) substituted aziridines **41** is reduced relative to the corresponding *N*-phthalimidoaziridines **42** (Scheme 37) at least in part because of the larger size of the quinazolinone relative to the phthalimido group.



Scheme 37

(ii) Conjugative effects

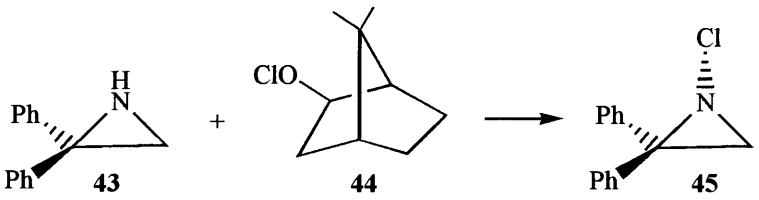
Attachment of an unsaturated group *e.g.* an alkoxycarbonyl CO_2R to the aziridine ring nitrogen lowers the inversion barrier (increases the inversion rate) as the result of conjugation with the *p*-orbital-contained unshared electron pair on the ring nitrogen in the transition state for inversion[51] (Scheme 38).



Scheme 38

(iii) σ-Electronegativity effects

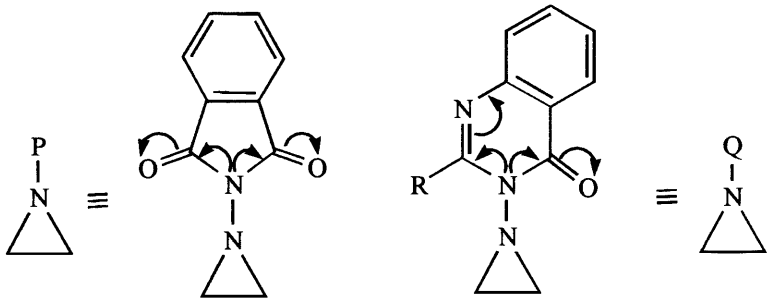
An electronegative but non-conjugating *N*-substituent on the aziridine nitrogen such as Br or Cl raises the barrier to inversion. The presence of single *N*-invertomers for *N*-phthalimido-aziridine in solution < –30 °C has been described previously (Scheme 31): the phthalimido group is a strongly electron-withdrawing and non-conjugating *N*-substituent. For *N*-chloroaziridines, the barrier is raised sufficient for isolation of *N*-invertomers at room temperature. Thus aziridine **43** is enantioselectively chlorinated by the enantiopure reagent **44**[52] (Scheme 39); the product **45** is racemised after 4 days at 0 °C.



Scheme 39

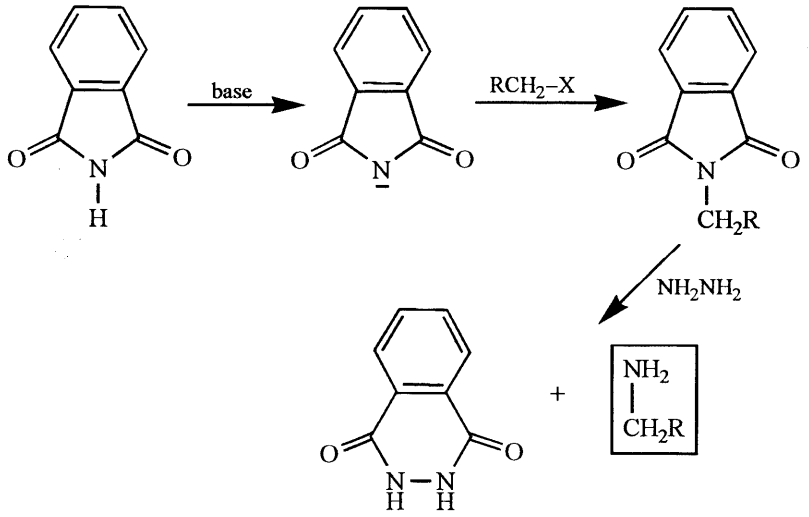
1.2.6 Rates of interconversion of N-invertomers in N-phthalimido- and N-(3,4-dihydro-4 -oxo-quinazolin-3-yl)aziridines

The *N*-phthalimido (P) and 3,4-dihydro-4-oxoquinazolin-3-yl (Q) substituents are more electron-withdrawing than an amino group because conjugation of the adjacent carbonyl or imine double bonds with the nitrogen lone pair (Scheme 40) renders the nitrogen more electron-withdrawing.



Scheme 40

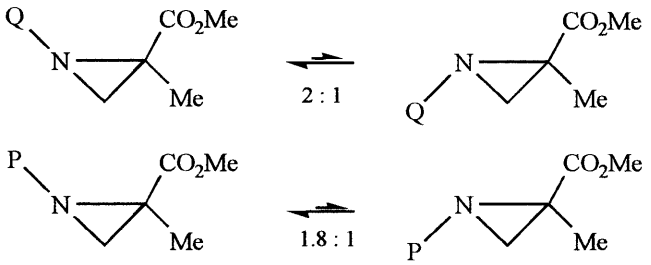
It is this conjugation which is responsible for the acidity of the N–H proton in phthalimide itself, an acidity which can be used to convert, for example, primary alkyl halides into the corresponding amine (Scheme 41) by nucleophilic displacement by the phthalimide anion. It is not surprising, therefore, that these heterocycles as electron-withdrawing aziridine *N*-substituents have the effect of raising the barrier to *N*-inversion over and above that of an amino group.



Scheme 41

1.2.7 N-Invertomer ratios in N-(P) and N-(Q)-substituted aziridines

When the two substituents on opposite sides of a disubstituted ring (1,1 or *trans*-1,2-substituted) are of comparable size, signals from both *N*-invertomers are visible in its NMR spectrum at room temperature (Scheme 42).

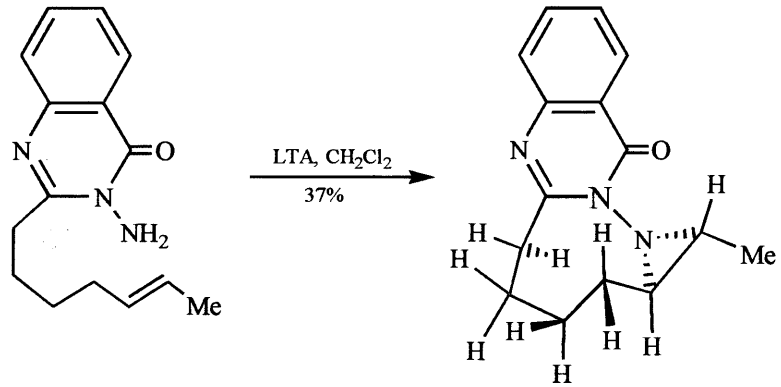


Scheme 42

In the NMR spectra of these aziridines, the ester methyl and the ring methyl signals *cis* to the P or Q groups are shielded but the aziridine ring proton signal *cis* to the P or Q group is deshielded relative to the *trans* ring proton. Consequently, distinguishing between the two *N*-invertomers is usually straightforward.[53]

1.2.8 Identification of the aziridinating agent in LTA oxidation of 3-aminoquinazolinones

The availability of a substituent R in the quinazolinone 2-position in **25** allows intramolecular aziridination to be studied by incorporation of double[54] or triple[55] bonds into this substituent. Work by Skinner[56] showed that LTA oxidation of 3-aminoquinazolinone **46** at high dilution in dichloromethane solution gave aziridine **47** (Scheme 43) whose NMR spectrum at 400 MHz indicated that the 8-membered ring was present as a single conformation (anancomeric) with the signals for each of the non-equivalent protons in the tetramethylene tether appearing as highly structured multiplets.

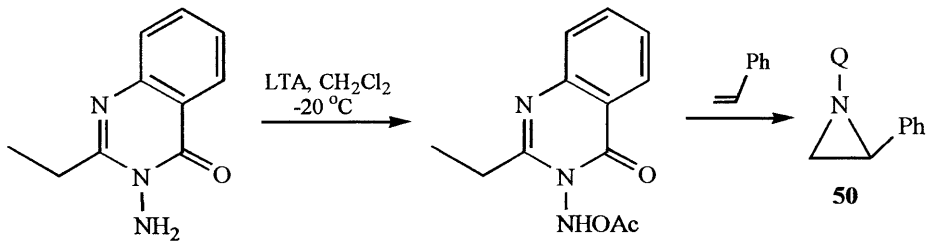


46 **47**

Scheme 43

Examination of this reaction by Grimshire[57] revealed that when the oxidation with LTA was carried out in deuterochloroform solution at –20 °C an NMR spectrum of the cold reaction mixture showed that no aziridine **47** had been formed but that the amino-group protons had disappeared. Only when the temperature of the solution was raised to >0 °C did the very characteristic multiplet signals from aziridine **47** appear. Thus reaction of LTA with 3-aminoquinazolinone **46** must have produced an intermediate which was stable at –20 °C but reacted with the double bond to give aziridine **47** at the higher temperature (>0 °C). Subsequently, it was shown by Kelly[57] that correspondingly stable (at –20 °C) intermediates

were formed by LTA oxidation of all 3-aminoquinazolinones including 3-amino-2-ethylquinazolinone **48**; in this case, the intermediate was shown to bring about aziridination of, for example, styrene added subsequently to the reaction mixture (Scheme 44).



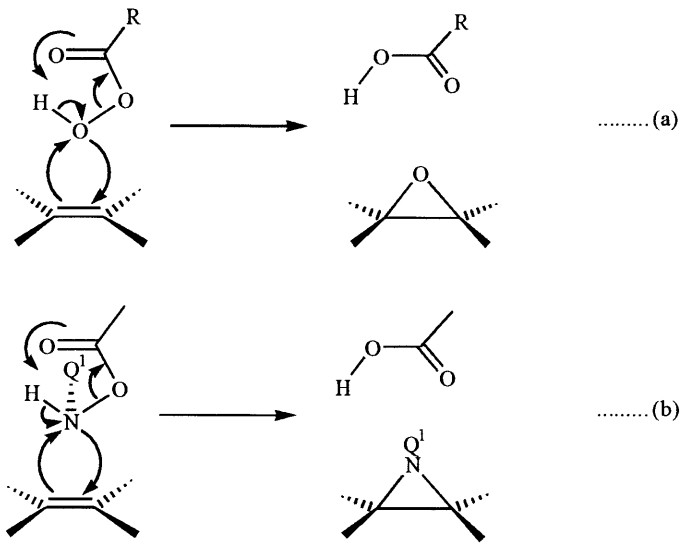
48 = Q^1NH_2 **49** = Q^1NHOAc

Scheme 44

The aziridination intermediate in Scheme 44 was identified as the 3-acetoxyamino-quinazolone **49** (Q^1NHOAc) by NMR (δ 2.15, $OCOCH_3$) and IR (γ_{max} 1768 cm^{-1}, $OCOCH_3$) spectroscopy. The rate of formation of aziridine **50** from Q^1NHOAc and styrene was first order in each suggesting that Q^1NHOAc **49** was the actual aziridinating agent and not a precursor of the *N*-nitrene. Subsequently, a route to authentic *N*(Q)-nitrenes became available (see later) whose reactivity was shown to be very similar to, but identifiably from, that of the corresponding QNHOAc intermediates.

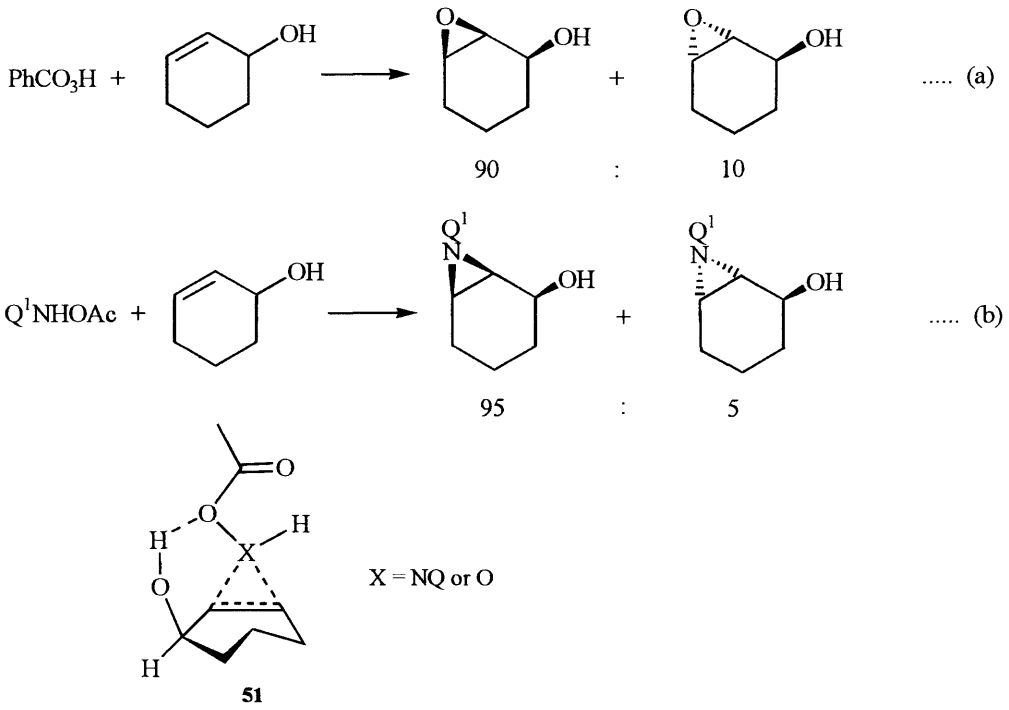
1.2.9 Comparison between aziridination of alkenes by Q^1NHOAc and epoxidation of alkenes by peroxyacids

With the finding that the actual aziridinating agents in these LTA oxidations of 3-aminoquinazolinones (QNH_2) were *N*-acetoxy-derivatives (QNHOAc), the analogy with the Bartlett mechanism[58] for epoxidation of alkenes with peroxyacetic acid became clear (Scheme 45).



Scheme 45

Support for this analogy, at least for the reaction of electron available alkenes, came from comparison of the stereochemistry of reactions of peroxybenzoic acid and of Q^1NHOAc with cyclohexenol (Scheme 46); in both cases the high *syn*-selectivity obtained is believed to result from intramolecular hydrogen bonding of the reagent with an allylic hydroxy group as in **51**.[59]



51

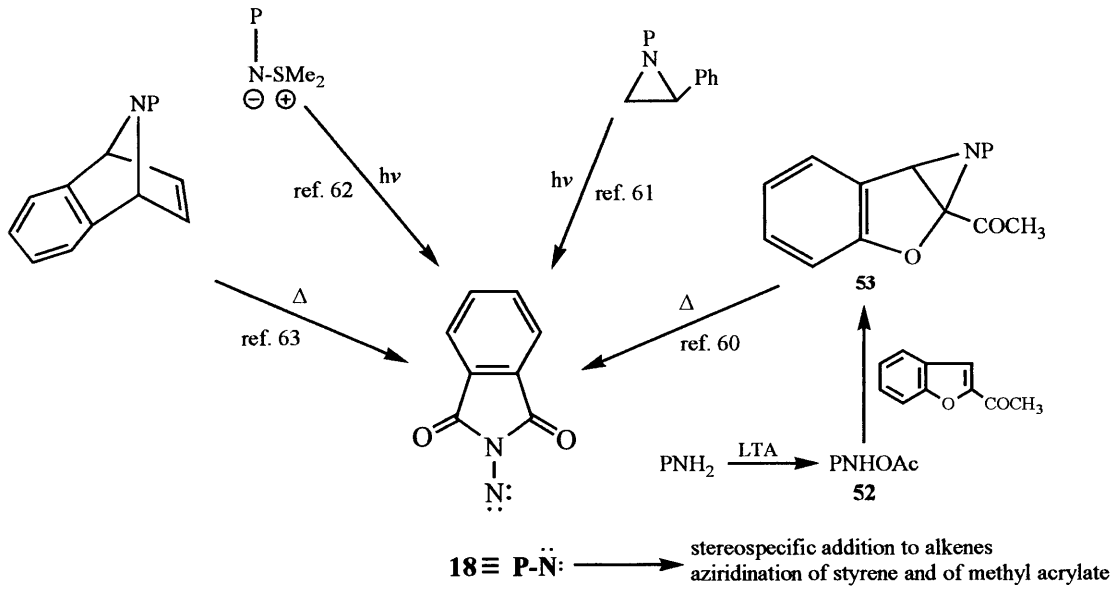
Scheme 46

However, one significant difference between epoxidation and aziridination of alkenes with these reagents is, as previously mentioned, their reactivity with, *e.g.* α,β-unsaturated esters: whereas QNHOAc aziridinates, for example, methyl acrylate in good yield, peroxyacids give poor yields of the corresponding epoxides.

1.2.10 N-Acetoxyaminophthalimide and N-phthalimidonitrene

In the LTA-mediated oxidative addition of *N*-aminophthalimide to alkenes, the aziridinating species was subsequently shown to be the corresponding *N*-acetoxyaminophthalimide **52** (PNHOAc), analogous to QNHOAc but which decomposes in solution at temperatures > −35 °C.[57] (The species involved in Scheme 32, therefore, should be PNHOAc **52**).

A number of routes[60-63] are available for the generation of *N*-phthalimidonitrene **18**, (PN̈:), which has a reactivity-profile very similar to that of PNHOAc **52** (Scheme 47).[63]



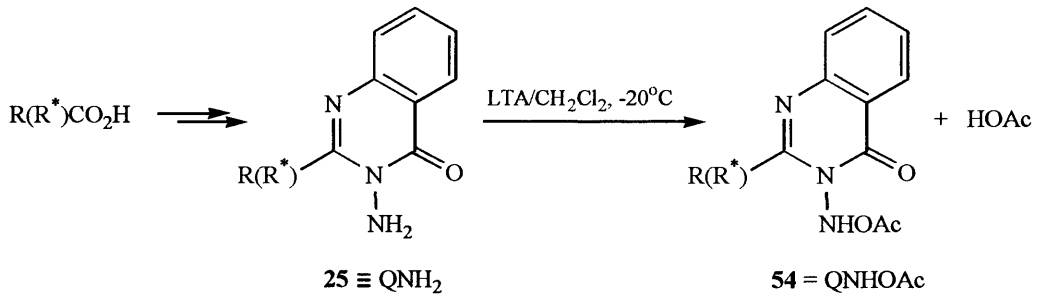
Scheme 47

Perhaps the most widely route used is that described by D. W. Jones[60] which involves heating the aziridine **53** with the alkene in boiling benzene; **53** is itself prepared by oxidative addition of *N*-aminophthalimide to 2-acetylbenzofuran - a reaction believed to involve PNHOAc **52** (see above).

It is the different selectivity between two alkenes (styrene and methyl acrylate) which, in a competitive reaction, distinguishes P – N̈: from PNHOAc with PN̈: having a relatively higher affinity for methyl acrylate at room temperature.

1.2.11 Properties of 3-acetoxyaminoquinazolinones QNHOAc

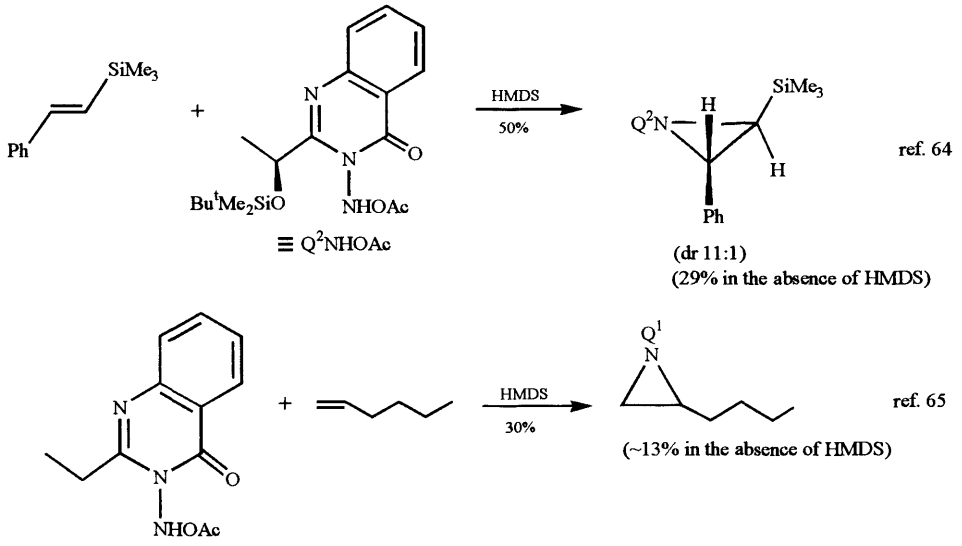
Excellent yields of the title compounds QNHOAc are obtained by slow addition of the 3-amino-2-substituted quinazolinone **25** (QNH_2) and LTA to a dichloromethane solution at –20 °C. Since QNH_2 compounds **25** are efficiently prepared from acids (Scheme 33) including chiral acids (R = R*), these aziridinating agents **54** are readily accessible (Scheme 48).



Scheme 48

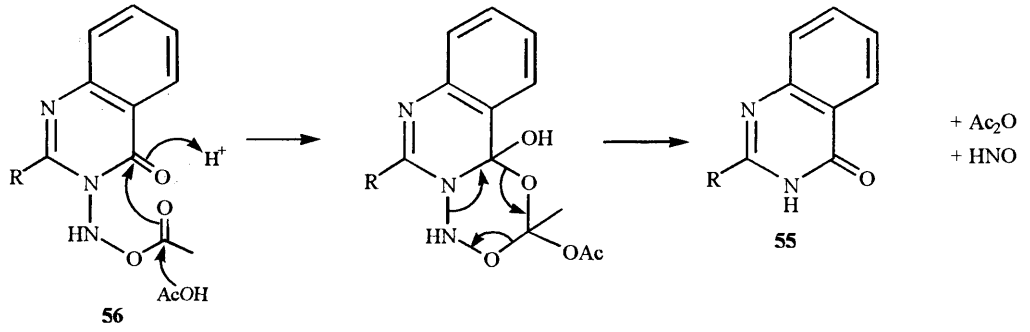
When prepared in dichloromethane or chloroform solution these QNHOAc compounds **54** (R = alkyl) are stable for only a few minutes above 0 °C but if the acetic acid co-produced in the acetoxylation step **25** → **54** (Scheme 48) is removed by addition of

hexamethyldisilazane (HMDS), they are stable for a longer time at this temperature. Yields of aziridines from the less reactive alkenes in Scheme 49a,b are raised by addition of HMDS because it scavenges the acetic acid produced both in the acetoxylation of QNH_2 and in the aziridination step and thereby prolongs the lifetime of QNHOAc.[64,65]



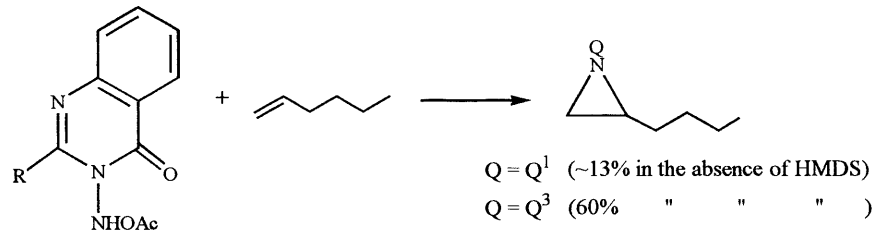
Scheme 49

The major products isolated from the acid-catalysed decomposition of these QNHOAc compounds are the 3H-quinazolinones (QH) **55** whose formation may take place as shown in Scheme 50; these QH compounds **55** are therefore the major products from unreactive alkenes. Protonation of the quinazolinone ring on the carbonyl carbon in **56** is particularly favoured by the aromaticity in the quinazolinium ion which results.



Scheme 50

Exceptionally, as was shown by Coogan,[66] 3-acetoxyamino-2-trifluoromethylquinazolinone (Q^3NHOAc) **57** is stable at room temperature in dichloromethane or chloroform solution for several hours presumably because its quinazolinone oxygen is less easily protonated by acetic acid. When Q^3NHOAc **57** is used in aziridination of less reactive alkenes the yields obtained are superior to those using 2-alkyl-substituted analogues, *e.g.* Q^1NHOAc **49** (Scheme 51) and are not increased by addition of HMDS to the reaction mixture.

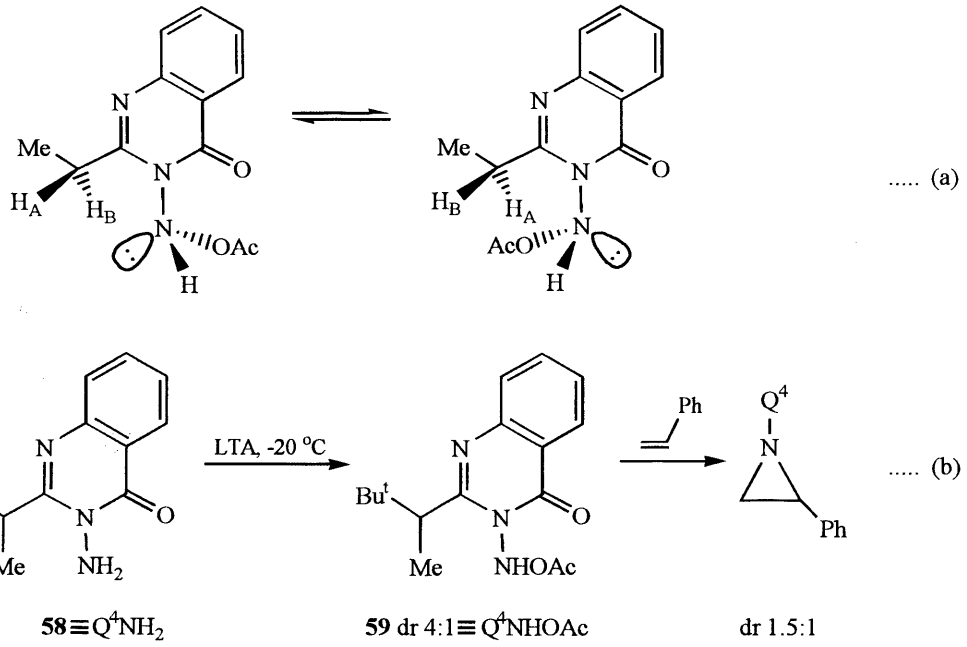


57 R = CF_3 ≡ Q^3NHOAc
49 R = Et ≡ Q^1NHOAc

Scheme 51

1.2.12 N-Inversion at the 3-acetoxyamino nitrogen of QNHOAc

The exocyclic nitrogen in these QNHOAc compounds is sp^3-hybridised, *i.e.* it is a chiral centre; thus the two protons of the methylene group CH_3CH_2 in the NMR spectrum of Q^1NHOAc **49** are diastereotopic and appear as an ABX_3 system; the magnetic environments of these methylene protons are exchanged by inversion at the nitrogen (Scheme 52a). When the 2-substituent on the quinazolinone is chiral, *e.g.* as in 3-aminoquinazolinone **58**, the two *N*-invertomers are diastereoisomeric in the derived Q^4NHOAc **59** and from NMR spectroscopy are present in a 4:1 ratio (Scheme 52b).[57]



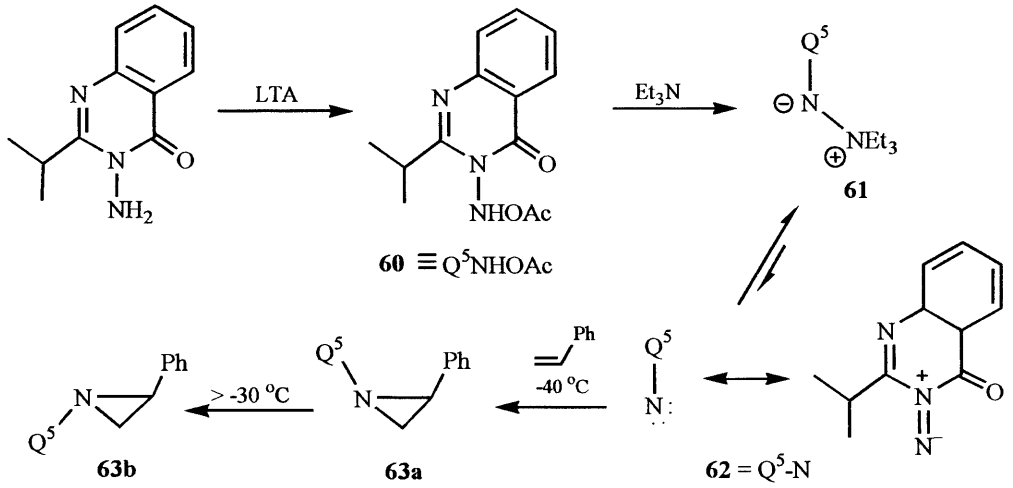
58≡Q^4NH_2 **59** dr 4:1≡Q^4NHOAc dr 1.5:1

Scheme 52

Attempts to separate these diastereoisomers have not been successful. Moreover, when the disappearance of **59** after the addition of styrene was monitored by NMR spectroscopy at −35 °C, the diastereoisomer ratio (dr) remained unchanged at 4:1 whereas the dr of the aziridine product was 1.5:1.[67] The conclusion from this and other similar experiments using QNHOAc compounds, is that *N*-inversion at the pyramidal nitrogen of the exocyclic acetoxyamino is slow on the NMR timescale but fast on the reaction (aziridination) timescale.

1.2.13 Aziridination of alkenes via (3,4-dihydro-4-oxoquinazolin-3-yl)-nitrenes (QN̈:)

Reaction of Q^5NHOAc[68] **60** with triethylamine in dichloroethane at –30 °C gave a solution of the ylide **61** which was assumed to be in equilibrium with the N(Q^5)-nitrene ($Q^5\ddot{N}$:) **62**; aziridination of added alkenes took place *via* the *N*-nitrene **62** (Scheme 53). The aziridination of alkenes by $Q^5\ddot{N}$: **62** even at a temperature of ~ –40 °C becomes significant in, for example, the aziridination of styrene since, by following the progress of the reaction using NMR, complete conversion initially to the *cis-N*-invertomer **63a** was observed with subsequent inversion to the *trans*-form **63b** taking place only on raising the temperature to –30 °C. [Contrast with the analogous aziridination of styrene with Q^1NHOAc described earlier where aziridine *N*-inversion is underway before aziridination is complete.]



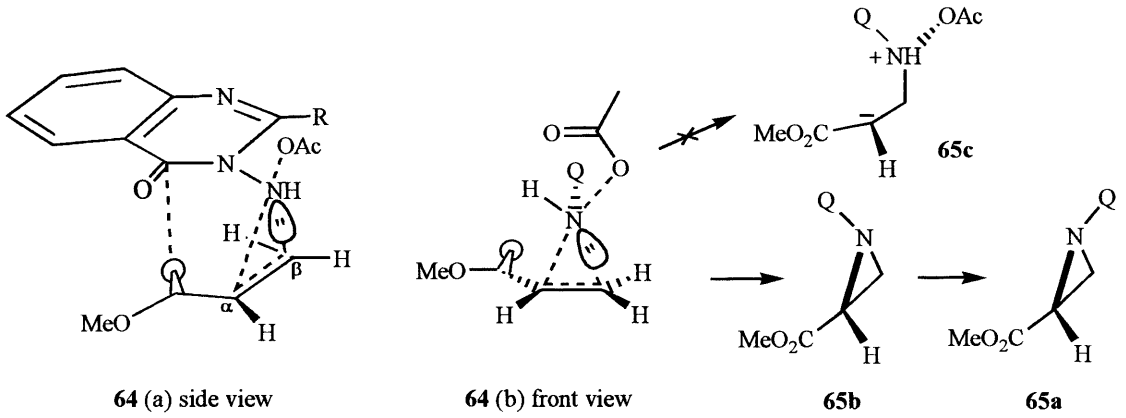
Scheme 53

The nitrene $Q^5\ddot{N}$: **62**, formed by reversible cleavage of the ylide **61**, like the corresponding Q^5NHOAc **60**, adds stereospecifically to *cis*- and *trans*-but-2-ene and adds to methyl acrylate as well as to styrene. Like the analogous phthalimidonitrene PN̈: (Scheme 47), it is distinguishable from the corresponding Q^5NHOAc by its selectivity in competitive reactions with two alkenes, *i.e.* it has a greater reactivity with methyl acrylate which may be the result of the more nucleophilic nitrogen arising from the resonance contribution in **62** (*cf.* the same explanation put forward earlier in Scheme 30).

1.2.14 The transition state for aziridination of alkenes using QNHOAc compounds

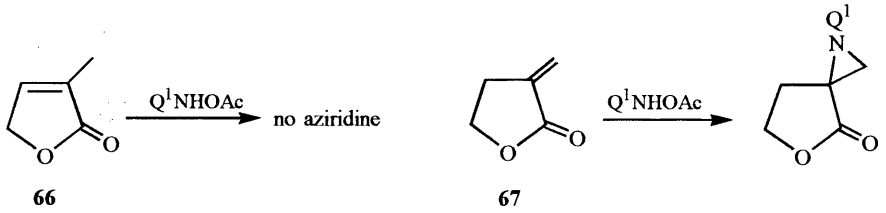
In the aziridination of *e.g.* styrene or of methyl acrylate by oxidative addition of *N*-aminophthalimide, (PNH_2) – now known to involve PNHOAc – the first formed aziridine *N*-invertomer has been shown to be the less stable one with P and Ph or CO_2Me *cis* (Scheme 31). The transition state leading to this *N*-invertomer with PNHOAc as the aziridinating agent and methyl acrylate as the alkene is the result of an attractive interaction between the π-electron-containing alkene substituent and P-ring as described previously (Scheme 32).

The TS$^{\#}$ (Scheme 54) for aziridination of methyl acrylate with QNHOAc **54** is believed to be analogous although, as mentioned previously, because the conversion of **65b** → **65a** is faster than aziridination of methyl acrylate, it is not possible to show that **65b** is the first-formed product by NMR spectroscopy.



Scheme 54

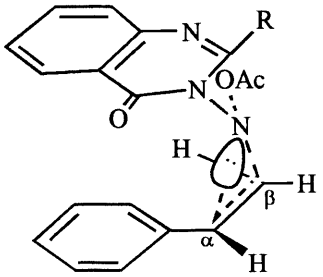
In **64** (Scheme 54) the secondary interaction between ester and Q-group can only be present if the α,β-unsaturated ester adopts the s-*cis* conformation. Attempted aziridination of the double bond in α,β-unsaturated γ-lactone **66** (Scheme 55) which cannot adopt this required s-*cis* conformation for the ester (lactone) yielded no aziridine product at all whereas the double bond in the s-*cis*-fixed α-methylene-γ-lactone **67** underwent aziridination in good yield.[57] Thus it appears that the 'secondary' interaction is of primary importance for the successful aziridination of these α,β-unsaturated esters; it is secondary only in the sense that it does not lead to bonding in the product.



Scheme 55

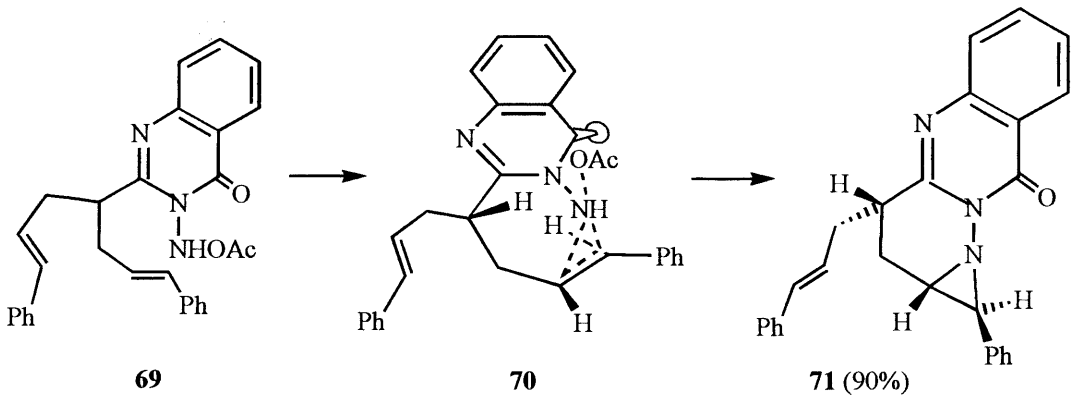
The secondary interaction between the (ester)C=*O* and the (Q)*C*=O as in **64** activates the alkene towards Michael addition at C_β by the lone pair on the acetoxyamino nitrogen *N*HOAc. At the same time, this interaction also reduces the electrophilicity of the Q-carbonyl group and thus increases the availability of the NHOAc lone pair since the Q-group is now less electron-withdrawing. Aziridine ring formation is completed by displacement of the acetoxy group from nitrogen (with inversion of configuration). In this TS$^{\#}$ **64**, therefore, bond formation between Q*N*HOAc and alkene C_β is running ahead of C_α–N bond formation but the reaction is concerted, *i.e.* there is a single TS$^{\#}$ and no dipolar intermediate **65c**.[69]

With electron-rich alkenes such as styrene, the TS$^{\#}$ geometry in **68** is assumed to be similar to that in **64** but with an attractive π–π interaction[70] between the phenyl ring and the quinazolinone carbonyl group.[71] Here, in contrast to the situation in **64**, C_β–N bond formation, with S_N2-type displacement of acetoxy, is believed to be running ahead of N–C_α bond formation; development of partial +ve charge at C_α is stabilised by the phenyl group. **64** and **68** have different orientations for their acetoxy groups corresponding to different configurations for the Q*N*HOAc chiral centre but, as was previously shown,[67] inversion at this nitrogen is fast on the timescale of the aziridination.



68

In contrast to the situation with aziridination of α,β-unsaturated esters, the secondary *endo*-overlap of the phenyl and the quinazolinone as in **68**, although preferred, is not mandatory for successful aziridination of styrene derivatives. Thus intramolecular aziridination in QNHOAc **69** (Scheme 56) where *endo*-phenyl/Q overlap is not possible for geometrical reasons, took place in excellent yield, presumably *via* TS$^{\#}$ **70** (there is a preference for a 7-membered TS$^{\#}$ in this reaction - see later); the aziridine product **71** was obtained as the single diastereoisomer shown as a result of a preference of the cinnamyl substituent for the equatorial-like position thus avoiding adverse interaction with QNH*OAc*[54] (at the time the reactive intermediate was believed to be the corresponding nitrene).



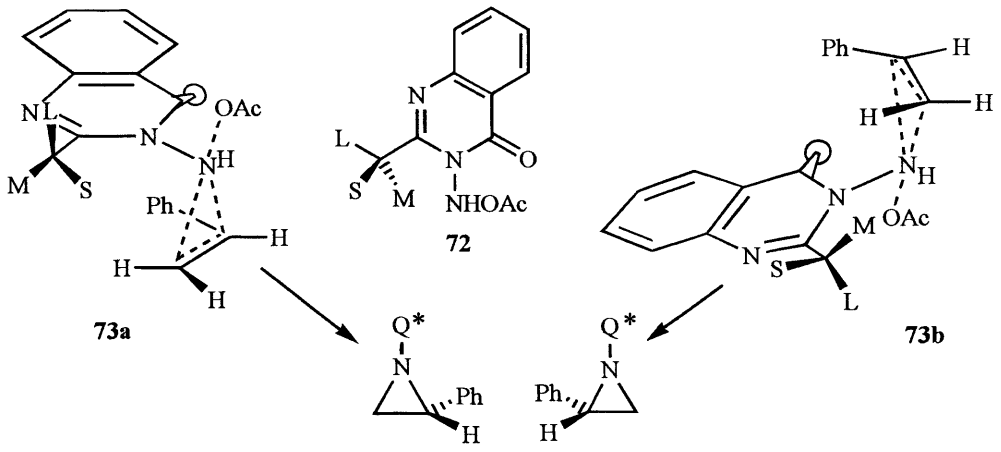
69 **70** **71** (90%)

Scheme 56

1.2.15 Diastereoselectivity in aziridinations using 3-acetoxyaminoquinazolinones

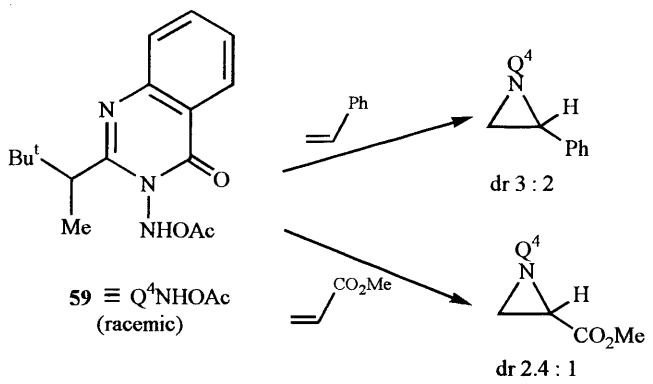
The presence of a chiral substituent on the Q2-position in QNHOAc means that aziridination of a prochiral alkene can lead to the formation of diastereoisomers.

The proximity of the chiral centre in the Q2-position of QNHOAc **72** to the alkene in the aziridination TS$^{\#}$ suggested that three-membered ring formation might take place diastereoselectively. Diastereoselectivity in these aziridinations is determined by which *face* of the prochiral alkene is attacked by QNHOAc **72**. Attack on each of the two faces of, for example, styrene is illustrated in Scheme 57 and diastereoselectivity will be obtained if TS$^{\#}$ **73a** is favoured over **73b** or *vice versa*. Note that in both of these TS$^{\#}$s, there is *endo*-overlap of Ph and Q rings and L is assumed to occupy the least hindered position in both cases.[72]



Scheme 57

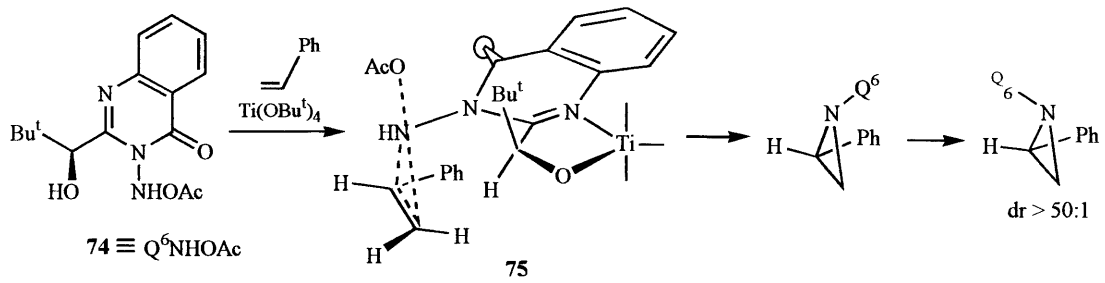
Using the 3-acetoxyaminoquinazolinone **59** (Q^{4}NHOAc), where *tert*-butyl, methyl and hydrogen are L, M and S respectively, and with the assumption that approach of the alkene is opposite the *tert*-butyl group, it is not clear that the *site preferences* for methyl and hydrogen in TS$^{\#}$ **73a** will be much preferred over those in TS$^{\#}$ **73b** and so diastereoselectivity would not be expected to be high, as found to be the case (Scheme 58).[73]



Scheme 58

Highly predictable site selectivity is possible in the TS$^{\#}$ for reaction of Q^{6}NHOAc **74** with alkenes in the presence of titanium(IV) *t*-butoxide (Scheme 59). The sense of diastereoselectivity in reaction with styrene is in agreement with an *in situ*-formed titanium alkoxide chelated with (Q)N–1 and a TS$^{\#}$ resembling **75**. The sites occupied by hydrogen

and by *t*-butyl are dictated by their differing bulk with the *t*-butyl group on the opposite side to the alkene. Consequently, the aziridination takes place highly diastereoselectively[72] (dr >50:1).

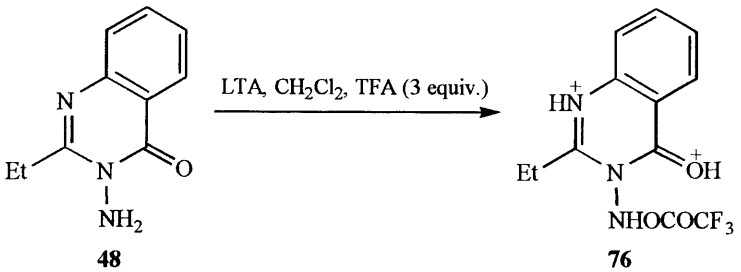


Scheme 59

1.2.16 Aziridination of alkenes using 3-amino-2-substituted quinazolin-4-(3H)-ones and lead tetraacetate-trifluoroacetic acid

Much of the work in this thesis is concerned with the effect of trifluoroacetic acid (TFA) on intramolecular reactions of QNHOAc compounds with aromatic rings tethered to the Q2-position and hence a detailed account of the effect of TFA on aziridination of alkenes with QNHOAc is given here.

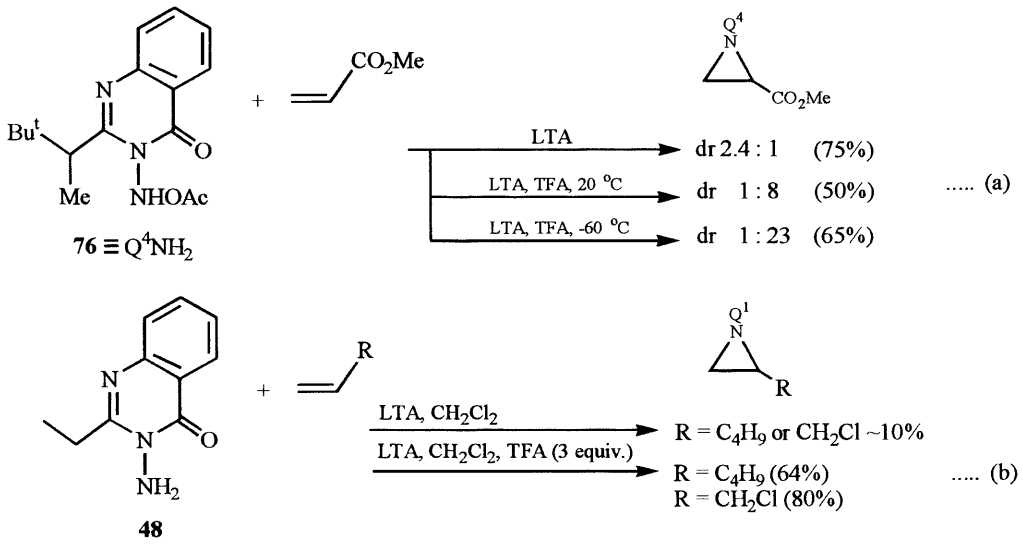
Although styrene and methyl acrylate react with Q^1NHOAc **49** to give the corresponding aziridines in 75% and 80% yields respectively, using only 1.5 mol eq. of alkenes, terminal alkenes such as hex-1-ene as previously mentioned gave yields of aziridine little better than 10%. The yields for epoxidation of terminal alkenes are improved by using buffered trifluoroperoxyacetic instead of peroxyacetic acid. In view of the apparent analogy between epoxidation using peroxyacids and aziridination using QNHOAc (Scheme 45), the effect of addition of TFA on aziridinations carried out *via* LTA-mediated addition of 3-aminoquinazolinones to alkenes was examined:[74] the assumption here was that either the acetoxy ligands on the lead in LTA would be replaced by trifluoroacetoxy ligands or exchange of acetoxy in QNHOAc by trifluoroacetoxy would take place, perhaps reversibly, giving Q^1NHOCOCF$_3$ **76** (Scheme 60).



Scheme 60

It had previously been shown by Tughan[73] that the presence of TFA unexpectedly improved the diastereoselectivity in aziridination of, for example, methyl acrylate by oxidative

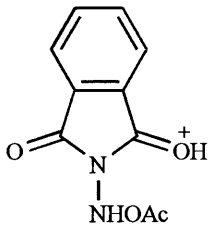
addition of Q^4NH_2 mediated by LTA (Scheme 61a) - at the time the intermediate was thought to be a *N*-nitrene. The presence of TFA in oxidative addition of Q^1NH_2 **48** to some otherwise unreactive alkenes greatly improved the yield of aziridines, *e.g.* hex-1-ene and allyl chloride (Scheme 61b). The same improvement in yield resulted from addition of a lead-free solution of Q^1NHOAc (held at –20 °C) to a solution of the alkene in dichloromethane containing TFA, *i.e.* the lead salts are not involved in this increase in yield.[74]



Scheme 61

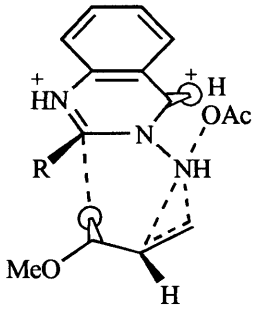
However, although NMR spectroscopic examination of solution of lead di-acetate free Q^1NHOAc in deuterochloroform at –40 °C in the presence of TFA (3 mol eq.) showed downfield shifts for the diastereotopic methylene protons of the ethyl group, the chemical shift of the *NH* proton was hardly affected and two acetate group methyl signals of equal intensity were visible, corresponding to free acetic acid (produced in the acetoxylation) and the QNHOAc-bound acetoxy group. So, in the presence of TFA, the acetoxy group appears to be neither rapidly exchanging nor to have been exchanged. Support for this conclusion came from the use of phenyl iodosoditrifluoroacetate (commercially available) or of lead tetra-trifluoroacetate in the oxidation, neither of which brought about the same enhancement of yield/diastereoselectivity as did addition of trifluoroacetic acid. The increased yields/diastereoselectivity in these aziridinations in the presence of TFA are, therefore, not the result of exchange of acetoxy by trifluoroacetoxy in Q^1NHOAc but must be a consequence of protonation of the quinazolinone ring. Since a minimum of three mole equivalents of TFA is required for enhancement of aziridination yields or diastereoselectivity, protonation on both the Q-carbonyl oxygen and on N-1 nitrogen as in **76** (Scheme 60) seems probable since these are likely to be the most basic sites in QNHOAc. Oxidation of *N*-aminophthalimide **24** with LTA in the presence of allyl chloride or hex-1-ene and TFA gave phthalimide (50–60%) as the only isolated product; *N*-aminophthalimide lacks the basic sites present in the quinazolone ring and so protonation will be less likely.

Thus protonation on a phthalimide carbonyl oxygen **77** is not favoured by aromaticity in the (hydroxy-substituted) hetero-ring as in the case with protonation of the quinazolinone carbonyl oxygen.[74]



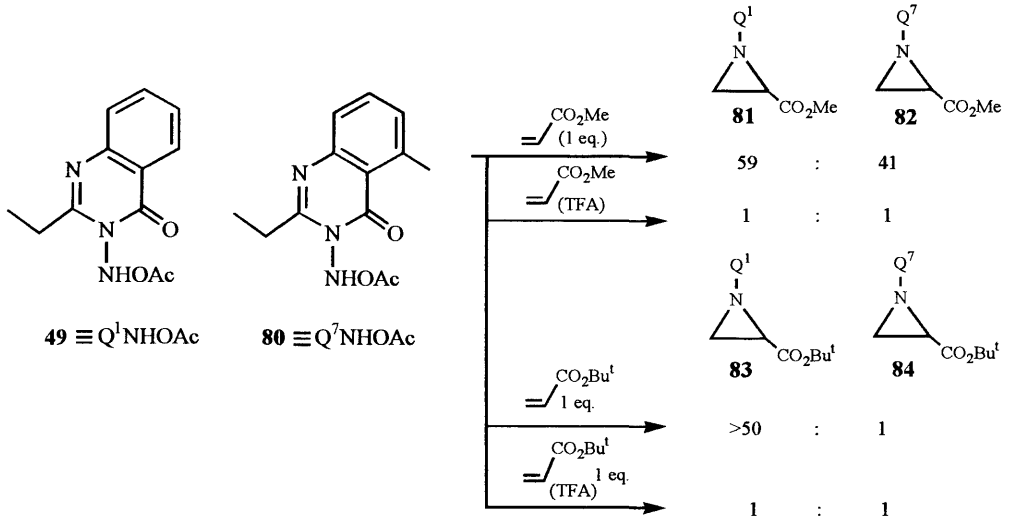
77

To account for the increase in diastereoselectivity brought about by TFA, it was earlier proposed by Tughan,[73] without experimental evidence, that protonation on *N*-1 of the quinazolinone ring resulted in a change in TS$^{\#}$ geometry from the usual (ester)C=*O*/(Q)*C*=O overlap in **64** (Scheme 54) to (ester)C=*O*/(Q)*C*=NH overlap as in **79**.



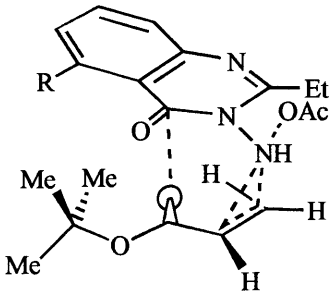
79

Thus the effect of N-1 protonation of the Q group is to favour overlap of the ester carbonyl oxygen with the now more electrophilic imine carbon **2** (*C*=$\overset{+}{\text{N}}$H). Experimental support for this proposed change in TS$^{\#}$ geometry has come from the work of Atkinson and Ulukanli[75] on competitive aziridination of α,β-unsaturated esters using the 3-acetoxyamino-quinazolinone **49** and its 5-methyl analogue **80** Q^{7}NHOAc (Scheme 62).

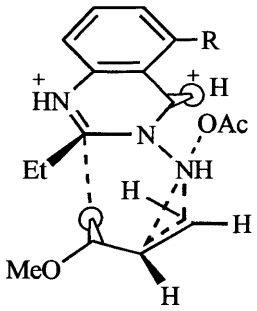


Scheme 62

Thus, in the competitive aziridination of methyl acrylate (1 eq.) by Q^1NHOAc **49** (1 eq.) and Q^7NHOAc **80** (1 eq.) only a slight excess of aziridine **81** over **82** was obtained. However, in competitive aziridination of *tert*-butyl acrylate (1 eq.) the aziridine **83** was produced in great excess over **84**. These changes can be rationalised in terms of $TS^{\#}$s **85a,b** and **86a,b** (Scheme 63) where a steric interaction between the 5-methyl and the *tert*-butyl group disfavours **85b** relative to **85a**.



85a R = H
85b R = Me



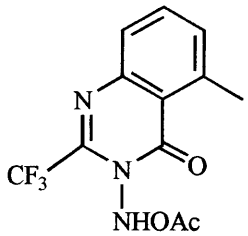
86a R = H
86b R = Me

Scheme 63

When these competitive aziridinations were carried out in the presence of TFA, however, 1:1 ratios of aziridine **81** : **82** and **83** : **84** were present in the crude reaction mixtures in each case. These gross changes in ratios in the presence of TFA are consistent with a switch in $TS^{\#}$ geometry to **86a,b** where the presence of the methyl group has no destabilising effect on $TS^{\#}$ **86b** relative to **86a** and so a 1:1 ratio of aziridines **83** and **84** is produced.

In the presence of TFA ($TS^{\#}$ **86a,b**) therefore, N-1 protonation of the quinazolinone takes place and the rate of aziridination is accelerated by the increased secondary interaction between the acrylate ester carbonyl oxygen and the $QC\overset{+}{=}NH$ which thereby facilitates Michael addition of the acetoxyamino nitrogen at C_β.

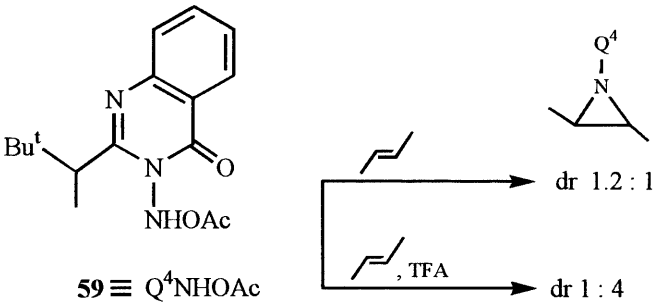
An analogous change in TS# geometry from (Q)*C*=O/(ester)C=*O* to (Q)*C*=N/(ester)C=*O* overlap was shown to occur using the 2-trifluoromethyl-1-substituted Q^8NHOAc **87** *even in the absence of TFA* using similar competitive aziridination reactions between Q^3NHOAc **57** and its 5-methyl-substituted analogue **87**.



87

Thus it appears that trifluoromethyl substituent is sufficiently electron-withdrawing to raise the electrophilicity at (Q)C–2 above that at C–4 and thereby bring about an analogous switch to that brought about by TFA.

Aziridination using QNHOAc-TFA cannot be applied to electron-rich alkenes, *e.g.* styrene which are polymerised by the TFA present. However, in aziridination of *trans*-but-2-ene with Q^4NHOAc **59**, the ratio of diastereoisomers obtained is changed from 1.2:1 in the absence of TFA to 1:4 in its presence (Scheme 64).[76]



Scheme 64

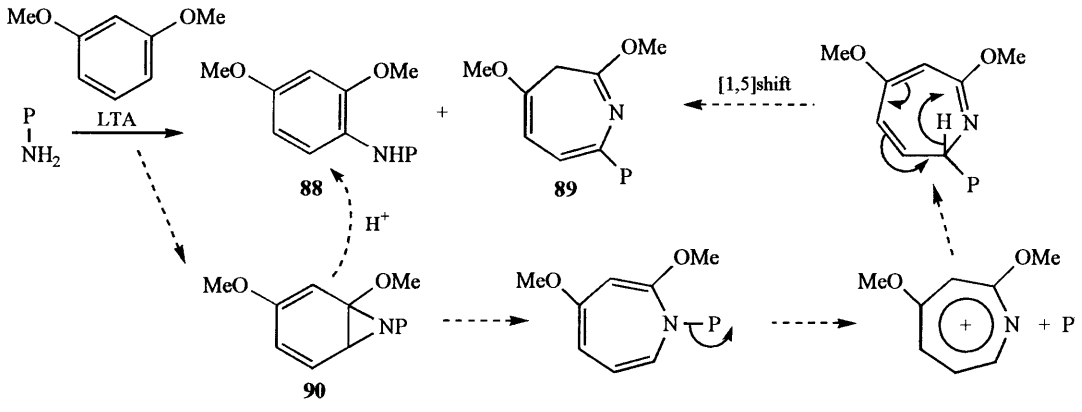
These results suggest that there is a secondary interaction between a methyl group of the alkene and, presumably, the (Q)C=O and that this interaction may also be switched to an alkene methyl/(Q)C=$\overset{+}{N}$H interaction in the presence of TFA.

1.2.17 Intermolecular aziridination of aromatic rings using PNHOAc 52 or PN̈: 18

Most of the work in this area is the work of D. W. Jones.[24,77,78]

In spite of the fact that the intermediate produced *in situ* by LTA oxidation of *N*-aminophthalimide, now known to be the *N*-acetoxyaminophthalimide **52**, adds to electron-rich and to electron-deficient alkenes, it fails to react with either benzene or anisole under normal conditions. Neither does reaction of these aromatic rings occur with phthalimidonitrene PN̈: **18**, generated by thermolysis of the 2-acetylbenzofuran-aziridination product **53** (Scheme 47).

Oxidative addition of *N*-aminophthalimide in the presence of a large excess of 1,3-dimethoxybenzene[24] gave the product **88** in 37% yield and a trace of the azepine **89** [Scheme 65, *cf.* Scheme 20].[27] Plausible intermediates in this and subsequent reaction schemes are indicated by dashed arrows.

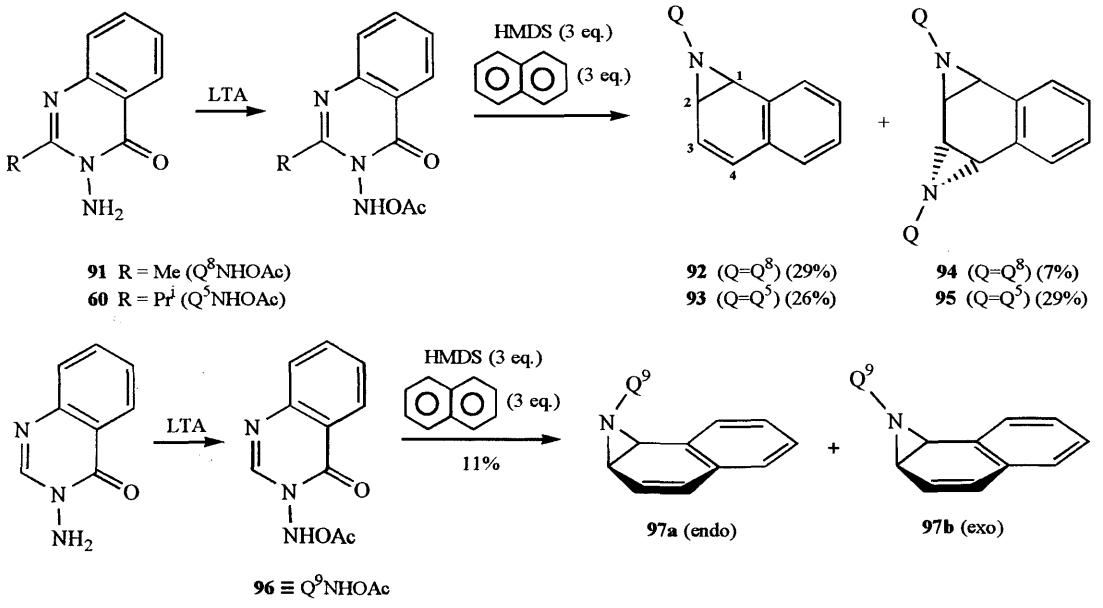


Scheme 65

It seems probable that the acetic acid, co-produced in this oxidation of *N*-amino-phthalimide with LTA, diverted the aziridinobenzene **90** to the substitution product **88** since the azepine **89** was formed as a major product by the mechanism suggested in Scheme **65** in the thermolysis of the phthalimidonitrene precursor **53** in benzene containing dimethoxy-benzene, conditions that avoid the production of acetic acid [*cf* Scheme 20].

1.2.18 Intermolecular aziridination of naphthalene using 3-acetoxyaminoquinazolinones

Intermolecular aziridination of naphthalene (3 eq.) with Q^5NHOAc **60** and with Q^8NHOAc **91** in the presence of HMDS (3 eq.) took place to give mono- and di-aziridination products **92-95** with the monoaziridine **92** being the major product (29%) from the reaction of Q^8NHOAc (Scheme 66). 1,2-Addition products in intermolecular reactions of naphthalene are seldom produced in yields greater than 1,2,3,4-addition products because after 1,2-addition, the remaining 3,4-double bond in the functionalised 6-membered ring will usually be more reactive than any of the double bonds in the parent naphthalene. Following these reactions by NMR at low temperature revealed that the kinetically-formed aziridine in each case was the *endo* as expected.[79]

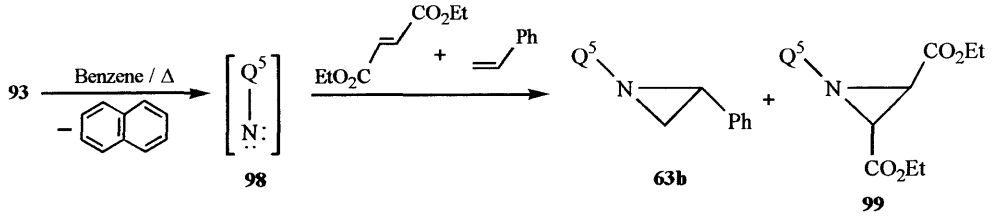


Scheme 66

Aziridination of naphthalene by *N*-acetoxyaminoquinazolinone **96** at –20 °C gave exclusively the corresponding *endo*-mono-aziridine **97a** (11%) from examination of the NMR spectrum of the crude reaction mixture and no bis-aziridine was formed: a mixture of *endo* and *endo-N*-invertomers **97a** and **97b** (~1:1) was present at room temperature.

Because, in this work, there appeared to be a correlation between the size of the Q2-substituent and the ratio of bis-aziridine to mono-aziridine formed, it was suggested that bis-aziridination took place only from the *exo-N*-invertomer; *endo* → *exo N*-inversion would be expected to be faster, the larger the Q2-substituent in Scheme 66.

Heating mono-aziridine **93** in benzene containing a mixture of styrene (3 eq.) and diethyl fumarate (3 eq.) gave the corresponding aziridines **63b** and **99** in a 1:1 ratio (Scheme 67). It is likely that the intermediate in this aziridination is the nitrene **98** as the same selectivity (1:1) for these two alkenes is found for this nitrene species generated by the route shown in Scheme 53.[79]

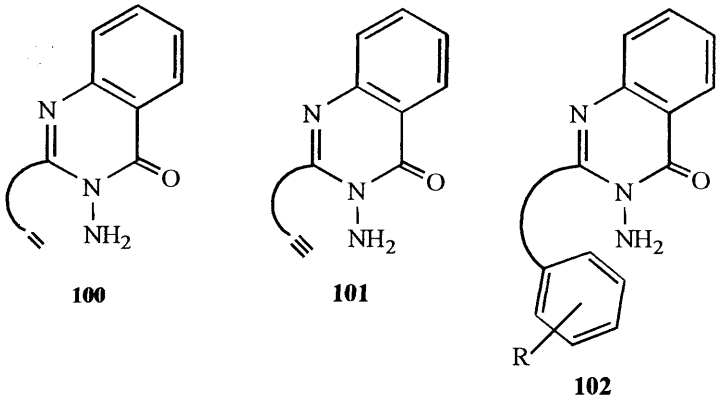


Scheme 67

1.2.19 Intramolecular aziridination of aromatic rings with QNHOAc and tether design

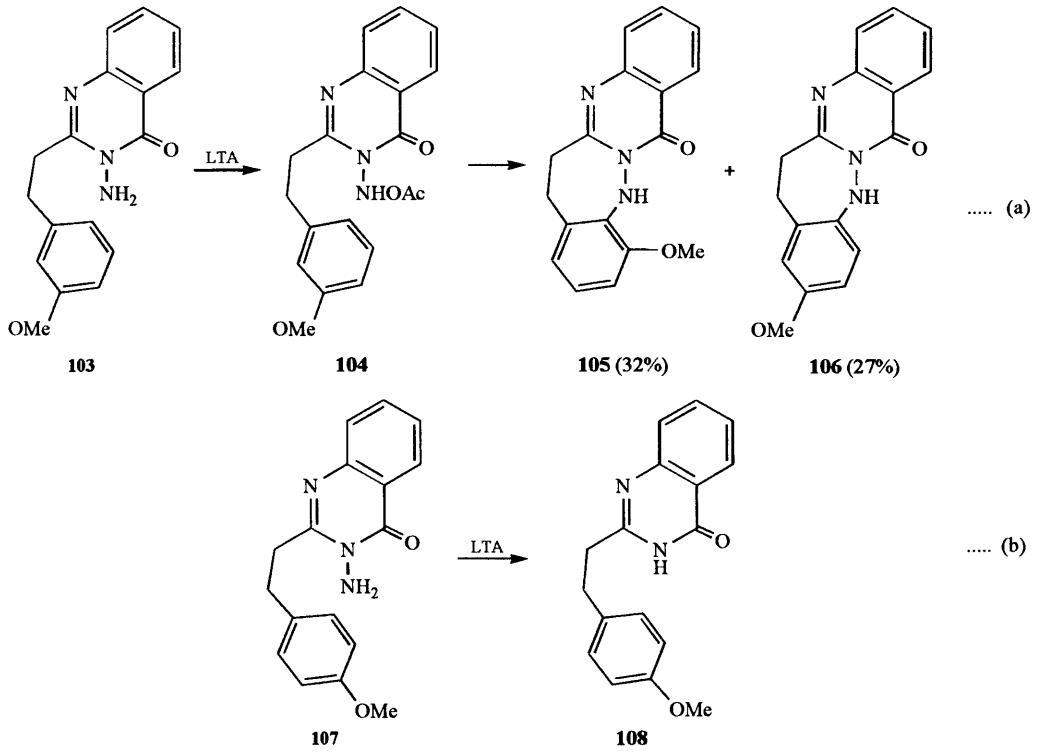
From the work done by Jones[24,25,77] described earlier (Scheme 65), electron-rich aromatic rings are able to react intermolecularly either with phthalimidonitrene PN̈: **18** or with what is now known to be *N*-acetoxyaminophthalimide **52**[63] and the isolated products from the reaction in Scheme 65 were either predominately the 3H-azepine **89** or the substitution product **88** according to whether acetic acid was present. The presence of at least two methoxy groups on the benzene ring was required for successful reaction.

From the early 1980s onwards, Atkinson *et al.* investigated the LTA-mediated oxidation of 3-aminoquinazolinones in which intramolecular reaction with double bonds **100**,[54,56] triple bonds **101**[55] or aromatic rings **102**[80,81] occurred. In each case, the reacting π-electron-containing functional group was tethered to the 2-position of the Q-ring by a carbon chain comprising at least two methylene groups.



The work to be described in this thesis is, for the most part, concerned with intra-molecular reactions of compounds resembling **102** and a detailed discussion of previous work done in this area is given here. The reactive intermediates were assumed at the time to be 3-nitrenoquinazolinones but are now known to be the 3-acetoxyaminoquinazolinones and are referred to as such in the following discussion. Initially, oxidations of the above QNH_2

102 compounds were studied using methoxyphenethyl as (Q)-2 substituents (Scheme 68). It was found that (a) a single methoxy substituent was sufficient for reaction with the aromatic ring to occur providing it was *meta* and (b) in the absence of a *meta*-methoxy, two methoxy groups were required, *e.g. ortho, para*. When no intramolecular reaction of the aromatic ring occurred, the only homogeneous product isolated was the 3H-quinazolinone *e.g.* **108** (Scheme 68b).

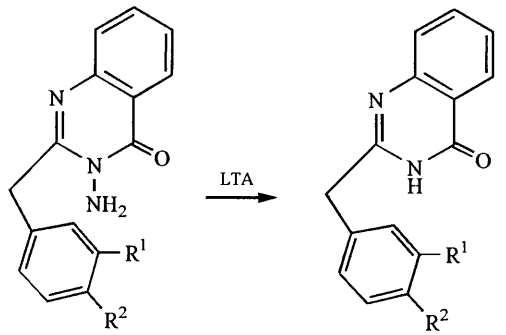


103 **104** **105** (32%) **106** (27%) ..... (a)

107 **108** ..... (b)

Scheme 68

In the LTA oxidation of 3-amino-2-(monomethoxyphenyl)quinazolinones **109** and **110** *i.e.* with a tether comprising one methylene group, no products from intramolecular reaction between the acetoxyamino group and the aryl ring were isolated, irrespective of the position of the methoxy group; again the only homogeneous products isolated were the 3H-quinazolinones **111** and **112** (Scheme 69).

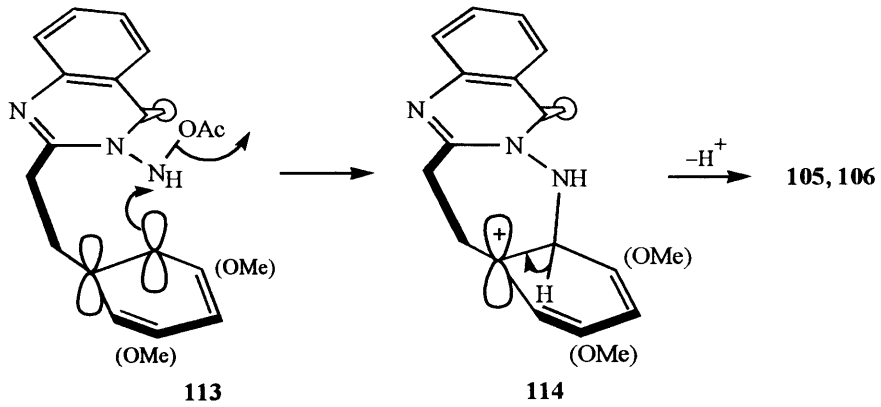


109 R^1 = H, R^2 = OMe
110 R^1 = OMe, R^2 = H

111 R^1 = H, R^2 = OMe
112 R^1 = OMe, R^2 = H

Scheme 69

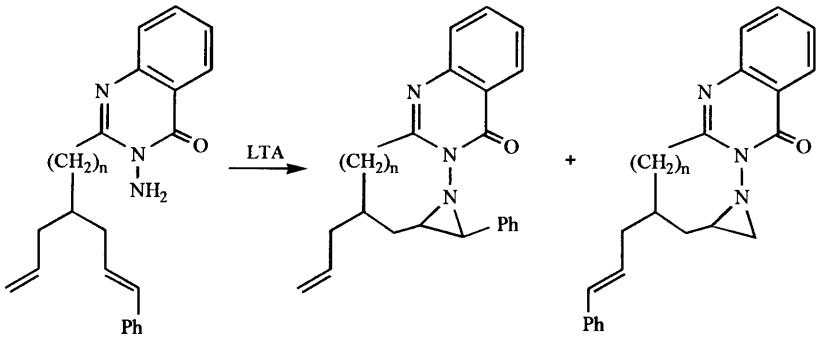
These results were rationalised by assuming that, in the transition state TS$^{\#}$ **113** for reaction of the QNHOAc with the aromatic ring, attack is geometrically constrained to take place *via* a 7-membered-containing ring **113** resulting in build up of carbocation character on C–1 in **114**. Stabilization of this carbocation is available by a methoxy substituent in the *meta*- position to the tether but not in the *ortho* or *para* (Scheme 70).[80]



Scheme 70

The products **105** and **106** are formed by loss of a proton from **114**, *i.e.* the reaction is in fact an electrophilic aromatic substitution on the aromatic ring by (Q)*N*HOAc and not an insertion into the aromatic C–H bond.

The conclusion that attack by the QNHOAc on the double bond of the aromatic ring is constrained to take place *via* a 7-membered ring was supported by a study of competitive intramolecular aziridination of the two double bonds in, *e.g.* compounds **115** and **116** (Scheme 71). The preference for attack on the phenyl-substituted double bond over the unsubstituted one in the bifurcated tether was very dependent on *n* (ratio 1.5:1 (n = 0) → 5.8:1 (n = 1) respectively) and consistent with significant carbocation build-up at the non-terminal double bond carbon when *n* = 0 (7-membered TS$^{\#}$) but a more concerted formation of the aziridine ring with *n* = 1 favouring attack on the phenyl-substituted double bond.[81]

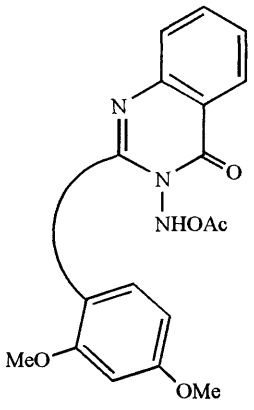


115 n = 0
116 n = 1

Scheme 71

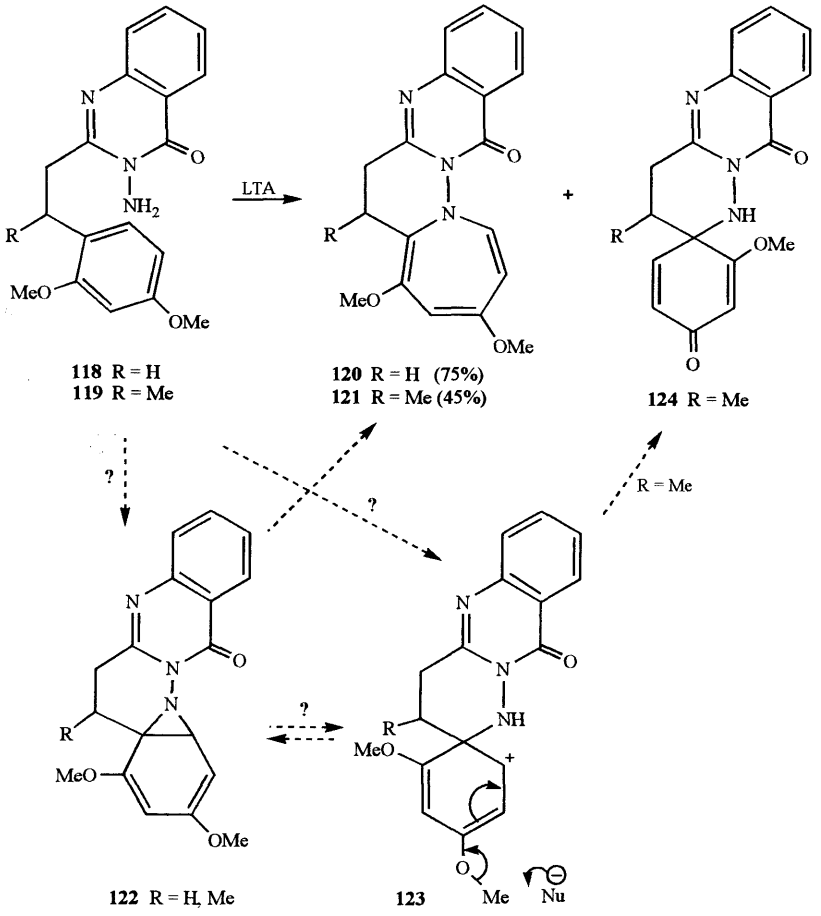
Atkinson and Gawad[82] studied the intramolecular reactions of QNHOAc compounds **117** having a (Q)-2 tethered 2,4-dimethoxyphenyl ring. They found that the nature of the

products was critically dependent on the number of methylene groups in the tether. The first-formed aziridines were invariably unstable and underwent further reaction (solvolysis) and the nature of the products, therefore, was dependent on the solvent that was used.



117

Thus, LTA oxidation of 2-(2,4-dimethoxyphenylethyl)-substituted quinazolones **118** and **119** in chloroform solution at room temperature gave the 1H-azepines **120** and **121** respectively[82a] (Scheme 72).

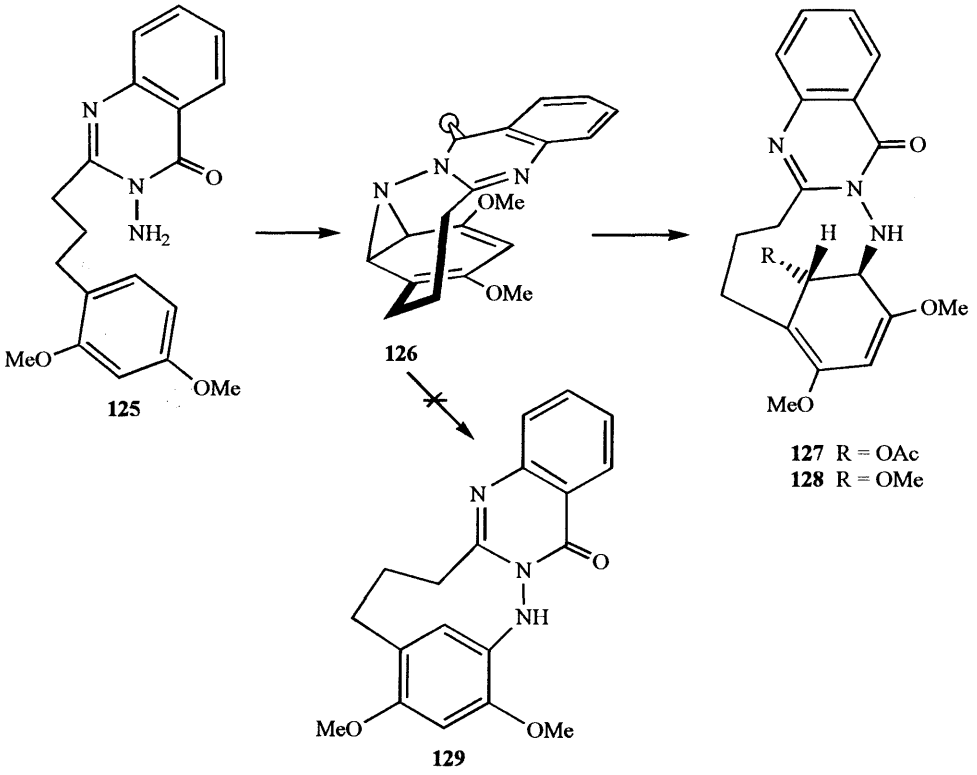


Scheme 72

1H-Azepines **120** and **121** were assumed to be formed *via* the benzeneimine intermediates **122** followed by $4\pi \rightarrow 6\pi$ electrocyclic ring-opening (cf. Scheme 20 in Part A).

Oxidation of QNH_2 **119** in methanol yielded no azepine **121** but the dienone **124**, formed, it was assumed, *via* the carbocation **123**. Atkinson and Gawad supposed that this species **123** was also a precursor of the aziridine **122**, *i.e.* that the presence of two methoxy substituents favours reaction *via* a 6-membered $TS^{\#}$. However, it was (and is) not clear whether aziridines **122** can be formed directly from the *N*-acetoxyamino compounds corresponding to QNH_2 **118** and **119**.

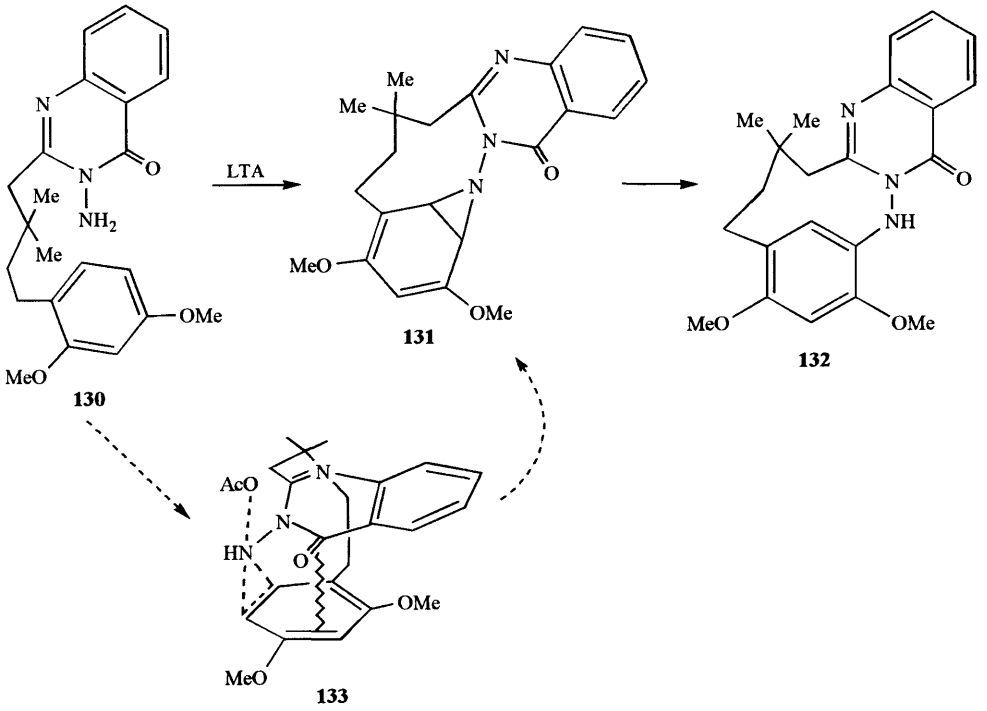
Very different results were obtained from oxidation of 3-amino-2-[3-(2,4-dimethoxyphenyl)propyl]quinazolinone **125** containing 3 carbons in the tether with LTA in benzene or chloroform and no azepine or dienone products analogous to those in Scheme 72 were isolated. The highly acid-sensitive product (27%) to which the bridged cyclohexadiene structure **127** was assigned (Scheme 73) was converted on attempted recrystallization from methanol into **128**, in which the acetoxy group had been replaced by a methoxy group. Oxidation of QNH_2 **125** with LTA in methanol also gave **128** directly in 29% yield. The precursor to cyclohexadiene **127** and the intermediate in conversion of **127** into **128** with retention of configuration was assumed to be aziridine **126** (Scheme 73).[82b]



Scheme 73

Elimination of the elements of acetic acid or methanol from cyclohexadienes **127** or **128** respectively, to give the aromatic dimethoxybenzene ring-containing derivative **129**, is prevented by the strain in this *meta*-cyclophane (Bredt's rule). However, oxidation in

benzene of QNH_2 **130** in which the dimethoxybenzene ring was tethered to the Q2-position by a chain of four carbons, gave a single crystalline product having the *meta*-cyclophane structure **132** (Scheme 74) *via*, it is assumed, aziridine **131**.[82c]

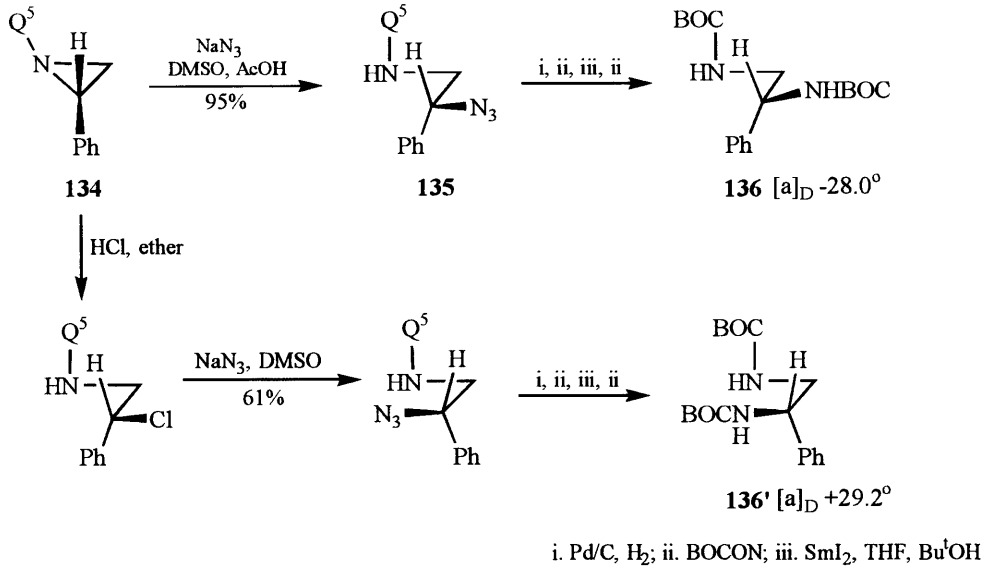


Scheme 74

The preference for intramolecular aziridination of the more distant 5,6-double bonds of the 2,4-dimethoxyphenyl ring in formation of **126** and **131** was in contrast to aziridination of the double bond of this ring adjacent to the tether in **122**. This difference was ascribed to preferred $TS^{\#}$s leading to aziridines **126** and **131** in which an attractive *endo*-interaction (*cf.* **68**) between a methoxylated double bond and the Q-carbon group was made possible by the increased tether length as illustrated in **133**.

1.2.20 N(Q)-aziridines as starting materials for preparation of chirons

A chiron is a small molecule containing one or two chiral centres and one or more functional groups which is available in enantiopure form.[83] Chirons are therefore useful for synthesis of target molecules in enantiopure form. The N(Q)-aziridines previously prepared in enantiopure form have (i) been ring-opened regiospecifically, (ii) have been freed from the Q group to provide useful chirons *e.g.* Scheme 75.[84]



Scheme 75

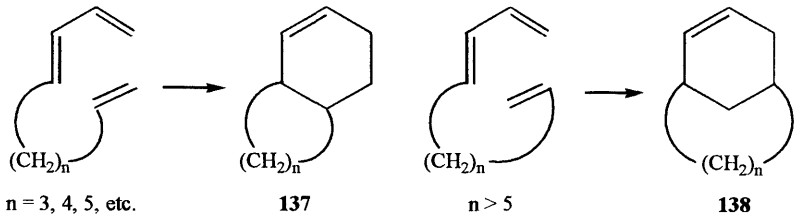
Cleavage of the Q^6-N bond was efficiently accomplished by samarium diiodide. By this means both enantiomers of the protected 1,2-diamine **136** and **136'** have been obtained.

Much of the work in this area has been directed towards using the Q-group on these aziridines to control the regio- and stereo-selectivity of the 3-membered ring-opening. The Q-group is also sufficiently electron-withdrawing to stabilise developing –ve charge on the nitrogen in aziridine ring-opening by nucleophiles, *e.g.* ring-opening of **134** → **135** by azide in Scheme 75.

1.3 Tether design in intramolecular reactions; application to intramolecular reactions of 3-acetoxyaminoquinazolinones

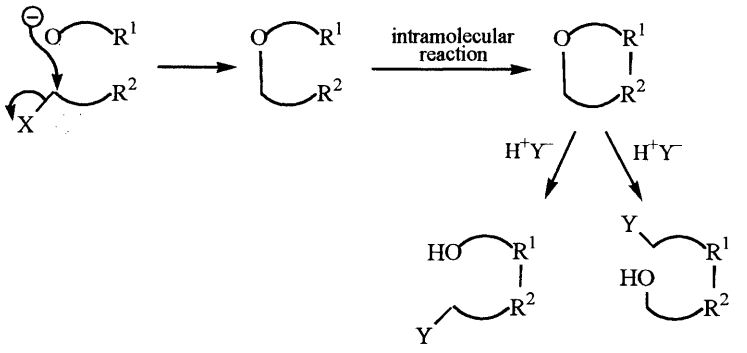
A properly designed tether can greatly increase the reaction rate between the two connected reactants by its favourable effect on the entropy of activation $\Delta S^{\#}$. An appropriately located chiral centre in the tether may also result in high diastereoselectivity in formation of the product. In many, if not most, cases the tether must be fissionable (disposable[85]) – it must be cleaved in a controlled way after intramolecular reaction to allow conversion to the required substituents in the product.

When considering tether length, the most important factor is that it must be sufficient to accommodate the $TS^{\#}$ for the reaction. Complete regioselectivity in a predictable sense results from limiting the tether length. Thus a 3- or 4-atom tether in the Diels-Alder reaction with the diene linked at its terminal position can only give the fused product **137**; with a longer tether, formation of the bridged product **138** becomes competitive (Scheme 76).



Scheme 76

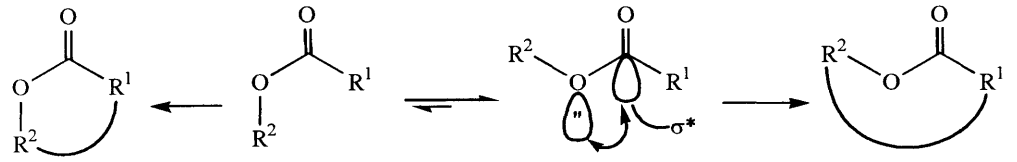
The fissionable element of the tether can also serve to link the two molecules to be reacted. Single atoms *e.g.* O, S, B or Si as atoms in the tether have been widely used because they allow easy linking of the reactants under mild conditions (Scheme 77).



Scheme 77

Cleavage of the C–O bond in the intramolecular cyclisation product can occur in two ways *i.e.* chemoselectivity cannot be guaranteed.

An ester is a potentially useful fissionable linkage in a tether because it is easily made from the corresponding alcohol/acid and also easily cleaved in the cyclised product. However, the ester does have a high preference for the s-*cis* **140** form over the s-*trans* **139** (Scheme 78).

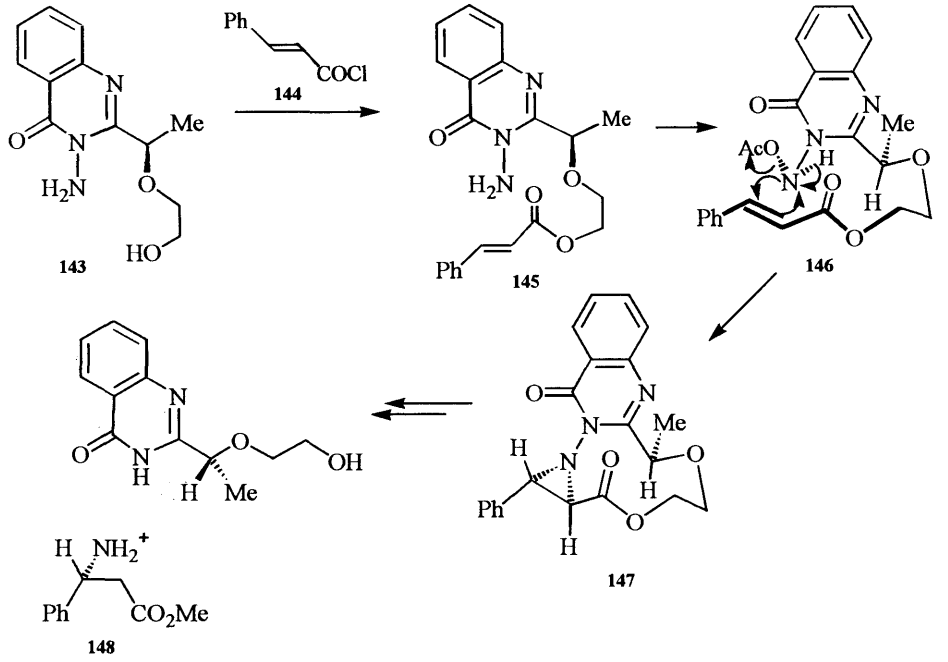


142 **139** s-*trans* **140** s-*cis* **141**

Scheme 78

This conformational preference arises as in **140** from overlap of the lone pair (n) in an sp^2 orbital on the ether-type oxygen with the σ* orbital of the C=O (n–σ*).[86] This preference for **140** means that cyclisation to **141** will require more atoms in the tether unless the cyclisation can be carried out at a temperature high enough to populate the s-*trans* conformation **139** and allow cyclisation directly to **142**.

Draycott *et al.*[87] have shown that intramolecular aziridination in LTA oxidation of **145** takes place completely diastereoselectively to give aziridine **147** (Scheme 79). The α,β-unsaturated acid *via* its acid chloride **144** was linked to the 3-aminoquinazolinone **143** bearing a terminal alcohol on the 2-substituent.

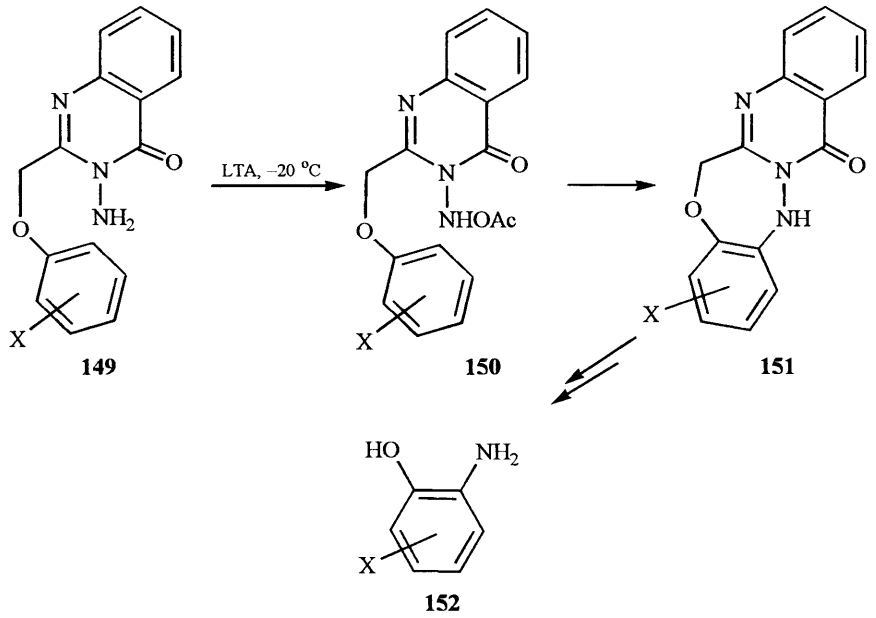


Scheme 79

In the TS[#] **146**, the preferred s-*cis* conformation of the ester can be nicely accommodated and the preferred equatorial location of the methyl group on the chain-like segment of the tether directs aziridination onto one diastereoface of the double bond, *i.e.* gives rise to a single diastereoisomer of the aziridine product **147**. One of the newly created chiral centres was retrieved in the conversion of **147** to the β-amino acid **148**. Since the QNH_2 **143** was enantiopure and the aziridination is completely diastereoselective, the amino acid **148** was recovered in enantiopure form.

In this thesis, our interest was the use of fissionable tethers in the intramolecular reaction of QNHOAc species with aromatic rings linked to the Q2-position. The advantage of having such a tether would be that the aromatic ring, modified by intramolecular reaction with QNHOAc could be freed from the Q-ring by fission of both the tether and the N–Q bond.

In Scheme 80, for example, intramolecular attack in **150** on the aromatic ring to give **151** followed by cleavage of the tether and the N–Q bond would give the corresponding *o*-aminophenol **152**.



149 **150** **151** **152**

Scheme 80

Efficient reductive cleavage of the Q–N bond can be accomplished (since 1992) using samarium iodide.[88] Although this reagent is expensive, it can be used in less than molar equivalent quantity in the presence of magnesium which reduces $Sm^{3+} \rightarrow Sm^{2+}$ *in situ*.[84]

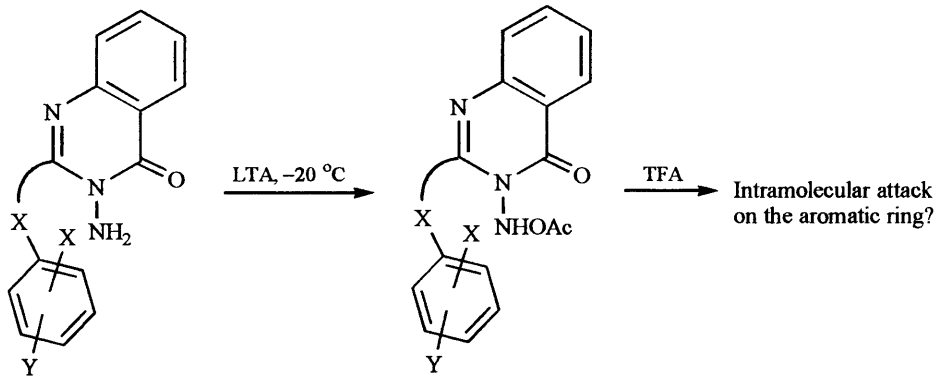
Since, as outlined above, there are ways in which the acetoxyamino group can attack the tethered aromatic ring other than that in Scheme 80, this strategy could be broadened to provide synthesis of other (Q–free) products from modification of the aromatic ring (including desaromatisation: see later).

CHAPTER 2

Intramolecular reactions of 3-acetoxyamino-2-(arylalkyl or aryloxyalkyl)quinazolin-4(3*H*)-ones

When the work described in this thesis was started in 1990, the beneficial effect of adding TFA on the yields of aziridines from QNHOAc compounds and less reactive alkenes had only recently been recognised.[74]

One of the initial objectives of the work described in this thesis was to examine whether the effect of adding TFA would be to bring about intramolecular reaction of QNHOAc compounds with otherwise unreactive aromatic rings tethered to the quinazolinone ring at C–2 (Scheme 81).



Scheme 81

The work of Gawad in this area,[82] referred to in the Introduction, had shown that attack on aromatic rings, activated towards electrophilic attack by the presence of two methoxy groups, took place to give a variety of products depending on the length of the (all-carbon) tether. Similarly (see Introduction), Woodthorpe *et al.*[80] had shown that any attack on ethyl-tethered monomethoxyphenyl rings was very dependent on the position of the methoxy group (Scheme 68). Thus, in the *p*-methoxyphenyl case **107**, no intramolecular reaction with (what is now known to be) the (Q)-3-acetoxyamino group took place and the only product was the 3*H*-quinazolinone **108**.

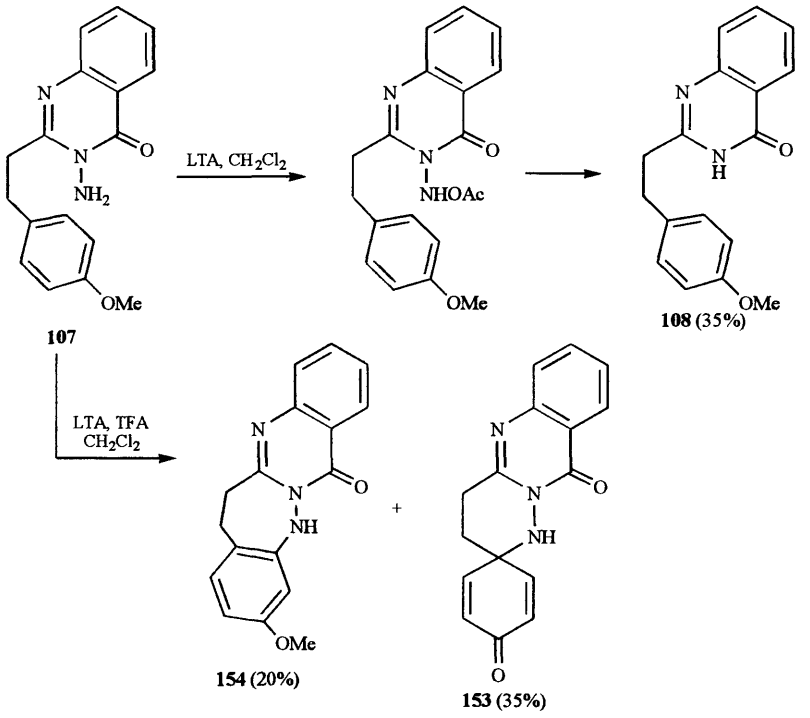
2.1 Reaction of QNH$_2$ 107 with LTA in the presence of TFA

In this work, the 3-aminoquinazolinone **107** was synthesised by the previously described method (Scheme 33) and the reaction with LTA carried out in the presence of TFA.

A discovery made in this work was that the highest yields of intramolecular reaction products in the presence of TFA were obtained when a lead-free solution of the QNHOAc compound, prepared by reaction of QNH$_2$ with LTA at ~ –15 °C, was added dropwise but briskly, whilst being maintained at < –10 °C, to a stirred solution of TFA (3 eq.) in dichloromethane held at room temperature. This procedure **B** was superior to that in which LTA was added to a solution of QNH$_2$ and TFA (procedure **C**), probably because intermolecular reactions of (protonated) QNHOAc with QNH$_2$ or with itself are avoided or minimised and intramolecular reaction, which takes place directly on addition to the dichloromethane-TFA solution, is favoured. On a small scale, the cold, practically lead-free solutions of the

QNHOAc required for dropwise addition above, can be prepared by carrying out the LTA oxidation of QNH_2 at –20 °C (see Experimental) and by filtering the solution using a Pasteur pipette and a cotton wool plug.

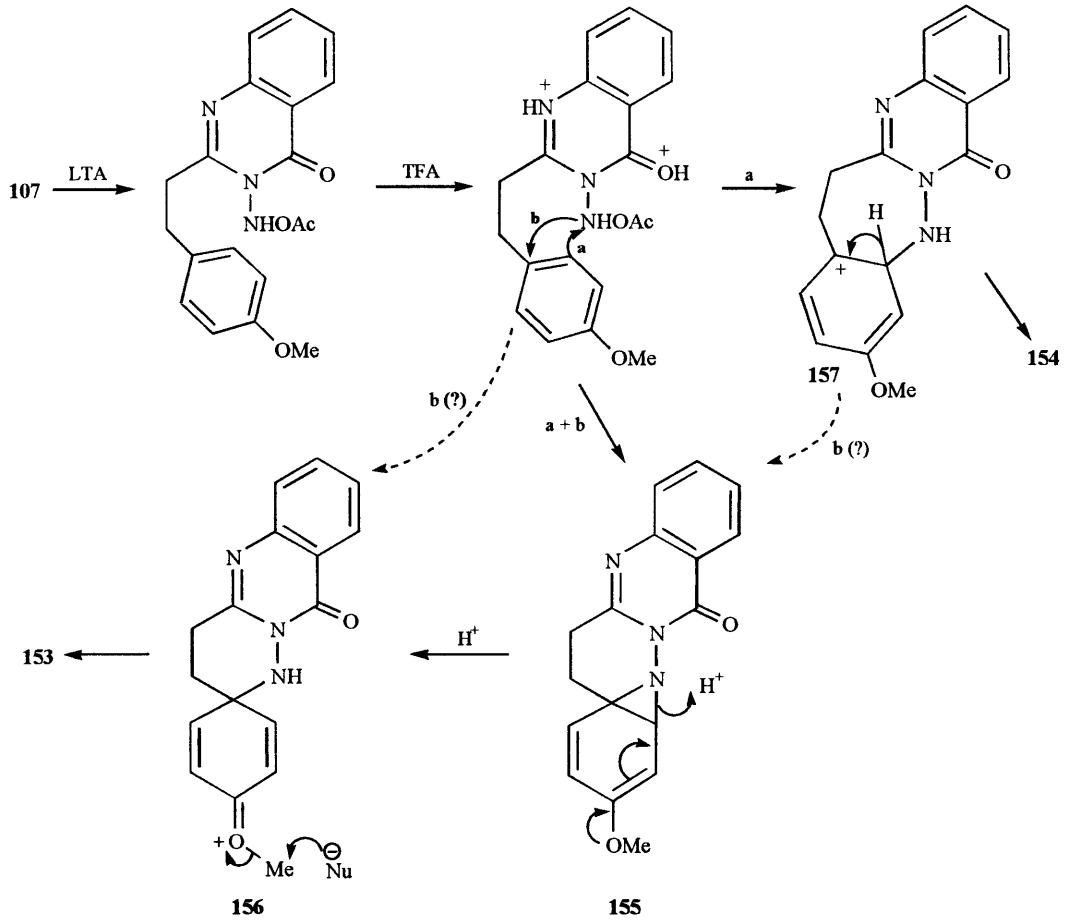
Using this procedure **B**, two products were isolated which were identified as the dienone **153** and the *ortho*-substitution product **154** (Scheme 82).



Scheme 82

Formulation of the 7-membered ring substitution product **154** was supported by the presence of an N–H in its IR spectrum (λ_{max} 3275 cm^{-1}), from its mass spectrum (M^+ 293) and, in particular, by the presence of signals in its NMR spectrum from a 1,2,4-trisubstituted aromatic ring including a doublet at δ 6.70 with *J* 3Hz for one of the *meta*-coupled protons. The structure of the dienone **153** was confirmed by its ^1H NMR spectrum with two doublets (further splitting visible since this is an AA'BB' system) at δ 6.9 and 6.2 and from characteristic peaks in the IR spectrum at λ_{max} 3215 (NH) and 1660 cm^{-1} (α,β-unsaturated ketone).

Formation of an analogous 4-(Q)-aminocyclohexadienone derivative **124** had been previously obtained by Gawad by oxidation of QNH_2 **119** with LTA in methanol[82a] (Scheme 72) and conceivably the mechanism of formation of the dienone **153** is analogous to that proposed by Gawad (b in Scheme 83).



Scheme 83

The benzenimine **155** is a possible primary product (in the *o,p*-dimethoxy analogue the major product in chloroform solution instead of methanol is the azepine from electrocyclic ring-opening of the analogous benzenimine - compare Introduction, Scheme 20) whose ring-opening to give **156** and hence dienone **153** in the presence of TFA would be expected to be very fast. However, ring-opening in the alternative sense to give **157** and hence, by proton loss, the 7-membered ring-containing *o*-substitution product **154** seems unlikely in view of the absence of any stabilisation of the carbocation by the methoxy group in **157**.

If benzenimine **155** is not a common intermediate, the genesis of carbocation **157** must be *via* direct attack on the *ortho*-position of the *para*-methoxyphenyl ring *via* a 7-membered $TS^{\#}$ as was previously proposed by Woodthorpe *et al.*[80] for the formation of the analogous *ortho*-substitution products from the *meta*-methoxyphenyl analogue **103** of QNH_2 **107**. In fact, it is possible that carbocation **157** is the common intermediate with benzenimine **155** formation competitive with proton loss to give *ortho*-substitution product **154**. If this is the case, it suggests that, at least in the presence of TFA, the aziridination in this case is a stepwise process with direct formation of a fully-developed albeit short-lived carbocation intermediate.

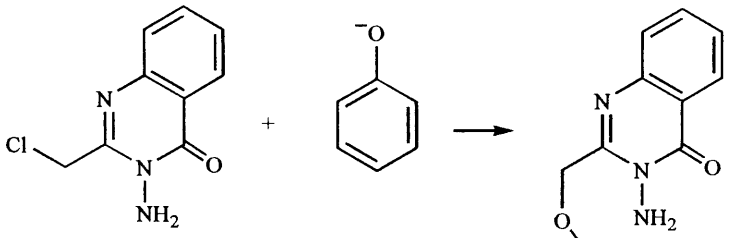
It is clear from the formation of dienone **153** and *ortho*-substitution product **154** that, just as the effect of adding TFA is to increase the yields of aziridines from unreactive alkenes so

its presence also facilitates attack on the less reactive aromatic ring in the intramolecular reaction in Scheme 82. It is also clear that the increased reactivity of the QNHOAc species in Scheme 82 in the presence of TFA is not dependent on, or mediated by, an *endo* interaction between the protonated Q-ring and the aromatic ring because any such interaction is absent in this case.

2.2 Reaction of QNH_2 159 containing an oxymethyl tether with LTA in the presence of TFA

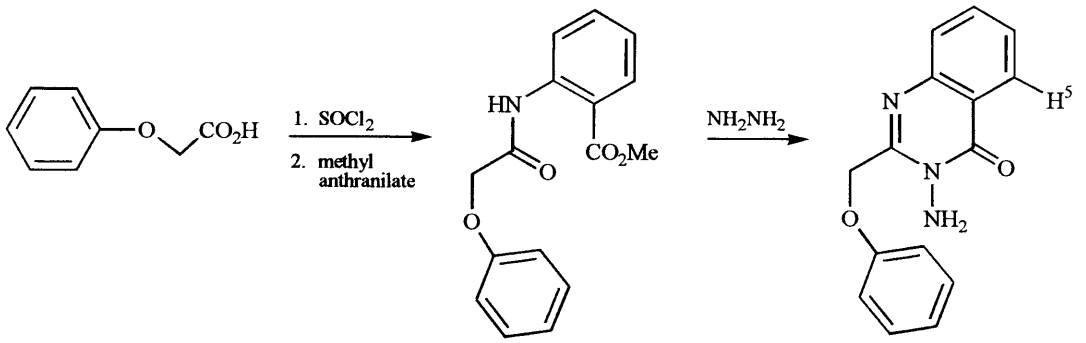
Following on from successful intramolecular reaction in LTA oxidation of QNH_2 **107** in the presence of TFA, the preparation and LTA oxidation of QNH_2 **159** was studied.

The oxymethyl tether in QNH_2 **159** was potentially advantageous being cleaved either by acid or by hydrogenolysis (the O–CH_2 bond is cleaved by samarium(II) reduction).[89] A potential application in *ortho*-amination of the phenoxy ring is described in the Introduction (Scheme 80). Although a possible direct route to QNH_2 **159** would be reaction of phenol as its anion with the known 3-amino-2-chloromethyl quinazolinone **158** (Scheme 84), its synthesis was in fact accomplished by the standard route shown in Scheme 85 taking advantage of commercially available phenoxyacetic acid.



158 **159**

Scheme 84

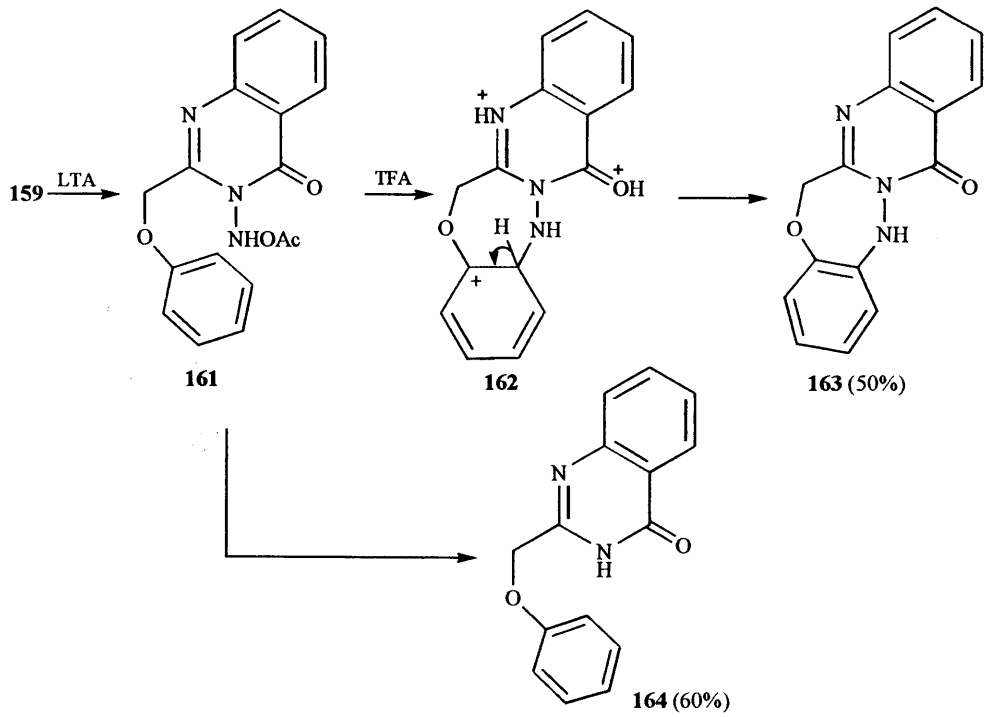


160 **159**

Scheme 85

In the general procedure exemplified in Scheme 85, the acid chloride formed with thionyl chloride was added, without purification, to methyl anthranilate (2 eq.) in ether and the insoluble solid methyl anthranilate hydrochloride separated by filtration. Unchanged methyl anthranilate was extracted from the ether solution with acid and the recovered *N*-acylamino-anthranilate *e.g.* **160** heated with hydrazine in ethanol or butanol. Where the starting acid was α-substituted, it was sometimes necessary to heat with hydrazine hydrate in ethanol in a sealed tube at ~120 °C for a few hours. All of the 3-aminoquinazolinones prepared in this work were crystalline compounds. In their NMR spectra, the H–5 proton in the aromatic ring (see **159**) is the lowest field proton at δ 8.2 and the NH_2 signal resonates at δ ~5.1 as a broadened singlet.

Reaction in QNHOAc **161** of the aromatic ring was expected to result in substitution in the *ortho*-position by analogy with analogous reaction of the 3-amino 2-[*m*-methoxyphenyl-ethyl]quinazolinone **103** (Scheme 68). Thus attack *via* the required 7-membered ring intermediate **162** (Scheme 86) would apparently be favoured by stabilisation of the carbocation by the adjacent oxygen in the tether and lead to the formation of *ortho*-substitution product **163** as in Woodthorpe's case discussed earlier.



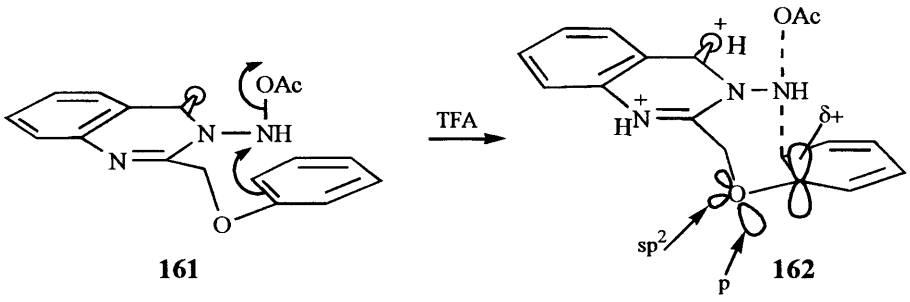
Scheme 86

However, in the event, reaction of QNH_2 **159** with LTA in dichloromethane in the absence of TFA gave none of the cyclised product **163**; the only identified product was the 3*H*-quinazolinone **164** in 60% yield (Scheme 86).

These 3*H*-quinazolinones were readily identifiable from M^+ in their mass spectra (loss of the elements of NH from the starting QNH_2) and from the presence of a broadened low field

(δ 8–10) signal for the N–H protons in their NMR spectra; the H–5 proton in the quinazolinone ring resonated at slightly lower field (δ 8.25–8.30) by comparison with this proton in QNH_2 compounds (δ 8.20). Most were polar, high melting (> 200 °C), crystalline compounds, insoluble in dry ether which often allowed their separation from other reaction products by trituration.

To understand the unexpected unreactivity of the oxyaryl ring towards the 3-acetoxy-amino group in **161**, it is necessary to examine the transition state ($TS^{\#}$) and, in particular, the orientation of the lone pairs on the oxygen in the tether, one of which must be available for stabilisation of the carbocation intermediate **162** (Scheme 87).



161 **162**

Scheme 87

Thus the 3-dimensional representation of the $TS^{\#}$ in **162** illustrates that the lone pair in the p-orbital of an sp^2-hybridised ether oxygen is orthogonal to the adjacent vacant p-orbital on the ring (the carbocation) and thus no stabilisation by p–p overlap of this oxygen of the carbocation is possible (stabilisation by either lone pair would also be minimal if the oxygen were regarded as sp^3-hybridised). Thus, since the carbocation-stabilising property of the ether oxygen is removed ('steric inhibition of resonance'), it acts only in an inductively electron-withdrawing sense and destabilises formation of the carbocation, *i.e.* attack on the aromatic ring is disfavoured more in this case than on the p-methoxyphenyl ring. [The corresponding methylene group in QNH_2 **107** constitutes an activating substituent.]

Again the more powerful reagent present in the presence of TFA was demonstrated by the isolation of the *ortho*-substitution product **163** (50%) when the oxidation of QNH_2 **159** was carried out using procedure **B**. This substitution product **163** contained only four aromatic protons other than those from the Q-ring and an N-H stretching frequency at 3250 cm^{-1} in the IR.

2.3 Intramolecular reactions of 3-acetoxyaminoquinazolinones with aromatic rings linked to the quinazolinone 2-position by a tether 3 atoms in length

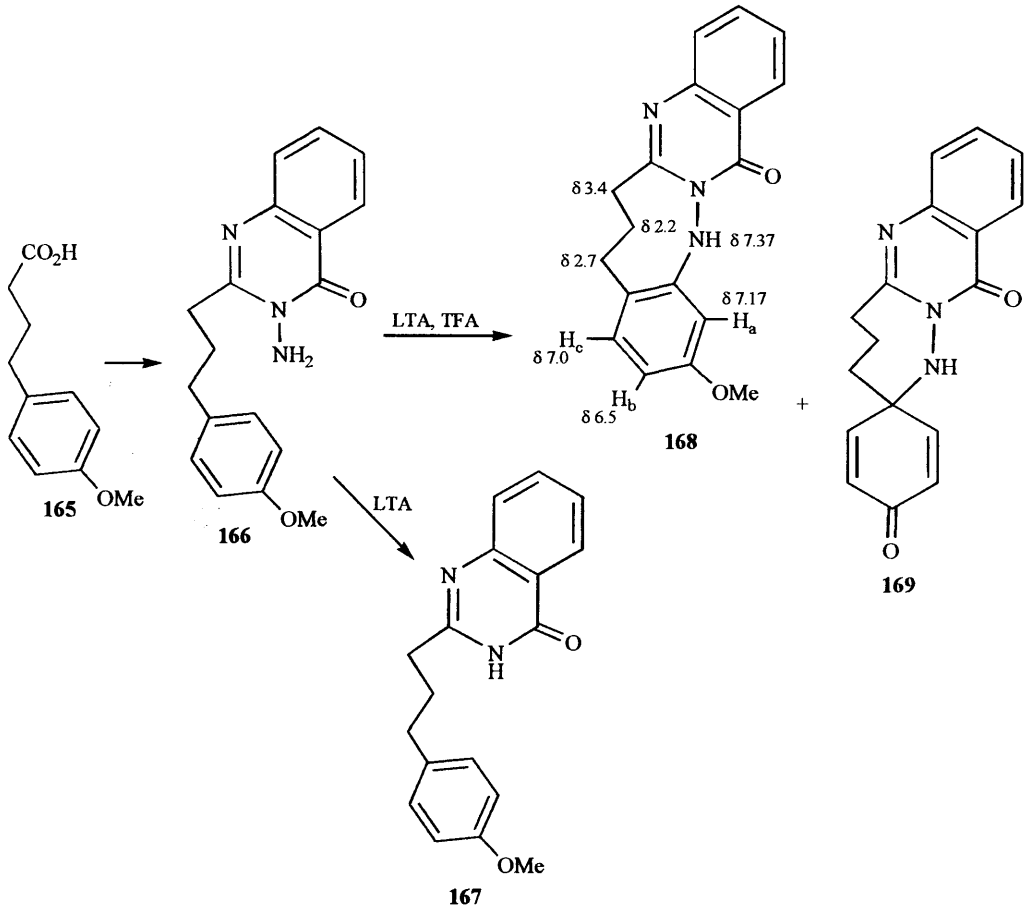
As previously outlined in the Introduction, the work of Gawad[82a-c] strongly suggested that *endo*-overlap of a tethered (dimethoxy-substituted) aromatic ring and the quinazolinone ring is important in intramolecular reactions of the intermediate QNHOAc compounds in

Schemes 73 and 74 when n in the tether is ≥ 3 though at the time the intermediates in these reactions were thought to be *N*-nitrenes.

It was of interest, therefore, to examine the intramolecular reactions of less reactive aromatic rings attached to the 2-position of QNHOAc compounds by a tether of 3 atoms and to investigate whether the presence of TFA brought about the intramolecular reaction of otherwise unreactive aromatic rings.

2.3.1 Oxidation of QNH_2 166 with LTA-TFA

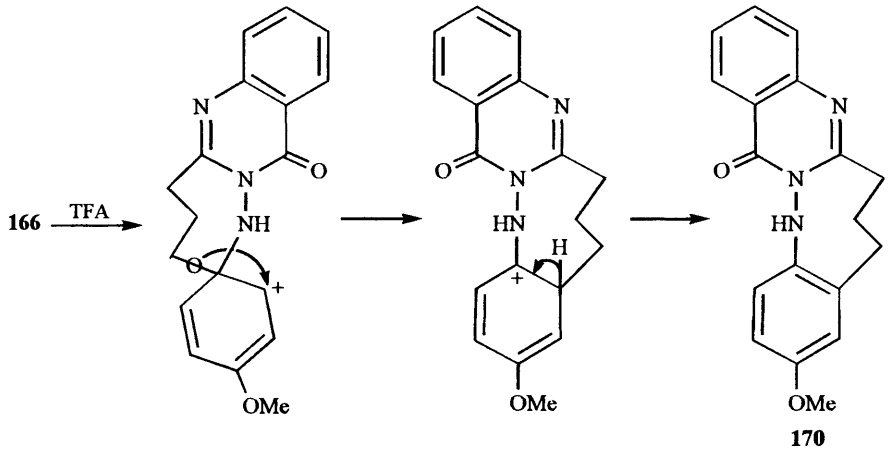
QNH_2 **166** (supplied by Dr. R. S. Atkinson) was prepared from the commercially available acid **165** in the usual way (Scheme 88). Oxidation in the absence of TFA gave 3H-quinazolinone **167** as the only pure compound isolated. Oxidation in the presence of TFA (procedure **B**) gave products analogous to those previously obtained from QNH_2 **107** namely *ortho*-substitution product **168** and dienone **169**. The structure of **168** was supported by ^1H NMR with the pattern of signals present indicating the presence of a 1,2,4-trisubstituted aromatic ring and by IR (NH 3280 cm^{-1}) and MS m/e 307.



Scheme 88

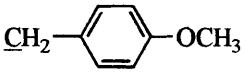
We were particularly concerned to eliminate structure **170** for this product – the result of possible rearrangement subsequent to attack on the *para*-methoxy-phenyl ring of **166** (Scheme 89) since an analogous rearrangement has been shown to occur in this work in

intermolecular reaction of *para*-xylene with 3-acetoxyamino-2-ethylquinazolinone (see Chapter 4).



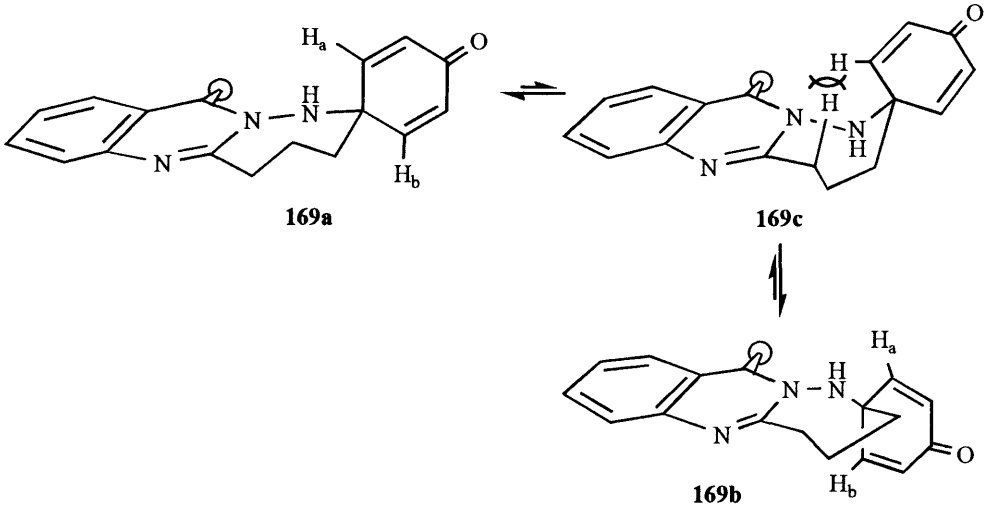
Scheme 89

A clear differentiation between **168** and **170** cannot confidently be made from the chemical shifts of protons in the methoxy-substituted aromatic ring. However, with the aid of a NOESY spectrum that identifies the protons which are close together in space, the structure was confirmed as **168** rather than **170**. Thus, the broadened singlet at δ 7.17 must be H_a and is close to the OMe at δ 3.72 and to NH at δ 7.37. The methoxy group is close to H_a and H_b (δ 6.5) and, most importantly, H_c at δ 7.0 is near the benzylic methylene group



at δ 2.7. Structure **170** cannot be fitted to these data.

The NMR spectrum of dienone **169** was of interest since the four dienone protons each appeared as non-equivalent doublets. It appears that in this compound, interconversion between the two conformations **169a** and **169b** is slow on the NMR timescale. Thus the chemical shift of proton H_a in **169a** is identical to that of proton H_b in **169b**.

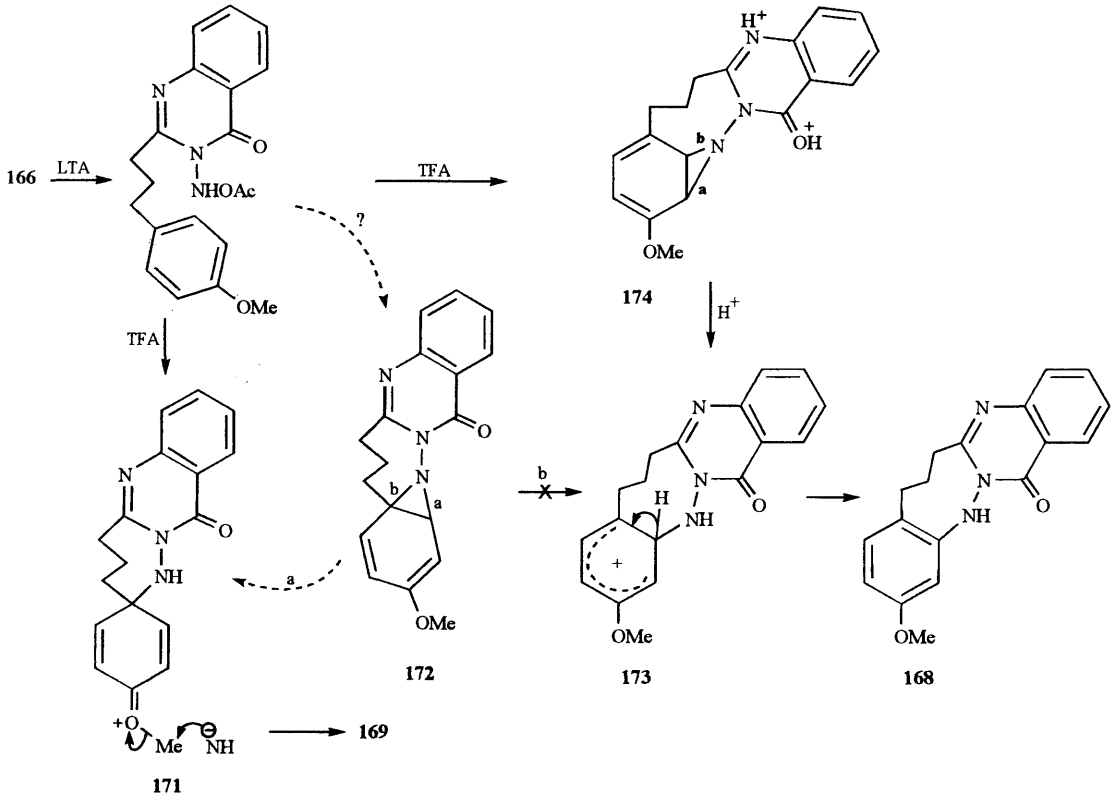


169a **169c** **169b**

No sign of coalescence was apparent when the NMR spectrum was run at 60 °C. The barrier to rotation around the *N-N* bond alone[88] would not be expected to be sufficient to account for this behaviour. It is possible that the barrier is raised because the first conformational change that includes *N-N* bond rotation leads to **169c** in which there is a severe H–H interaction between a dienone and tether proton as shown and so this conformational change must be coupled with that taking place within the rest of the 7-membered ring thus raising the energy barrier significantly.

Mechanisms for formation of 168 and 169

In the intramolecular reaction of the intermediate QNHOAc from QNH_2 **166** (Scheme 90) the precedent for reaction *via* a 7-membered transition state and the stabilizing effect of the methoxy group suggest that formation of the *spiro*-intermediate **171** should be highly favoured. The formation of the benzeneimine **172**, if it occurred, would be unlikely to lead to the substitution product **168** *via* **173** by cleavage of bond b. Likewise, direct formation of **173** *via* an 8-membered ring and a less stable carbocation than **171** seems unlikely. A more likely origin of **168** is from initial attack *via* alternative benzenimine **174** which corresponds to the first intermediate **126** in Gawad's reaction[82b] mechanism using QNH_2 **125**, the *o,p*-dimethoxy analogue of **166** (Scheme 73).

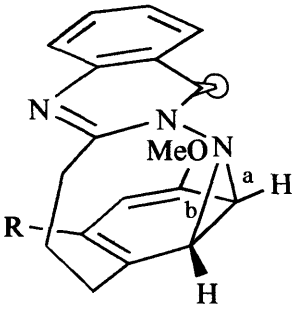


Scheme 90

In the ring-opening of Gawad's benzeneimine **126** breakage of bond b is favoured over bond a because of the stabilizing effect of the two methoxy groups on the incipient

carbocation formed. This carbocation is trapped either by acetic acid when the reaction is carried out in dichloromethane or by methanol when carried out in methanol.

If benzeneimine **174** is indeed an intermediate in the formation of the substitution product **168** why should the regioselectivity of the aziridine ring-opening be opposite to that of the benzeneimine **126** *i.e.* why should breakage of ring bond a be favoured over ring b? Benzeneimines **174** and **126** would be expected to have the stereostructures shown below, the result in each case of $TS^{\#}$s in which the diene residue in the aromatic ring is *cis* to the quinazolinone ring. It is certain that the ring strain present in these benzeneimines is better alleviated on breakage of ring a (to form the carbocation **173**) than by cleavage of ring b. The complementary regioselectivity in cleavage of the aziridine ring bonds in **174** and **126** could arise because, for cleavage of ring b, stabilisation of the incipient carbocation is at a premium to compensate for the strain relief accompanying breakage of ring a. Thus the presence of the second methoxy group in **126** is critical for preferential cleavage of ring b whereas **174** opens at ring bond a to give carbocation **173** and hence *ortho*-substitution product **168** by proton loss.



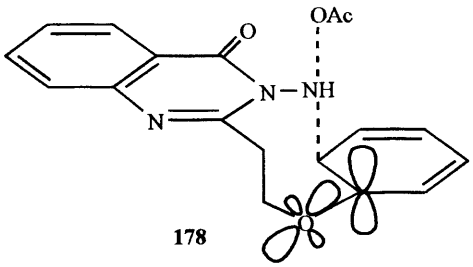
126 R = OMe
174 R = H

The conclusion is, therefore, that in the TFA-catalysed intramolecular reaction in Scheme 90, competitive attack on the *ipso* position to give **171** (possibly *via* aziridine **172**) and on the 2,3-bond to give aziridine **174** occurs leading to the products **169** and **168**.

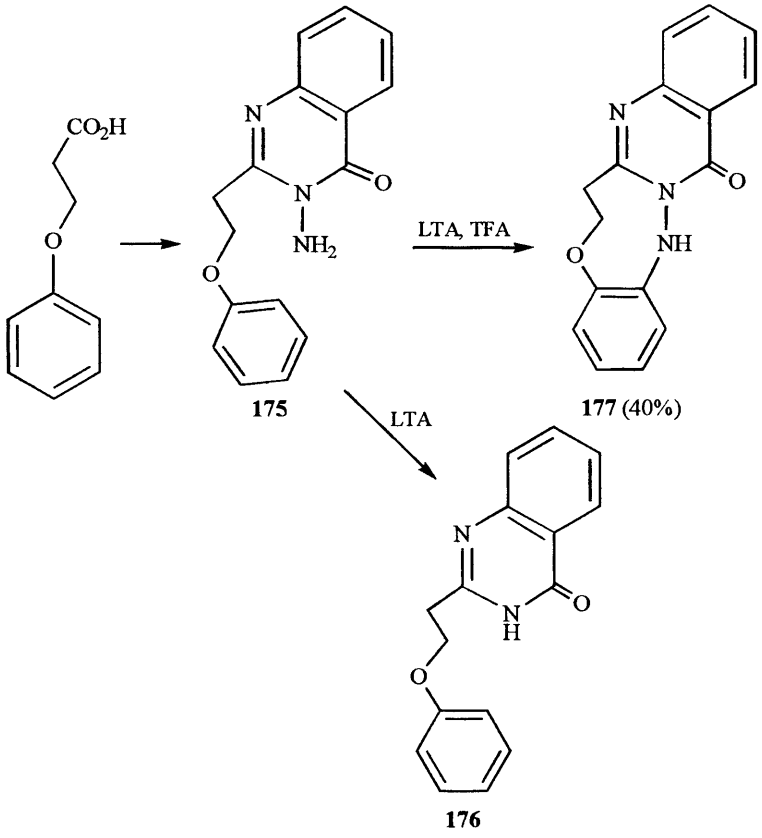
2.3.2 Oxidation of QNH_2 175 containing an oxyethyl tether with LTA-TFA

Synthesis of QNH_2 **175** was accomplished in the usual way from the again commercially available β-phenoxypropionic acid. Oxidation in the absence of TFA gave only 3H-quinazolinone **176** but, in the presence of TFA, the *ortho*-substitution product **177** was isolated in 40% yield (Scheme 91). Its MS (M^+ 279) corresponded to the loss of two protons from QNH_2 **175** and the ^1H NMR indicated that only 8 aromatic protons were present.

It is likely that with an additional atom in the tether by comparison with QNH_2 **159**, better overlap of the oxygen p-orbital with the incipient carbocation is possible in **178** but is still not sufficient to allow reaction in the absence of TFA.



178

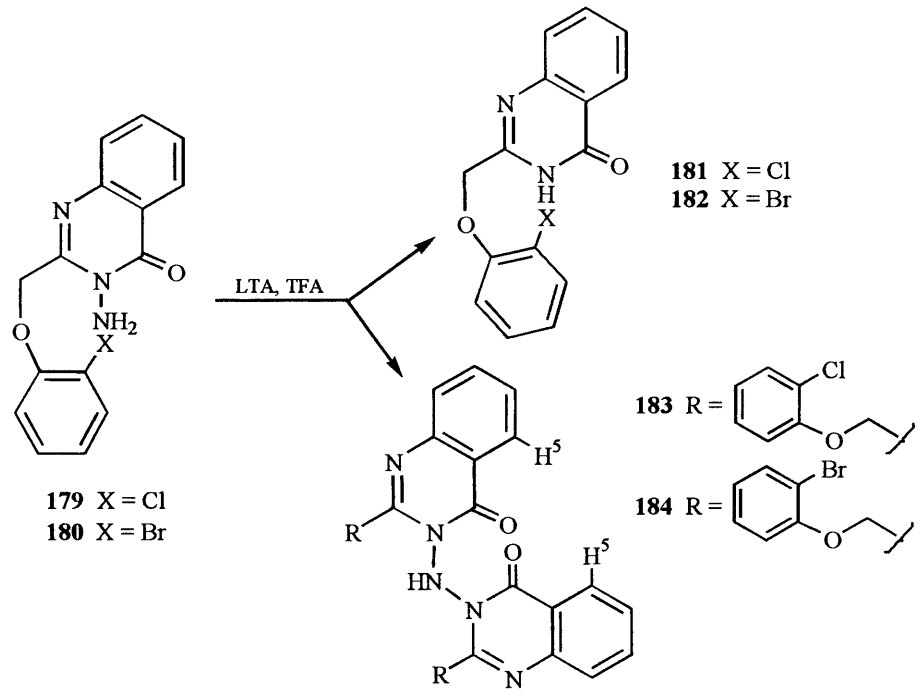


175 177 (40%) 176

Scheme 91

2.4 Intramolecular reactions of 3-acetoxyamino-2-[2-mono-(or di)halophenoxymethyl] quinazolin-4(3H)-ones

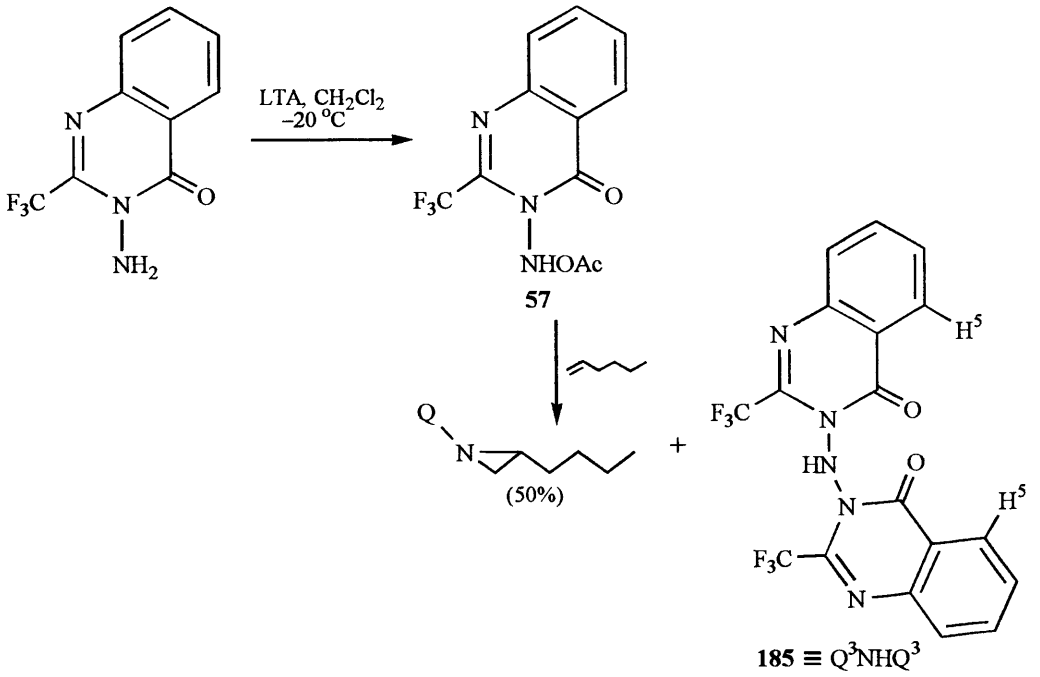
Intramolecular reactions between the QNHOAc group and less reactive tethered aromatic rings as in Schemes 82, 88 and 91 are facilitated by the presence of TFA in the reaction medium. Up to this point only unsubstituted aromatic rings or those containing only one methoxy (alkoxy) group had been examined. It was of interest to test whether the presence of TFA would render the QNHOAc nitrogen sufficiently electrophilic to attack even deactivated aromatic rings. Accordingly, the 3-aminoquinazolinones **179** and **180** were prepared by the usual route from the corresponding acids (Scheme 92).



Scheme 92

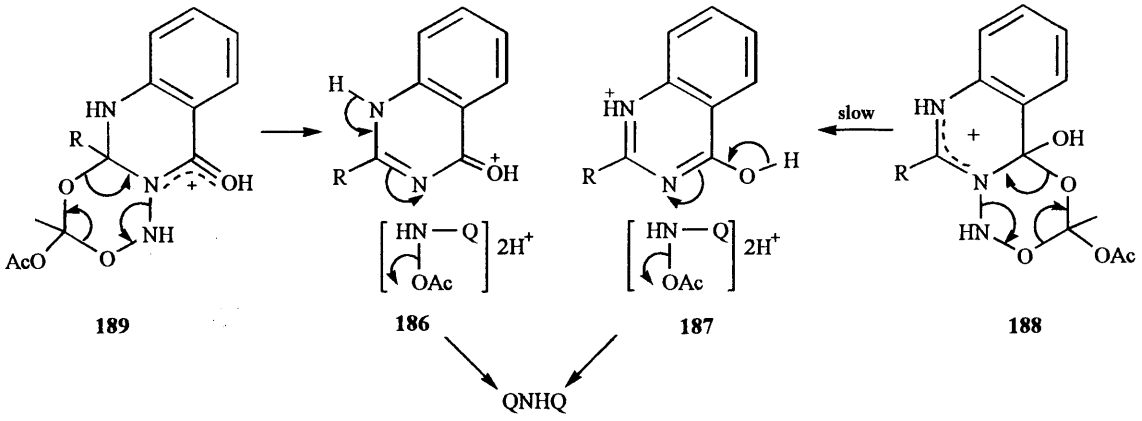
By reactions of each of these 3-aminoquinazolinones with LTA in dichloromethane at –20 °C in the presence of TFA, a crystalline product that was less soluble in ethanol was isolated directly from the crude reaction mixture in each case leaving the corresponding 3*H*-quinazolinone compounds **181** or **182** in the ethanolic filtrate. The structures of these two isolated crystalline products were identified from their ^{1}H NMR, IR and mass spectra as the *N,N-bis*(3,4-dihydro-4-oxoquinazolin-3-yl)amines (QNHQs), **183** and **184**. The identity of these QNHQs was suggested from the characteristically sharp low-field NH proton signals in their ^{1}H NMR spectra at δ 9.9 and 9.8 respectively which integrated in each case to half of the signals assigned to the QH-5 protons. An accurate mass determination (FAB) for **184** confirmed the molecular formula as $C_{30}H_{21}N_5O_4Br_2$.

An analogous Q^3NHQ^3 compound **185** was first isolated by Coogan[66] from Q^3NHOAc **57** (in the absence of TFA) and its structure was confirmed by X-ray crystallography (Scheme 93). These QNHQ products had never been found otherwise as decomposition products in the absence of TFA.



Scheme 93

The mechanism for formation of QNHQ compounds **183** and **184** is intriguing but not completely clear; formally they arise from reactions of the corresponding QNHOAc compound with an enol tautomer of the 3*H*-quinazolinone (as in either **186** or **187** - Scheme 94).



Scheme 94

In fact this mechanism is very likely bound up with decomposition of the QNHOAc compounds in the presence and absence of TFA. The greater stability of QNHOAc compounds in the absence of acetic acid has been referred to in the Introduction and leads to increased yields of aziridine (Scheme 49). How can this acid sensitivity of QNHOAc be reconciled with the beneficial effect of TFA addition on the yields of, in many cases, the same alkenes? One possibility is that, in the suggested mechanism for acid-catalysed decomposition of QNHOAc (Scheme 50), fragmentation of the intermediate **188**, now protonated on N1, is grossly retarded because of resonance stabilisation by N3.

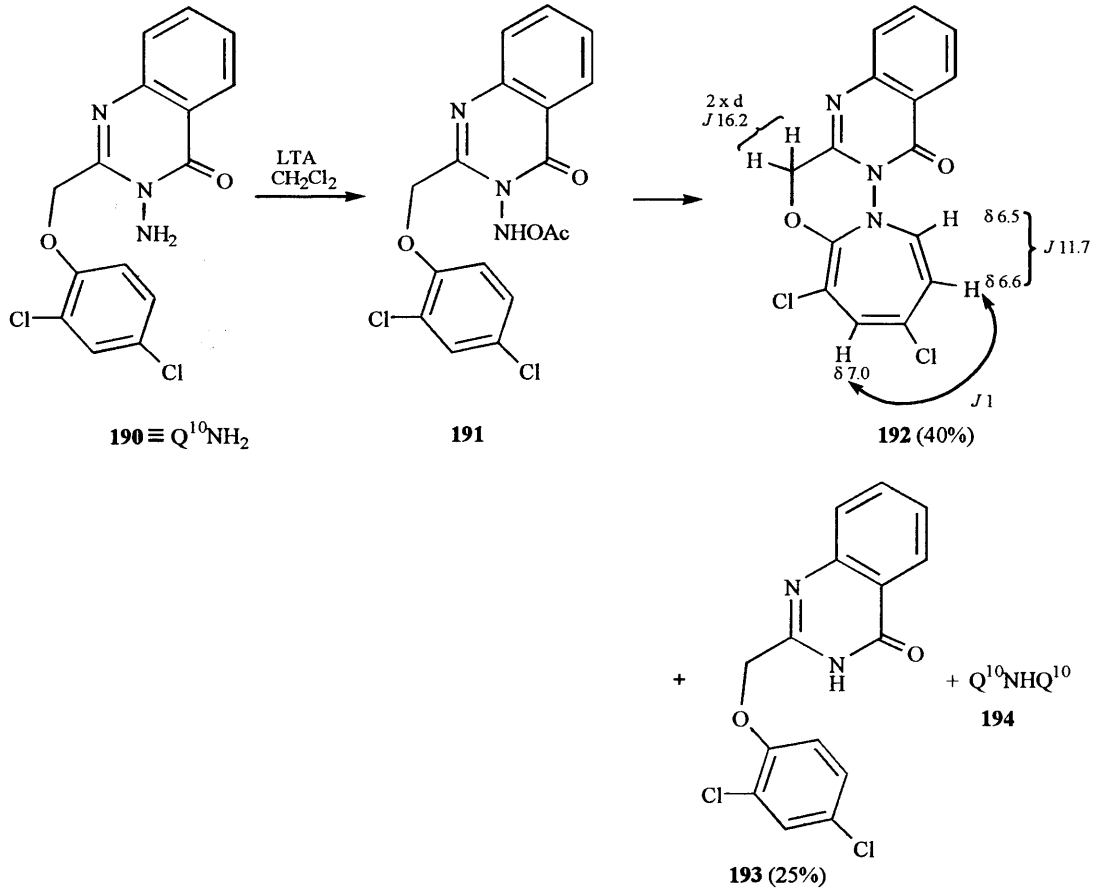
Alternatively, intramolecular attack by the (Q)-acetoxyamino group may be diverted onto the now more electrophilic (Q)$C{=}\overset{+}{N}H$ to give **189** (Scheme 94) and fragmentation of this intermediate be retarded relative to an increased rate of aziridination by the diprotonated QNHOAc. Intra-molecular attack in this alternative sense would be all of a piece with the switch in TS$^{\#}$ geometry in aziridinations brought about by the presence of TFA (Scheme 63) or by the use of the 2-trifluoromethyl-substituted Q^3NHOAc **57**.

Formation of QNHQ compounds in TFA, therefore, may result from capture of the 1H-enol by the more reactive diprotonated QNHOAc as in **186**.

2.4.1 Oxidation of QNH_2 190 with LTA

In view of the absence of any reaction products from intramolecular attack in Scheme 92 on the aromatic rings, it was most surprising to find that such reactions did occur in the case of the *o,p*-dichlorophenoxymethyl substituted QNH_2 **190** *even in the absence of TFA*. (Only QH compounds **181** and **182** were obtained in Scheme 92 in the absence of TFA.)

3-Aminoquinazolinone **190** was prepared by the standard route and oxidised by LTA in dichloromethane at –20 °C in the absence of TFA. Three crystalline products were isolated by chromatography on deactivated silica whose structures were assigned as **192**, **193** and **194** (Scheme 95).



190 ≡ $Q^{10}NH_2$ **191** **192** (40%) **194** **193** (25%)

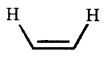
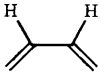
Scheme 95

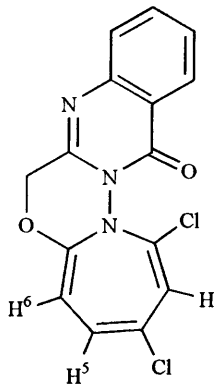
Examination of the ^{1}H NMR spectrum of the most polar compound **193** (mp. 210–213 °C) showed it was the 3*H*-quinazolinone with δ 9.5 (s, NH), 8.3–6.72 [m, 4H(Q) + 3H(Ar)] and 5.1 (s, C*H*$_2$–O); an accurate mass determination showed a molecular formula of $C_{15}H_{10}N_2O_2Cl_2$. The second most polar crystalline product was isolated in 20% yield, mp. 273–275 °C and its $Q^{10}NHQ^{10}$ structure **194** was indicated by the characteristically sharp low-field NH proton signal at δ 9.7 in its ^{1}H NMR spectrum: accurate mass measurement (FAB) confirmed the expected molecular formula as $C_{30}H_{19}N_5O_4Cl_4$.

The fact that $Q^{10}NHQ^{10}$ **194** is produced in the absence of TFA suggests that there is an alternative route to this compound analogous to that suggested in Scheme 94. Since QNHQ compounds **183** and **184** are not products in Scheme 92 in the absence of TFA, the additional chlorine substituent on the aromatic ring in QNH_2 **190** must be playing an as yet unexplained role in formation of **194**.

The least polar crystalline product in Scheme 95, isolated in 40% yield, mp. 193–196 °C was identified as the azepine **192**.

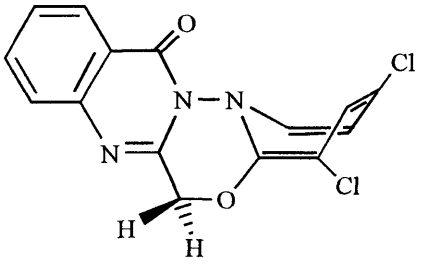
Important features of ^{1}H NMR spectrum of azepine **192** are:

(a) the coupling constant between the two vicinal protons H-6 and H-7 of 11.7 Hz which is in good agreement with that (11.9 Hz) between H-6 and H-7 protons in Gawad's 3,5-dimethoxyazepine ring-containing analogous compound **120** and larger by ~2 Hz than would be expected for coupling between two vicinal aromatic protons. The size of this coupling constant also supports a double bond between the two coupled protons  rather than a single bond  as in **195**;



195

(b) the non-equivalence of the two protons within the methylene group which is also present in the protons in both methylene groups in **120** and **192** can be ascribed to a boat-like conformation for the azepine ring as in **192'**. As with Gawad's azepine **120**,[82a] boat-to-boat ring flipping, which would interconvert the environments of the diastereotopic hydrogens in the O–CH_2 group, must be slow on the NMR timescale (but see later);



192'

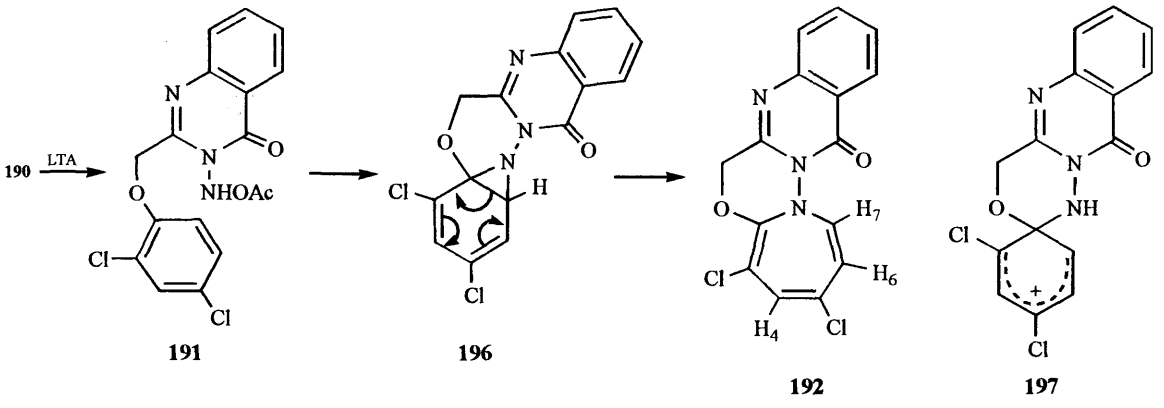
(c) the chemical shifts of the azepine ring protons in **120** and **192** are widely different for H-6 and H-4 but very similar for H-7 which is consistent with pronounced deshielding by the chlorine atoms only of their neighbouring protons (H-7 is deshielded by the adjacent azepine ring nitrogen in both cases).

(d) Structure **195** is also eliminated based on the similarity in δ of the two vicinally coupled azepine ring protons H-6 and H-7; the effect of the oxygen on the azepine at C-7 would be expected to raise H-6 to higher field.

An accurate mass determination confirmed the molecular formula of azepine **192** as $C_{15}H_{10}N_3O_2Cl_2$ and there was no NH stretching in the IR.

Mechanism of formation of the 1-H-azepine 192

Formation of the 1-*H*-azepine **192** can be assumed to take place by a mechanism analogous to that proposed by Gawad[82a] for formation of **120** except that the aziridinating species is now known to be the QNHOAc compound **191** and not the corresponding nitrene. Thus aziridination of the C_1-C_6 double bond to give **196** and then $4\pi \rightarrow 6\pi$ electrocyclic ring-opening would result in the formation of the azepine **192** (Scheme 96).

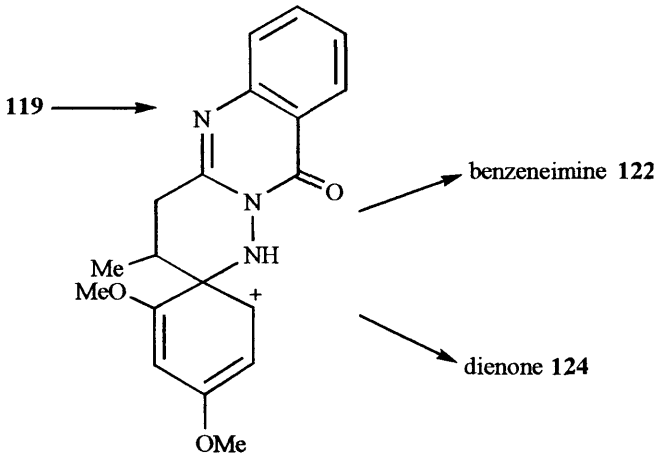


Scheme 96

The reactivity of the 2,4-dichlorophenyl ring in **191** by comparison with the unreactivity of the 2-chlorophenyl ring in Scheme 92 is surprising. It appears that, notwithstanding the preference for attack on the *ortho*-position *via* a 7-membered $TS^{\#}$ in these reactions, the presence of the two chlorines allows aziridination to take place with N–C_1 running ahead of

C_6–N bond formation, *i.e.* with attack on the *ipso*-position *via* 6-membered TS$^{\#}$. The resulting partial carbocation would be (weakly) stabilised by both chlorine atoms.

Whether the carbocation **197** is fully formed is not clear. If it were, an analogy between this reaction and that of Gawad can be drawn if it is assumed that aziridination in Gawad's case takes place *via* a dimethoxy analogue **198**. This would necessitate a not unreasonable revision of the mechanism given previously in Scheme 72 to one in which the carbocation **198** is the common intermediate in formation of benzenimine and dienone.

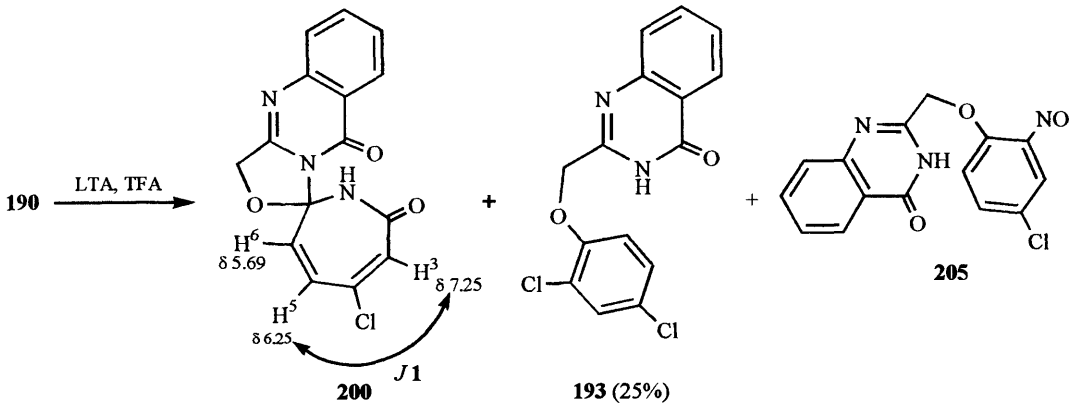


198

Thus the effect of dimethoxy or dichloro substitution in the aromatic ring is to facilitate reaction *via* a 6-membered TS$^{\#}$.

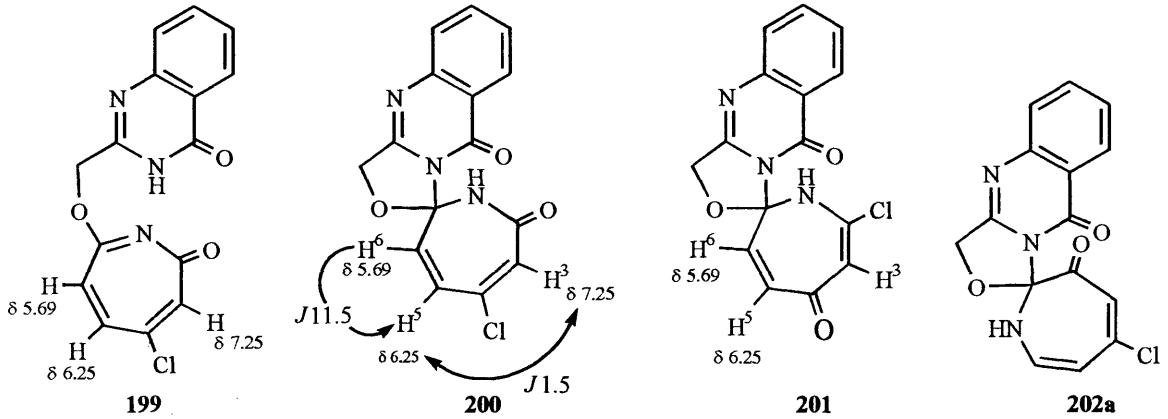
2.4.2 Oxidation of QNH$_2$ 190 with LTA/TFA using procedure B

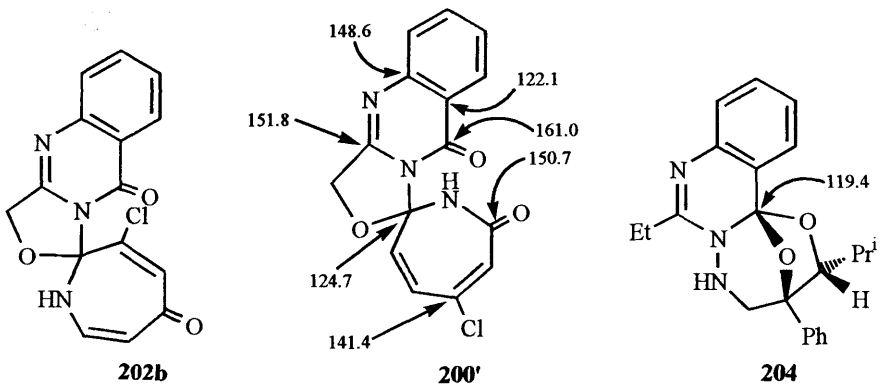
From oxidation of the 3-aminoquinazolinone **190** with LTA/TFA using procedure **B**, three crystalline products were also isolated by chromatography (Scheme 97). The first eluted compound (25% yield), mp. 166–168 °C had a molecular mass corresponding to $C_{15}H_{10}N_3O_3Cl$ *i.e.* with loss of a chlorine and gain of an oxygen atom together with loss of the elements of acetic acid from QNHOAc **191**. Apart from an apparently unperturbed quinazolinone ring with H-5 at δ 8.1, the NMR spectrum showed the presence of three hydrogens having a 1,2,4-relationship with $J_{1,2}$ 11.5 and $J_{2,4}$ 1.5 Hz. The 11.5 Hz coupling is in agreement with two vicinal protons on a double bond in an azepine ring. Apart from a singlet δ 5.2 for the two protons in the methylene group adjacent to the Q ring, the highest field proton resonates at δ 5.7.



Scheme 97

With the assumption that the chlorine has been replaced by a carbonyl group on the 7-membered ring, structural formulae **199–201** and **202a/b** for this compound can be considered. Although the 1-*H*-azepin-2-one ring system in **199** is known, it is very uncommon, non-aromatic and difficult to make[90,91] and for this reason alone **199** seems unlikely as the structure.

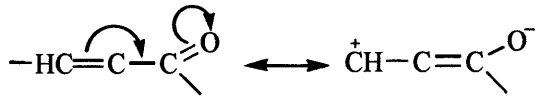




The ^{13}C NMR spectrum also does not support assignment of structure **199** since the 3 quaternary carbons of the azepinone ring can be assigned at 150.7, 141.4 and 124.7 ppm (after subtraction of the 4 known quaternary ^{13}C signals for the quinazolinone from the total of 7 quaternary signals observed). Since the carbonyl carbon is likely to be that at 150.7, the

imidate carbon O–*C*=N in structure **199** would have to resonate at 124.7 which is at unreasonably high field for such a carbon (expected value ~ 160 ppm).

Since there appears to be no vicinal coupling between the NH proton and an adjacent azepine ring proton, structures **200** and **201** must be preferred over **202a** and **202b**. A distinction between these two in favour of **200** can be made on the basis of the relative chemical shift positions of the two vicinal protons H-5 and H-6, α and β to the carbonyl group in **201**. The signal at δ 6.25 is assigned to H-5 because it has a 1 Hz coupling with H-3. It is well known that the β-proton resonates at up to ~1 ppm to lower field than the α-proton in the α,β-unsaturated ketone systems as a result of the resonance effect;



so the ordering of the chemical shifts of H-5 and H-6 in structure **201** is not as expected. On the other hand, since the azepinone structure is very likely not planar, a similar lower chemical shift for H-6 than H-5 in **200** is feasible.

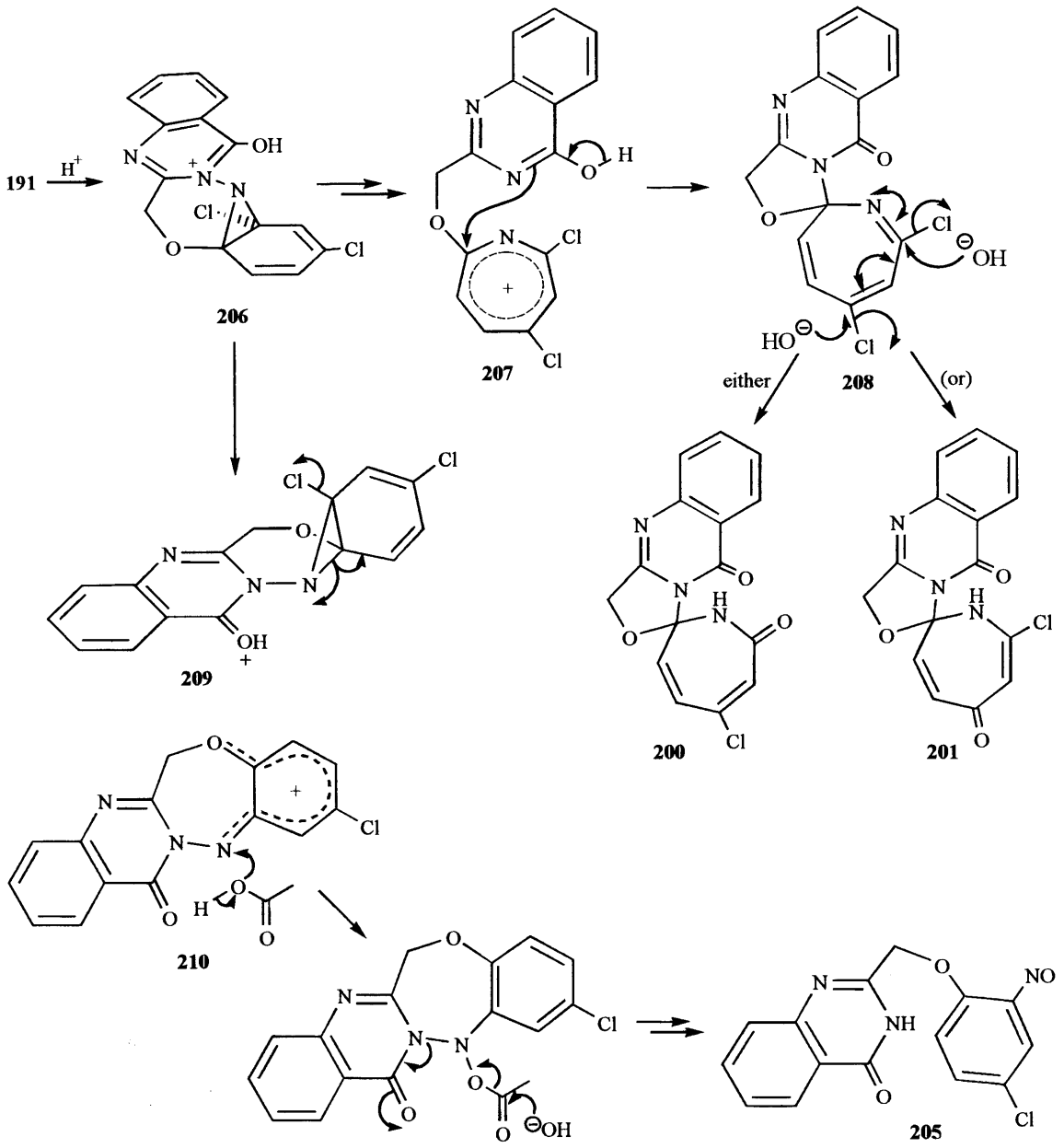
With assignments of quaternary ^{13}C signals (structure **200'**) as indicated, the chemical shift of the *spiro*-carbon approximates to that of the *spiro* carbon in compound **204** (δ 119.4) (the structure of **204** was confirmed by an X-ray crystal structure determination[71]).

The two protons in the methylene group in structure **200** are intrinsically non-equivalent and yet appear as a singlet in the NMR spectrum of this compound. However, it is noteworthy that unlike the (oxy)methylene group in azepine **195**, there is no obviously preferred conformation in **200** which would be more likely to enhance the non-equivalence of these two protons.

The second-eluted product in oxidation of QNH_2 **190** with LTA in the presence of TFA had mp. 224–226 °C and was formulated as the 3*H*-quinazolinone **205** in which the *ortho*-chlorine of the dichlorophenoxy group had been replaced by a nitroso group. Its NMR spectrum showed a significantly smaller (aromatic) vicinal coupling constant (*J* 8.5 Hz) for H-5 and H-6 than for compounds **195** and **200** and a *meta*-coupling (2.5 Hz) that confirmed the 1,2,4-substitution of the ring. The NH signal of δ 9.6 is typical of a 3*H*-quinazolinone.

The most polar product from the reaction in Scheme 97 was the 3*H*-quinazolinone **193** identical with that isolated previously (Scheme 95).

In the mechanism of formation of both azepinone **200** and 3*H*-quinazolinone **205** (Scheme 98) it is proposed that aziridination of the 1,2-bond of the dichlorophenoxy ring in QNHOAc **191** occurs in the presence of TFA in contrast to aziridination of the 1,6-bond in formation of azepine **195** in the absence of TFA.



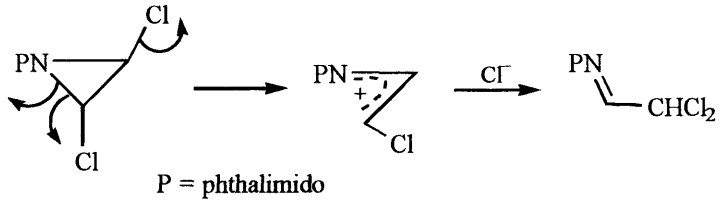
Scheme 98

When protonated, the Q group becomes a good leaving group and electrocyclic ring-opening ($4\pi \rightarrow 6\pi$) in the benzenimine **206** followed by cleavage of the *N–N* bond (loss of QH) gives the aromatic azatropylium cation **207** (*cf.* Scheme 65). Capture of this cation by the 3*H*-quinazolinone nitrogen will lead to dichloroazepine **208** which, being an imidoyl chloride, would be expected to be easily hydrolysed in the basic work-up giving azepinone **200**.

In benzeneimine **206**, attack on the chlorine-substituted double bond of the aromatic ring has made another mode of decomposition possible which is a $0\pi \rightarrow 2\pi$ electrocyclic ring-opening of the aziridine with loss of the chloride anion as in **209** to form a stabilised carbocation **210**. Attack on nitrogen in **210** by a nucleophile *e.g.* acetic acid, present in the solution will be favoured because the aromatic benzene ring is thereby regenerated. Facile

hydrolysis of the resulting ester in the basic work-up and tautomerism to the *o*-nitroso-substituted benzene ring in 3*H*-quinazolinone **205** is to be expected.

The electrocyclic ring-opening of the 2-chloro aziridine and loss of chloride above is precedented as in the rearrangement of the aziridine in Scheme 99.[30]



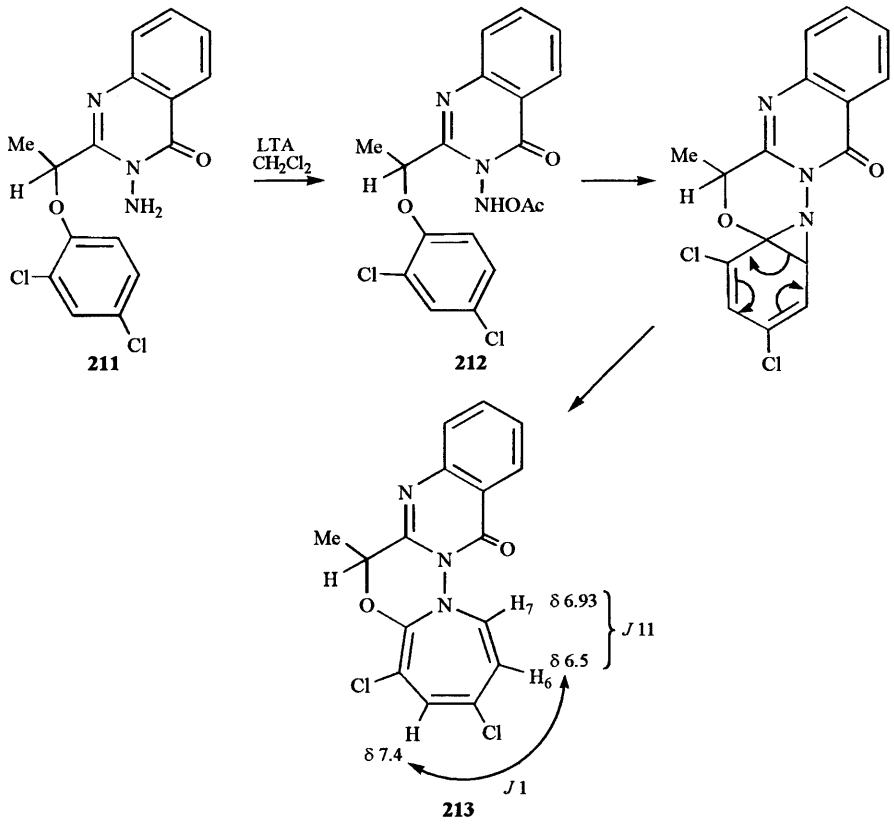
P = phthalimido

Scheme 99

A discussion of the different regioselectivity in intramolecular reactions of QNHOAc **191**, brought about by TFA, is given later (see below).

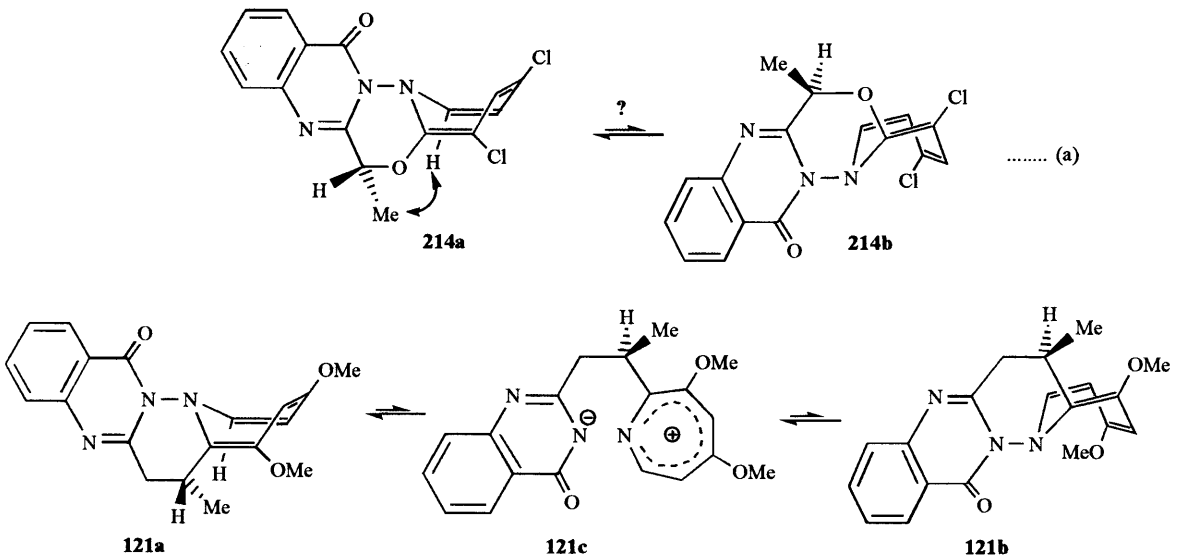
2.4.3 Oxidation of QNH_2 211 by LTA in dichloromethane

Oxidation of the title compound, prepared in the usual way with LTA, was studied to provide further evidence for the assigned structures of products isolated from the previous oxidations of QNH_2 **190**. In the absence of TFA, a single product was obtained from the crude reaction mixture by trituration with ethanol in 45% yield, mp. 174–175 °C (Scheme 100). The azepine structure **213** was assigned to this compound which has the characteristic coupling constant of 11 Hz between H-6 and H-7 but the chemical shift of H-7 at δ 6.93 is lowered by comparison with that of the desmethyl analogue **192** (δ 6.50) and with Gawad's dimethoxy analogue **120** (δ 6.54).



Scheme 100

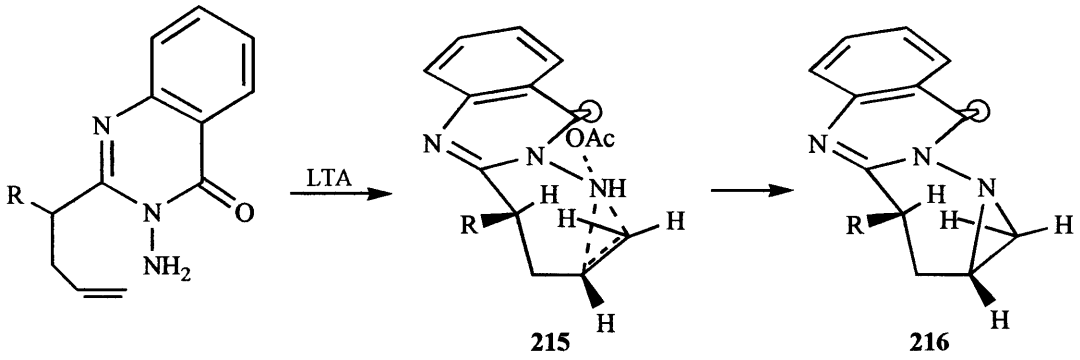
The proximity of the methyl group to H-7 in **213** could account for its downfield shift if the conformation of this azepine ring is as indicated in **214a**. This explanation raises two questions: (i) why is the equilibrium between **214a** and its ring-flipped form **214b**, shown to be present in the corresponding dimethoxyphenyl (ethyl) analogue of Gawad (Scheme 101), not established and/or (ii) why is **214a** preferred over the presumably as, or more, stable **214b**?



Scheme 101

Conceivably equilibration **121a** ⇌ **121b** in Gawad's dimethoxy-substituted azepine could take place *via* the dimethoxy-substituted and hence stabilised azatropylium ion-containing species (**121c** in Scheme 101) rather than by boat-to-boat conformational interconversion as previously envisaged.[82a] The higher barrier to interconversion between azepines **214a** and **214b** could, therefore, be raised because of the lesser stabilisation of the TS$^{\#}$ for formation of the (dichloro)azatropylium cation corresponding to **121c**.

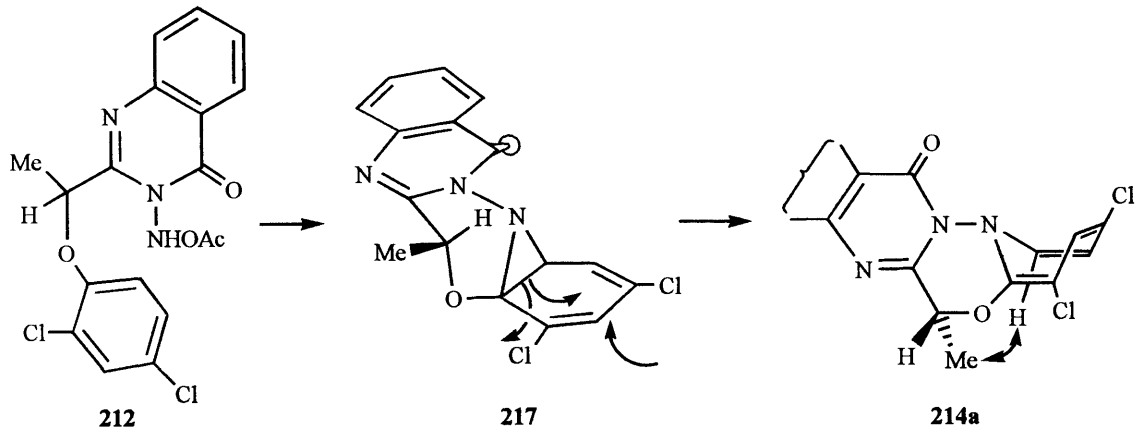
The answer to the question in (ii) above may lie in the stereochemistry of the initial aziridination. The intramolecular oxidative aziridination of a variety of 2-[but-(2-substituted)-3-ene-1-yl]-3-aminoquinazolinones was previously carried out by Woodthorpe and Skinner[54] and, in particular, by Grimshire (Scheme 102).[81]



Scheme 102

In every case the aziridination was completely diastereoselective in the sense shown in **216** as deduced from the magnitude of the coupling constants in the conformationally-fixed product. The explanation given for this diastereoselectivity at the time was the preference of the R group for an 'equatorial' position on the tether in the TS$^{\#}$ **215** with the nitrene the aziridinating species. With the knowledge that the acetoxyaminoquinazolinone is the actual aziridinating agent, it can be seen that placement of the R group equatorially avoids the interaction that would ensue with QNH*OAc* if R were in the axial position; reaction *via* a 7-membered TS$^{\#}$ is assumed (see 1.2.19).

In the intramolecular aziridination of QNHOAc **212**, therefore, the completely diastereo-selective formation of benzeneimine **217** and, by electrocyclic ring-opening, conformation **214a** for the azepine can be anticipated (Scheme 103); note that the enforced mode of electrocyclic ring-opening delivers the boat conformation illustrated in **214a**. The formation of azepine **214a**, according to this explanation, is under kinetic control.

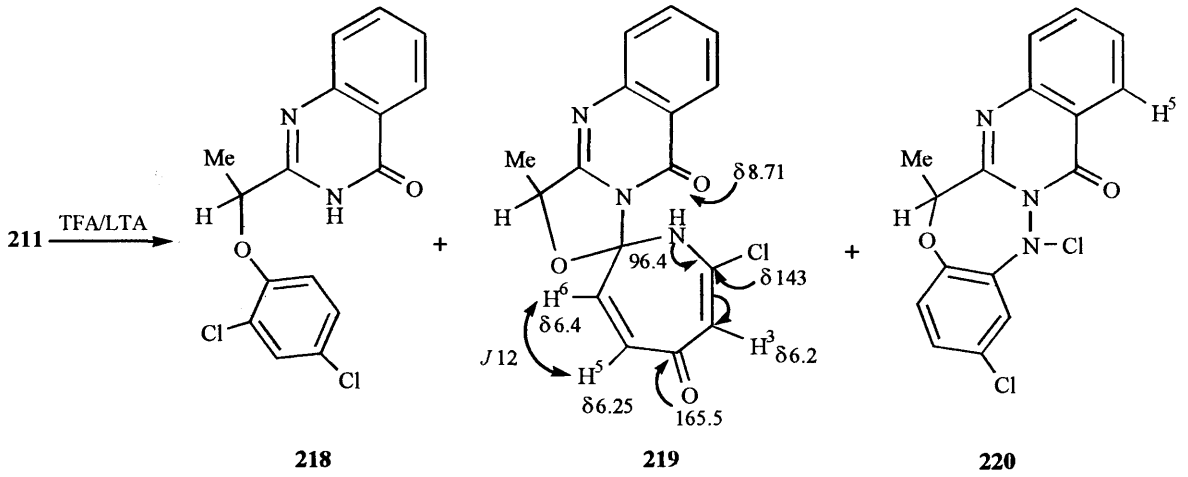


Scheme 103

It appears, therefore, that oxidation of QNH_2s **190** and **211**, in the absence of TFA, proceed in the same way to give analogous products.

2.4.4 Oxidation of QNH_2 211 in the presence of TFA using procedure B

Three crystalline products were obtained from this reaction and were separated by chromatography. The first eluted, with mp. 160–162 °C (25%) was identified by NMR (δ 9.6, NH), IR (ν_{max} 3060) and an accurate mass determination as the 3*H*-quinazolinone **218** (Scheme 104).



Scheme 104

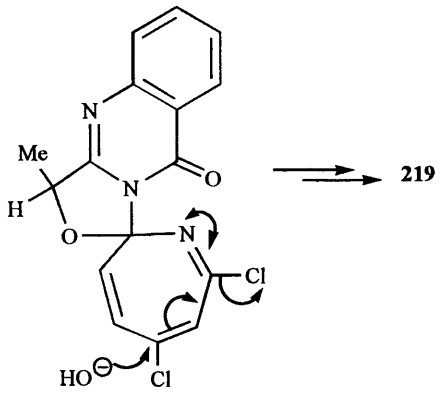
The formula of the second product eluted, mp. 185–187 °C (30%) corresponded, from its accurate mass determination as in the case of azepinone **200** previously, to replacement of a chlorine by an oxygen atom and loss of acetic acid from **212**. As in **200** also, the presence of two vicinal protons on a double bond with *J* 12 Hz suggests an azepinone structure.

However, this product does not appear to have a structure analogous to that of azepinone **200** because the differences in chemical shifts of *e.g.* the azepine ring protons are substantially greater than would be expected as a result of introduction of the additional

methyl group. Likewise there are differences in ^{13}C chemical shifts for the azepine ring quaternary carbons which point to the same conclusion (see **219** and **200'**).

The data for this product mp. 160–162 °C strongly suggest an azepinone structure and azepin-4-one **219** (Scheme 104) could account for the changes in ^{1}H and ^{13}C chemical shifts particularly if the 7-membered ring has a conformation which is not completely planar. Thus H-3 at δ 6.2 (see **219**) would be relatively shielded by virtue of its attachment to the β-carbon of an enamine (arrows in **219**) and H-6 would be at lower field because it is now β to a carbonyl group. The ^{13}C resonance of the azepinone carbonyl carbon in **219** is at lower field than in **200** (165.5 *v* 150.7 ppm) because is it more ketonic as a result of the likely non-planarity of the vinylogous amide system HN–C=C–C=O.

This azepinone could arise (Scheme 105) from attack on a dichloroazepine intermediate analogous to **208** in Scheme 98, at the chlorine-bearing carbon C-4.



Scheme 105

It is not clear is why different chlorine-bearing carbons are attacked depending on whether a methyl group is present or not in the tether. Since azepinone **219** contains two chiral centres it could exist as diastereoisomers but the single set of signals for this compound in its ^{1}H NMR and ^{13}C spectra suggests that it is diastereoisomerically pure.

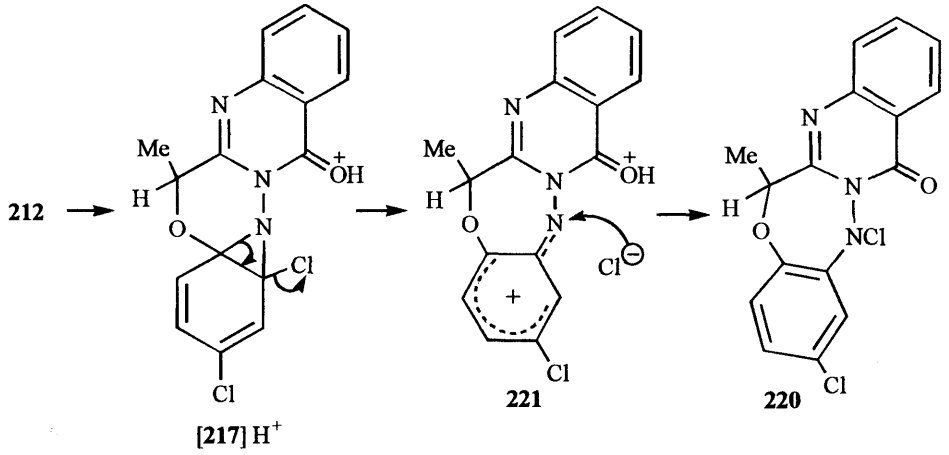
When azepine **213** was treated with TFA/CH_2Cl_2 under the conditions used in the TFA-catalysed LTA oxidation of QNH_2 **211**, it was recovered largely unchanged. Thus the mechanism for formation of azepinone **219** does not involve acid catalysed reaction of azepine **213**.

The more polar product isolated by chromatography from intramolecular reaction of QNHOAc **212** in the presence of TFA was isolated in 20% yield with mp. 174–175 °C and was assigned the *N*-chloro structure **220** as in Scheme 104.

No *o*-nitroso-derivative analogous to **205**, previously isolated from intramolecular reaction of QNHOAc **191** in the presence of TFA, was isolated. The ^{1}H NMR spectrum of **220** did not show any signal for an NH but three (1,2,4-disposed) aromatic protons on the aromatic ring were present at δ 7.0 (d, *J* 1.5, H-4), 6.59 (dd, *J* 8.5 and 1.5, H-2) and 6.4 (d,

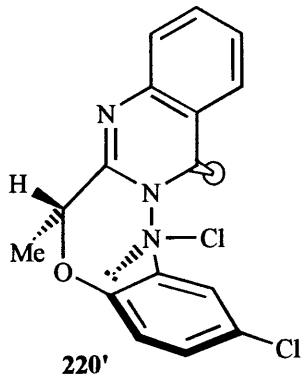
J 8.5, H-1). The molecular mass confirmed the presence of two chlorine atoms in the product $C_{16}H_{11}N_3O_2Cl_2$ (Na) and a major peak at 335 corresponding to loss of a chlorine atom as would be expected. There is a significant downfield shift (δ8.3 → 8.8) for the QH-5 which is not unexpected since this chemical shift is dependent on the substitution at the exocyclic nitrogen. Attempts to replace the chlorine on nitrogen by hydrogen using zinc and acid did not give any homogeneous product although the starting material was not recovered.

The *N*-chloro-benzo-oxadiazepino-[2,3-b]quinazolinone product **220** formally arises by insertion into the *ortho*-carbon chlorine bond of the dichlorophenoxy ring in QNHOAc **212** and its mechanism of formation is of great interest. By analogy with the proposed mechanism for formation offered previously for the *ortho*-nitroso-containing 3*H*-quinazolinone **205** (see Scheme 98), trapping of the analogous carbocation intermediate **221** by chloride released in the electrocyclic ring-opening, would give rise to **220** directly (Scheme 106).



Scheme 106

An obvious question which arises here is why the analogous carbocation intermediates **210** (in Scheme 98) and **221** (in Scheme 106) lead in the former case to the ortho-nitroso-containing 3*H*-quinazolinone **205** and the latter case to **220**. It is possible that the *N*-chloro compound analogous to **220** is also formed in the case of **210** but its formation is reversible leading eventually to **205**. The stability of *N*-chloro compound **220** may be ascribed to the presence of the methyl in the tether if this group holds the 7-membered ring in a conformation which retards solvolysis of chloride. Thus a conformation **220'** could be preferred for **220** where loss of the chlorine would be in the plane of the benzene ring, *i.e.* there would be no stabilisation of the incipient cation. The presence of the methyl group could destabilise formation of the *N*-invertomer. Clearly further work is necessary to establish this explanation.



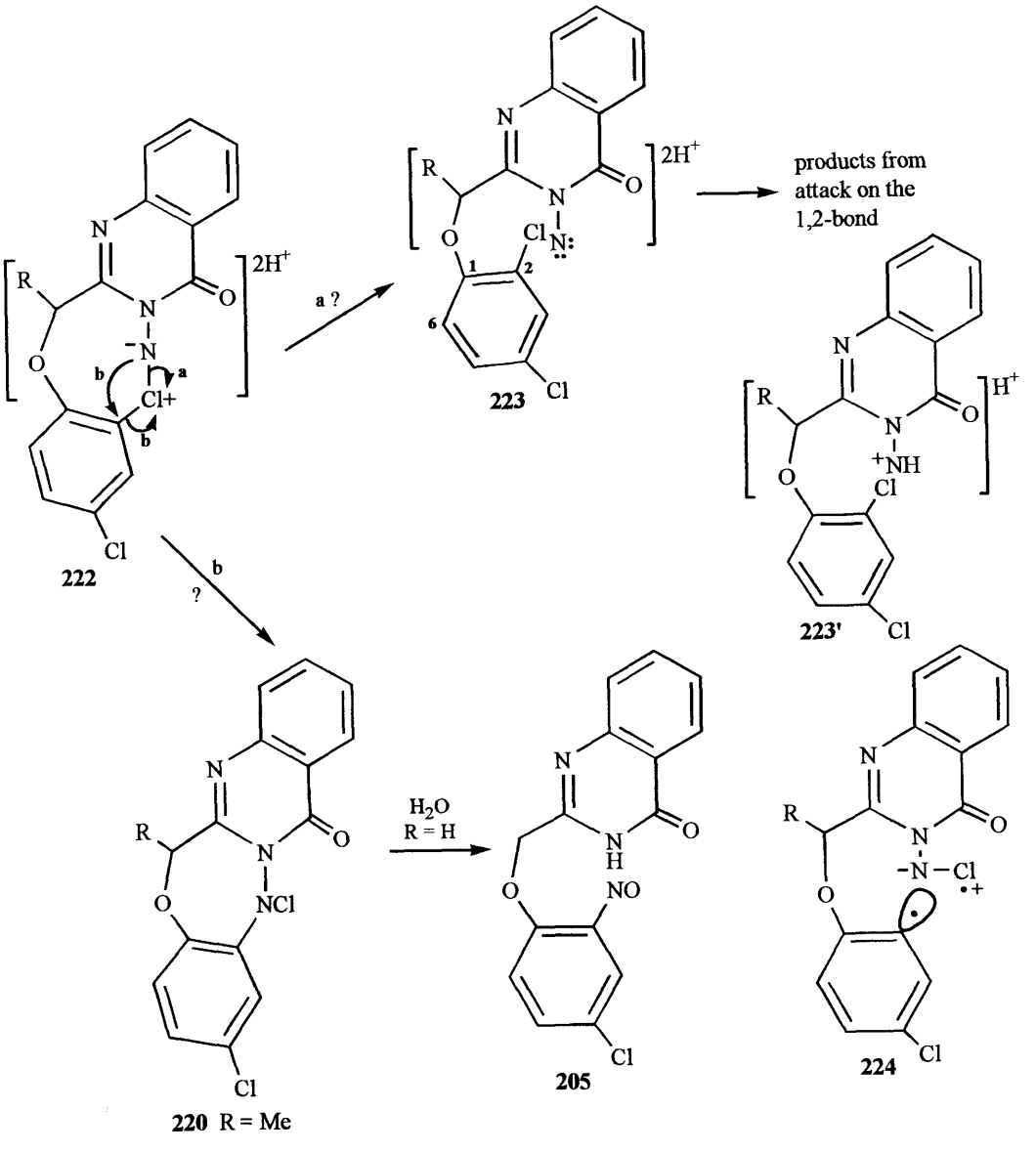
220'

The isolation of *o*-nitroso derivative **205**, *N*-chloro compound **220** and azepinones **200** and **219** suggests that *the double bond of the dichlorophenoxy ring which is aziridinated is changed from 1,6 in the absence of TFA to 1,2- in its presence.*

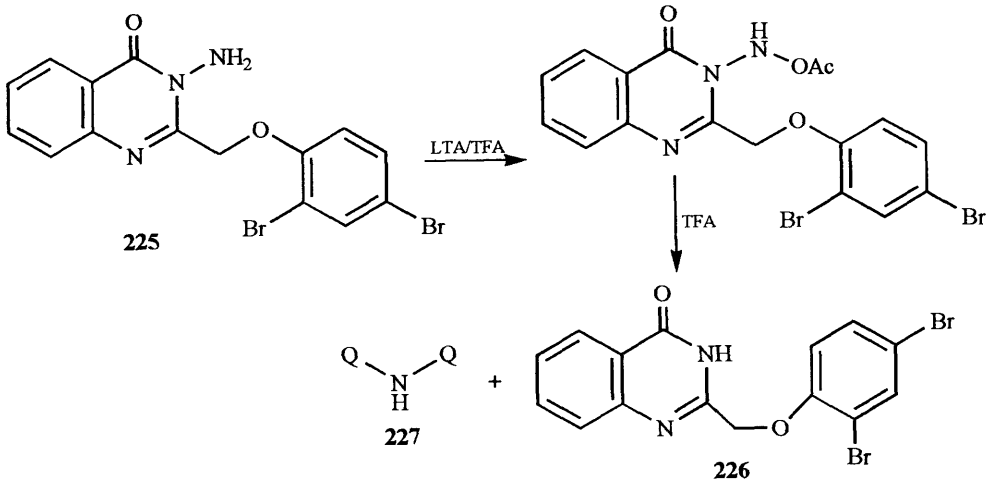
It is logical to assign this change in regioselectivity to the presence of the *ortho*-chlorine atom in the cases where TFA is present in the oxidations, *i.e.* attack takes place initially by the more reactive (di)-protonated QNHOAc[74] intermediate on the *ortho*-chlorine atom to give the ylide **222** in its protonated form (Scheme 107).

What is not clear is how attack on the 1,2-double bond occurs in **222** and whether the protonated nitrene **223** or the nitrenium ion **223'** is involved. Any mechanism must assign a role to the *para*-chlorine since QNH_2 **179** does not undergo attack on the *ortho*-chlorophenoxy ring under the same reaction conditions. Neither does any attack on the 2,4-dibromophenoxy ring occur in reaction of QNH_2 **225** under the conditions of procedure **B** (Scheme 108). Previous methods[68,79] for generating (3,4-dihydro-4-oxo-quinazolin-3-yl)nitrenes (QNs) analogous to **223** are not tolerant of acid solution so there is no precedented reaction of these species in acid available.

The mechanism of formation of 3*H*-quinazolinone **205** and of *N*-chloro compound **211** could proceed *via* path b in Scheme 107 involving a Steven's rearrangement. However, Steven's rearrangements of this type do not appear to be common probably because the aryl radical in the radical pair intermediate **224** is non-stabilised (Scheme 107).



Scheme 107



Scheme 108

The apparent absence of attack on the *ortho*-bromine by the acetoxyamino nitrogen in Scheme 108 (*cf.* Scheme 107) could arise from preferential reaction of the 'hard' acetoxyamino nitrogen with the 'hard' chlorine rather than the softer bromine (the hard acid soft base principle).[92]

Summary

Whereas oxidations of QNH_2s **107**, **159**, **166** and **175** by LTA gave only the corresponding QH derivatives, in the presence of TFA, products from intramolecular attack on the respective aromatic rings – either *ortho*-substitution products or (for **107** and **166**) dienones – are obtained.

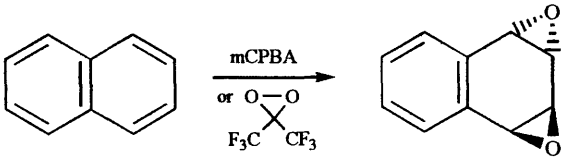
Oxidation of QNH_2 **190** and of **211** (containing an additional methyl group in the tether) gave analogous azepines **192** and **213** even in the absence of TFA as a result of attack on the 1,6-double bond of the 2,4-dichlorophenoxy ring. In the presence of TFA, different but related products, azepinones **200** and **219**, QH **205** and *N*-chloro derivative **220**, are obtained from QNH_2s **190** and **211** respectively. It is postulated that these products arise from attack on the 1,2-double bond of the dichlorophenoxy ring, a result of preliminary attack by the more reactive protonated QNHOAc species on the *ortho*-chlorine substituent in each case.

CHAPTER 3

Intramolecular reactions of 3-acetoxyamino-2-(α- or β-naphthylalkyl- or α- or β-naphthoxymethyl)quinazolin-4(3*H*)-ones

Intermolecular aziridination of naphthalene with 3-acetoxyaminoquinazolinones[79] in the presence of hexamethyldisilazane (HMDS) has been previously discussed in the Introduction and gives a mixture of mono-aziridines **92** and **93** and bis-aziridines **94** and **95** respectively (Scheme 66).

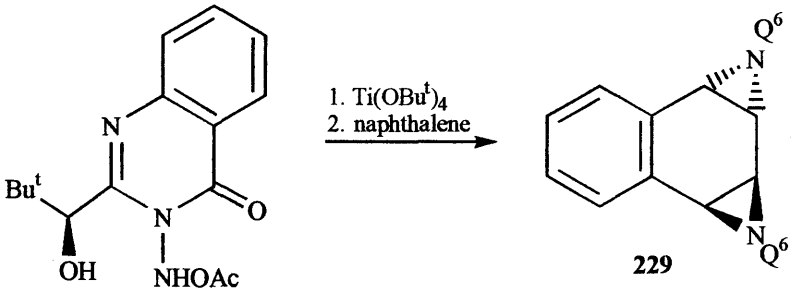
The isolation of monoaziridines **92** and **93** was surprising as the remaining (styrenoid) double bond in the aziridinated 6-membered ring would be expected to be much more reactive than any bond in naphthalene. In fact, epoxidation with *m*-chloroperoxybenzoic acid (mCPBA)[93] or with trifluoromethyl-methyl dioxirane[94] gave only bis-epoxidation product **228** (Scheme 109).



228

Scheme 109

Although the monoaziridination of naphthalene in this work was of interest, the yields were low and attempts to carry out the reaction diastereoselectively using the enantiopure Q^6NHOAc **74** in the presence of titanium(IV) *t*-butoxide gave only the bis-aziridine **229** (Scheme 110).



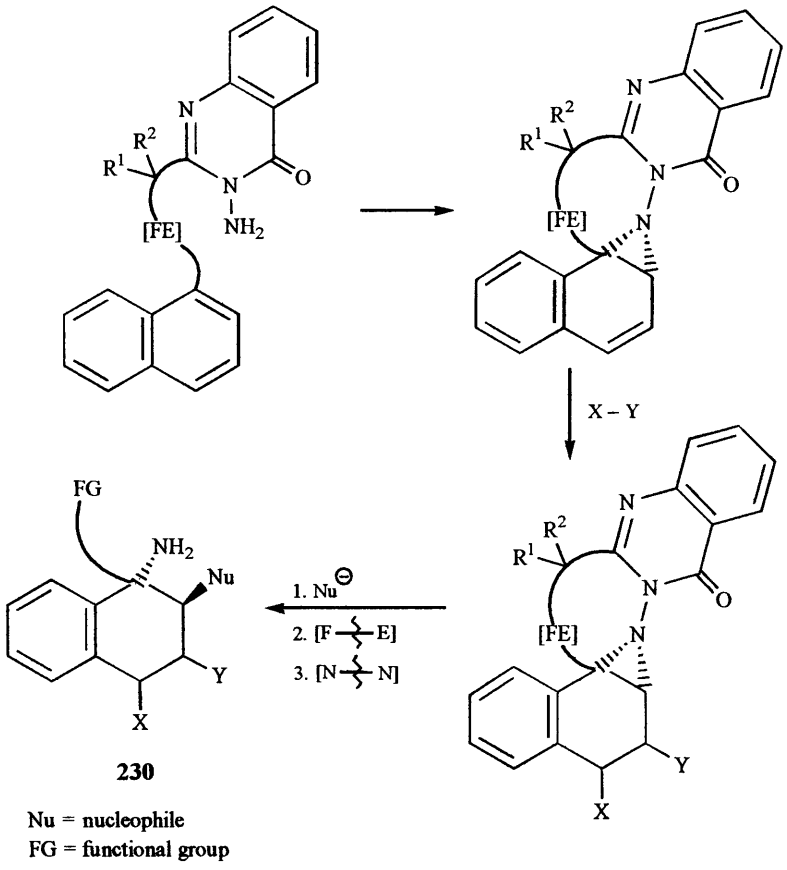
74 ≡ Q^6NHOAc

Scheme 110

The work described in this Chapter (which was initiated prior to the intermolecular reactions of naphthalene and QNHOAc above) deals with intramolecular aziridination of naphthalene rings that are tethered to the 2-position of the 3-acetoxyaminoquinazolinone.

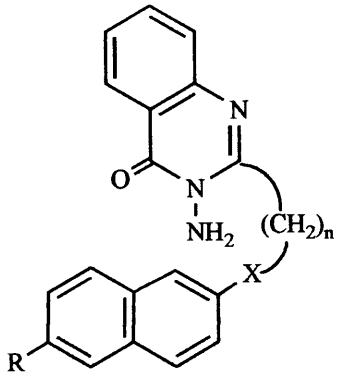
Intramolecular aziridination of these compounds, if successful, would lead only to mono-aziridination products. Eventually, we hoped to also incorporate a chiral centre in enantiopure form in the tether and to obtain complete diastereoselectivity in the aziridination. By incorporating a fissionable element [FE] also in the tether (see Introduction), diastereoselective aziridination followed by (i) addition to the styrenoid double bond, (ii) aziridine ring-opening, (iii) *N-N* bond cleavage and (iv) cleavage of the

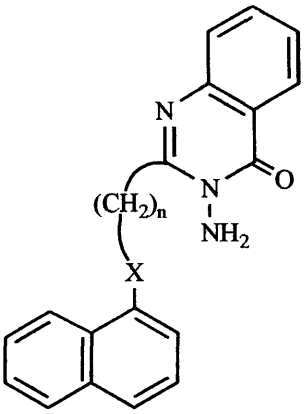
[FE] would lead to a 1,2,3,4-tetra-substituted-1,2,3,4-tetrahydronaphthalene **230** as a single stereoisomer (Scheme 111).



Scheme 111

As a preliminary, we synthesized the 3-aminoquinazolinones **231**–**238** in order to examine the effects of changes in the length and composition of the tether and, in **234**, substitution in the naphthalene ring on intramolecular aziridination *via* the corresponding 3-acetoxyamino-quinazolinones. All these 3-aminoquinazolinones were prepared from the corresponding acids *via* the route analogous to that in Scheme 114 (for **236**) except **238** for which the acid chloride from the commercially available acid [(*S*)-Naproxen] was prepared by treatment of the sodium salt with oxalyl chloride.



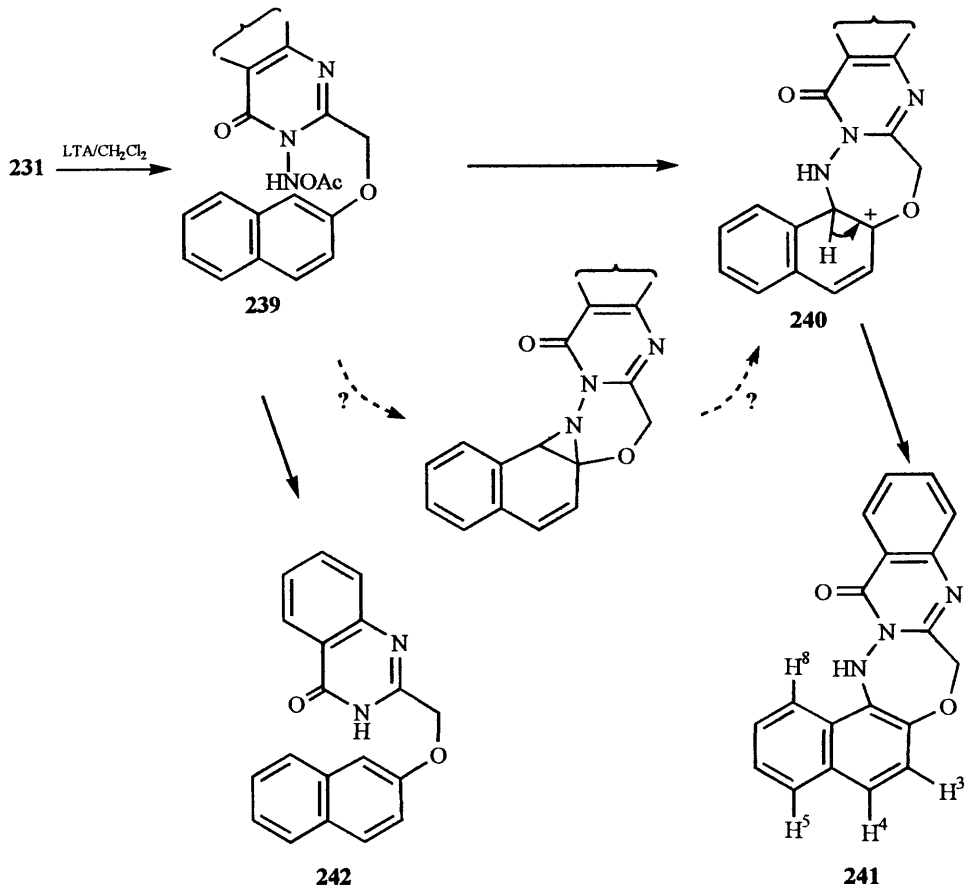


231 X = O, n = 1, R = H
232 X = CH_2, n = 1, R = H
233 X = CH_2, n = 2, R = H
234 X = CH(CH_3), n = 0, R = OMe

235 X = O, n = 1
236 X = CH_2, n = 0
237 X = CH_2, n = 1
238 X = CH_2, n = 2

3.1 Oxidation of 3-amino-2-(2-naphthoxymethyl)quinazolin-4(3H)-one, QNH_2 231 with LTA

Reaction of the title 3-aminoquinazolinone QNH_2 **231** with LTA in the absence of TFA by using the standard procedure gave two crystalline products **241** and **242** (Scheme 112) that were separated by flash chromatography. The less polar product was crystallised from ethanol in 40% yield and was identified as the substitution product **241** from a consideration of all its spectroscopic data. The ^1H NMR (400 Hz) spectrum showed a sharp NH proton (exchangeable D_2O) at δ 8.6 ppm and only 10 aromatic protons including the H-3, H-4, H-5 and H-8 protons which appeared as four doublets. An accurate mass determination corresponded to the expected formula $C_{19}H_{13}N_3O_2$. This substitution product **241** was presumed formed by addition of QNHOAc **239** to the 1,2-double bond of the naphthalene *via* the carbocation intermediate **240** either directly or *via* the aziridine, with subsequent loss of a proton.

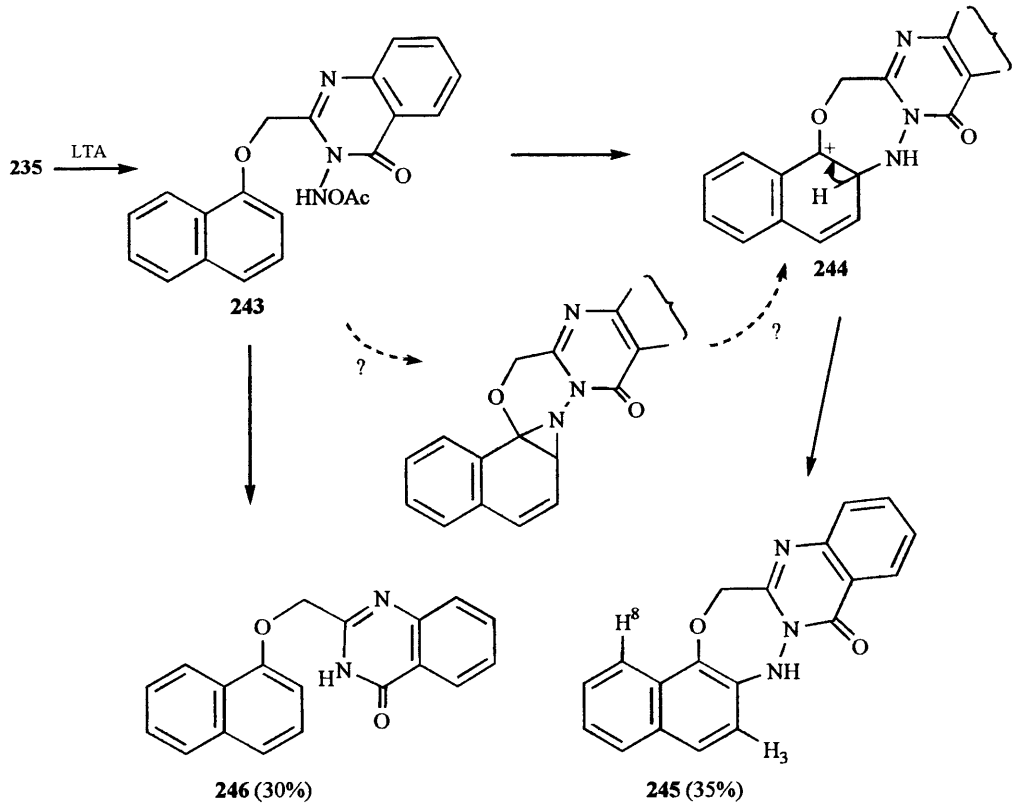


Scheme 112

A more polar product (R_f 0.6) was also obtained in crystalline form, mp. 232–235 °C, in 30% yield. Its accurate mass and high melting point supported assignment of the 3H-quinazolinone structure **242** with a characteristic broadened low field NH peak in the aromatic region.

3.2 Oxidation of 3-amino-2-(1-naphthoxymethyl)quinazolin-4(3H)-one, QNH_2 235 by LTA

Oxidation of the QNH_2 **235** by the standard procedure was also carried out with LTA/CH_2Cl_2 at –20 °C (Scheme 113). Two crystalline products were again isolated by chromatography whose ^1H NMR spectra suggested that their structures **245** and **246** were analogous to **241** and **242** isolated previously. The substitution product **245** was isolated in 35% yield. Its ^1H NMR spectrum showed a low-field doublet with very small additional splitting (*meta*-coupling) at δ 8.3 which probably corresponds to H-8. An accurate mass determination corresponded to $C_{19}H_{13}N_3O_2$ as required. The second isolated product **246** mp. 168–170 °C, obtained in 30% yield, was assigned the QH structure **246** from its ^1H NMR spectrum with a signal for NH at δ 9.9 ppm; an accurate mass determination was in agreement with loss of NOAc from QNHOAc **243**.

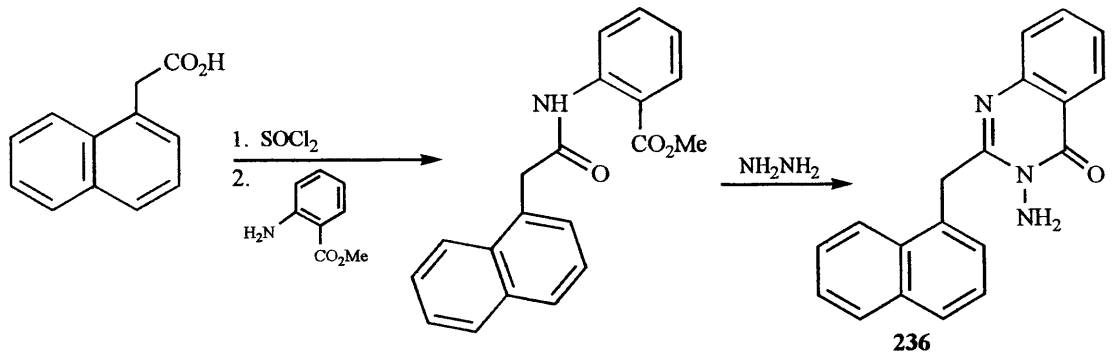


Scheme 113

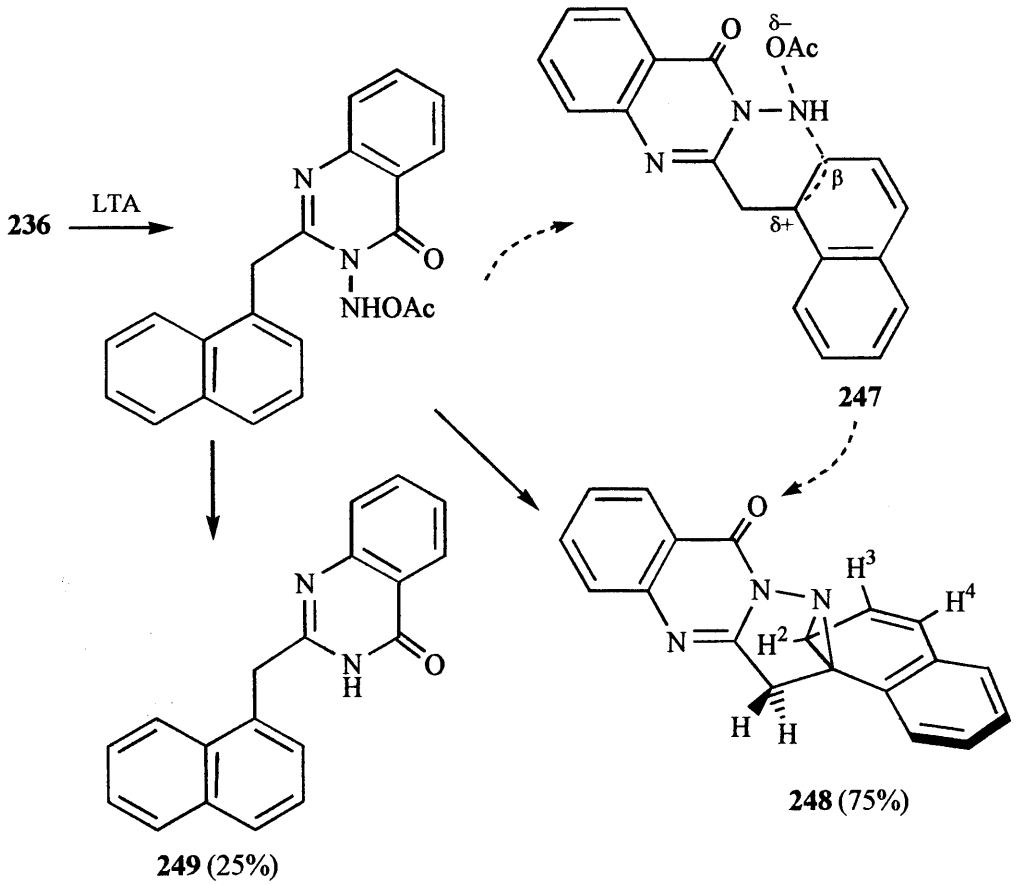
The methanism of formation of substitution products **241** and **245** are presumably analogous to those discussed earlier for formation of the corresponding phenoxy analogues. 2-Naphthoxymethyl-substituted QNH_2 compounds **231** and **235** are benzo analogues of 2-phenoxymethyl QNH_2 compound **159**. The steric inhibition of resonance which prevents stabilisation of the incipient carbocation and hence intramolecular attack on the phenoxy ring in **159**, in the absence of TFA (Scheme 87) is presumably also present in formation of carbocations **240** and **244**. However, the additional benzene ring allows benzyl/cinnamyl stabilisation in formation of these carbocation intermediates. If aziridines are intermediate in these reactions they will be very short-lived.

3.3 Oxidation of 3-amino-2-(1-naphthylmethyl)quinazolin-4(3H)-one QNH_2 236 by LTA/CH_2Cl_2

Oxidation of 3-aminoquinazolinone **236** (Scheme 114) by LTA in dry dichloromethane at –20 °C gave two crystalline products that were separated by fractional crystallization from ethanol. The less soluble was isolated in 75% yield, mp. 165–170 °C and identified as the monoaziridine **248** from its ^1H NMR spectrum (Scheme 115). The most revealing features in this spectrum were (i) the appearance of a doublet at δ 6.69 with *J* 9 Hz for H-4 and a double doublet at δ 6.38 with *J* 9 and 5.9 Hz for H-3 which is also vicinally-coupled to H-2; (ii) the appearance of the two protons in the tether as an AB-system (*J* 18.8) at δ 4.59 and 3.90. The molecular mass corresponded to $C_{19}H_{13}N_3O$.



Scheme 114

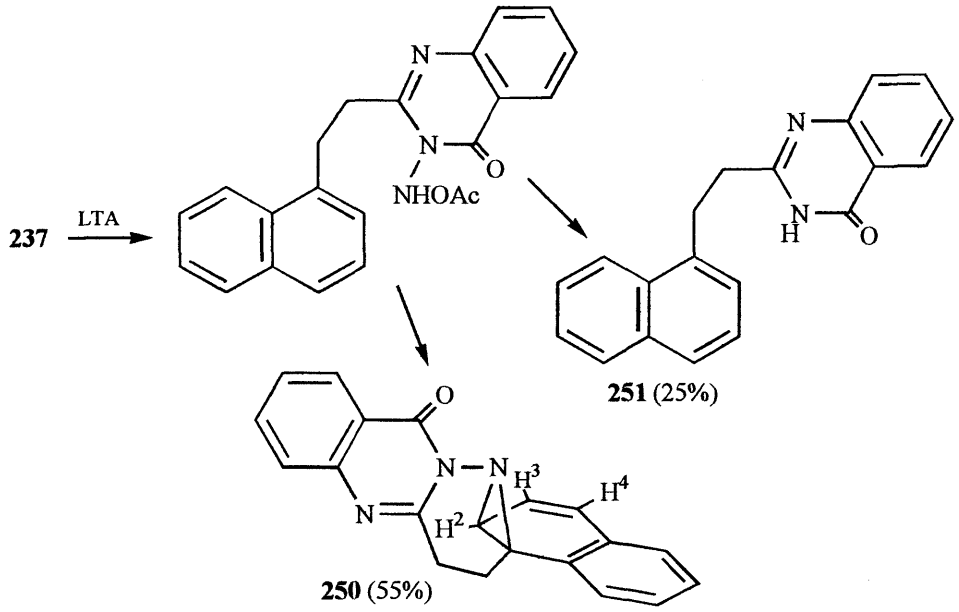


Scheme 115

The crystalline product more soluble in ethanol was separated in 25% yield, mp. 285-288 °C and identified as the QH **249**; its ^{1}H NMR spectrum showed a single broad peak for a NH proton at δ 8.9 and its mass spectrum showed a molecular ion peak M^+ at 286. These assigned structures **248** and **249** were also supported by microanalysis. The yield of **248** (75%) is remarkably high considering that previous work had suggested a preference for cyclisation *via* a 7-membered TS$^{\#}$ (Scheme 70). However, it was pointed out that cyclisation *via* a 6-membered TS$^{\#}$ (*e.g.* **247**) becomes feasible when stabilisation of the carbocation is sufficient (*cf.* Scheme 72).

3.4 Oxidation of 3-amino-2-(1-naphthylethyl)quinazolin-4(3H)-one QNH_2 237 by LTA/CH_2Cl_2

Oxidation of QNH_2 **237** by LTA/CH_2Cl_2 at −20 °C also gave two crystalline oxidation products that were separated by flash chromatography. The less polar product was isolated in 55% yield, mp. 175–180 °C and, from its ^1H NMR spectrum, formulated as the mono-aziridine **250** (Scheme 116); H-4 appeared as a doublet at δ 6.69 with *J* 9.5 Hz, H-3 as a double doublet at δ 6.58 with *J* 9.5 and 4.8 Hz and H-2 as a doublet at δ 3 with *J* 4.8 Hz, *i.e.* values very similar to those for aziridine **248**. Neither the ^1H NMR nor the IR spectrum of aziridine **250** showed any signal for an NH proton.



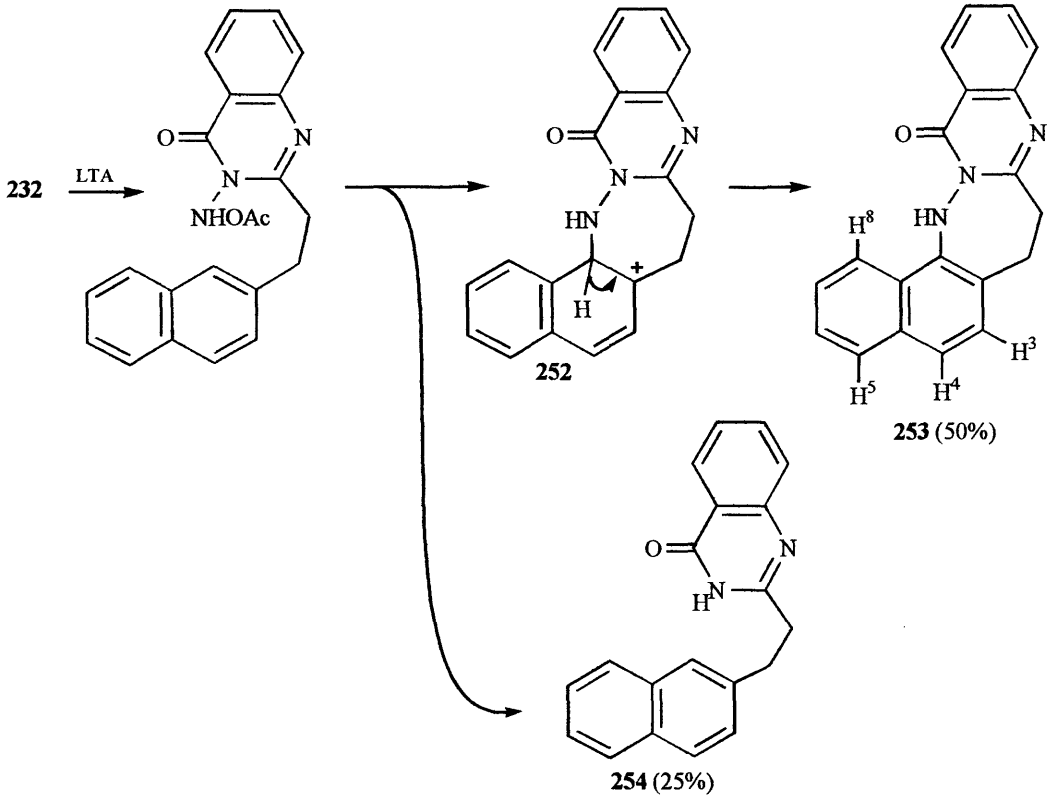
Scheme 116

The more polar product (25%) mp. 232–234 °C was again identified as the 3H-quinazolinone **251** from its exchangeable (D_2O) NH proton at δ 8.9 and molecular mass determination.

3.5 Oxidation of 3-amino-2-(2-naphthylethyl)quinazolin-4(3H)-one, QNH_2 232 by LTA/CH_2Cl_2

Attempted intramolecular aziridination using QNH_2 **232** by the usual method also gave two crystalline products that were separated by flash chromatography. The less polar, isolated in 50% yield, mp. 168–170 °C was identified as the substitution product **253** in agreement with its molecular mass (Scheme 117). Except for the 4 protons in the tether and the N*H* (δ 8.8) only 10 aromatic protons appeared in its ^1H NMR spectrum including doublets at δ 8.2, *J* 8.5 Hz and δ 7.1 ppm, *J* 8.5 Hz. A most interesting feature in its ^1H NMR was the non-equivalence of the 4 protons within the two methylene groups in the tether which appeared as two structured multiplets between δ 3.7–3.45 ppm. Clearly, conformational change in the

7-membered ring is not sufficiently fast to render the two protons within each methylene group equivalent.



Scheme 117

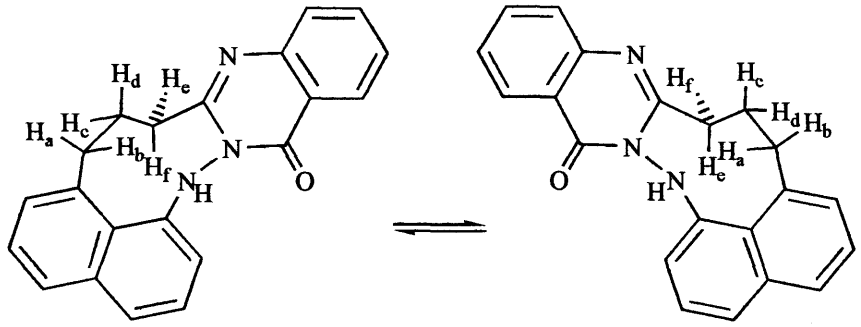
The more polar product (25%) mp. 172–173 °C was identified as the 3H-quinazolinone **254** from the presence of 11 aromatic protons and a singlet corresponding to the NH proton at 10.8 ppm in its ^{1}H NMR spectrum and signals at 300 (MH^+) and 299 (M^+) in its mass spectrum. The isolation of aziridine **250** in Scheme 116 but substitution product **253** in Scheme 117 may reflect the greater stability of the β-carbocation **252** over the α-carbocation which would be formed from the intermediate QNHOAc compound in Scheme 116. Alternatively, it may be that the aziridine analogous to **250** is not stable to the acetic acid co-produced in the reaction in Scheme 117.

3.6 Oxidation of 3-amino-2-(1-naphthylpropyl)quinazolin-4(3H)-one QNH_2 238 with LTA/CH_2Cl_2

Attempted intramolecular aziridination of QNH_2 **238** by LTA/CH_2Cl_2 at –20 °C gave the substitution product **255** (45%), mp. 174–175 °C (Scheme 118) after separation by chromatography from 3H-quinazolinone **256**. This compound **255** showed interesting features in its ^{1}H NMR spectrum that were consistent with a conformational change taking place in the molecule at a rate close to the NMR timescale. Thus there was a broadened signal at δ 5.0 ppm and all signals from protons in the tether were likewise broadened though still resonating at different δ values, whereas the aromatic proton signals were sharp.

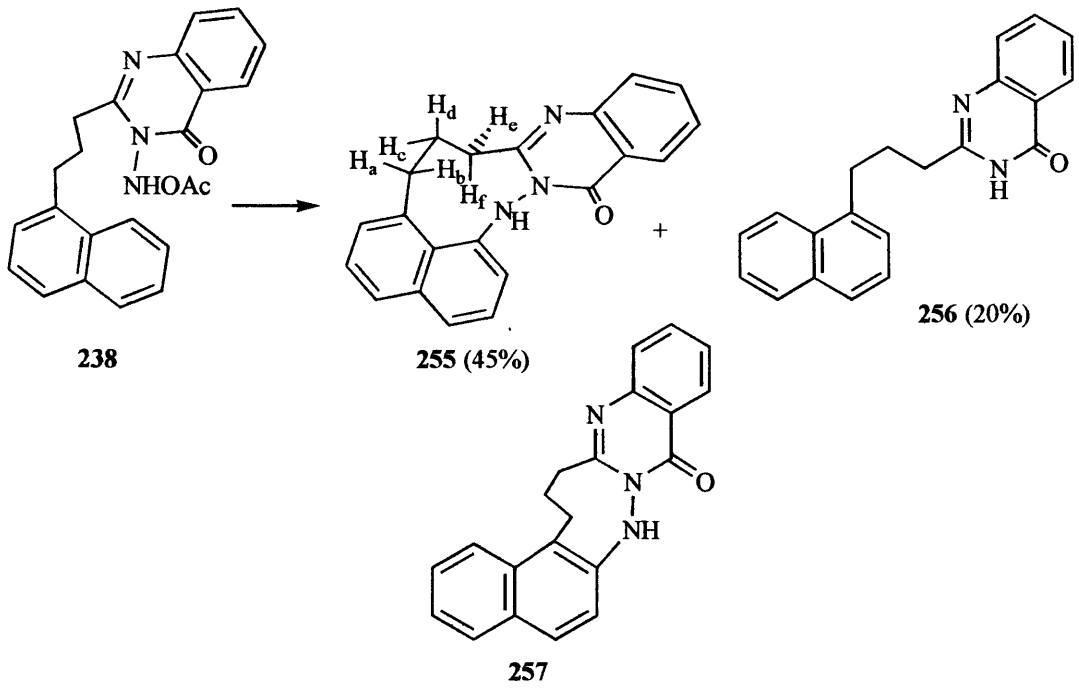
The ^{1}H NMR spectrum run at low temperature confirmed the assigned conformation for the 9-membered ring in this product **255**. The two protons H_f and H_e both appeared as doublets of doublets at δ 2.85 (*J* 12 and 7.2 Hz) and 2.75 (*J* 12 and 7.2 Hz) and not doublets of doublets of doublets as would be expected because *J* H_fH_c ~0 Hz and also *J* H_eH_d ~ 0 Hz since H_e and H_f have ~90° dihedral angles with H_d and H_c respectively. Likewise H_a and H_b appeared as two doublets of doublets at δ 3.15 (*J* 12.8 and 7.2 Hz) and δ 5.0 (*J* 12.8 and 6.8 Hz) respectively because of the ~90° dihedral angles they have with H_c and H_d respectively; H_b is at such low field (δ 5 ppm) by comparison with H_a because it is close in space to either the *NH* proton or to the lone pair of electrons on the exocyclic nitrogen.

On heating, the spectrum shows clearly that coalescence of signals is occurring. The first two signals to coalesce (T = 323 K) are H_e and H_f, the two closest together at δ 2.85 and 2.75 and by raising the temperature to more than 323 K this signal is beginning to sharpen up to become a triplet. The process which is becoming fast on the NMR timescale on heating is interconversion of two enantiomeric forms of the molecule **255a** and **255b**.



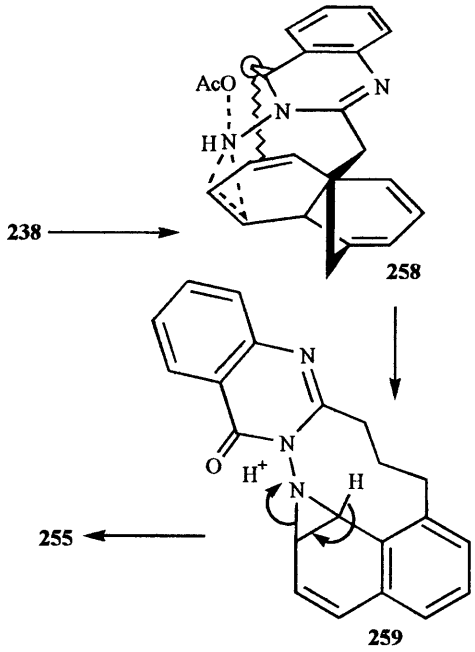
255a **255b**

In this flipping of the ring, the pairs of protons on each carbon of the tether interchange their environments, hence the coalescence. The only other structure possible for this substitution product is **257** (Scheme 118) but analogous compounds containing this trimethylene linkage (see below) do not show such high barriers to conformational change in the trimethylene-containing ring.



Scheme 118

The substitution product **255** is believed to be formed *via* the aziridine **259** by the route shown in Scheme 119; aziridination in **238** takes place preferentially with the bond in the distant aromatic ring possibly through TS$^{\#}$ **258** in which π bonds of Q(C=O) and Q(C=N) are overlapping with the naphthalene π-bonds in a way known to be favoured for this type of reaction (see **68** Introduction).

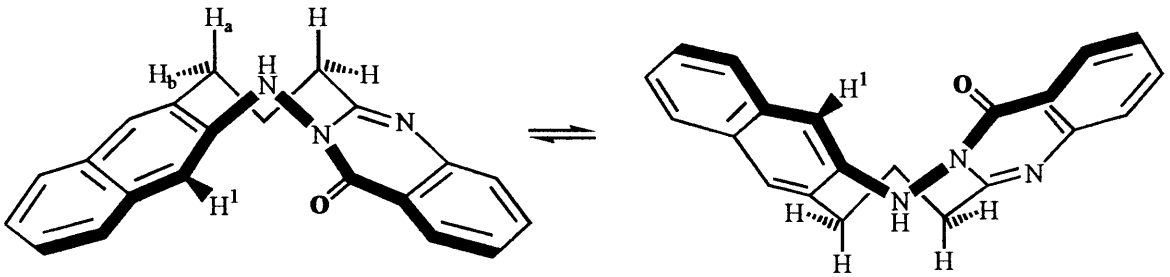


Scheme 119

The 3H-quinazolinone **256** (Scheme 118) has a low-field broad NH signal at δ 10.65 ppm and has the methylene protons of the tether appearing as two triplets and a multiplet, *i.e.* indicating the conformational freedom present in this tether.

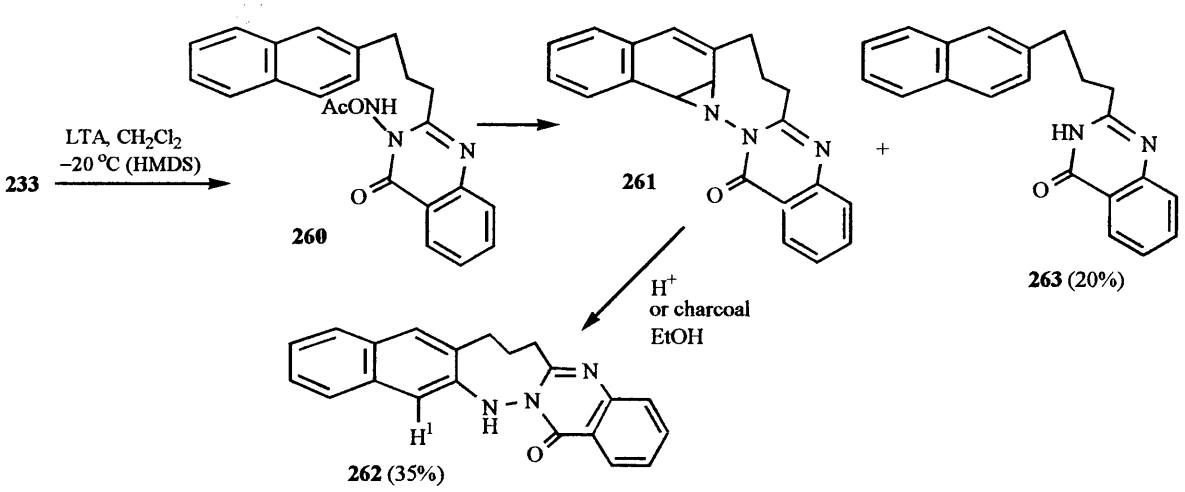
3.7 Oxidation of 3-amino-2-(2-naphthylpropyl)quinazolin-4(3H)-one, QNH_2 233 by LTA/ CH_2Cl_2

Attempted intramolecular aziridination of **233** by LTA/CH_2Cl_2 at −20 °C gave two crystalline products that were separated by chromatography. The less polar product isolated in 35% yield, mp. 166–168 °C, was identified as the substitution product **262** (Scheme 120). Like the previous compound **255**, its ^{1}H NMR spectrum showed broadened signals for all the protons in the tether with a conformational change in the 8-membered ring interconverting, *e.g.* H_a and H_b (topomerisation) which is becoming slow on the NMR time-scale (**262a** **262b**).



262a **262b**

A broadened signal at δ 8.2 ppm was shown not to be the *NH* proton, by shaking with D_2O. It belongs to H-1: the N*H* signal is present in the aromatic proton multiplet between δ 7.8–7.35. The structure of the substitution product **262** was confirmed also by X-ray crystallography (Fig. 1) and shows the high symmetry of the 8-membered ring 'butterfly' conformation.



Scheme 120

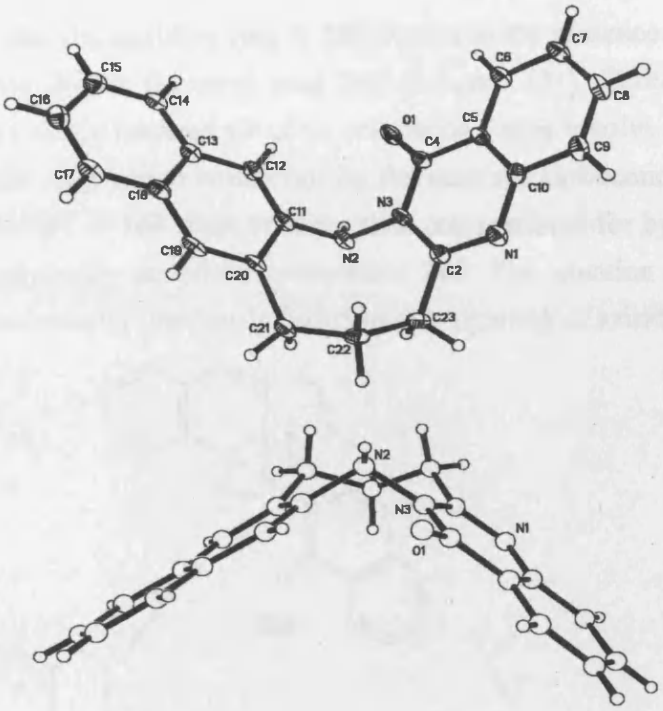


Fig. 1 X-ray crystal structure of **262**

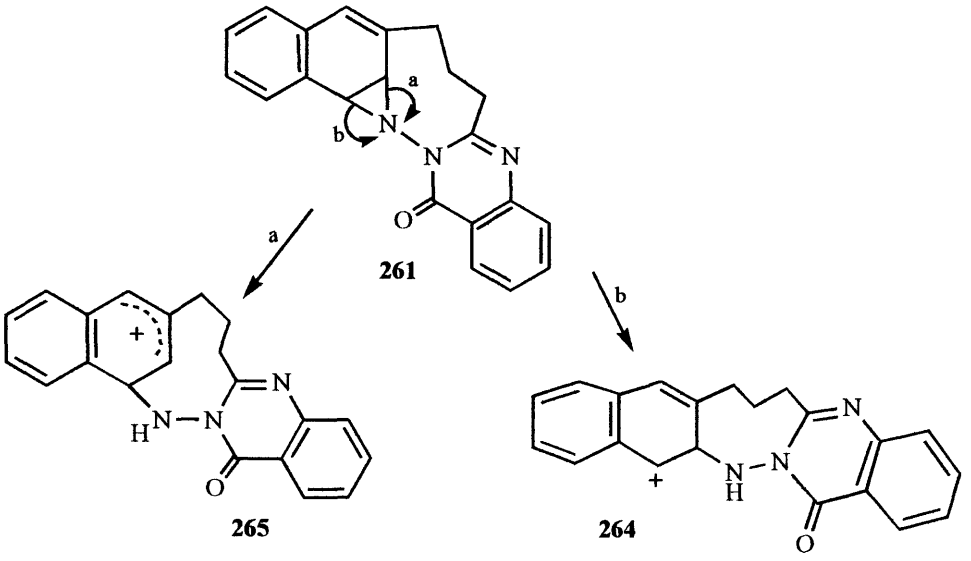
The more polar product isolated in 20% yield, mp. 209–210 °C was identified as the 3H-quinazolinone compound **263** with a low-field proton for a N*H* proton at δ 10.8 and the protons in the tether appearing as two triplets and a multiplet at δ 3.28, 2.9 and 2.33 respectively. The mass spectrum showed a peak at 337 for MNa^+ and another peak at 315 for MH^+.

On repeating the intramolecular aziridination of **233** in the presence of HMDS at −15 °C a crystalline product was isolated (59%) mp. 141–143 °C identified as the aziridine **261**, the precursor of the substitution product **262**. The structure of the aziridine **261** was supported by the presence of two coupled aziridine ring protons at δ 3.98 and 4.66 (*J* 6 Hz).

An attempt was made to catalytically reduce the double bond in the now non-aromatic ring aziridine **261** with 5% palladium on carbon in ethanol for 1h but instead of reduction of the double bond, formation of the previously isolated substitution product **262** took place. It was subsequently found that the substitution product **262** was also obtained from the aziridine **261** by treating it with just cold acetic acid. The reagent mediating the isomerization of the aziridine **261** to the substitution product **262** in the attempted hydrogenation appears to be charcoal because the same isomerisation was brought about by stirring in ethanol with charcoal alone though not with just ethanol.

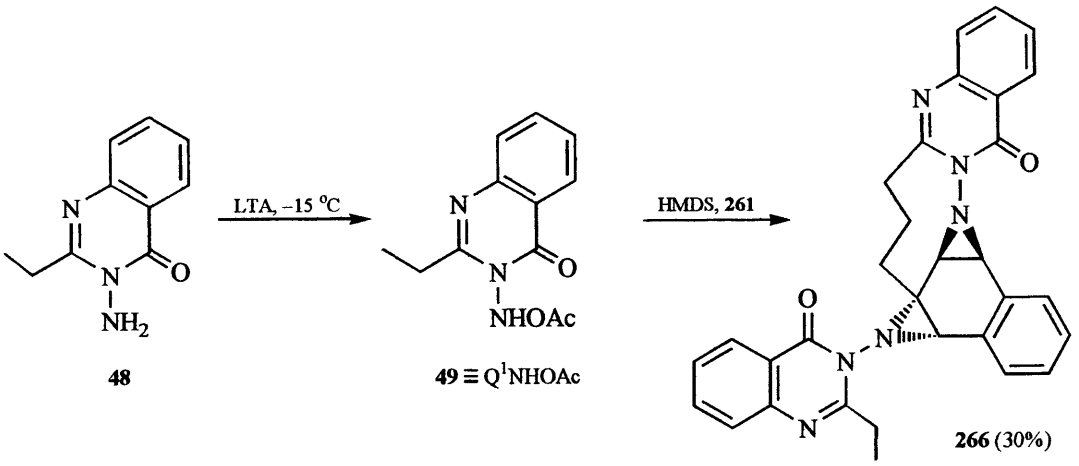
This aziridine **261** is formed from intramolecular reaction of the 3,4-double bond in the original naphthalene. Aziridination of the 3,4- and not the 1,2-double bond can be attributed to a favourable *endo*-overlap of the quinazolinone ring carbonyl group with the adjacent double bond of the naphthalene (that common to both rings) analogous to that shown in $TS^{\#}$ **258**.

It is interesting that the aziridine ring in **261** breaks in the presence of acid in such a way that the carbocation **264** is favoured over **265** (Scheme 121). Carbocation **264** might be expected to be less stable because all of its resonance forms involve loss of aromaticity of the second aromatic ring which would not be the case for carbocation **265**. However, this apparent lesser stability in **264** must be more than compensated for by the strained tether in formation of the allylically-stabilised carbocation **265**. The situation here is reminiscent of the different regioselectivity previously found in ring-opening of aziridines **126** and **174**.



Scheme 121

In order to demonstrate that further addition to the remaining (styrenoid) double bond in aziridine **261** was possible (*cf.* Scheme 111), further aziridination with Q^1NHOAc **49** was carried out (Scheme 122). In this reaction Q^1NHOAc **49** was prepared in solution at −15 °C by portionwise addition of LTA to Q^1NH_2 **48**; HMDS was then added to remove any excess acetic acid followed directly by addition of the aziridine **261** and then the reaction mixture was slowly warmed to room temperature. After purification, a high melting point white solid (242–243 °C) was obtained and identified as the bis-aziridine **266** with two aziridine ring proton signals as doublets at δ 3.69 and 4.34, *J* 8 Hz and one at δ 4.23 (as a broadened singlet. The mass spectrum showed a molecular ion peak at 515 (MH^+). It is assumed that the stereostructure of the bis-aziridine **266** is as illustrated with attack of Q^1NHOAc **49** being directed onto the opposite face of the double bond to the existing aziridine ring.

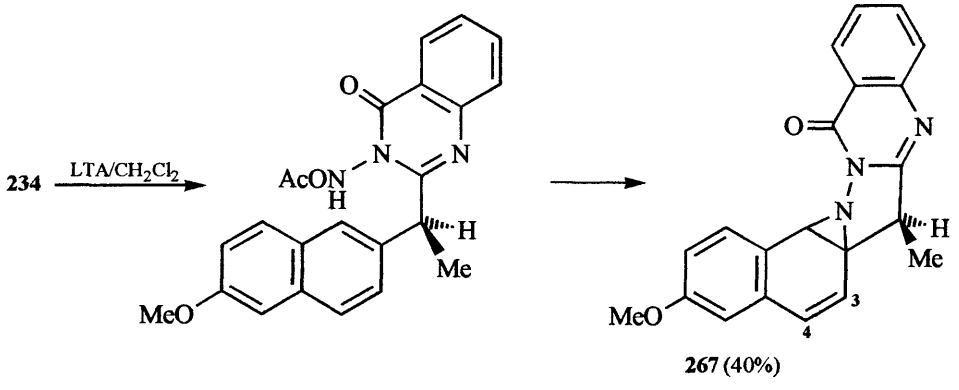


Scheme 122

In principle, other reagents could be added to the 3,4-position of aziridine **261** and hence lead to 1,2,3,4-substituted tetrahydronaphthalenes after ring-cleavage and *N–N* bond reduction (see Scheme 111).

3.8 Oxidation of 3-amino-2-[2-(S)-(6-methoxynaphthy)ethyl]quinazolin-4(3H)-one 234 by LTA/CH_2Cl_2

Oxidation of QNH_2 **234** by LTA/CH_2Cl_2 at –20 °C gave a crystalline product (40%) mp. 188–191 °C whose ^1H NMR spectrum supported its assigned structure as the mono-aziridine **267** (Scheme 123) showing a singlet for the 3-membered ring proton at δ 3.7 and two doublets at δ 6.9 and 6.55 (*J* 9.5 Hz) for H-4 and H-3 respectively. The ^1H NMR also showed a quartet at δ 4.25 (*J* 8.3 Hz) for C*H*–CH_3 the methoxy methyl as a singlet at 4.05 and a doublet at 2.05 (*J* 8.3 Hz) for CH–C*H*$_3$. An accurate mass determination showed the formula to be $C_{21}H_{17}N_3O_2$ as required for aziridine **267**. The data above suggest that this intramolecular aziridination does have the potential to be highly diastereoselective with the configurations at the newly created aziridine ring chiral centres controlled by that in the tether (*cf.* Scheme 111) although the configurations at the new chiral centres in **267** have yet to be determined.



Scheme 123

3.9 Summary

Intramolecular reactions of QNHOAc compounds derived from QNH_2s **231–238** gave the corresponding aziridines or their ring-opened products (formally aromatic substitution products), sometimes in good yields but generally accompanied by QH compounds in ~20% yield.

When the tether is at least 3 atoms in length, the preference for a secondary overlap between the Q-ring and an unreacting double bond in the naphthalene leads unexpectedly to aziridination of a more distant double bond than that attached to the tether.

In one of these compounds **234**, prepared from enantiopure (*S*)-Naproxen, the intramolecular reaction is highly, or even completely, diastereoselective.

The styrenoid double bond remaining in aziridine **261** has been further aziridinated showing that functionalisation using this strategy to give a single diastereoisomer of a 1,2,3,4-tetrasubstituted tetrahydronaphthalene is feasible.

The 8- or 9-membered rings in some of these substitution products show retarded conformation changes (topomerisation) on the ^{1}H NMR scale.

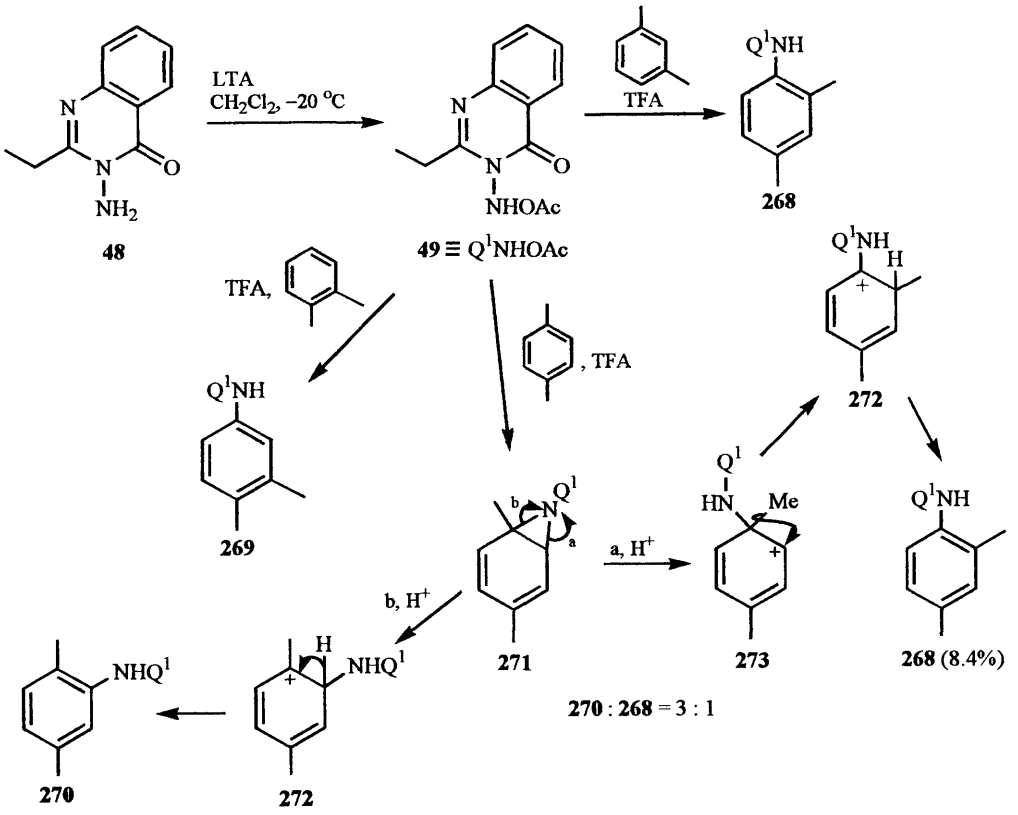
CHAPTER 4

Intermolecular reactions of 3-acetoxyamino-2-ethylquinazolin-4(3H)-one with xylenes and with toluene in the presence of TFA

The increased reactivity of QNHOAc compounds in intramolecular reactions with a tethered aromatic ring in the presence of TFA led us to examine intermolecular reactions of the title compound in the presence of TFA with the less reactive aromatic compounds xylene and toluene. Reaction of 3-acetoxyaminoquinazolinone **49** with the different isomers of xylene and with toluene was successful in the presence of TFA under the same conditions devised previously for the intramolecular aziridination of less reactive aromatic rings. In the absence of TFA no products of intermolecular reaction of the QNHOAc with these aromatic rings were obtained.

4.1 Reaction of meta, ortho and para-xylenes

In the case of *meta*-xylene the yield of the substitution product **268** was 22%. Under the same conditions the yield of the corresponding substitution product **269** using *ortho*-xylene was 42%. Reaction of QNHOAc **49** in the presence of *para*-xylene and TFA gave a mixture of two products which were difficult to separate. Careful chromatography over kieselgel gave incomplete separation but a pure sample of each component was obtained. The major product was the expected substitution product **270**. The minor product was identical to that obtained from *meta*-xylene above, *i.e.* substitution product **268**. The ratio of the major: minor (**270** : **268**) in the crude reaction mixture was ~3:1 from NMR examination of the crude reaction product. The absence of any *meta*-xylene in the *para*-xylene sample used in the reaction was confirmed by NMR spectroscopy. The rearranged substitution product **268** is assumed to be formed from the presumed aziridine intermediate **271** *via* ring-opening in an acid medium and migration of a methyl group to form a more stable carbocation **272** followed by loss of a proton (Scheme 124). Opening of aziridine **271** in the alternative regiosense and loss of a proton would give **270**. That competitive ring-opening of aziridine occurs in both regiosenses is not surprising given the likely similar stabilities of the two carbocations involved.



Scheme 124

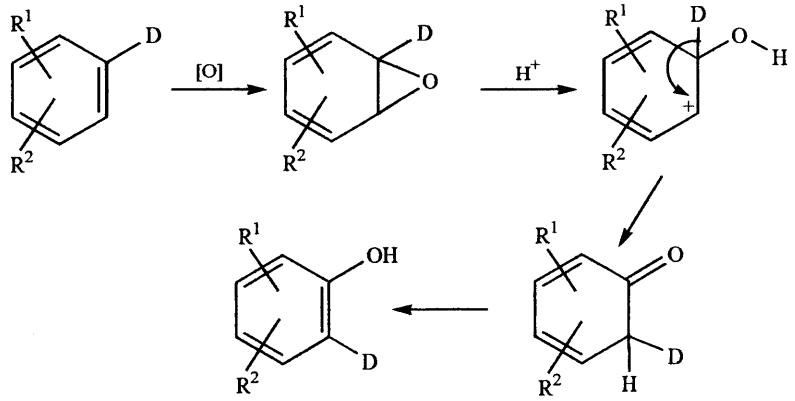
The structures of the substitution products **268**, **269** and **270** were supported by ^1H NMR, IR and microanalysis. The *meta*-substitution product **268**, mp 138–140 °C included in its ^1H NMR a single proton for NH at δ 6.9 ppm and two of the aromatic protons were visible at δ 6.85 (d, *J* 9) and δ 6.19 (d, *J* 9 and 1.5) ppm. The methylene group of the ethyl appeared as a multiplet at δ 2.8–3.1 ppm whereas the methyl group CH_2CH_3 appeared as a triplet (*J* 8 Hz) at 1.4 ppm (see below). The IR spectrum showed a sharp peak at 3320 cm^{-1} for the NH proton.

For the *ortho*-substituted isomer **269**, mp. 138–139 °C the aromatic protons appeared as a doublet at δ 6.45 (*J* 9 Hz), a doublet of doublets at δ 6.35 (*J* 9 and 2 Hz) and a doublet at δ 6.40 (*J* 2 Hz) ppm. As in the *meta*-substitution product **268** the CH_2CH_3 signal of the ethyl group appeared as a multiplet. The IR spectrum showed a sharp NH peak at 3260 cm^{-1}.

In the ^1H NMR spectrum of the *para*-xylene derived substitution product **270** the NH proton appeared as a singlet at δ 6.9 ppm and the three aromatic protons as two doublets (*J* 9 Hz) at ~7.18 and 6.7 ppm and the third as a singlet at ~6.19 ppm. Again the ethyl group showed a multiplet for its CH_2 group signal. The IR spectrum of **270** showed a sharp NH peak at ~3310 cm^{-1}.

The multiplet in each of the ^1H spectra of compounds **268**, **269** and **270** for the CH_2 of the respective ethyl groups arises from restricted rotation around the *N-N* bond which leads to the protons in this methylene group becoming non-equivalent on the ^1H NMR timescale.[88]

The methyl migration involved in formation of **268** from reaction of *para*-xylene with QNHOAc **49** (Scheme 124) is analogous to the 'NIH shift' found in the epoxidation of a number of aromatic compounds (Scheme 125) in which migration of the proton is demonstrated by means of deuterium labelling.[95]



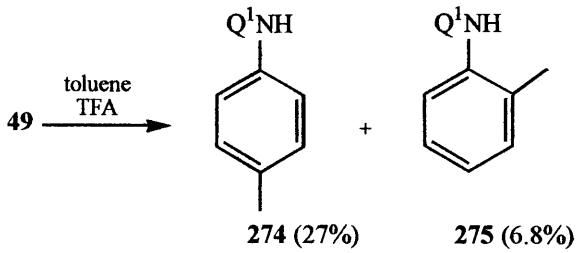
Scheme 125

4.2 Reaction of Q¹NHOAc 49 with toluene in the presence of TFA

The title reaction gave a mixture of *para*- and *ortho* substitution products **274** and **275**, separable by chromatography in a ratio of 4:1 (Scheme 126). Accurate mass determinations showed that both of them corresponded to $C_{17}H_{17}N_3O$. The *para*-substitution of the major isomer was confirmed by the presence of two doublets (*J* 9 Hz) at δ 7.1 and 6.6 ppm for the four aromatic ring protons on the toluene-derived aromatic ring. By contrast, the four neighbouring protons on this ring in the minor isomer gave a more complex set of signals. As in the xylene derived substitution products, the CH_2CH_3 signal is a multiplet for the same reason given above.

It was in our attempts to react toluene with Q¹NHOAc in the presence of TFA that the higher yield and cleaner product using procedure **B** became apparent, *i.e.* addition of pre-formed Q¹NHOAc to a solution of toluene and TFA in dichloromethane.

The mechanism for formation of these substitution products of xylene and toluene may involve aziridines as intermediates (*cf.* **271**). However, we have no evidence that substitution does not take place directly to give the corresponding carbocation directly (*e.g.* **272** and **273** from *para*-xylene).



Scheme 126

CHAPTER 5

Experimental

Experimental

^{1}H Nuclear magnetic resonance (NMR) spectra were recorded on Bruker ARX 250, DPX 300 or DRX 400 (MHz) spectrometers. Chemical shifts are reported as δ in units of parts per million (ppm) relative to tetramethylsilane (δ 0.00 singlet) in deuterated chloroform ($CDCl_3$) ($C\mathit{H}Cl_3$ δ 7.26 singlet) at 250 MHz unless otherwise stated. ^{13}C NMR spectra were recorded on an ARX 250 (75 MHz); the following abbreviations are used; s, singlet; d, doublet; t, triplet; q, quartet; h, heptet; m, multiplet; dd, doublet of doublets; ddd, doublet of doublet of doublets; br, broad; azir, aziridine; Ph, phenyl; Q, quinazolinone. Coupling constants (*J* values) are reported in Hertz (Hz) and evaluated using a WIN NMR computer software (PC version).

Infrared spectra (IR) of all compounds were recorded in dichloromethane (CH_2Cl_2) using a Perkin Elmer PE 298 infrared spectrophotometer and measured in units of cm^{-1}; the following abbreviations are used; s, strong; m, medium; w, weak. Mass spectra were recorded on a Kratos Concept 1H Magnetic Sector Mass Spectrometer using Mach 3 software and all spectra were determined in units of mass relative to charge (m/z) with electron impact (EI) ionisation or fast atom bombardment (FAB) (giving MH^+); only peaks ≥ 20% of the base peak are given. The X-ray crystal structure was carried out by Dr J. Fawcett and Dr D. R. Russell at the University of Leicester. Melting points were obtained on a Kofler 'hot stage' and are uncorrected.

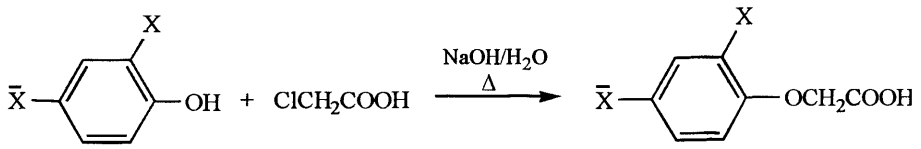
Silica gel [(Sorbasil) C60, 35–70 μ, supplied by Prolabo] chromatographic purification was performed using silica packed glass columns (various sizes). The amount of silica used was approximately 40–60 times by weight relative to material applied to the column. The eluting solvents (light petroleum (bp 60–80°) : ethyl acetate mixture in all cases), were reagent grade and used as received. All crude products were examined by Thin Layer Chromatography (TLC) prior to purification. TLC was performed on silica gel 60 F_{254} on aluminium sheets with a 0.2 mm layer manufactured by Merck & Co. and the visualising agent was UV fluorescence (254 nm).

All reaction solvents were purified and dried according to procedures given in "Purification Organic Solvents" by Perrin & Armarego. Dichloromethane was distilled from CaH2 and stored over 4Å molecular sieves. Tetrahydrofuran (THF) was distilled from sodium and benzophenone immediately prior to use. Ether (diethyl ether) was dried over sodium wire and dry ethanol was prepared by distillation from magnesium and iodine. Saturated aqueous hydrogen carbonate solution was routinely used in the work up of aziridinations. Magnesium or sodium sulphate were routinely used as drying agents. Removal of solvent under reduced pressure was carried out using a Buchi rotary evaporator and a water pump unless otherwise indicated.

Lead tetra-acetate was freed from acetic acid under reduced pressure prior to use. All other reactants were reagent grade and were used as received.

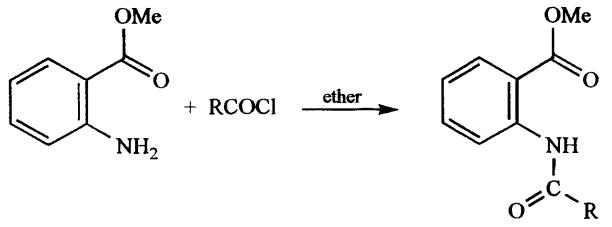
Preparation of phenoxyacetic acid derivatives

A mixture of halophenol (0.05 mol) and chloroacetic acid (0.05 mol) was heated under reflux with stirring with a solution of sodium hydroxide (0.112 mol) in water (25 cm^3) for 2h. The reaction mixture was diluted with water (150 cm^3), filtered if necessary, acidified with dilute hydrochloric acid then extracted with ether (3 × 20 cm^3). After drying the combined ether extracts and then evaporating under reduced pressure, the residue was crystallised from the appropriate solvent.



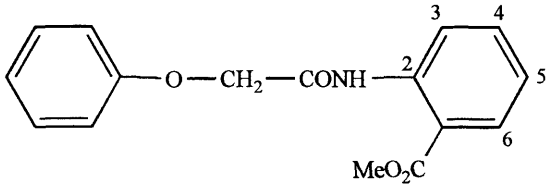
a X = $\bar{X}$ = Cl; b X = H, $\bar{X}$ = Cl; c X = H, $\bar{X}$ = Br; d X = $\bar{X}$ = Br

General procedure for the synthesis of methyl-N-substituted carbonyl anthranilates



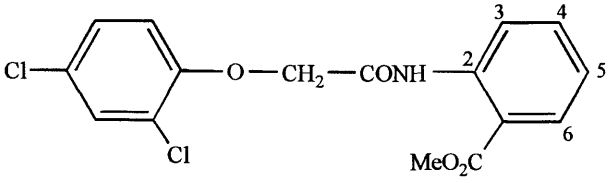
The appropriate acid (0.02 mol) was heated under reflux with thionyl chloride (0.10 mol) until it dissolved and then the reaction mixture set aside overnight at room temperature. Excess thionyl chloride was removed under reduced pressure using a water pump and a solution of the residue in dry ether (10 cm^2) was added dropwise but briskly to a solution of methyl anthranilate (0.04 mol) in dry ether (100 cm^3) with efficient stirring. The mixture was set aside overnight and then the solid methyl anthranilate hydrochloride was filtered off and washed with dry ether, the combined ether filtrates washed with hydrochloric acid (2M; 4 × 25 cm^3) and then water before drying and evaporation to give the product usually as a crystalline solid. The following amides were obtained by the above procedure:

(i) methyl N-2-phenoxyethanoylanthranilate 160



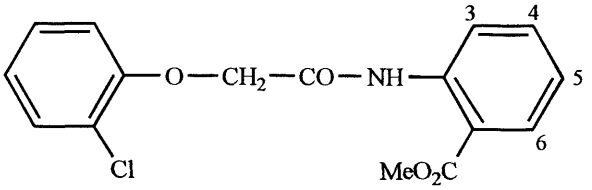
using phenoxyacetic acid as colourless crystals (77%), mp. 81-83 °C (from ethanol) (Found: C, 67.5; H, 5.4; N, 4.95. $C_{16}H_{15}NO_4$ requires C, 67.5; H, 5.5; N, 4.9%); δ_H 12.0 (1H, s br, NH), 8.75 (1H, dd, *J* 8 and 1, H-3), 7.99 (1H, dd, *J* 7 and 2, H-6), 7.60-6.85 [7H, m, H-4, H-5, 5 × C*H*(OPh)], 4.55 (2H, s, CH_2) and 3.85 (3H, s, CH_3); ν_{max}/cm^{-1} 3225 br (NH) and 1700s (CO); *m/z* (%) 285 (M^+) (base), 192 (11), 178 (42), 146 (100) and 132 (54);

(ii) methyl N-2-(2,4-dichlorophenoxy)ethanoylanthranilate



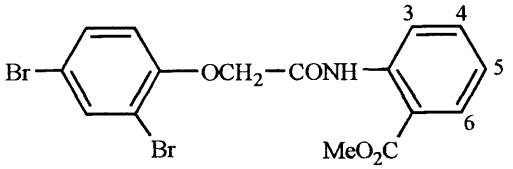
using acid as colourless crystals (70%), mp. 113-115 °C (from ethanol) (Found: C, 54.5; H, 3.75; N, 4.0. $C_{16}H_{13}NO_4Cl_2$ requires C, 54.25; H, 3.7; N, 3.95%); δ_H 11.80 (1H, s br, NH), 8.75 (1H, dd, *J* 8 and 1, H-3), 8.05 (1H, dd, *J* 7 and 2, H-6), 7.65-6.85 [5H, m, H-4, H-5 and 3 × H (2,4-diClAr)], 4.75 (2H, s, CH_2) and 3.90 (3H, s, CH_3); *m/z* (%) 354 (M^+) (base), 318 (29), 286 (21), 191 (25), 178 (15), 146 (100), 133 (95), 119 (15) and 104 (11);

(iii) methyl N-2-(chlorophenoxy)ethanoylanthranilate



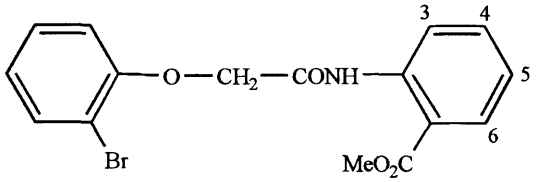
using acid b as colourless crystals (80%) (from ethanol-water), mp. 94-95 °C (Found: C, 60.0; H, 4.3; N, 4.2. $C_{16}H_{14}NO_4Cl$ requires C, 60.1; H, 4.4; N, 4.4%); δ_H 11.80 (1H, s br, NH), 8.75 (1H, dd, *J* 8 and 1, H-3), 8.05 (1H, dd, *J* 7 and 2, H-6), 7.58 (1H, ddd, *J* 8, 8 and 2, H-4), 7.40-6.90 [5H, H-5, 4 × C*H* (2-ClAr)], 4.70 (2H, s, CH_2) and 3.89 (3H, s, CH_3); ν_{max}/cm^{-1} 3220 br (NH) and 1690s (CO), *m/z* (%) 319 (M^+, 18), 284 (100), 252 (26), 178 (13), 146 (86) and 132 (48);

(iv) methyl N-2-(2,4-dibromophenoxy)ethanoylanthranilate



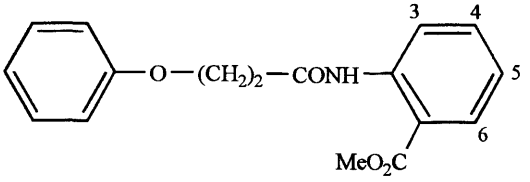
using acid d as colourless crystals (75%) mp. 103-105 °C (from EtOH/CH_2Cl_2) (Found: C, 43.2; H, 29.3; N, 13.5. $C_{16}H_{13}NO_4Br_2$ requires C, 43.35; H, 29.35; N, 31.6); δ_H 11.96 (1H, s br, NH), 8.71 (1H, dd, *J* 8 and 1, H-3), 8.1 (1H, dd, *J* 7 and 2, H-6), 7.79-6.81 [5H, m, H-4, H-5 and 3 × CH (2,4-diBrAr)]. 4.70 (2H, s, CH_2) and 3.90 (3H, s, CH_3); *m/z* (%) 466 (MNa^+, 100), 444 (MH^+, 50), 288 (39), 222 (86) and 102 (68);

(v) methyl N-2-(2-bromophenoxy)ethanoylanthranilate



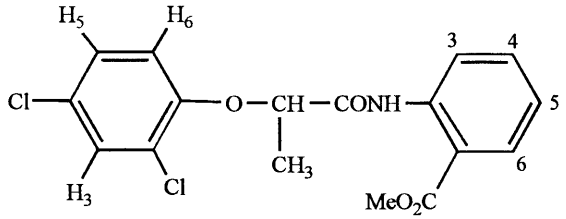
using acid c as colourless crystals (80%) mp. 90-92 °C (from ethanol-water) (Found: C, 52.5; H, 3.7; N, 3.8. $C_{16}H_{14}NO_4Br$ requires C, 52.75; H, 3.85; N, 3.85); δ_H 11.80 (1H, s br, NH), 8.70 (1H, dd, *J* 8 and 1, H-3), 8.00 (1H, dd, *J* 7 and 2, H-6), 7.63-6.87 [6H, H-4, H-5 and 4 × CH (*o*-BrAr)], 4.70 (2H, s, CH_2) and 3.90 (3H, s, CH_3);

(vi) methyl N-3-phenoxypropanoylanthranilate



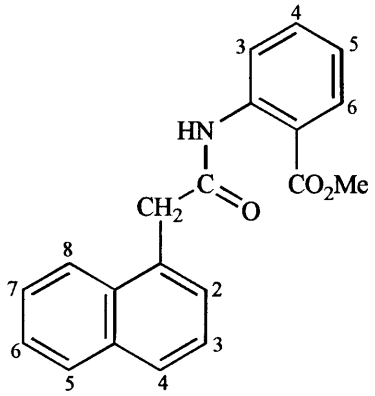
using 3-phenoxypropionic acid as colourless crystals (66%), mp. 78-80 °C (from ethanol) (Found: C, 68.15; H, 5.8; N, 4.65. $C_{17}H_{17}NO_4$ requires C, 68.2; H, 5.7; N, 4.7%); δ_H 11.20 (1H, s br, NH), 8.70 (1H, dd, *J* 8 and 1, H-3), 7.95 (1H, dd, *J* 7 and 2, H-6), 7.60-6.85 [7H, m, H-4, H-5, 5 × CH(Ph)], 4.35 (2H, t, *J* 6, CH_2), 3.85 (3H, s, CH_3) and 2.85 (2H, t, *J* 6, CH_2); γ_{max}/cm^{-1} 3318 br (NH), 1708s (CO) and 1625s; *m/z* (%) 299 (M^+) (base), 206 (41), 174 (29), 151 (94), 132 (13), 119 (53) and 107 (19);

(vii) methyl N-2-(2,4-dichlorophenoxy)propanoylanthranilate



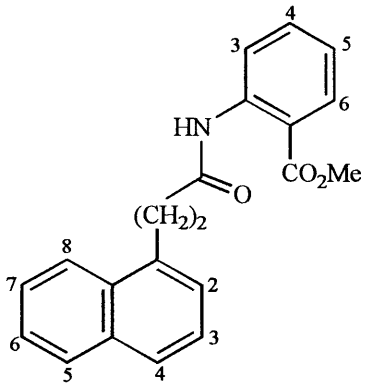
using 2-(2,4-dichlorophenoxy)propionic acid as colourless crystals (75%), mp. 87-80 °C (from methanol) (Found: C, 55.4; H, 4.0; N, 3.7. $C_{17}H_{15}NO_4Cl_2$ requires C, 55.6; H, 4.1; N, 3.8%); δ_H 11.86 (1H, s br, NH), 8.70 (1H, dd, *J* 8 and 1, H-3), 8.0 (1H, dd, *J* 7 and 2, H-6), 7.55 (1H, ddd, *J* 8, 7 and 2, H-4), 7.4 [1H, d, *J* 2, H-3 (2,4-diClAr)], 7.19-7.07 [2H, m, H-5 and H-5 (2,4-diClAr)], 6.8 [1H, d, *J* 7, H-6 (2,4-diClAr)], 4.72 (1H, q, *J* 6, C*H*-CH_3), 3.88 (3H, s, OCH_3) and 1.71 (3H, d, *J* 6, CH_3-CH), *m/z* (%) 390 (MNa^+, 100), 368 (MH^+, 66) and 260 (18);

(viii) methyl N-2-(1-naphthylethanoyl)anthranilate



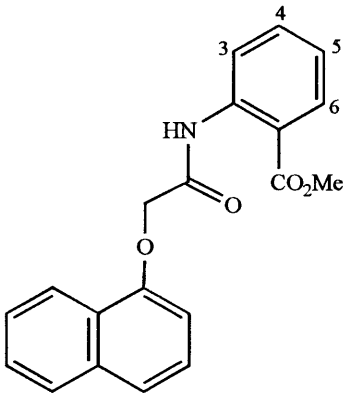
using 1-naphthylethanoic acid as a colourless solid (83%), mp. 113-115 °C (from ethanol); δ_H 10.95 (1H, br s, NH), 8.75 (1H, dd, *J* 8 and 1, H-3), 8.10 (1H, dd, *J* 7 and 2, H-6), 7.95-7.70 (2H, m, H-4 and H-5), 7.65-6.85 [7H, m, 7 × CH (naphth)], 4.25 (2H, s, CH_2) and 7.30 (3H, s, CH_3); γ_{max}/cm^{-1} 3265br (NH), 1700s (CO), 1685s (CO) and 1600s; *m/z* (%) 319 (M^+, 18) (base), 178 (26), 168 (32), 146 (100), 141 (59) and 115 (38);

(ix) methyl N-3-(1-naphthyl)propanoylanthranilate



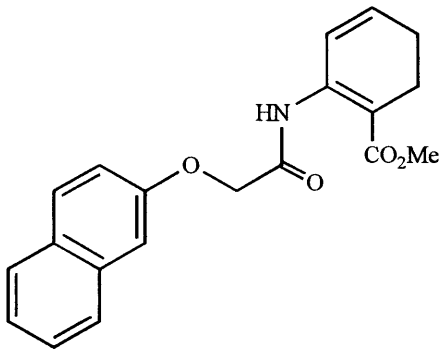
using 1-naphthylpropionic acid as a colourless solid (80%), mp. 83-85 °C (from ethanol) (Found: C, 75.05; H, 5.85; N, 4.1. $C_{21}H_{19}NO_3$ requires C, 75.0; H, 5.75; N, 4.2%); δ_H 11.00 (1H, br s, NH), 8.75 (1H, dd, *J* 8 and 1, H-3), 8.15-6.90 [10H, m, H-4, H-5, H-6, 7 × CH (naphth)], 3.85 (3H, s, CH_3), 3.50 (2H, m, CH_2CH_2) and 2.80 (2H, m, 2H, CH_2CH_2); γ_{max}/cm^{-1} 3260br (NH), 1705s (CO) and 1675s; *m/z* (%) 333 (M^+, 37), 301 (19), 154 (62), 151 (98) and 141 (100);

(x) methyl N-2-(1-naphthoxy)ethanoylanthranilate



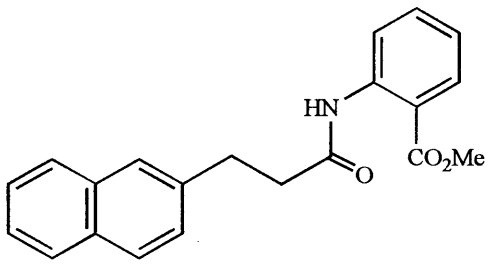
using 1-naphthoxyethanoic acidas colourless crystals (75%), mp. 141-143 °C (from ethanol) (Found: C, 71.5; H, 5.1; N, 4.2. $C_{20}H_{17}NO_4$ requires C, 71.6; H, 5.05; N, 4.15%); δ_H 8.9 [2H, m, 2 × CH(Ar)], 8.15 [1H, d, *J* 9, 1 × CH(Ar)], 7.9 [1H, d, *J* 9, 1 × CH(Ar)], 7.7-7.6 [4H, m, 4 × CH(Ar)], 7.5 [1H, dd, *J* 9.5 and 9.5, 1 × CH(Ar)], 7.3 (1H, dd, *J* 9.5 and 9.5, 1 × CH(Ar)], 7.0 [1H, d, *J* 9, 1 × CH(Ar)] 4.9 (2H, s, -OCH_2), 4.9 (3H, s, $COCH_3$) and 1.7 (1H, br s, NH); *m/z* (%) 358 (MNa^+, 100), 301 (15) and 102 (90%);

(xi) methyl N-2-(2-naphthoxy)ethanoylanthranilate



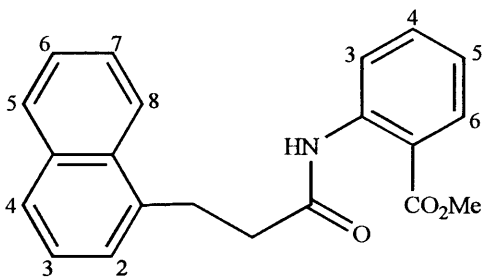
using 2-naphthoxyethanoic acid as a colourless crystalline product (75%), mp. 103-105 °C (from ethanol) (Found: C, 71.45; H, 5.0; N, 4.1. $C_{20}H_{17}NO_4$ requires C, 71.6; H, 5.0; N, 4.5); δ_H 9.0 [1H, d, *J* 9.5, C*H*(Ar)], 8.2 [1H, d, *J* 9.5, 1 × CH(Ar)], 8-7.85 [3H, m, 3 × CH(Ar)], 7.75 (1H, dd, *J* 8.5 and 8.5, 1 × Ar-H), 7.7-7.5 [3H, m, 3 × CH(Ar)], 7.4 [1H, d, *J* 8.5, 1 × CH(Ar)], 7.3 [1H, dd, *J* 8.5 and 8.5, 1 × CH(Ar)], 4.9 (2H, s, OCH_2), 4.1 (3H, s, CH_3) and 1.8 (1H, br s, NH);

(xii) methyl N-3-(2-naphthyl)propanoylanthranilate



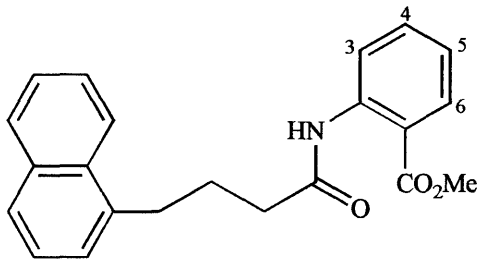
using 3-(2-naphthyl)propionic acid (prepared by Mr D. Messenger in the University of Leicester) as a crystalline product (75%), mp. 66-68 °C (from methanol) (Found: C, 75.1; H, 5.7; N, 4.0. $C_{21}H_{19}NO_3$ requires C, 75.0; H, 5.75; N, 4.2%); δ_H 11.0 (1H, br s, NH), 8.72 (1H, dd, *J* 8 and 1, H-3), 8.0 (1H, dd, *J* 7 and 1, H-6), 7.9-7.35 [8H, m, 8 × CH(Ar)], 7.05 [1H, m, CH(Ar)], 3.85 (3H, s, CO_2Me), 3.22 (2H, t, *J* 6, CH_2) and 2.85 (2H, t, *J* 6, CH_2); *m/z* (%) 356 (MNa^+, 100) and 102 (8);

(xiii) methyl *N*-3-(1-naphthyl)propanoylanthranilate



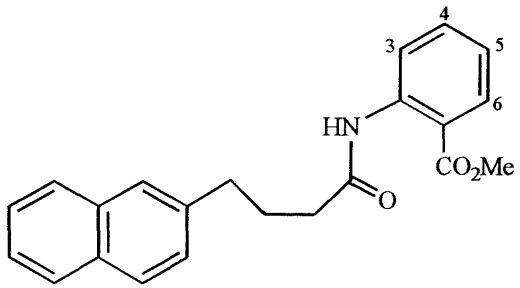
using 3-(1-naphthyl)propionic acid (prepared by Mr D. Messenger in the University of Leicester) as a colourless solid (75%), mp. 83-85 °C (from ethanol) (Found: C, 75.05; H, 5.85; N, 4.1. $C_{21}H_{19}NO_3$ requires C, 75.0; H, 5.75; N, 4.2%); δ_H 11.0 (1H, br s, NH), 8.75 (1H, dd, *J* 8 and 1, H-3), 8.15-6.90 [10H, m, 10 × CH(Ar)], 3.85 (3H, s, CH_3), 3.50 (2H, m, CH_2-CH_2CO) and 2.80 (2H, m, CH_2-CH_2CO); γ_{max}/cm^{-1} 3260br (NH), 1705s (CO) and 1675s (CO); *m/z* (%) 333 (M^+, 37), 301 (19), 154 (62), 151 (98) and 141 (100);

(xiv) methyl N-4-(1-naphthyl)butanoylanthranilate



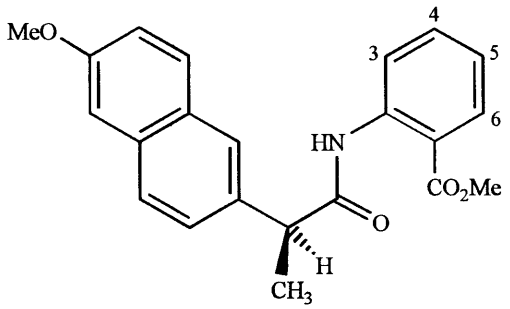
using 4-(1-naphthyl)butanoic acid (prepared by Mr D. Messenger in the University of Leicester) as an oily colourless product (70%); δ_H 11.0 (1H, br s, NH), 8.8 (1H, dd, *J* 8.5 and 1.2, H-3), 8.1 [1H, dd, *J* 9 and 1, CH(naphth)], 7.9 (1H, dd, *J* 7 and 1, H-6), 7.8 [1H, dd, *J* 9 and 1, CH(naphth)], 7.6 [1H, dd, *J* 7 and 1, CH(naphth)], 7.5-7.3 [5H, m, 5 × CH(Ar)], 7.0 (1H, ddd, *J* 8, 8 and 1, H-5), 3.8 (3H, s, CO_2CH_3), 3.4 (2H, t, *J* 6, CH_2), 3.2 (2H, t, *J* 6, CH_2) and 2.1 (2H, m, CH_2); γ_{max}/cm^{-1} 3300s, 1690s and 1585s;

(xv) methyl *N*-4-(2-naphthyl)butanoylanthranilate



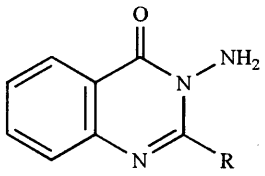
using 4-(2-naphthyl)butanoic acid (prepared by Mr D. Messenger in the University of Leicester) as an oily colourless product (80%); δ_H 10.9 (1H, br s, NH), 8.9 (1H, dd, *J* 8 and 1, H-3), 8.0 (1H, dd, *J* 7 and 2, H-6), 7.7-7.8 [3H, m, 3 × CH(naphth)], 7.5 (1H, ddd, *J* 8, 8 and 2, H-4), 7.4-7.3 [4H, m, 4 × CH(naphth)], 7.0 (1H, ddd, *J* 8, 8 and 2, H-5), 3.9 (3H, s, CO_2CH_3), 3.2 (2H, t, *J* 6, CH_2), 2.85 (2H, t, *J* 6, CH_2) and 1.6 (2H, m, CH_2-CH_2-CH_2); γ_{max}/cm^{-1} 3225s, 1676s and 1585;

Preparation of (S)-methyl N-2-(2,6-methoxynaphthyl)propanoylanthranilate



Naproxen (Aldrich: (*S*)-(+) 6-methoxynaphthyl-α-methylacetic acid) (3.49 g, 0.01 mol) was added to a solution of sodium metal (0.23 g, 0.01 mol) in dry methanol (50 cm^3). After evaporation of the methanol the residue was triturated with dry ether and the insoluble sodium salt separated and converted into its acid chloride by suspending it in dry benzene (20 cm^3), treating with 4 drops of dry pyridine and then, whilst cooling the solution in ice, adding oxalyl chloride (3 cm^3).[96] After the mixture had been stirred for 5 min, the benzene and excess of oxalyl chloride were removed under reduced pressure and a solution of methyl anthranilate (3.02 g, 0.02 mol) in dry ether (50 cm^3) added to the residue with stirring. The mixture was set aside for 3h, the solid methyl anthranilate hydrochloride and sodium chloride filtered off and washed with dry ether and the combined ether filtrates washed four times with hydrochloric acid (2M) and then with water before being dried and evaporated. The anthranilate was obtained as a colourless oil which was used without further purification (75%); δ_H 11.16 (1H, s br, NH), 8.8 (1H, dd, *J* 8 and 1, H-3), 8.1 (1H, dd, *J* 7 and 1, H-6), 7.85 [1H, d, *J* 11, 1 × CH(Ar)], 7.8-7.7 [3H, m, 3 × CH(Ar)], 7.59-7.3 [4H, m, 4 × CH(Ar)], 4.0 (3H, s, OCH_3), 3.96 (1H, m, C*H*-CH_3), 3.9 (3H, s, CO_2Me) and 1.8 (3H, d, *J* 7, CH-C*H*$_3$); *m/z* (%) 386 (MNa^+, 100), 364 (MH^+, 10), 185 (16) and 102 (65).

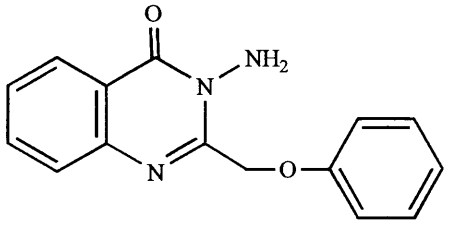
General procedure for the synthesis of 3-amino-2-substituted quinazolin-4(3H)-ones



The appropriate N-acylanthranilate (0.02 mol) and hydrazine hydrate (95%, 0.10 mol) were dissolved in n-butanol (20 cm^3) and heated under reflux for 6-8h. Cooling in ice gave a crystalline product which was filtered off and dried.

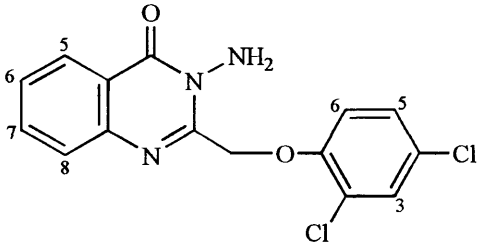
The following were prepared by this method:

(i) 3-amino-2-(phenoxymethyl)quinazolin-4(3H)-one 159



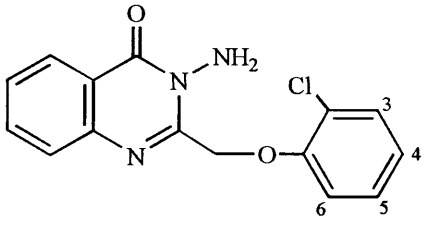
as colourless crystals (85%), mp. 146-148 °C (from methanol) (Found: C, 76.5; H, 5.0; N, 15.7. $C_{15}H_{13}N_3O_2$ requires C, 76.4; H, 4.9; N, 15.7%); δ_H 8.25 (1H, d, *J* 8, H-5), 7.75-6.90 [8H, 3 × CH(Q) + 5 × H(Ar)], 5.3 (2H, s, CH_2) and 4.6 (2H, s, NH_2); γ_{max}/cm^{-1} 3310br, 3260w, 1675s and 1600s; *m/z* (%) 267 (M^+, 52), 251 (25), 236 (11), 95 (20), 174 (11) and 145 (46);

(ii) 3-amino-2-(2,4-dichlorophenoxymethyl)quinazolin-4(3H)-one 190



as colourless crystals (85%), mp. 201-206 °C (from ethanol) (Found: C, 53.5; H, 3.35; N, 12.5. $C_{15}H_{11}N_3O_2Cl_2$ requires C, 53.6; H, 3.3; N, 12.5%); δ_H ($CDCl_3$ + 2 drops of TFA) 8.45 [1H, dd, *J* 8 and 1, H-5(Q)], 8.07 [1H, ddd, *J* 8, 8 and 1, H-7(Q)], 7.75 [1H, d, *J* 8, H-8(Q)], 7.61 [1H, ddd, *J* 8, 8 and 1, H-6(Q)], 7.41 [1H, d, *J* 3, H-3(Ar)], 7.25 [1H, dd, *J* 9 and 3, H-5(Ar)], 7.15 (1H, d, *J* 9, H-6(Ar)], 5.7 (2H, s, CH_2) and 5.3 (2H, s, NH_2); γ_{max}/cm^{-1} 3309br, 3260w, 1675s and 1605s; *m/z* (%) 336 (19) (M^+, base), 300 (100), 285 (15), 263 (12), 175 (30) and 144 (95);

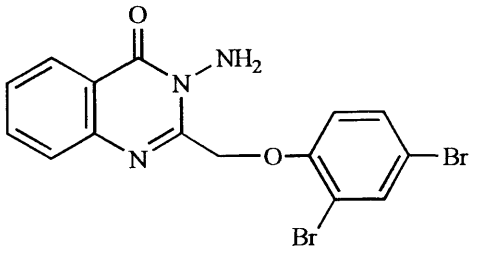
(iii) 3-amino-2-(2-chlorophenoxymethyl)quinazolin-4(3H)-one 179



as colourless crystals (70%), mp. 203-205 °C (from ethanol) (Found: C, 59.6; H, 4.1; N, 13.9. $C_{15}N_{12}N_3O_2Cl$ requires C, 59.7; H, 4.0; N, 13.95; δ_H 8.3 [1H, d, *J* 8, H-5(Q)], 7.81-

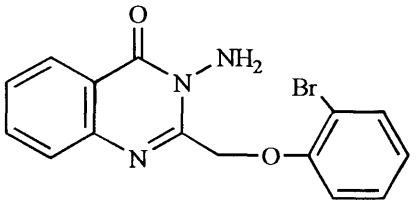
6.90 [5H, m, C*H*(Q) + 4 × H(Ar)], 5.45 (2H, s, CH_2) and 5.31 (2H, s, NH_2); *m/z* (%) 301 (M^+, 8), 266 (100) and 145 (55);

(iv) 3-amino-2-(2,4-dibromophenoxymethyl)quinazolin-4(3H)-one 225



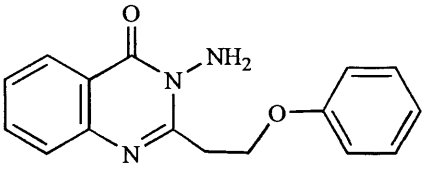
as colourless crystals (80%), mp. 218-220 °C (from ethanol) (Found: C, 42.1; H, 2.4; N, 9.7. $C_{15}H_{11}N_3O_2Br_2$ requires C, 42.35; H, 2.6; N, 9.9. δ_H 8.2 [1H, d, *J* 8, H-5(Q)], 8.0 [1H, ddd, *J* 8, 8 and 1, H-7(Q)], 7.72 [1H, d, *J* 8, H-8(Q)], 7.59 [1H, ddd, *J* 8, 8 and 1, H-6(Q)], 7.4-7 [3H, m, 3 × CH(Ar)], 5.65 (2H, s, CH_2) and 5.3 (2H, s, NH_2);

(v) 3-amino-2-(2-bromophenoxymethyl)quinazolin-4(3H)-one 180



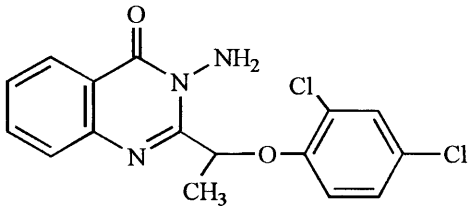
as a colourless solid (60%), mp. 210-211 °C (from ethanol) (Found: C, 52.1; H, 3.2; N, 12.2. $C_{15}H_{12}N_3O_2Br$ requires C, 52.0; H, 3.45; N, 12.15%); δ_H [1H, d, *J* 8, H-5(Q)], 7.75 [2H, m, H-7(Q) and H-8(Q)], 7.5 [2H, m, H-6(Q) and C*H*(Ar)], 7.3 [1H, m, C*H*(Ar)], 7.15 [1H, d, *J* 8, C*H*(Ar)], 6.9 [1H, m, C*H*(Ar)], 5.50 (2H, s, CH_2) and 5.32 (2H, s, NH_2); *m/z* (%) 347 (MH^+), 329 (10), 266 (100) and 145 (64);

(vi) 3-amino-2-(2-phenoxyethyl)quinazolin-4(3H)-one 175



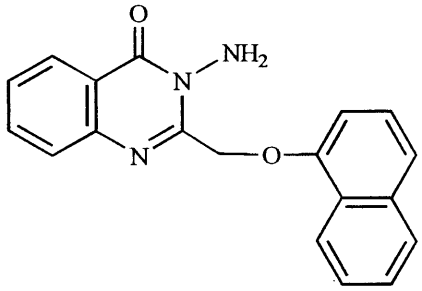
as a colourless solid (14%), mp. 162-165 °C (from ethanol) (Found: C, 68.1; H, 5.45; N, 14.9. $C_{16}H_{15}N_3O_2$ requires C, 68.3; H, 5.35; N, 14.95%); δ_H 8.20 [1H, d, *J* 8, H-5(Q)], 7.70-6.85 [8H, m, 3 × CH(Q) and 5 × CH(Ar)], 5.10 (2H, s, NH_2), 4.41 (2H, t, *J* 6, CH_2-CH_2O) and 3.50 (2H, *J* 6, C$H_2$$CH_2O$); γ_{max}/cm^{-1} 3320s, 3260w, 1680s and 1560s; *m/z* (%) 281 (M^+, 22), 186 (81), 174 (98) and 130 (36);

(vii) 3-amino-2-[1-(2,4-dichlorophenoxyethy)]quinazolin-4(3H)-one 211



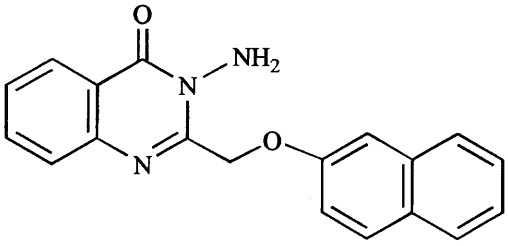
as a colourless crystalline compound (75%), mp. 168-170 °C (from methanol) (Found: C, 55.1; H, 3.6; N, 12.2. $C_{16}H_{13}N_3O_2Cl_2$ requires C, 55.0; H, 3.5; N, 12.0%); δ_H 8.30 [1H, d, *J* 8, H-5(Q)], 7.8-7.0 [6H, m, 3 × C*H*(Q) and 3 × CH(Ar)], 5.85 (1H, q, *J* 6, C*H*-CH_3), 5.22 (2H, s, NH_2) and 1.9 (3H, d, *J* 6, CH_3-CH); γ_{max}/cm^{-1} 3320s, 3259w and 1680s;

(viii) 3-amino-2-(1-naphthoxymethyl)quinazolin-4(3*H*)-one 235



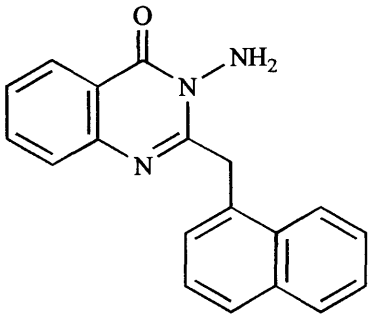
as colourless crystals (70%), mp. 202-204 °C (from ethanol) (Found: C, 71.7; H, 4.6; N, 13.1. $C_{19}H_{15}N_3O_2$ requires C, 71.9; H, 4.7; N, 13.2%); δ_H 8.3 [1H, d, *J* 8, H-5(Q)], 8.2 [1H, dd, *J* 7.5 and 1.2, H-7(Q)], 7.7-7.3 [8H, m, H-8(Q) and 7 × CH(naphth)], 7.1 [1H, dd, *J* 8, H-6(Q)], 5.5 (2H, s, NH_2) and 5.33 (2H, s, CH_2O);

(ix) 3-amino-2-(2-naphthoxymethyl)quinazolin-4(3H)-one 231



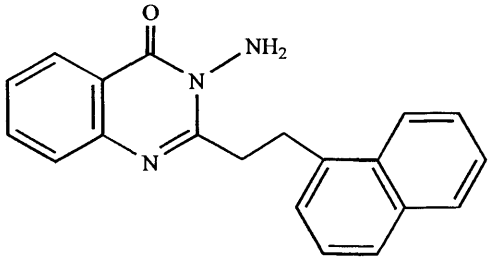
as colourless crystals (75%), mp. 111-113 °C (from methanol) (Found: C, 71.8; H, 4.7; N, 13.3. $C_{19}H_{15}N_3O_2$ requires C, 71.9; H, 4.7; N, 13.2%); δ_H 8.0 [1H, d, *J* 8, H-5(Q)], 7.73-7.0 [10H, m, 3 × CH(Q) and 7 × CH(naphth)], 5.3 (2H, s, NH_2) and 5.2 (2H, s, CH_2O); *m/z* (%) 318 (MH^+, 100), 206 (12) and 176 (10);

(x) 3-amino-2-(1-naphthylmethyl)quinazolin-4(3H)-one 236



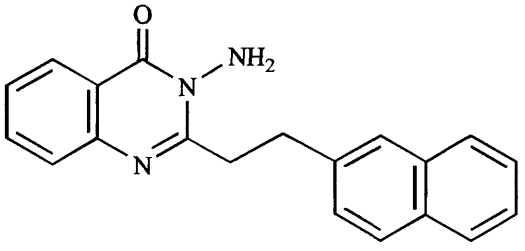
as colourless crystals (60%), mp. 203-205 °C (from ethanol) (Found: C, 75.6; H, 5.15; N, 14.05. $C_{19}H_{15}N_3O$ requires C, 75.75; H, 5.0; N, 13.95%); δ_H 8.15-8.45 [2H, m, H-5(Q) and H-7(Q)], 7.85-7.21 [9H, m, 2 × CH(Q) and 7 × C*H*(naphth)], 4.85 (2H, s, CH_2) and 4.65 (2H, s, NH_2); γ_{max}/cm^{-1} 3300s, 3260w, 1670s and 1615s; *m/z* (%) 301 (M^+) (base), 285 (31), 271 (33), 141 (42) and 115 (33);

(xi) 3-amino-2-(1-naphthylethyl)quinazolin-4(3H)-one 237



as a colourless crystalline product (75%), mp. 161-163 °C (from ethanol) (Found: C, 75.9; H, 5.55; N, 13.4. $C_{20}H_{17}N_3O$ requires C, 76.15; H, 5.45; N, 13.3%); δ_H 8.1-8.2 [2H, m, 2 × C*H*(Q)], 8.3-8.1 [9H, m, 2 × CH(Q) and 7 × CH(naphth)], 4.68 (2H, s, NH_2) and 3.69-3.32 (4H, m, CH_2-CH_2); γ_{max}/cm^{-1} 3270s, 3240w, 1660s and 1620s; *m/z* (%) 315 (M^+, 100), 297 (43), 284 (25), 141 (100) and 115 (65);

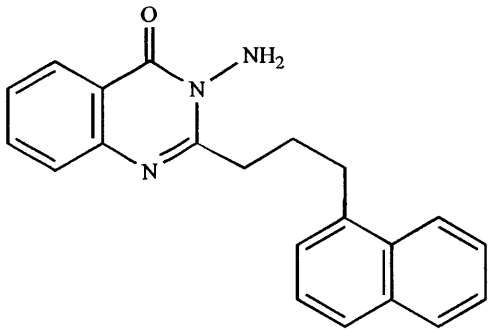
(xii) 3-amino-2-(2-naphthylethyl)quinazolin-4(3H)-one 232



as a colourless crystalline compound (75%), mp. 155-157 °C (from methanol) (Found: C, 76.0; H, 5.5; N, 13.4. $C_{20}H_{17}N_3O$ requires C, 76.15; H, 5.3; N, 13.3%); δ_H 8.2 [1H, d, *J* 8,

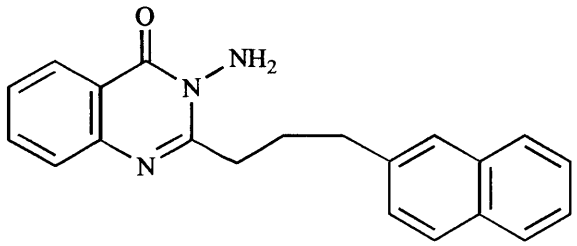
H-5(Q)], 7.8-7.39 [10H, m, 3 × CH(Q) + 7 × CH(naphth)], 4.7 (2H, s, NH_2) and 3.4-3.2 (4H, m, CH_2-CH_2); *m/z* (%) 338 (MNa^+, 30), 316 (MH^+, 48) and 102 (100);

(xiii) 3-amino-2-[3-(1-naphthyl)propyl]quinazolin-4(3H)-one 238



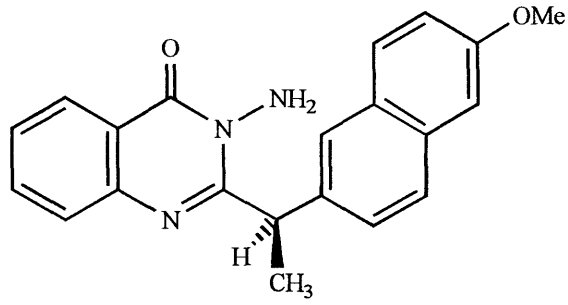
as a white crystalline compound (70%), mp. 164-166 °C (from chloroform-petroleum ether) (Found: M^+ 329.4005. $C_{21}H_{19}N_3O$ requires M^+ 329.4006); δ_H 8.2 [1H, *J* 8, H-5(Q)], 8.16 [1H, d, *J* 8.5, H-8(Q)], 7.83 [1H, d, *J* 7.9, C*H*(Ar)], 7.76-7.65 [3H, m, 3 × C*H*(Ar)], 7.54-7.33 [5H, m, 5 × C*H*(Ar)], 4.77 (2H, s, NH_2), 3.3 (2H, t, *J* 8, CH_2), 3.1 (2H, t, *J* 8, CH_2), 2.2 (2H, m, CH_2-CH_2-CH_2);

(xiv) 3-amino-2-[3-(2-naphthyl)propyl]quinazolin-4(3H)-one 233



as a white crystalline product (70%), mp. 167-170 °C (from ethanol) (Found: C, 76.5; H, 5.7; N, 12.7. $C_{21}H_{19}N_3O$ requires C, 76.6; H, 5.8; N, 12.8%); δ_H 8.22 [1H, d, *J* 8, H-5(Q)], 8.15 [1H, dd, *J* 8.5 and 1, H-8(Q)], 7.9 [dd, *J* 9 and 1, C*H*(naphth)], 7.8-7.4 [8H, 2 × H(Q) and 6 × C*H*(naphth)], 4.79 (2H, s, NH_2), 3.3 (2H, t, *J* 8, CH_2), 3.15 (2H, t, *J* 8, CH_2) and 2.3 (2H, m, $CH_2CH_2CH_2$); γ_{max}/cm^{-1} 3318w, 3208w, 1660s and 1585s; *m/z* (%) 352 (MNa^+) (base), 330 (MH^+, 76), 304 (20) and 139 (25);

(xv) 3-amino-2-[1-(6-methoxynaphthyl)ethyl]quinazolin-4(3H)-one 234

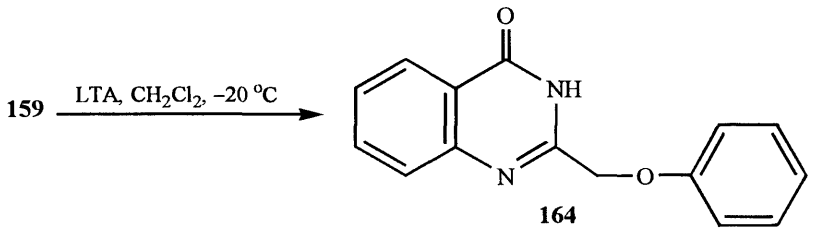


After refluxing for 18h as a white solid (80%) mp. 140-142 °C (from methanol); δ_H 8.25 [1H, d, *J* 8, H-5(Q)], 7.9-7.6 [5H, m, 5 × CH(Ar)], 7.5-7.4 [2H, m, 2 × CH(Ar)], 7.15 [2H, m, 2 × CH(Ar)], 5.0 (1H, m, C*H*-CH_3), 4.8 (2H, s, NH_2), 3.9 (3H, s, OCH_3) and 1.76 (3H, d, *J* 6, CH-CH_3); *m/z* (%) 368 (MNa^+, 21), 346 (MH^+, 29), 301 (17), 130 (20) and 102 (100).

General procedure A for the oxidation of 3-aminoquinazolinones with lead tetraacetate in the absence of trifluoroacetic acid

The 3-aminoquinazolinone (1 eq.) and acetic acid-free lead tetraacetate (LTA) (1.03-1.25 mol eq.) were added alternately and continuously in very small portions over 15 min. to a vigorously stirred solution of dry dichloromethane (1 cm^3/100 mg of 3-aminoquinazolinone) cooled with a dry ice-acetone bath held at –20 °C to –25 °C. The mixture was then stirred for a further 10 min. at this bath temperature which was then allowed to rise to ambient over 20–25 min. with stirring throughout. The lead diacetate was separated, more dichloromethane (15 cm^3) added and the organic solution washed successively with saturated aqueous sodium hydrogen carbonate and water then dried and the solvent removed by evaporation under reduced pressure.

Oxidation of 3-amino-2-(phenoxymethyl)quinazolin-4(3H)-one 159



164

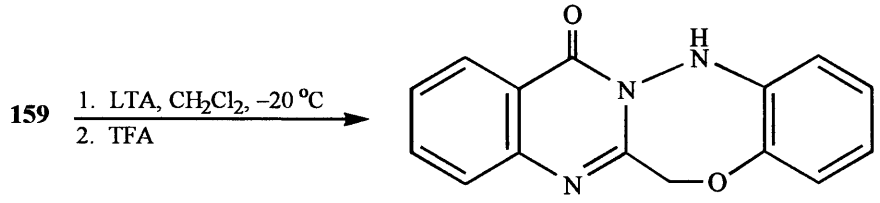
The general procedure **A** was followed using 3-aminoquinazolinone **159** (1 g, 3.5 mmol) and LTA (1.7 g, 1.03 mol eq.) in dichloromethane (10 cm^3). The crude product crystallized on addition of ethanol to give *2-phenoxymethylquinazolin-4(3H)-one* **164** (0.6 g, 60%) as colourless crystals, mp. 237–239 °C, R_f = 0.64 (Found: C, 71.5; H, 4.9; N, 11.2. $C_{15}H_{12}N_2O_2$ requires C, 71.4; H, 4.8; N, 11.1%); δ_H 8.30 [1H, d, *J* 8, H-5(Q)], 7.82–6.90 [8H, m, 3 × C*H*(Q), 5 × C*H*(Ar) and NH] and 5.1 (2H, s, CH_2); γ_{max}/cm^{-1} 3190w, 3130w, 1670s and 1615s; *m/z* (%) 252 (M^+, 45), 234 (13), 159 (26) and 132 (33).

General procedure B for the oxidation of 3-aminoquinazolinones with lead tetraacetate in the presence of trifluoroacetic acid

Solid 3-aminoquinazolone (1 mol eq.) and powdered acetic acid-free lead tetraacetate (LTA) (1.1 mol eq.) were added alternately and continuously in very small portions over 15 min. to a vigorously stirred solution of dry dichloromethane (1 cm^3/100 mg of 3-aminoquinazolinone) cooled with a dry ice-acetone bath held at –20 °C to –25 °C. After addition, the mixture was stirred for a further 5 min. Before insoluble lead diacetate was separated without allowing the temperature of the solution to rise > –10 °C (on a small scale a Pasteur pipette can be used) and the cold dichloromethane solution added dropwise over ~2 min. to a stirred solution of trifluoroacetic acid (TFA) (2.5 cm^3) in dichloromethane (10 cm^3) held at room temperature. After addition of further dichloromethane (15 cm^3), the

solution was washed successively with aqueous saturated sodium hydrogen carbonate and water, dried and the solvent removed by evaporation under reduced pressure.

Oxidation of 3-amino-2-(phenoxymethyl)quinazolin-4(3H)-one 159 in the presence of TFA

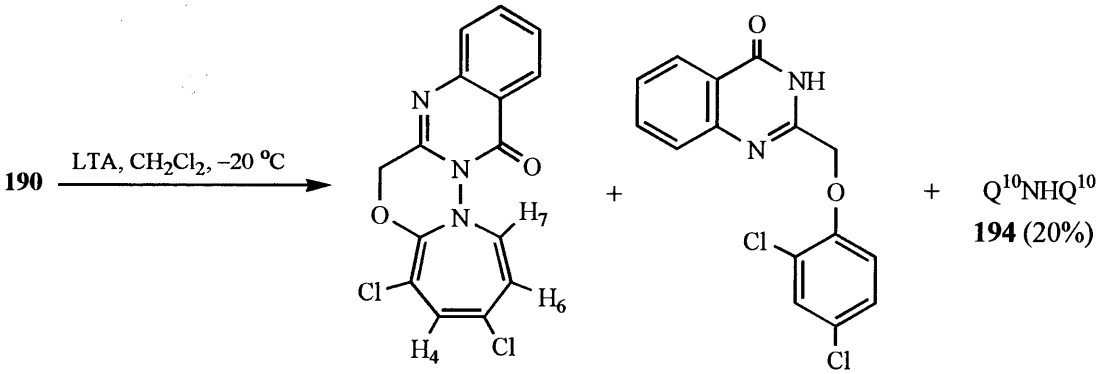


163

General procedure **B** was followed using 3-aminoquinazolinone **159** (1 g, 3.5 mmol) and LTA (1.9 g, 1.03 mol eq.) in dichloromethane (10 cm^3) and gave a gelatinous product which solidified on trituration with dry ether. Crystallization gave *benzo-1,4,5-oxadiazepino[3,4-b]quinazolinone* **163** as a colourless crystalline product (0.5 g, 50%) mp. 247–248 °C, R_f = 0.92 (from pyridine) (Found: C, 67.85; H, 4.2; N, 15.75. $C_{15}H_{11}N_3O_2$ requires C, 67.9; H, 4.2; N, 15.84%); δ_H ($CDCl_3$ + 2 drops of TFA) 8.43 [1H, dd, *J* 8 and 1.2, H-5(Q)], 8.08 [1H, ddd, *J* 7, 8 and 1, H-7(Q)], 7.93 [1H, d, *J* 8, H-8(Q)], 7.83 [1H, ddd, *J* 7, 8 and 1.2, H-6(Q)], 7.35 (1H, br s, NH), 7.13–6.73 [4H, m, 4 × C*H*(Ar)] and 5.83 (2H, s, CH_2); γ_{max}/cm^{-1} 3250s, 1660s and 1600s; *m/z* (%) 265 (M^+), 236 (39) and 160 (22).

Oxidation of 3-amino-2-(2,4-dichlorophenoxymethyl)quinazolin-4(3H)-one 190

(i) In the absence of TFA



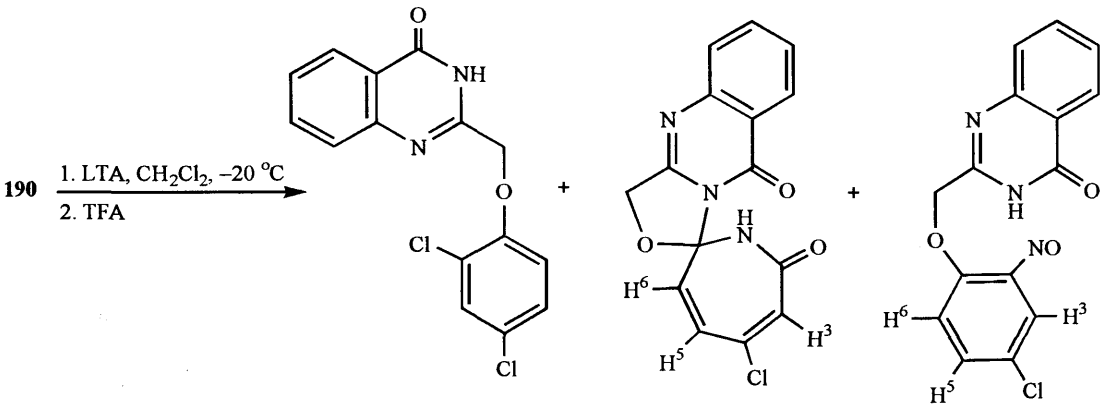
192 (40%) **193** (25%)

General procedure **A** was followed using 3-aminoquinazolinone **190** (1 g, 0.003 mmol) and LTA (1.66 g, 1.25 mol eq.) in dry dichloromethane (15 cm^3) and the crude product was chromatographed over silica, eluting with light petroleum ethyl–ethyl acetate (3:1). The first eluted product (R_f 0.7) was the *azepine* **192** as a colourless solid (0.4 g, 40%), mp. 193–196 °C (from ether/light petroleum) (Found: MH^+ 334.015. $C_{15}H_9N_3O_2Cl_2$ requires MH^+ 334.015); δ_H 8.3 [1H, dd, *J* 8.1 and 1.2, H-5(Q)], 7.9-7.1 [3H, m, 3 × C*H*(Q)], 7.0 (1H, d, *J*

1, H-4 azepine), 6.6 (1H, dd, *J* 11.7 and 1, H-6 azepine), 6.5 (1H, d, *J* 11.7, H-7 azepine), 5.05 (1H, d, *J* 16.2, C*H*HO) and 4.9 (1H, d, *J* 16.2, CH*H*O); γ_{max}/cm^{-1} 1680s, 1650s and 1610s; *m/z* (%) 334 (M^+, 62), 287 (10), 285 (51) and 159 (95).

The second-eluted product (R_f 0.6) was the 3*H*-quinazolinone **193** as a colourless solid (0.22 g, 25%), mp. 210–213 °C (from ethanol/CH_2Cl_2) (Found: M^+ 321.162. $C_{15}H_{10}N_2O_2Cl_2$ requires M^+ 321.162); δ_H 9.8 (1H, s, NH), 8.1 [1H, d, *J* 8.2, H-5(Q)], 8.3–6.72 [6H, m, 3 × C*H*(Q) and 3 × C*H*(Ar)] and 5.1 (2H, s, CH_2-O); γ_{max}/cm^{-1} 3000s, 1665s and 1600s. Further elution with the same solvent mixture gave *bis(3,4-dihydro-4-oxoquinazolin)-3-yl)amine* **194** as a colourless solid (0.2 g, 20%), mp. 273–275 °C (from ethanol/ CH_2Cl_2) (Found: M^+ 655.322. $C_{30}H_{19}N_5O_4Cl_2$ requires M^+ 655.323); δ_H 9.85 (1H, s, NH), 8.1 [2H, dd, *J* 8 and 1.2, 2 × H-5(Q)], 7.8–7.6 [4H, m, 2 × H-7(Q)] and 2 × C*H*(Ar)], 7.5–7.4 [4H, m, 2 × H-8(Q) and 2 × C*H*(Ar)], 7.3–7.1 [4H, m, 2 × H-6(Q) and 2 × CH(Ar)] and 5.9 (4H, s, 2 × CH_2O).

(ii) In the presence of TFA

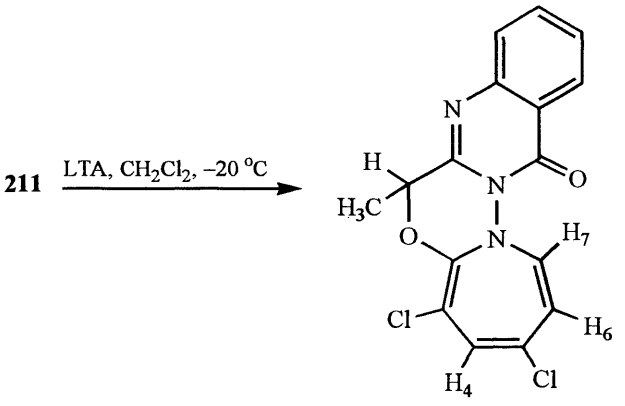


General procedure **B** was followed using 3-aminoquinazolinone **190** (1 g, 3 mmol) and LTA (1.66 g, 1.25 mol eq.) in dry dichloromethane (15 cm^3) at –20 °C and the 3-acetoxyamino-quinazolone solution was added to a solution of TFA (2 cm^3) and dichloromethane (5 cm^3). Chromatography of the crude product over silica, eluting with light petroleum–ethyl acetate (2:1) gave *3H-quinazolinone* **193** (0.2 g, 20%) identical with that isolated previously. Further elution with the same solvent mixture gave *azepinone* **200** as a colourless solid (0.25 g, 25%), mp. 166–168 °C (from ethanol) (Found: M^+ 315.715. $C_{15}H_{10}N_3O_3Cl$ requires M^+ 315.715); δ_H 9.8 (1H, s, NH), 8.1 [1H, d, *J* 8, H-5(Q)], 8.2–7.5 [3H, m, 3 × C*H*(Q)], 7.2 (1H, d, *J* 1.5, H-3), 6.25 (1H, dd, *J* 11.5 and 1.5, H-5), 5.7 (1H, dd, *J* 11.5 and 1, H-6) and 5.2 (2H, s, CH_2O); δ_C 7 × quaternary *C* at 161.0, 151.8, 150.7, 148.6, 141.4, 124.7 and 122.1, 7 × *C*H at 135.3, 130.9, 128.4, 127.7, 127.5, 127.1 and 115.9] and *C*H_2 (68.7); *m/z* (%) 315 (M^+, base), 175 (100), 160 (10) and 132 (19).

Further elution with the same solvent mixture gave *2-(4-chloro-2-nitrosophenoxymethyl)-quinazolin-4(3H)-one* **205** (0.19 g, ~25%) (R_f 0.6) as a colourless crystalline solid, mp. 222–224 °C (from ethanol) (Found: M^+ 315.713. $C_{15}H_{10}N_3O_3Cl$ requires M^+ 315.715); δ_H 9.6 (1H, s br, NH), 8.3 [1H, dd, *J* 8.2 and 1, H-5(Q)], 7.85 [1H, ddd, *J* 8.2, 7 and 1, H-7(Q)], 7.7 [1H, d, *J* 7, H-8(Q)], 7.5 [1H, ddd, *J* 8.2, 7 and 1, H-6(Q)], 7.4 [1H, d, *J* 2.5, H-3(Ar)], 7.25 [1H, dd, *J* 8.5 and 2.5, H-5(Ar)], 7.0 [1H, d, *J* 8.5, H-6(Ar)] and 5.1 (2H, s, OCH_2); δ_C 7 × quaternary *C* at 161.8, 153.0, 148.5, 142.0, 125.7, 123.0 and 121.9; 7 × *C*H at 134.9, 129.8, 128.5, 127.7, 127.4, 126.2 and 116.1 and CH_2; γ_{max}/cm^{-1} 3185w, 1680s, 1660w, 1628w and 1500w; *m/z* (%) 315 (M^+, 11), 176 (12), 175 (92), 160 (14) and 132 (15).

Oxidation of 3-amino-2-[1-(2,4-dichlorophenoxyethyl)]quinazolin-4(3H)-one 211 by LTA in dichloromethane

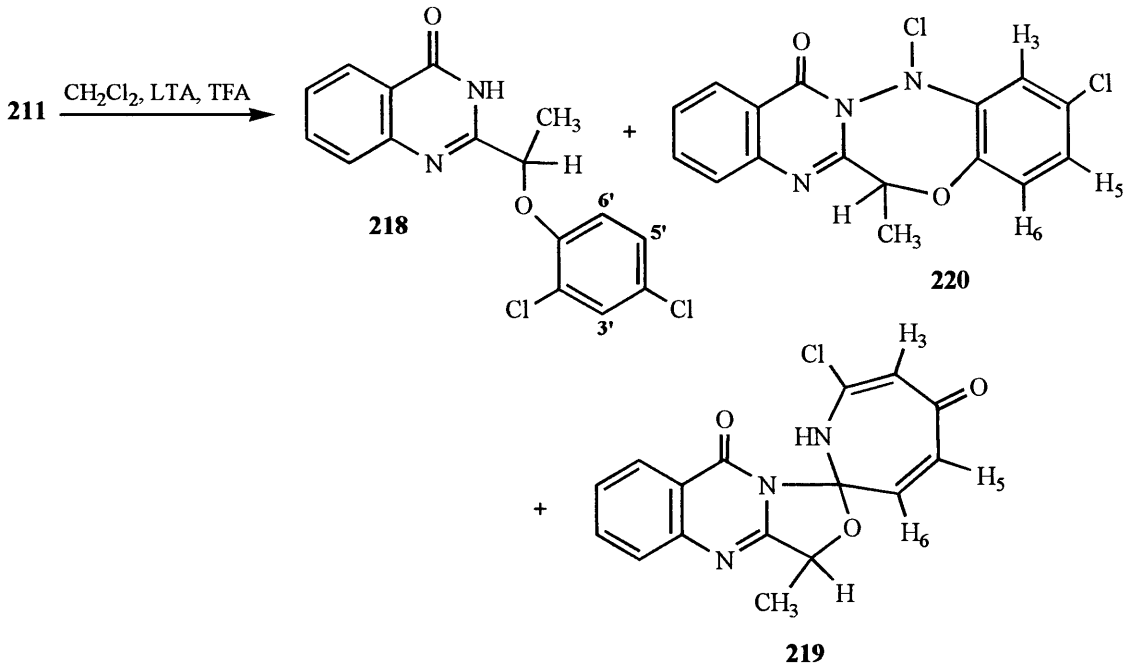
(i) In the absence of TFA



213

General procedure **A** was followed using 3-aminoquinazolinone **(211)** (1 g, 0.029 mol) and LTA (1.39 g, 0.31 mol) in dry dichloromethane (15 cm^3). The crude product was crystallised from ethanol to give *azepine* **213** as a colourless solid (0.42 g, 45%), mp. 174–175 °C (Found: M^+ 347.018. $C_{16}H_{11}N_3O_2Cl_2^{35}$ requires M^+ 347.019); δ_H 8.8 [1H, d, *J* 8.1, H-5(Q)], 7.8–7.2 [3H, m, 3 × CH(Q)], 7.4 (1H, d, *J* 1, H-4), 6.93 (1H, d, *J* 11, H-7), 6.5 (1H, dd, *J* 11 and 1, H-6), 5.32 (1H, m, C*H*-CH_3) and 1.8 (3H, d, *J* 6, CH_3-CH); *m/z* (%) 370 (MNa^+, 60), 348 (MH^+, 35) and 191 (100).

(ii) In the presence of TFA



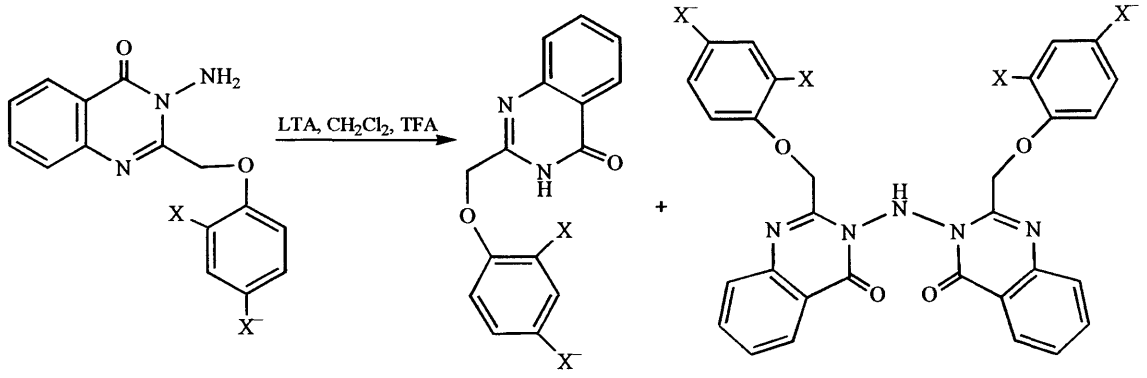
General procedure **B** was followed using 3-aminoquinazolinone **211** (1 g, 3 mmol), LTA (1.39 g, 1.1 mol eq.), dry dichloromethane (15 cm^3) at –20 °C and the solution added to TFA (2 cm^3) in dichloromethane (10 cm^3). Chromatography of the crude product over silica, eluting with light petroleum–ethyl acetate (2:1) gave *3H-quinazolinone* **218** as a colourless solid (0.2 g, 25%); mp. 160–162 °C (R_f = 0.6) (Found: MH^+ 335.0355. $C_{16}H_{13}N_2O_2Cl_2$ requires MH^+ 335.0354); δ_H 9.6 (1H, s br, NH), 8.2 [1H, dd, *J* 7.5 and 1.5, H-5(Q)], 7.8 [1H, dd, *J* 7.5 and 1.5, H-8(Q)], 7.79 [1H, dd, *J* 7 and 1.5, H-5(Ar)], 7.5 [1H, ddd, *J* 8, 7.5 and 1.5, H-7(Q)], 7.4 [1H, d, *J* 1.5, H-3(Ar)], 7.19 [1H, dd, *J* 7 and 1, H-6(Ar)], 6.99 [1H, d, *J* 8, H-6(Q)], 5.31–5.2 (1H, m, C*H*-CH_3) and 1.7 (3H, d, *J* 6, CH_3-CH); *m/z* (%) 335 (M^+, 65), 333 (100), 127 (11) and 113 (57).

Further elution with the same solvent mixture gave *azepinone* **219** as a colourless solid (0.3 g, 30%), mp. 185–187 °C (from ethanol) (R_f 0.5) (Found: M^+ 330.064. $C_{16}H_{13}N_3O_3Cl$ requires M^+ 330.082); δ_H 8.71 (1H, s, NH), 8.29 [1H, d, *J* 8, H-5(Q)], 7.86–7.5 [3H, m, H-6, H-7, H-8(Q)], 6.4 (1H, d, *J* 12, H-6), 6.25 (1H, dd, *J* 12 and 1.5, H-5), 6.2 (1H, d, *J* 1.5, H-3), 5.2 (1H, q, *J* 6, C*H*-CH_3) and 1.8 (3H, d, *J* 6, CH_3-CH); δ_C 165.6 [C=O(azep)], 159.1 [C=O(Q)], 154.15 [*C*=N(Q)], 149.2 [*C*N=C(Q)], 142.89 (*C*=Cl), 140.6 (*C*H=), 135.4 (CH=), 5 × *C*H (129.0, 127.9, 127.6, 127.2 and 126.6), 121.7 [*C*=CO(Q)], 96.4 (spiro *C*), 74.7 (*C*H-CH_3) and 17.8 (*C*H_3-CH); *m/z* (%) 352 (MNa^+, 80), 330 (M^+, 100) and 173 (52).

Further elution with the same solvent mixture gave *dihydro-N-chlorooxadiazepine* **220** (0.19 g, 20%) as a colourless crystalline solid, mp. 174–175 °C (from ethanol) (Found: MH^+ 348.0307. $C_{16}H_{11}N_3O_2Cl_2$ + H requires M^+ 348.0307); δ_H 8.8 [1H, d, *J* 8, H-5(Q)], 7.8–7.5 [2H, m, 2 × C*H*(Q)], 7.46 [1H, m, H-6(Q)], 7.0 [1H, d, *J* 1.5, H-3(Ar)], 6.59 [1H, dd, *J* 8.5 and 1.5, H-5(Ar)], 6.4 [1H, d, *J* 8.5, H-6(Ar)], 5.1 (1H, q, *J* 6, C*H*-CH_3) and 1.5

(3H, d, *J* 6, C*H*$_3$-CH); *m/z* (%) 370 (MNa^+, ^{35}Cl, 100), 348 (MH^+, ^{35}Cl, 40), 314 (27) and 102 (28).

Oxidation of 3-amino-2-(2-chlorophenoxymethyl)quinazolin-4(3H)-one 179 in the presence of TFA



179, X = Cl, $\overline{X}$ = H
225, X = $\overline{X}$ = Br
180, X = Br, $\overline{X}$ = H

181, X = Cl, $\overline{X}$ = H
226, X = $\overline{X}$ = Br
182, X = Br, $\overline{X}$ = H

183, X = Cl, $\overline{X}$ = H
227, X = $\overline{X}$ = Br
184, X = Br, $\overline{X}$ = H

General procedure **B** was followed using **179** (1 g, 3.3 mmol), LTA (1.6 g, 1.1 mol eq.) in dichloromethane (15 cm^3) at –20 °C. Triturating the crude product with dry ether gave *bis-[3,4-dihydro-4-oxo-2-(2-chlorophenoxymethyl)quinazolin-3-yl]amine* **183** (0.3 g, 30%) as a colourless crystalline solid; mp. 190–192 °C (from chloroform-ethanol) (Found: M^+ 586.414. $C_{30}H_{21}N_5O_4Cl_2$ requires M^+ 586.414); δ_H 9.9 (1H, s, NH), 8.15 [1H, d, *J* 8, 2 × H-5(Q)], 7.65 [2H, m, 2 × H-7(Q)], 7.51–7.20 [10H, m, 4 × C*H*(Q) and 6 × C*H*(Ar)], 7.05 [2H, m, 2 × C*H*(Ar)] and 6.0 (4H, s, 2 × CH_2); *m/z* (%) 586 (M^+, 16), 282 (50), 177 (51) and 102 (100).

After separation of the QNHQ compound **183** above and evaporation of the ether, crystallization of the residual product from ethanol gave *3H-quinazolinone* **181** (0.2 g, 20%) as a colourless solid, mp. 130–132 °C, R_f = 0.64; (Found: M^+ 286.707. $C_{15}H_{11}N_2O_2Cl$ requires M^+ 286.707); δ_H 9.8 (1H, s, NH), 8.3 [1H, d, *J* 8, H-5(Q)], 7.81–7.41 [3 × C*H*(Q)], 7.29 [2H, m, 2 × C*H*(Ar)], 7.1 [2H, m, 2 × C*H*(Ar)] and 5.15 (2H, s, C*H*$_2$); γ_{max}/cm^{-1} 3060w, 1700s and 1610s; *m/z* (%) 287 (MH^+, 71), 154 (100) and 136 (82).

Oxidation of 3-amino-2-(2,4-dibromophenoxymethyl)quinazolin-4(3H)-one 225 in TFA

General procedure **B** was followed using 3-aminoquinazolone **225** (1 g, 2.4 mmol), LTA (1.14 g, 1.1 mol eq.) in dry dichloromethane (15 cm^3). Trituration of the crude product with dry ether as described in the previous experiment gave the analogous *bis-[3,4-dihydro-4-oxo-2-(2,4-dibromophenoxymethyl)quinazolin-3-yl]amine* **227** as a colourless crystalline solid (0.2 g, 20%), mp. 195–196 °C (from CH_2Cl_2-ethanol) (Found: M^+ 833.093.

$C_{30}H_{19}N_5O_4Br_4$ requires M^+ 833.094); δ_H 9.85 (1H, s, NH), 8.2 [2H, d, *J* 8, 2 × H-5(Q)], 7.80–7.66 [4H, 2 × H-7(Q) and 2 × H-8(Q)], 7.50–7.37 [4H, m, 2 × H-6(Q) and 2 × C*H*(Ar)], 7.20 [4H, m, 4 × C*H*(Ar)] and 5.99 (4H, s, 2 × CH_2).

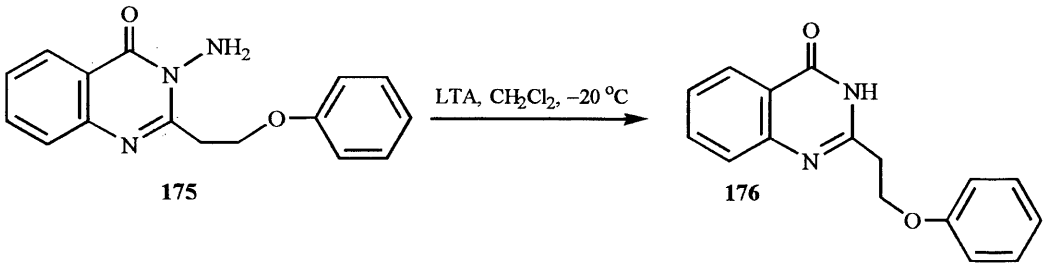
Evaporation of the ether filtrate and crystallization of the residue from ethanol gave the *3H-quinazolinone* **226** as a colourless crystalline solid (0.4 g, 40%), mp. 220–223 °C (from ethanol) (Found: C, 44.1; H, 2.4; N, 6.90. $C_{15}H_{10}N_2O_2Br_2$ requires C, 43.9; H, 2.4; N, 6.82%); δ_H 8.3 [1H, d, *J* 8, H-5(Q)], 7.8–7.4 [4H, m, 3 × C*H*(Q) and C*H*(Ar)], 7.23 [1H, s, CH(Ar)], 6.89 [1H, d, *J* 9, C*H*(Ar)] and 5.1 (2H, s, CH_2); *m/z* (%) 411 (MH^+, 3), 331 (97), 329 (100), 159 (50) and 132 (77).

Oxidation of 3-amino-2-(2-bromophenoxymethyl)quinazolin-4(3H)-one 180

General procedure **B** was followed using 3-aminoquinazolinone **180** (1 g, 3 mmol) and LTA (1.4 g, 1.1 mol eq.). Triturating the crude product with ether gave *bis-[3,4-dihydro-4-oxo-2-(2-bromophenoxymethyl)quinazolin-3-yl]amine* **184** as a colourless crystalline solid (0.32 g, 30%), mp. 156–158 °C (from CH_2Cl_2-ethanol) (Found: M^+ 675.011. $C_{30}H_{21}N_5O_4Br_2$ requires M^+ 675.011); δ_H 9.80 (1H, s, NH), 8.15 [2H, d, *J* 8, 2 × H-5(Q)], 7.70 [2H, m, 2 × H-7(Q)], 7.55–7.35 [4H, m, 4 × C*H*(Q)], 7.25–6.89 [8H, m, 8 × C*H*(Ar)] and 5.95 (4H, s, 2 × CH_2); *m/z* (%) 675 (M^+, 30), 331 (100), 265 (56), 176 (67) and 144 (45).

Oxidation of 3-amino-2-(2-phenoxyethyl)quinazolin-4(3H)-one 175

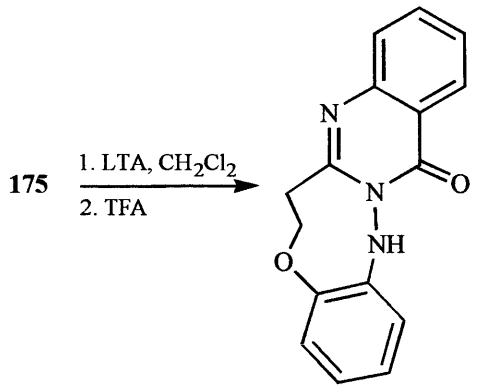
(i) In the absence of TFA



175 **176**

General procedure **A** was followed using 3-aminoquinazolone **175** (0.3 g, 1 mmol), LTA (0.52 g, 1.1 mol eq.) in dry dichloromethane (5 cm^3). The crude product was crystallised from ethanol to give 3*H*-quinazolinone **176** (0.1 g, 35%) as a colourless crystalline product, mp. >230 °C (decomp.) (Found: C, 72.2; H, 5.25; N, 10.6. $C_{16}H_{14}N_2O_2$ requires C, 72.2; H, 5.25; N, 10.5); δ_H 8.3 [1H, *J* 8, H-5(Q)], 7.8–6.9 [9H, 3 × C*H*(Q), 5 × C*H*(Ar) and NH], 4.4 (2H, t, *J* 6, CH_2CH_2O) and 3.5 (2H, *J* 6, CH_2CH_2O).

(ii) In the presence of TFA

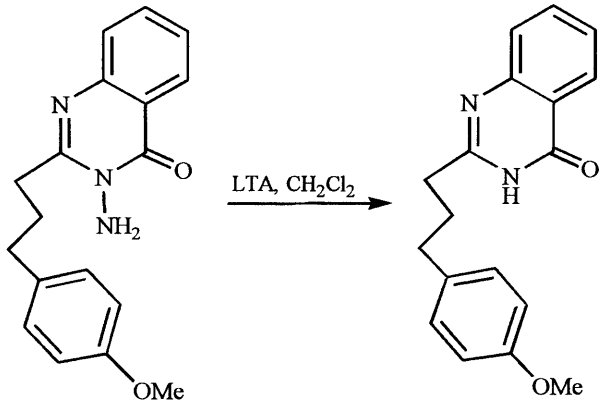


177

General procedure **B** was followed using 3-aminoquinazolinone **175** (0.3 g, 1 mmol), LTA (0.52 g, 1.1 mol eq.) and TFA (2 cm^3). Trituration of the crude product with ethanol gave the *benzo-1,5,6-oxadiazolino[4,5-b]quinazolinone* **177** (0.12 g, 40%) as colourless crystals, mp. 178–180 °C (from ethanol) (Found: C, 68.75; H, 4.75; N, 15.15. $C_{16}H_{13}N_3O_2$ requires C, 68.8; H, 4.7; N, 15.05%); δ_H 8.12 [1H, d, *J* 8, H-5(Q)], 7.70–6.90 [8H, m, 3 × C*H*(Q), 4 × C*H*(Ar) and NH], 4.50 (2H, t, *J* 6, OCH_2CH_2) and 3.60 (2H, *J* 6, CH_2-CH_2O); γ_{max}/cm^{-1} 3328s, 1660s and 1595s; *m/z* (%) 279 (M^+, 43), 171 (71), 144 (20), 130 (11) and 119 (70).

Oxidation of 3-amino-2-[3-(4-methoxyphenyl)propylquinazolin-4(3H)-one 166

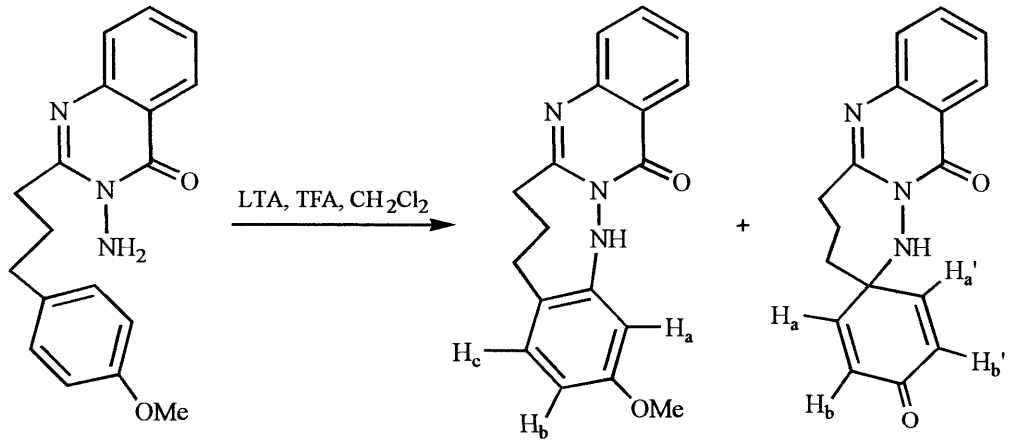
(i) In the absence of TFA



166 **167**

General procedure **A** was followed using 3-aminoquinazolone **166** (supplied by Dr. R. S. Atkinson) (0.5g, 2 mmol), dry LTA (0.78 g, 1.1 mol eq.) and dry dichloromethane (15 cm^3). Triturating the crude product with ethanol gave *3H-quinazolinone* **167** (0.17 g, 35%) as a colourless crystalline solid, mp. 142–145 °C (from ethanol); δ_H 8.27 [1H, d, *J* 8.1, H-5(Q)], 7.8 [1H, ddd, *J* 8.1, 7.5 and 1, H-7(Q)], 7.7 [1H, d, *J* 7.5, H-8(Q)], 7.5 [1H, ddd, *J* 8.1, 7.5 and 1, H-6(Q)], 7.4–7.5 [2H, m, 2 × C*H*(Ar)], 7.18 [1H, s, NH), 7.0 [1H, d, *J* 9, C*H*(Ar)], 6.65 [1H, *J* 9, C*H*(Ar)], 3.82 (3H, s, OCH_3), 3.4 (2H, m, CH_2), 2.8 (2H, m, CH_2) and 2.2 (m, CH_2); *m/z* (%) 295 (M^+, 100), 173 (13), 160 (65) and 136 (23).

(ii) In the presence of TFA

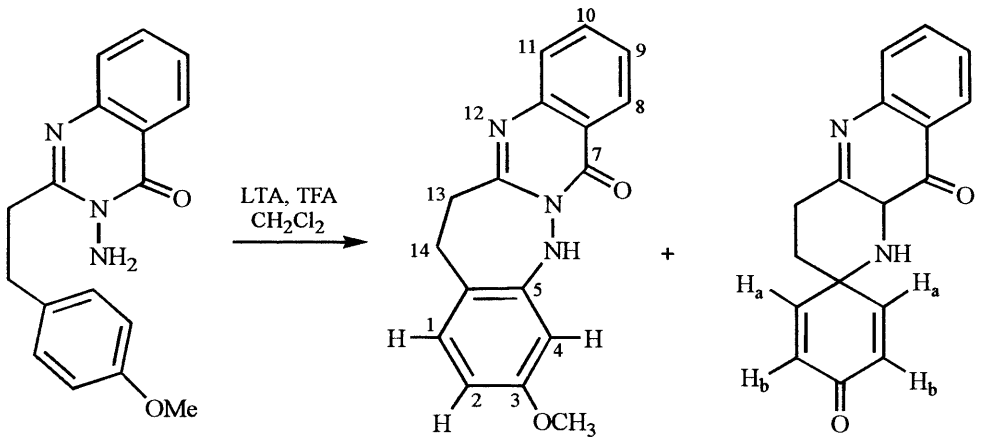


166 **168** **169**

General procedure **B** was followed using 3-aminoquinazolone **166** (0.5 g, 2 mmol), powdered dry LTA (0.78 g, 1.1 mol eq.) and dry dichloromethane (15 cm^3) and adding the 3-acetoxyaminoquinazolinone solution to a solution of dichloromethane (10 cm^3) and TFA (2 cm^3). Triturating the crude product with ethyl acetate gave the *methoxybenzo-1,2-diazolino[2,3-b]quinazolinone* **168** (0.2 g, 40%), mp. 167–169 °C (from ethanol) (Found: C, 70.1; H, 5.7; N, 13.65. $C_{18}H_{17}N_3O_2$ requires C, 70.35; H, 5.6; N, 13.65%); δ_H [1H, d, *J* 8, H-5(Q)], 7.80–7.4 [3H, m, 3 × C*H*(Q)], 7.37 (1H, s, NH), 7.10 [1H, d, *J* 3, C*H*(Ar) *ortho* to NH], 7.0 [1H, d, *J* 8, C*H*(Ar) *meta* to NH], 6.5 [1H, dd, *J* 8 and 3, C*H*(Ar) *para* to NH], 3.72 (3H, s, OCH_3), 3.4 (2H, t, *J* 7, Q-CH_2-CH_2CH_2), 2.7 (2H, m, Q-CH_2-CH_2-CH_2) and 2.20 (2H, m, Q-CH_2-CH_2-CH_2); γ_{max}/cm^{-1} 3280s, 1660s and 1610s; *m/z* (%) 307 (M^+, base), 292 (11), 210 (16), 183 (16), 159 (68) and 147 (29). The substitution pattern in the methoxy-aromatic ring was confirmed by a NOESY spectrum (see text).

After separation of **168** and evaporation of ethyl acetate, addition of light petroleum (4 drops) and trituration gave the *spirodienone* **169** (0.12 g, 25%) as colourless crystals, mp. 198–200 °C, R_f = 0.31 (from ethyl acetate-light petroleum) (Found: C, 69.7; H, 5.1; N, 14.4. $C_{17}H_{15}N_3O_2$ requires C, 69.6; H, 5.1; N, 14.3%); δ_H 8.25 [1H, d, *J* 8.1, H-5(Q)], 7.81 [1H, ddd, *J* 7.5, 8 and 1, H-7(Q)], 7.75 [1H, d, *J* 7.5, H-8(Q)], 7.55 [1H, ddd, *J* 7.5, 8 and 1, H-6(Q)], 7.1 [1H, dd, *J* 10 and 1.5, H_a(Ar)], 6.89 [1H, dd, *J* 10 and 1.5, H_b(Ar)], 6.65 (1H, s, NH), 6.4 [1H, dd, *J* 10 and 1, H_c(Ar)], 3.6 (2H, m, CH_2), 3.1 (2H, m, CH_2) and 2.2 (2H, m, CH_2); γ_{max}/cm^{-1} 3230s, 1660s and 1605s.

Oxidation of 3-amino-2-[2-(4-methoxyphenyl)ethyl]quinazolin-4(3H)-one 107 in the presence of TFA

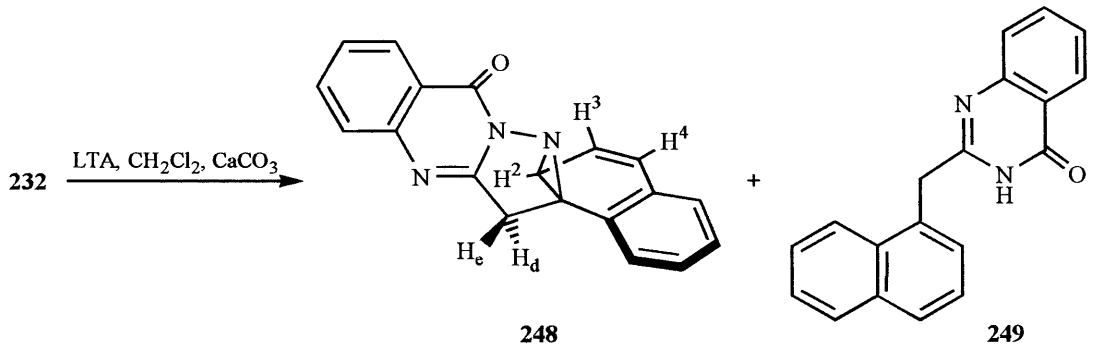


107 **154** **153**

Procedure **B** was followed using equimolar quantities of both the 3-aminoquinazolinone **107** (0.16 g, 2 mmol) and LTA (0.99 g, 1.1 mol eq.). The crude product obtained after evaporating the dichloromethane solution was chromatographed over silica. Elution with ethyl acetate-light petroleum (2:1) gave the *methoxybenzo-1,2-diazepino[2,3-b]quinazolinone* **154** (0.17 g, 35%) as a colourless crystalline solid, mp. 156–158 °C (from ethanol) (Found: C, 69.6; H, 5.1; N, 14.3. $C_{17}H_{15}N_3O_2$ requires C, 69.6; H, 5.1; N, 14.3%); δ_H 8.24 [1H, d, *J* 8 and 1.3, H-8(Q)], 7.86 (1H, s, NH), 7.7–7.6 [2H, m, H-10(Q) and H-11(Q)], 7.45 [1H, ddd, *J* 8, 7.2 and 1.3, H-9(Q)], 7.0 [1H, d, *J* 9, H-1(Ar)], 6.70 [1H, d, *J* 3, H-4(Ar)], 6.61 [1H, dd, *J* 9 and 3, H-2(Ar)], 3.80 (3H, s, OCH_3), 3.55 (2H, t, *J* 7, CH_2-CH_2) and 3.26 (2H, t, *J* 7, CH_2-CH_2); γ_{max}/cm^{-1} 3270w, 1655s and 1598s; *m/z* (%) 293 (M^+, 14), 278 (13), 160 (27), 146 (15) and 120 (18).

Further elution with ethyl acetate-light petroleum (2:1) gave *spirodienone* **153** as a colourless crystalline solid (0.1 g, 20%), mp. 195–200 °C (from ethyl acetate-light petroleum) (Found: C, 68.6; H, 4.8; N, 15.0. $C_{16}H_{13}N_3O_2$ requires C, 68.8; H, 4.65; N, 15.05%); δ_H 8.2 [1H, d, *J* 8, H-5(Q)], 7.80–7.35 [3H, m, H-6, H-7 and H-8(Q)], 7.0 (1H, s, NH), 6.85 and 6.20 (4H, 2 × *d*, *J* 10, AA'XX' system, 2 × H_a and 2 × H_b), 3.11 (2H, t, *J* 7, QCH_2CH_2) and 2.20 (2H, t, *J* 7, Q-CH_2CH_2); γ_{max}/cm^{-1} 3225s (NH), 1660w and 1605w; *m/z* (%) 279 (M^+, 87), 159 (100), 120 (30) and 116 (16).

General Procedure C for the oxidation of 3-aminoquinazolinones with lead tetra-acetate (LTA) exemplified by oxidation of 3-amino-2-(1-naphthylmethyl)quinazolin-4(3H)-one 232



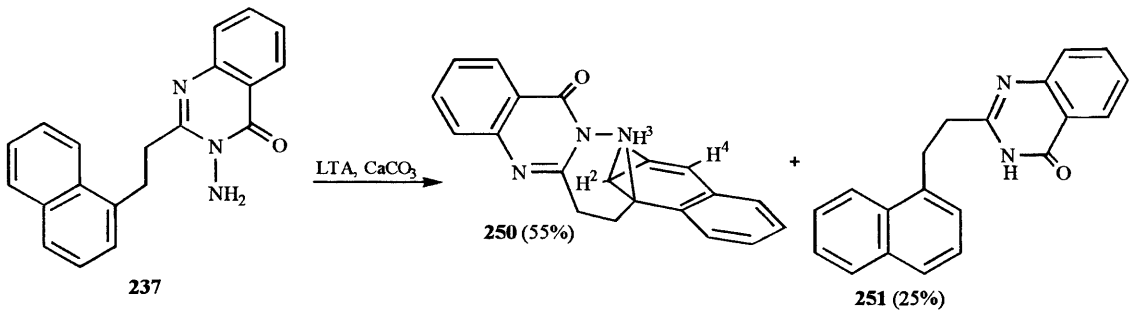
248 **249**

Solid 3-aminoquinazolinone **232**, (1g, 3 mmol) and powdered dry (LTA) (1.5 g, 1.01 mol eq.) were alternately and continuously added in very small quantities to a magnetically-stirred mixture of dry dichloromethane (40 cm^3) and dry $CaCO_3$ (1 g) over a period of 15 mins at –20 °C. Insoluble solids were separated off at this temperature (on a small scale a Pasteur pipette can be used) and the clear solution which contained the cold 3-acetoxyaminoquinazolinone was added dropwise but briskly, allowing minimal warming, to a stirred mixture of dry dichloromethane (40 cm^3) and dry $CaCO_3$ (1 g) held at room temperature. The reaction mixture was left to stir for an additional 10 min at room temperature and the reaction mixture then washed with saturated aqueous sodium hydrogen carbonate solution before being dried and evaporated under reduced pressure.

Crystallization of the crude product gave the *aziridine* **248** as colourless crystals (75%) mp. 205–207 °C (from ethanol) (Found: C, 76.15; H, 4.35; N, 14.05. $C_{19}H_{13}N_3O$ requires C, 76.25; H, 4.3; N, 14.5%); δ($CDCl_3$) 8.30 [1H, d, *J* 8, H-5(Q)], 7.75–7.26 [7H, m, 3 × C*H*(Q) and 4 × C*H*(Ar)], 6.69 (1H, d, *J* 9, H-4), 6.38 (1H, dd, *J* 9 and 5.9, H-3), 4.59 (1H, d, *J* 18.8, C*H*H), 3.90 (1H, d, *J* 18.8, CH*H*) and 3.19 (1H, d, *J* 5.9, H-2); γ_{max}/cm^{-1} 1668s, 1625w and 1608w; *m/z* (%) 299 (M^+, 100), 286 (17), 271 (29), 139 (14) and 120 (15).

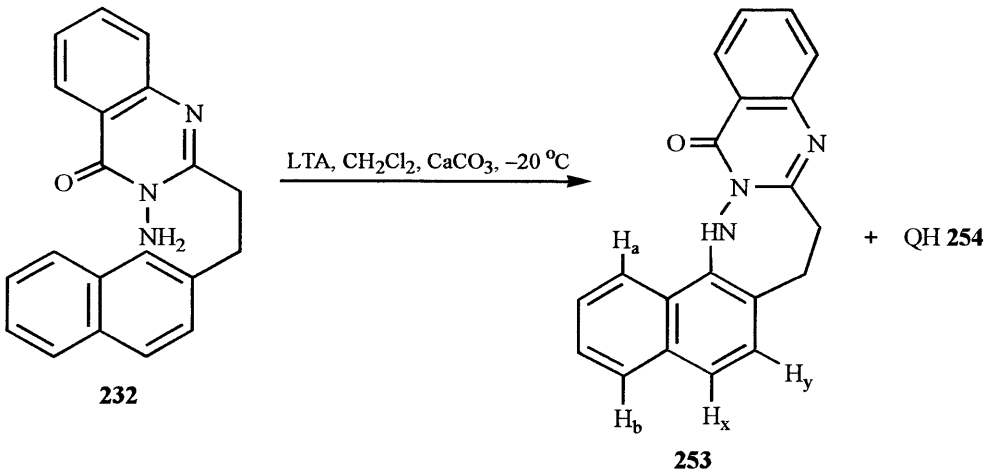
Concentration of the filtrate left after the separation of the aziridine **248** gave *2-(α-naphthylmethyl)quinazolin-4(3H)-one* **249**, mp. 285–288 °C (decomp.) (from ethanol/H_2O) (Found: M^+ 286.327. $C_{19}H_{14}N_2O$ requires M^+ 286.327); δ($CDCl_3$) 8.90 (1H, br, s, *N*H), 8.2 [1H, d, *J* 8, H-5(Q)], 8.15–8.05 [10H, 3 × CH(Q) and 7 × C*H*(Ar)] and 3.2 (2H, s, CH_2); *m/z* (%) 286 (M^+, 47), 271 (100), 257 (17), 173 (21), 156 (66), 141 (29) and 115 (56).

Oxidation of 3-amino-2-(1-naphthylethyl)quinazolin-(3H)-one 237



A lead diacetate-free cold (–20 °C) solution of 3-acetoxyaminoquinazolinone in dry dichloromethane (25 cm^3) prepared as described previously (general procedure **A**) from **237** (0.32 g, 1 mmol) and dry LTA (0.5 g, 1.1 mol eq.) at –20 °C was added to dichloromethane (20 cm^3) containing calcium carbonate (1 g) and the resulting mixture stirred for 15 min. before its temperature was allowed to rise to ambient by removal of the cooling bath. After working-up, the crude reaction product was purified by chromatography (eluent 2:1 light petroleum–ethyl acetate) to yield the *aziridine* **250** as a colourless crystalline compound (55%), mp. 175–180 °C (from ethanol) (Found: C, 76.4; H, 4.95; N, 13.3. $C_{20}H_{15}N_3O$ requires C, 76.6; H, 4.8; N, 13.4%), δ($CDCl_3$) 8.29 [1H, d, *J* 8, H-5(Q)], 7.75–7.2 [7H, m, 3 × C*H*(Q) and 4 × C*H*(Ar)], 6.69 (1H, d, *J* 9.5, H-4), 6.58 (1H, dd, *J* 9.5 and 4.8, H-3), 3.3 (4H, m, CH_2–CH_2) and 3.0 (1H, d, *J* 4.8, H-2); γ_{max}/cm^{-1} 1668s and 1600w; *m/z* (%) 313 (M^+, 79), 285 (11), 167 (17), 158 (35), 144 (15), 127 (11) and 120 (11). Further elution with the same solvent mixture gave *3H-quinazolinone* **251** (25%), mp. 232–234 °C (from ethanol) (Found: M^+ 299.3513. $C_{20}H_{15}N_2O$ requires M^+ 299.3513); δ($CDCl_3$) 10.85 (1H, br s, NH), 8.3 [1H, dd, *J* 8.1 and 1.2, 5-H(Q)], 7.7–7.3 [10H, m, 3 × H(Q) + 7 × H(Ar)], 3.3 (2H, t, *J* 8, CH_2) and 3.0 (2H, t, *J* 8, CH_2).

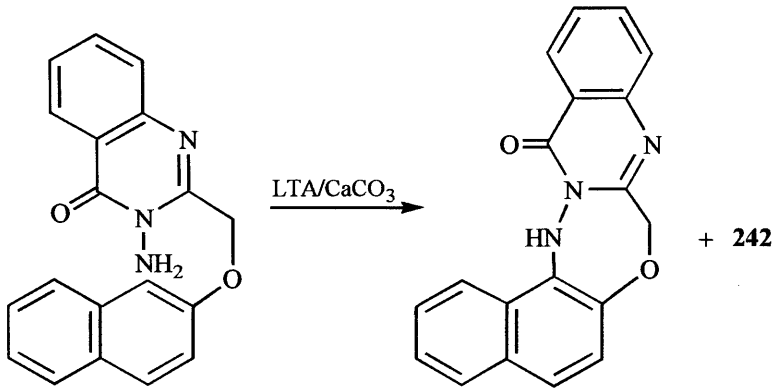
Oxidation of 3-amino-2-(2-naphthylethyl)quinazolin-4(3H)-one 232



General procedure **C** was followed using 3-aminoquinazolone **232**, (0.32 g, 1 mmol) and dry LTA (0.5 g, 1.1 mol eq.) in dichloromethane (40 cm^3). After work-up, the crude product was purified by chromatography (eluent light petroleum – ethyl acetate 2:1) to yield the *substitution product* **253** as a colourless solid (50%) mp. 168–170 °C (from ethyl acetate) (Found: M^+ 313.3580. $C_{20}H_{15}N_3O$ requires M^+ 313.3580); δ($CDCl_3$) 8.8 (1H, s, NH), 8.55 [1H, dd, *J* 8 and 1.2, 5-H(Q)], 8.20 (1H, d, *J* 8.5, H-4), 7.82–7.3 (7H, m, ArH), 7.1 (1H, d, *J* 8.5, H-3) and 3.7–3.45 (4H, m, CH_2–CH_2).

Further elution gave the *3H-quinazolinone* **254** as a colourless crystalline product (25%) mp. 172–173 °C (ethanol) (Found: M^+, 299.3458. $C_{20}H_{15}N_2O$ requires M^+ 299.3459); δ($CDCl_3$) 10.9 (1H, br s, NH), 8.17 [1H, dd, *J* 1.2 and 8, 5-H(Q)], 7.78–7.39 [10H, m, 3 × H(Q) + 7 × H(Ar)], 3.3 (2H, t, *J* 8, CH_2) and 3.1 (2H, t, *J* 8, CH_2); *m/z* 300 (MH^+, 10), 299 (M^+, 37) and 62 (100).

Oxidation of 3-amino-2-(2-naphthoxyethyl)quinazolin-4(3H)-one 231

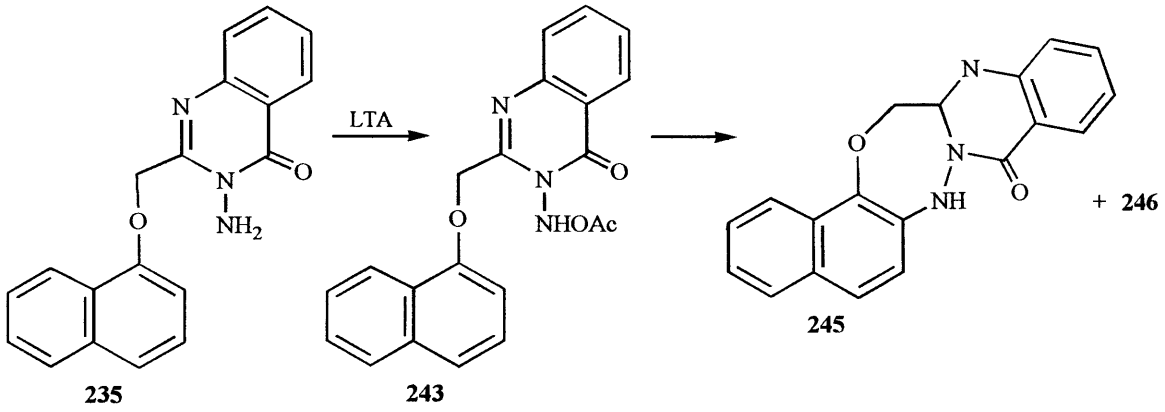


231 **241**

General procedure **C** was followed using 3-aminoquinazolone **231**, (0.5 g, 1.5 mmol), LTA (0.7 g, 1.01 mol eq.) and dry dichloromethane (40 cm^3). Crystallization of the crude product gave the *substitution product* **241** as a colourless crystalline solid (0.2 g, 40%), mp. 185–187 °C (from ethanol) (Found: M^+ 315.318. $C_{19}H_{13}N_3O_2$ requires M^+ 315.3198); δ 8.6 (1H, s, NH), 8.34 [1H, dd, *J* 8.7, H_c), 8.20 [1H, dd, *J* 8 and 1, 5-H(Q)], 7.85–7.79 [2H, m, 7-H and 8-H(Q)], 7.8 1H, d, *J* 8.8, H(Ar)], 7.65 [1H, ddd, *J* 8, 7.9 and 1, 6-H(Q)], 7.59–7.54 (2H, m, ArH), 7.52 [1H, d, *J* 8.8, H(Ar)], 7.42 [1H, ddd, *J* 8.8, 8.5 and 1, H(Ar)], 7.11 [1H, d, *J* 8.8, H(Ar)] and 5.7 (2H, s, –OCH_2).

On concentration of the filtrate left after separation of **241** gave *3H-quinazolinone* **242** as colourless crystals (30%) (0.15 g), mp. 232–235 °C (from ethanol) (Found: M^+ 302.3317. $C_{19}H_{14}N_2O_2$ requires M^+ 302.3318); δ 8.3 [1H, dd, *J* 8 and 1, 5-H(Q)], 7.3–6.7 [11H, m, 5 × H(Q) + 7 × H(Ar), NH] and 5.5 (2H, s, OCH_2).

Oxidation of 3-amino-2-(1-naphthoxymethyl)quinazolin-4(3H)-one 235

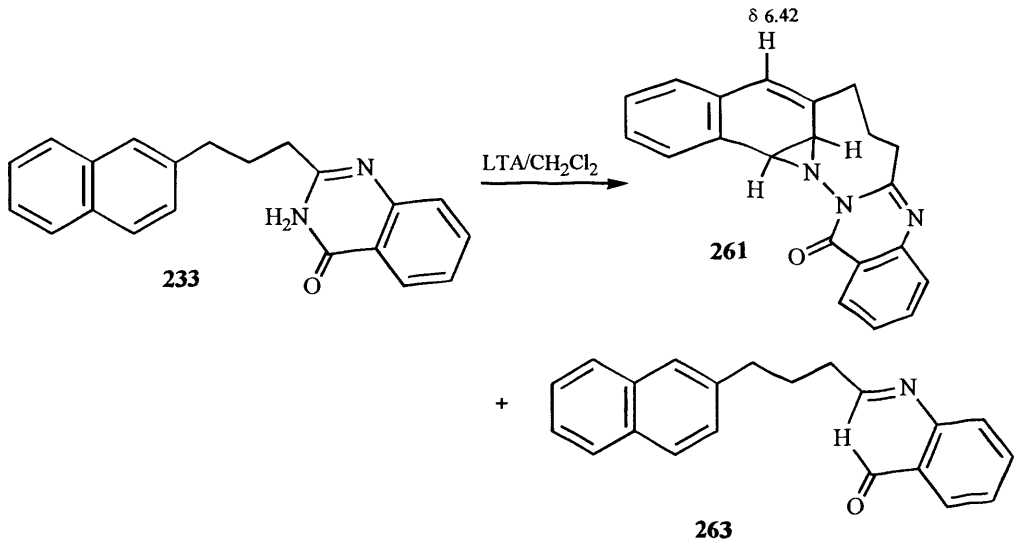


235 243 245

A solution of 3-acetoxyaminoquinazolinone **243** was prepared as described previously (general procedure **C**) from **235** (0.5 g, 1.6 mmol) and LTA (0.7 g, 1.01 mol eq.) in dry dichloromethane (40 cm^3) at –20 °C. After addition to the dichloromethane/$CaCO_3$ solution the reaction mixture gave a brown residue (0.45 g) from which two crystalline products were separated on chromatography (eluent 2:1 light petroleum–ethyl acetate). The first isolated product (R_f 0.8) was separated as a colourless crystalline solid (0.16 g, 35%), mp. 237–239 °C (from ethanol) and it was identified as the *substitution product* **245** (Found: M^+ 315.1008. $C_{19}H_{13}N_3O_2$ requires M^+ 315.1008); δ 8.31 [1H, dd, *J* 8 and 1.5, H(Ar)], 8.15 [1H, dd, *J* 7.9 and 1.2, 5-H(Q)], 7.98 (1H, s, NH), 7.84–7.79 [2H, m, 7-H, 8-H(Q)], 7.72 [1H, dd, *J* 7.9 and 1.2, 6-H(Q)], 7.69–7.55 [1H, m, H(Ar)], 7.5–7.4 [3H, m, 3 × H(Ar)], 7.24 [1H, d, *J* 8.5, H(Ar)] and 5.8 (2H, s, OCH_2); *m/z* 315 (M^+, 100%), 286 (47), 156 (42), 128 (27) and 102 (17).

Further elution with the same solvent mixture gave *3H-quinazolinone* **246** as a colourless crystalline solid (0.13 g, 30%), mp. 168–170 °C (from ethanol) (Found: M^+ 302.3218. $C_{19}H_{14}N_2O_2$ requires M^+ 302.3218); δ 9.9 (1H, br, NH), 8.4–8.2 [2H, m, 5-H(Q), 1H(naph.)], 7.9–7.2 [8H, m, 7-H(Q), 8-H(Q) and 6 × H(Ar)], 6.9 [1H, *J* 7.9, 6-H(Q)] and 5.3 (2H, s, OCH_2); *m/z* 303 (MH^+, 100%), 160 (21) and 143 (30). This crystalline product was identified as the Q^6H **15**.

Oxidation of 3-amino-2-(2-propylnaphthalene)quinazolin-4(3H)-one 233

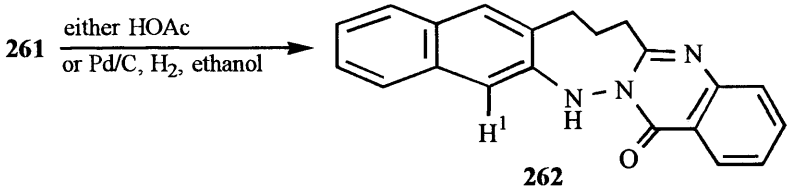


LTA (0.81 g, 1.2 mol eq.) and **233** (0.5 g, 1.5 mmol) were added portionwise and simultaneously to stirred, dry dichloromethane (100 cm^3) held over 20 min. After work-up using general procedure **C**, the organic layer was dried and evaporated under reduced pressure to give an orange residue. Trituration with ethyl acetate afforded *aziridine* **261** as a colourless solid (292 mg, 59% yield), mp. 141–143 °C (from ethanol); δ 7.78 [1H, d, *J* 9.6, 5-H(Q)], 7.54 [2H, m, H-7 and H-8(Q)], 7.41 [1H, d, *J* 9.6, H(Ar)], 7.26 [1H, dd, *J* 8.4 and 8.4, 6-H(Q)], 7.04–7.16 (2H, m, 2 × ArH), 6.70 [1H, d, *J* 8.4, H(Ar)], 6.42 (1H, s, C*H*=), 4.66 (1H, d, *J* 6, azir. H), 3.98 (1H, m, C*H*), 2.39–2.57 (2H, m, CH_2) and 2.17–2.32 (1H, m, C*H*); *m/z* (%) 350 (MNa^+, 67), 328 (MH^+, base), 315 (32), 304 (14) and 139 (90).

The *3H-quinazolinone* **263** (20%) was obtained from the ethyl acetate filtrate after removal of aziridine **261** by crystallisation, mp. 205–210 °C (from ethanol) (Found: MH^+ 315.3938. $C_{21}H_{19}N_2O$ requires MH^+ 315.3939); δ 10.84 (1H, br s, NH), 8.2 [1H, d, *J* 8, 5-H(Q)], 8.1 (1H, m, 1 × Ar-H), 7.8–7.2 [9H, 3 × H(Q) + 6 × H(Ar)], 3.28 (2H, t, *J* 9, CH_2), 2.9 (2H, *J* 9, CH_2) and 2.33 (2H, m, CH_2); *m/z* (%) 337 (MNa^+, 23), 315 (MH^+, 81), 104 (100) and 102 (30).

Ring opening of aziridine 261

(i) with acetic acid



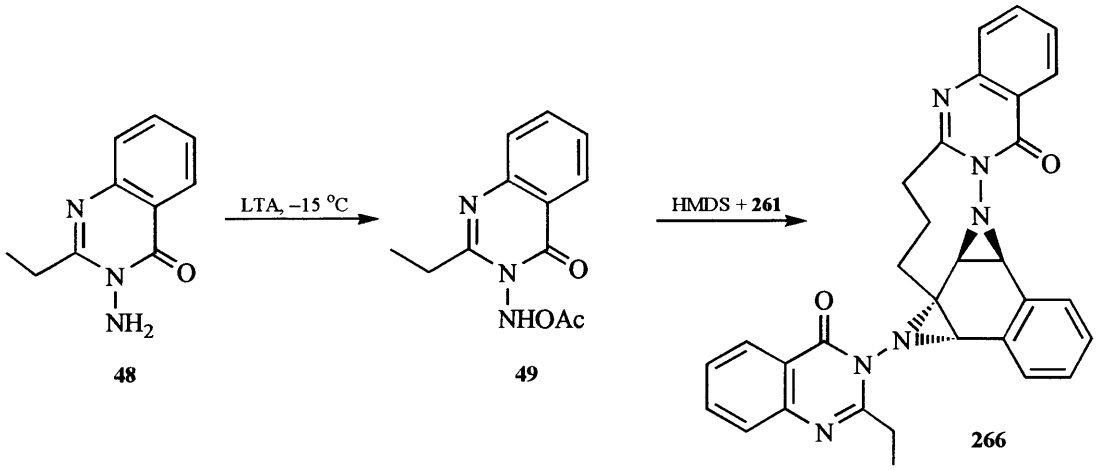
262

An excess of acetic acid (0.5 cm^3) was added to a stirred solution of **261** (0.1 g, 0.31 mmol) in dichloromethane (15 cm^3). After 10 min. the solution was washed with saturated Na_2CO_3 solution, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The resultant solid was crystallized from ethanol yielding a light pink crystalline compound (67 mg, 67% yield) that was identified as the *naphtho-1,2-azocino[2,3-b]quinazolinone* **262**, mp. 166–168 °C (Found: MH^+ 328.1449. $C_{21}H_{18}N_3O$ requires MH^+ 328.1449); δ 8.13 [1H, d, *J* 9.6, 5-H(Q)], 8.02 [1H, br s, H(Ar)], 7.71 [1H, d, *J* 9.6, H(Q) or H(Ar)], 7.50–7.65 [4H, m, 3 × H(Q)/(Ar) + N-H], 7.48 [1H, s, H(Ar)], 7.25–7.36 [3H, m, 3 × H(Q)/(Ar)], 3.32 (2H, br s, CH_2), 2.94 (2H, br s, CH_2) and 2.20 (2H, br s, CH_2); *m/z* (%) 350 (MNa^+, 34), 328 (MH^+, 88), 301 (base), 229 (26), 199 (73) and 139 (15). A crystal of **262** obtained from ethanol was used for an X-ray structure determination (see Fig. 1).

(ii) using catalytic hydrogenation

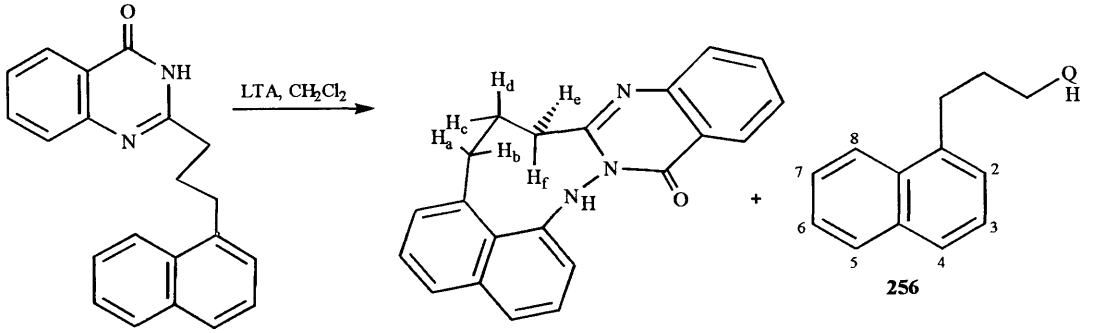
To a solution of aziridine **261** (0.1 g, 0.31 mmol), dissolved in ethanol (2 cm^3) was added palladium on carbon (0.05 g, 5%) and the mixture stirred vigorously under a hydrogen atmosphere for 1h. Dichloromethane (10 cm^3) was then added and the mixture filtered through Celite and the catalyst washed with more dichloromethane (10 cm^3). The solvent was then removed by evaporation under reduced pressure and the resultant oil triturated with ethanol and filtered affording a white powder (24 mg, 24% yield). NMR examination showed this to be compound **262** identical with that isolated above.

Intermolecular aziridination of the 3,4-double bond in the aziridine 261 to form bis-aziridine 266



LTA (0.33 g, 1.15 mol eq.) was added slowly but constantly over 7 min. to a stirred solution of 3-amino-2-ethylquinazolin-4(3*H*)-one **48** (0.12 g, 0.65 mmol) in dichloromethane (1 cm^3) at −15 °C, then HMDS (0.13 cm^3, 1.08 mol) was added, followed by the solid aziridine **261** (0.2 g, 0.65 mmol) and then the cool bath was removed. After stirring for 1h at room temperature, dichloromethane (20 cm^3) was added and the suspension washed with saturated sodium carbonate solution and then with water. The organic layer was dried over Na_2SO_4, filtered and evaporated under reduced pressure to afford a pink-orange micro-crystalline solid (300 mg). A portion of this material (250 mg) was then purified by flash chromatography, eluting with 7:1 ethyl acetate - light petroleum (60–80 °C). The solid from this fraction was triturated with ethyl acetate, collected by filtration and crystallized from ethyl acetate by first dissolving in a few drops of dichloromethane to afford a white solid (79 mg, 32% yield), mp. 242–243 °C that was identified as the *bis-aziridine* **266**; δ 8.28 [2H, d, *J* 7, 2 × Ar-H, 5-H(Q)], 7.98 [1H, m, H(Ar/Q)], 7.76 (2H, ddd, *J* 7.6, 7.6 and ~1.5, 2 × H(Q/Ar)], 7.69 [1H, d, *J* 8, H(Q/Ar)], 7.65 [1H, d, *J* 7.6, H(Q/Ar)], 7.46–7.53 [4H, m, 4 × H(Q/Ar)], 4.34 (1H, d, *J* ~8, azir. ring-H), 4.23 (1H, s, azir. ring-H), 3.69 (1H, d, *J* 8, azir. ring-H), 3.64 (1H, d, *J* 10.4, C*H*H), 3.26 (1H, dq, *J* 16.4 and 7.2, CH*H*CH_3), 2.94 (1H, dq, *J* 16.4 and 7.6, C*H*HCH_3), 2.66–2.78 (1H, m, C*H*H), 2.25–2.39 (1H, m, CH*H*), 2.24–2.13 (1H, m, CH*H*), 1.88 (1H, ddd, *J* 14.8, 7.6 and 1.6, C*H*H) and 1.45 (3H, t, *J* 7.2, CH_2-C*H*$_3$); *m/z* (%) 537 (MNa^+, base), 515 (MH^+, 24), 315 (11) and 139 (62).

Oxidation of 3-amino-2(1-propylnaphthalene)quinazolin-4(3H)-one 238

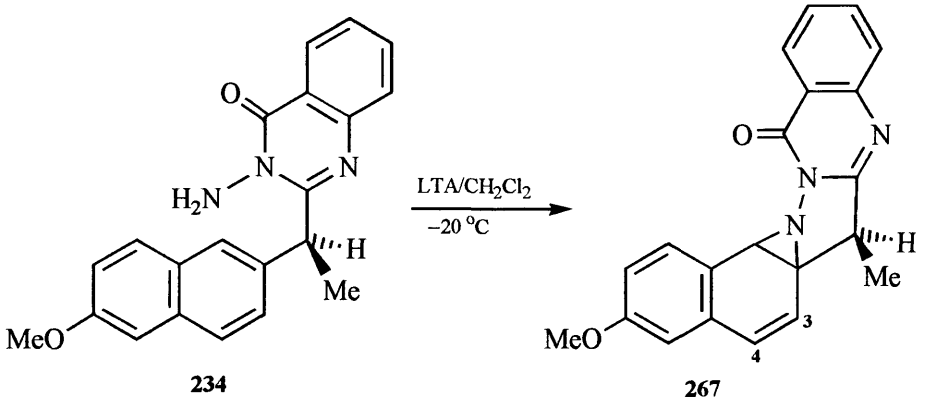


238 **255** **256**

General procedure **C** was used for the oxidation of 3-aminoquinazolinone **238** (0.5 g, 1.5 mmol) with LTA (0.94 g, 1.4 mol eq.) and dry dichloromethane (100 cm^3). The crude reaction mixture left after evaporation of the organic layer was purified by chromatography (eluent 1:2 ethyl acetate - light petroleum). The first eluted fraction was obtained as a white crystalline solid identified as *naphtho-azanino[2,3-b]quinazolinone* **255** (0.2 g, 45%), mp. 174–175 °C (from ethanol) (Found: MH^+ 328.1450. $C_{21}H_{18}N_3O$ requires 328.1450); δ 8.40 [1H, d, *J* 8.1, 5-H(Q)], 7.9 (1H, br s, NH), 7.85–7.28 [9H, m, 3-H(Q), 6 × H(Ar)], 5.0 (1H, dd, *J* 12.8 and 6.8, H_b), 3.15 (1H, dd, *J* 12.8 and 7.2, H_a), 2.85 (1H, dd, *J* 12.0 and 7.2, H_e), 2.75 (1H, dd, *J* 12.0 and 7.2, H_f), 2.5 (1H, m, H_d) and 2.15 (1H, m, H_c).

The second eluted fraction was also obtained as a colourless crystalline compound (0.1 g, 20% yield) and identified as the *3H-quinazolinone* **256**, mp. 198–201 °C (from ethanol) (Found: MH^+ 315.1497. $C_{21}H_{19}N_2O$ requires MH^+ 315.1497); δ 10.65 (1H, br s, NH), 8.25 [1H, d, *J* 8, 5-H(Q)], 8.13 [1H, dd, *J* 8 and 1.5, 8-H(Q)], 7.87–7.25 [9H, m, 2 × H(Q), 7 × H(naphth)], 3.25 (2H, t, *J* 8, CH_2), 2.8 (2H, t, *J* 8, CH_2) and 2.3 (2H, m, CH_2); *m/z* (%) 337 (MNa^+, 22), 315 (M^+, 100) and 102 (53).

Oxidation of (S)-3-amino-2-[1-(6-methoxynaphthyl)ethyl]quinazolin-4(3H)-one 234



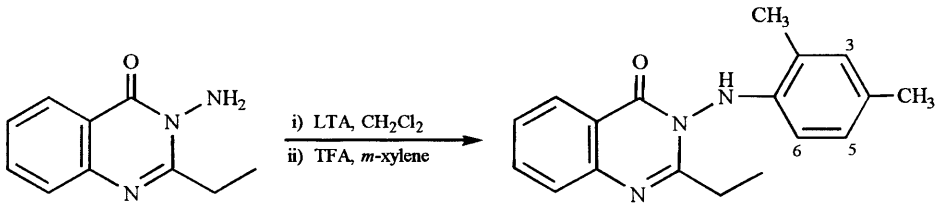
234 **267**

The general method **C** was applied using **234** (0.5 g, 1.5 mmol), LTA (0.7 g, 1.1 mol eq.) and dry dichloromethane (100 cm^3). After normal work-up of the reaction, the residue left after evaporation of the organic solvent was crystallised from methanol to give the *aziridine*

267 as a colourless crystalline solid (0.2 g, 40% yield), mp. 188–191 °C (Found: MH^+ 344.1400. $C_{21}H_{17}N_3O_3$ requires MH^+ 344.1399); δ 8.55 [1H, d, *J* 8, 5-H(Q)], 8–7.8 [2H, m, 2 × H(Q/Ar)], 7.7–7.6 [2H, m, 2 × H(Q/Ar)], 7.05 [1H, dd, *J* 8 and 1.5, H_d(Ar)], 7.0 [1H, d, *J* 1.5, H_e(Ar)], 6.90 (1H, d, *J* 9.5, H-4), 6.55 (1H, d, *J* 9.5, H-3), 4.3 (1H, q, *J* 9, C*H*-CH_3), 4.05 (3H, s, OCH_3), 3.7 (1H, s, H_e) and 2.1 (3H, d, *J* 9, CHC*H*$_3$); *m/z* (%) 366 (MNa^+, 100), 344 (MH^+, 38) and 102 (60).

Intermolecular aziridination of aromatic compounds using 3-amino-2-ethylquinazolin-4(3H)-one 49 in the presence of TFA

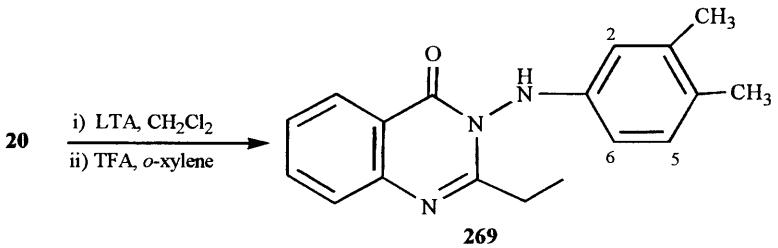
(i) using m-xylene



48 **268**

Following procedure **B** solid 3-aminoquinazolone **48** (1 g, 5 mmol) and dry LTA (2.58 g, 1.1 mol eq.) were added alternately and continuously in small portions to a stirred solution of dry dichloromethane (20 cm^3) at –20 °C over a period of 15 min. The resulting cold solution of the 3-acetoxyaminoquinazolinone freed from lead di-acetate was then added dropwise to a stirred solution of *m*-xylene (1.5 g, 14 mmol) and TFA (1.8 cm^3) in dry dichloromethane (5 cm^3) held at room temperature. After addition the reaction mixture was washed with aqueous sodium hydrogen carbonate solution, dried and evaporated. The crude product (0.4 g) was crystallized to give *3-arylaminoquinazolinone* **268** (0.34 g, 22% based on **48**) as a colourless solid, mp. 137–140 °C (from ethyl acetate–petroleum ether) (Found: C, 73.6; H, 6.6; N, 14.3. $C_{18}H_{19}N_3O$ requires C, 73.7; H, 6.5; N, 14.35%); δ_H 8.2 [1H, d, *J* 8, H-5(Q)], 7.75–7.00 [5H, m, 3 × CH(Q), H-3(Ar) and NH], 6.85 [1H, d, *J* 9, H-5 or 6(Ar)], 6.19 [1H, d, *J* 9, H-6 or 5(Ar)], 2.86 (2H, m, C*H*$_2$-CH_3), 2.35 (3H, s, CH_3), 2.2 (3H, s, CH_3) and 1.4 (3H, t, *J* 7, CH_2C*H*$_3$); γ_{max}/cm^{-1} 3320s (NH), 1690s (CO) and 1600s; *m/z* (%) 293 (M^+, 62), 174 (21), 120 (100) and 119 (43).

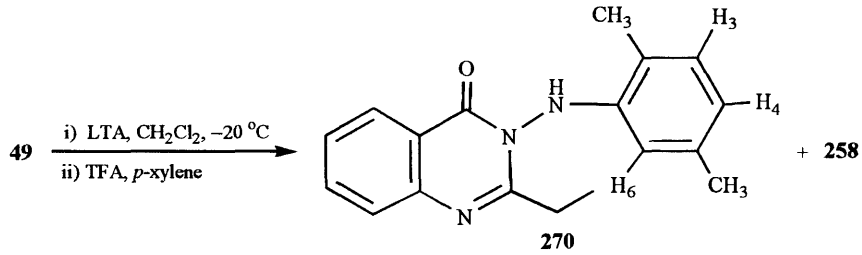
(ii) using o-xylene



269

The reaction **48** was carried out as described previously but using *o*-xylene instead of the *m*-xylene. The crude product was crystallized from ethanol to give *3-arylaminoquinazolinone* **269** (0.65 g, 42% based on **49**), mp. 138–139 °C (Found: C, 73.55; H, 6.6; N, 14.3. $C_{18}H_{19}N_3O$ requires C, 73.7; H, 6.55; N, 14.35%); δ_H 8.10 [1H, d, *J* 8, H-5(Q)], 7.70–7.10 [4H, m, 3 × CH(Q) and NH], 6.45 [1H, d, *J* 9, H-5(Ar)], 6.4 [1H, d, *J* 3, H-2(Ar)], 6.35 [1H, dd, *J* 9 and ~2, H-(Ar)], 2.9 (2H, m, CH_2CH_3), 2.1 (6H, s, 2 × CH_3) and 1.3 (3H, t, *J* 7, CH_2CH_3); γ_{max}/cm^{-1} 3260s (NH), 1600s (CO) and 1600s; *m/z* (%) 293 (M^+, 67), 174 (35) and 173 (50).

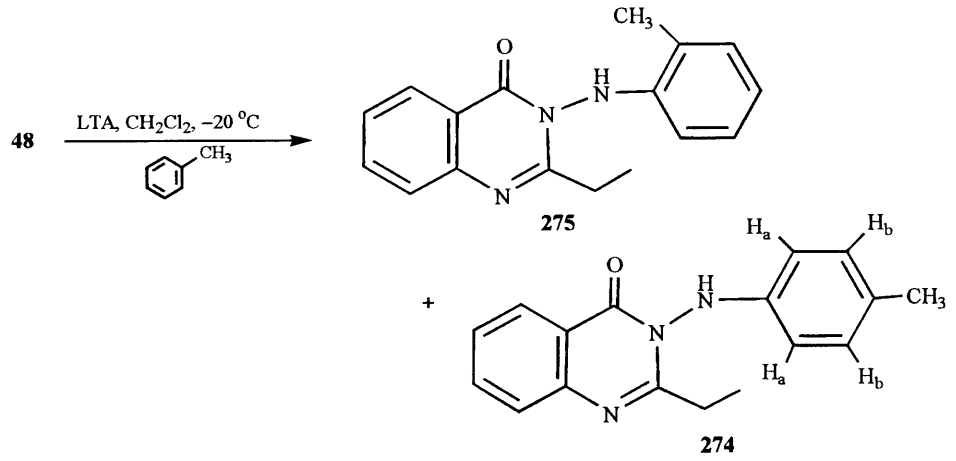
(iii) using p-xylene



258 : **261** [1 : 3]

The procedure described above for *m*-xylene was followed using QNH_2 **49** (1 g, 5 mmol), LTA (2.58 g, 1.1 mol eq.), TFA (1.8 cm^3) and *p*-xylene (1.5 g, 0.015 mol) in dry dichloromethane (20 cm^3). After work-up, the residue was purified by flash chromatography eluting with light petroleum ether–ethyl acetate (3:1). The first fraction eluted (R_f 0.8) gave *3-arylaminoquinazolinone* **270** as colourless crystals (0.2 g, 13% based on 49), mp. 139–141 °C (from ethanol) (Found: C, 73.6; H, 6.6; N, 14.4. $C_{18}H_{19}N_3O$ requires C, 73.7; H, 6.55; N, 14.3%); δ_H 8.2 [1H, d, *J* 8, H-5(Q)], 7.79–6.9 [5H, m, 3 × CH(Q), NH, H-6 (Ar)], 6.9 [1H, d, *J* 9, H-4 or 3(Ar)], 6.19 [1H, d, *J* 9, H-3 or 4(Ar)], 2.9 (2H, m, CH_2CH_3), 2.39 (3H, s, CH_3), 2.2 (3H, s, CH_3) and 1.3 (3H, t, *J* 7, CH_2CH_3); γ_{max}/cm^{-1} 3310s, 1675s and 1600s. Further elution with the same solvent mixture afforded a colourless crystalline solid (0.13 g, 8.4%) whose ^1H NMR spectrum showed it to be identical with the previously isolated 3-[2,4-dimethylphenyl]amino-2-ethylquinazolinone **268**.

(iv) using toluene



The general procedure described above for *m*-xylene was applied using **49** (1 g, 5 mmol), LTA (2.58 g, 1.1 mol eq.), TFA (1.8 cm^3) and toluene (1.4 g, 15 mmol) in dry dichloromethane (20 cm^3). After work-up the residue was purified by flash chromatography and elution with light petroleum - ethyl acetate (3:1). The first fraction (R_f 0.9) afforded *3-[2-methylphenyl]amino-2-ethylquinazolinone* **275** (100 mg, 6.8%) as colourless crystals, mp. 90–92 °C, R_f = 0.9 (from ethanol/water) (Found: M^+ 279.3350. $C_{17}H_{17}N_3O$ requires M^+ 279.3354); δ_H 8.2 [1H, d, *J* 8, H-5(Q)], 7.81–7.65 [3H, m, NH and 2 × H(Q/Ar)], 7.5 [1H, d, *J* 8, H(Q/Ar)], 7.4 [2H, m, 2 × H(Q/Ar)], 7.25 [2H, m, 2 × H(Q/Ar)], 2.5–2.2 (5H, m, CH_2CH_3) and 1.25 (3H, t, *J* 6, CH_2CH_3); *m/z* (%) 279 (M^+, 100), 278 (72), 175 (18) and 154 (12).

Further elution with the same solvent mixture gave a second crystalline product R_f (0.8) (0.4 g, 27% based on **49**) identified as *3-[4-methylphenyl]amino-2-ethylquinazolinone* **274**, mp. 105–107 °C (from ethanol); δ_H 8.25 [1H, d, *J* 8, H-5(Q)], 7.8–7.7 [2H, m, 2 × CH(Q)], 7.5–7.4 [1H, m, CH(Q)], 7.15 (1H, br s, NH), 7.7 [2H, dd, *J* 9.5 and 1, 2 × H_a or H_b(Ar)], 6.6 [2H, dd, *J* 9.5 and 1, 2 × H_b or H_a(Ar)], 3.1–2.8 (2H, m, CH_2CH_3), 2.25 (3H, s, CH_3) and 1.4 (3H, t, *J* 6, CH_2CH_3); *m/z* (%) 302 (MNa^+, 12), 280 (MH^+, 35) and 279 (M^+, 100).

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