STUDIES ON INTRAMOLECULAR TRAPPING OF N-NITRENES.

by

MICHAEL J. GRIMSHIRE

A Thesis submitted in partial fulfilment of the requirements for the Degree of Doctor of Philosophy in the Faculty of Science at the University of Leicester.

1985

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To Mum & Dad, Grandad, and family

"Some men see things that are and ask why? I dream of things that never were and ask why not?"

ROBERT F. KENNEDY

ACKNOWLEDGEMENTS

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ABSTRACT

Studies on the Intramolecular Trapping of N-Nitrenes.

M.J. Grimshire

The research described in this Thesis is an investigation of the intramolecular trapping of N-nitrenes by alkenes and alkynes.

In the former case, the objective was to try to obtain a description of the transition state geometry for concerted addition of nitrenes to double bonds. This was attempted by a study of intramolecular nitrene additions since in the latter, some control over the approach geometry of the interacting components can be exercised by design of the molecular framework. From the effect of changes in this framework upon the characteristics of the cycloaddition, and in particular upon its concertedness, an ideal configuration for the participating atoms (i.e. transition state geometry) was definable.

2H-azirines are obtained in greatly improved yields in the intramolecular trapping of N-nitrenes by comparison with the analogous intermolecular trapping.

Analysis of the n.m.r. spectra of these azirines together with the X-ray crystal structure of one of them reveals that a preference for near-coplanarity of three of the bonds at the spiro-centre results in conformational anchoring of the five-membered ring. (Examination of all the azirine ring containing structures in the Cambridge crystallographic data file shows that all of these also show the same near-coplanarity of azirine C-C bond and substituent bonds at the spiro-centre).

Attempts to trap a presumed 1H-azirine intermediate were unsuccessful. This is probably the result not only of their anti-aromatic character but also that migration of the N-N bond in the 1H-azirine delivers the 2H-azirines, in the cases studied, directly in their most stable conformations.

INDEX

INDEX (Continued).

PART 1

INTRODUCTION

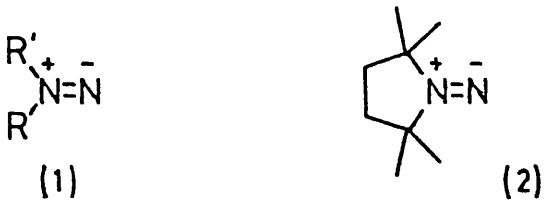
1.1. Introduction to heterocyclic N-nitrenes.

1.1.1.

Nitrenes are reactive intermediates containing a nitrogen atom with an incomplete electron shell, R-N, the nitrogen analogue of carbenes. There are several types of nitrene with differing properties and behaviour, such as alkyl nitrenes, R-N; vinyl nitrenes, H_2C=CH-N; aryl nitrenes, Ar-N; alkoxycarbonyl nitrenes, RO_2C-N; together with a range of nitrenes attached to elements other than carbon of which the largest amount of published work relates to those nitrenes attached to nitrogen, the aminonitrenes, R_2N-N. In these latter cases, the nitrogen (N-1) bonded to the electron deficient nitrogen (N-2) can be substituted by alkyl groups or aryl groups, or alternatively form part of a heterocyclic ring.

1.1.2. 1,1-Diazenes.

When the substituents on N-1 are alkyl groups, the transient species are more properly described as 1,1-diazenes (1).[1-4] Work by Dervan *et al*[5-8] has shown that delocalisation of the electron pair of N-1 into a vacant p orbital on N-2 in 1,1-diazene (2) is substantial. (Figure 1).



(1) (2)

Fig.1

A consequence of this formal double bond between the two nitrogens is a suppression of the nitrene character of the 1,1-diazene. (Figure 2).

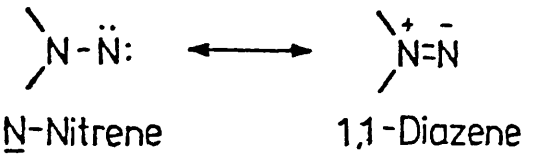


Fig.2

1.1.3. Heterocyclic N-nitrenes.

Oxidation of N-aminoheterocyclic compounds generates the corresponding heterocyclic N-nitrenes. Oxidation can be accomplished by lead tetra-acetate (LTA)[9,10] or benzene iodosodiacetate ($PhI(OAc)_2$).[11] (Figure 3).

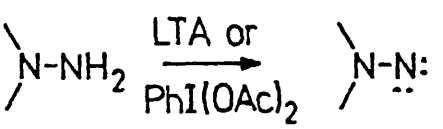
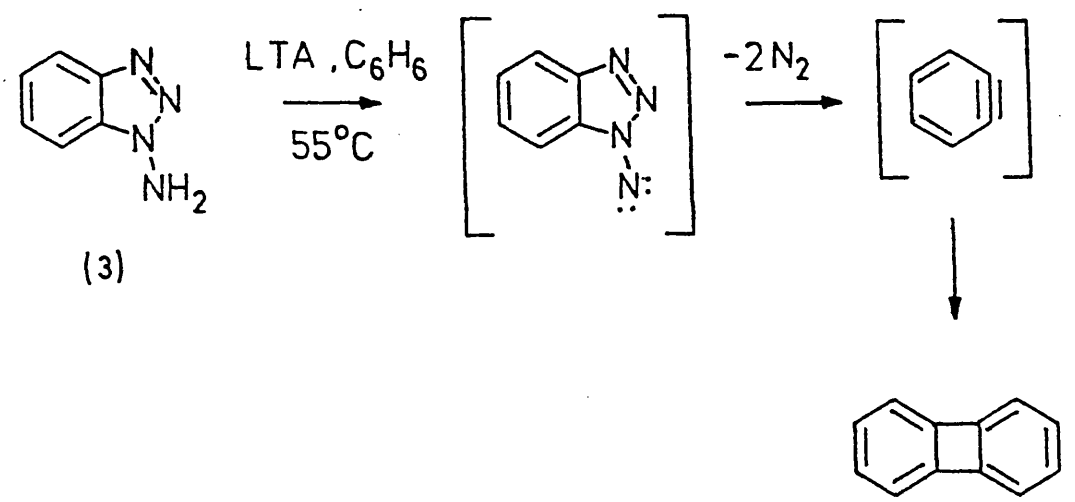


Fig.3

The reactivity of a number of heterocyclic N-nitrenes has been examined by Rees et al and tends to fall into two distinct classes.



(3)

(83%)

Fig.4

One group does not undergo intermolecular reactions but spontaneously rearranges or fragments. The best known example is the oxidation of N-aminobenzotriazole (3) which generates benzyne.[12] (Figure 4).

The other group of heterocyclic N-nitrenes gives N-nitrenes on oxidation whose intramolecular decay is sufficiently retarded for them to be trapped intermolecularly.[13-15] Characteristically they yield aziridines when oxidised in the presence of alkenes. They include the nitrenes derived from oxidation of N-aminophthalimide (NAP) (4), N-aminobenzoxazolinone (5), N-aminoquinazolinone (6), N-aminoquinolone (7), N-aminopyrrole (8), N-aminotriazole (9), N-aminotriazolinone (10), and N-aminobenzimidazole (11). (Figure 5).

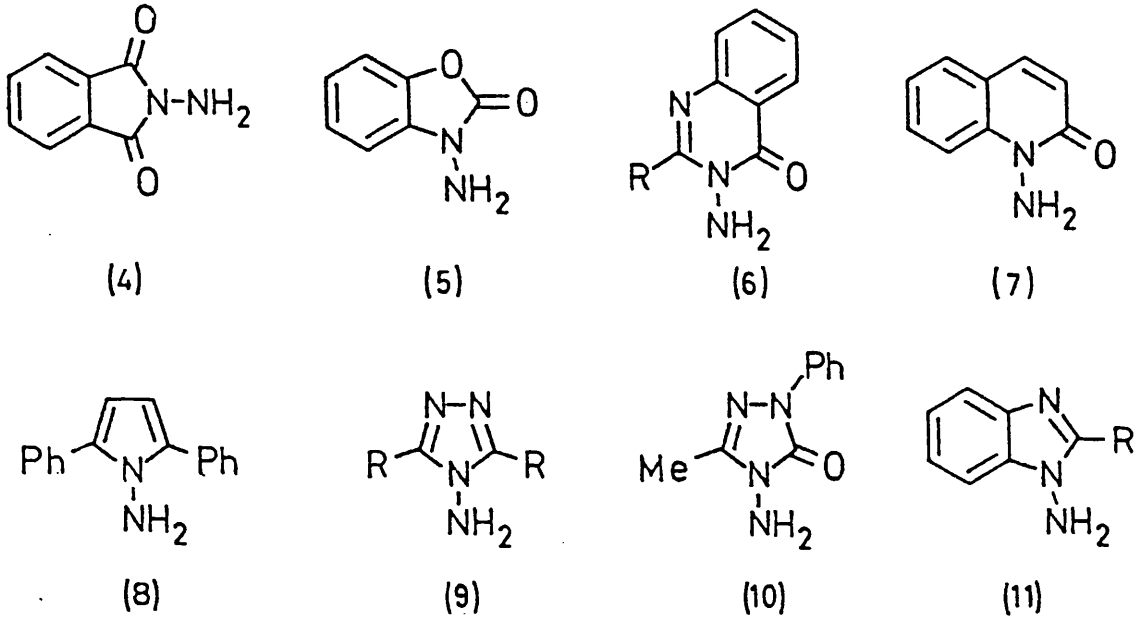


Fig.5

Examination of these heterocycles reveals that they all contain features that will reduce the availability of the substituted nitrogen (N-1) lone pair for donation to the nitrene. Thus one or both of the

N-1 substituents is a carbonyl or imino function, or else the N-1 lone pair is part of an aromatic ring. Competition for the N-1 lone pair by its substituents has two important consequences: nitrene behaviour of N-2 is made manifest, and the tendency for elimination of nitrogen is reduced since the N=N bond order is effectively reduced. (Figure 2).

Of interest is the behaviour of the nitrene derived by oxidation of N-aminotriazole (12)[16] in the presence of alkenes in that it undergoes intramolecular fragmentation in competition with addition to the alkene. (Figure 6).

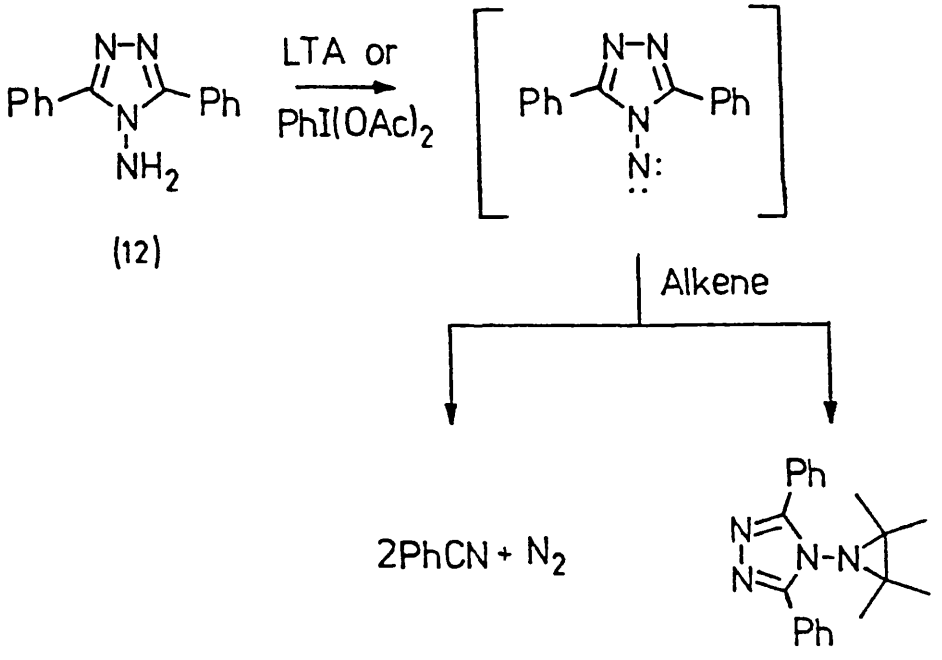
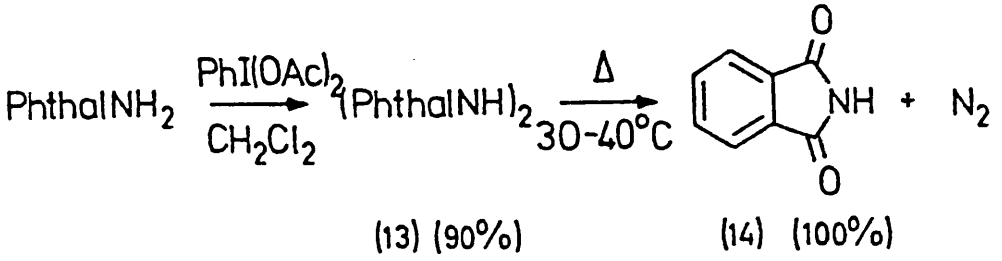


Fig.6

The nitrenes derived from oxidation of (4) - (11) can be trapped by a wide variety of reagents, via insertion into π-bonds and attack on lone pairs of electrons on heteroatoms. There are no products from proven direct insertion into σ-bonds.

When nitreneophilic traps are absent, de-amination results. This

arises it is thought, from attack of the nitrene on unoxidised amino-compound.[17] Oxidation of N-aminophthalimide (NAP) with benzene iodosodiacetate allows isolation of the tetrazane (13), which is the presumed intermediate in the formation of phthalimide (14).[18] (Figure 7).



(13) (90%) (14) (100%)

Fig.7

The amount of de-amination obtained as a by-product is dependent, therefore, on the nitreneophilicity of the trap.

1.1.4. Evidence for an N-nitrene description of the intermediates in oxidations of N-aminoheterocycles.

In oxidation of NAP with LTA, the evidence against an oxidising agent-nitrene complex (nitrenoid) description for the reactive intermediate is the generation, by three other methods, of a species showing the same reactivity. (Figure 8).

In every case the nitrene was trapped stereospecifically by cis (and trans) alkenes and (methods a and b) reacted readily with both electron-rich and electron-deficient alkenes, behaving, in fact, exactly as the species resulting from LTA oxidation of NAP.

The oxidation of N-aminotriazole (12)[16] in the presence of alkenes with either LTA or phenyl iodosodiacetate (Figure 6) gave the same ratio of fragmentation to aziridine formation, again implying a common intermediate in both oxidations.

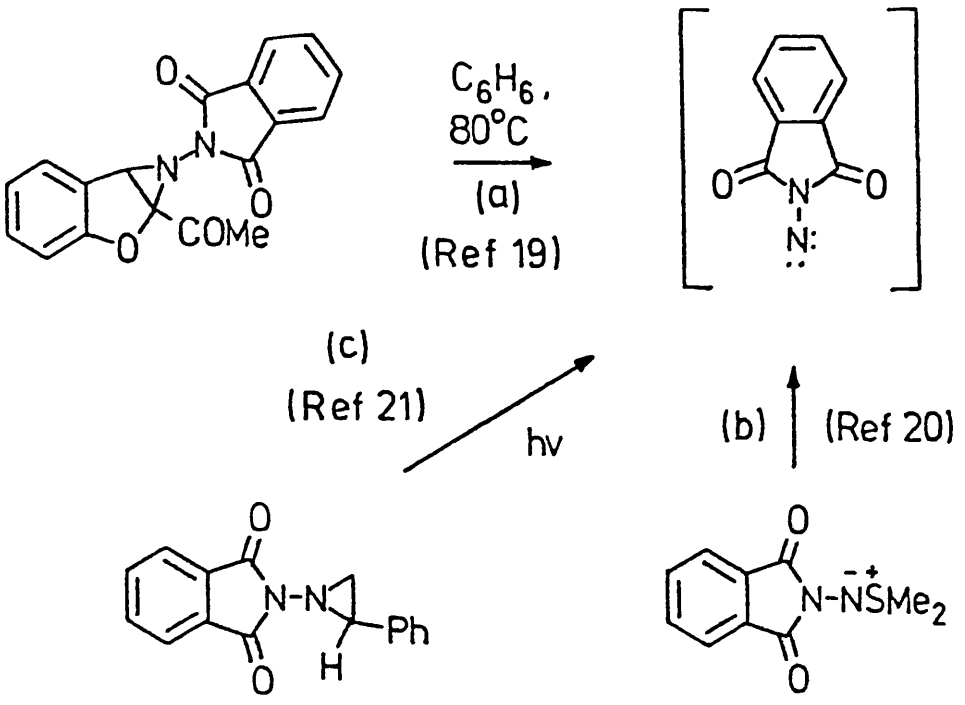


Fig.8

1.1.5. Trapping by Alkenes to give Aziridines.

Addition of singlet nitrenes to alkenes should be concerted with the alkene configuration retained in the aziridine, whereas addition of triplet nitrenes occurs via biradical intermediates in which the spins of the electrons are parallel. Before ring closure can take place to give the aziridine, spin inversion must occur. Spin inversion may be a slow process compared to carbon-carbon bond rotation and so stereospecificity may be lost (Skell's hypothesis).

From the stereospecificity of their reactions with alkenes, particularly with acyclic cis-alkenes, it appears that all the nitrenes derived from oxidation of (4) - (11) have singlet ground states: no experimental evidence is available to suggest that they react via anything other than the singlet state. Calculations of the electronic states of these nitrenes support assignment of the singlet state as the ground

state.[22,23]

The preferred geometry of the transition state for concerted addition of singlet N-nitrenes to alkenes is unknown, but it is assumed to be one in which maximum overlap between complementary HOMO and LUMO pairs of nitrene and alkene is attained. The following description satisfactorily fulfils this requirement. (Figure 9).

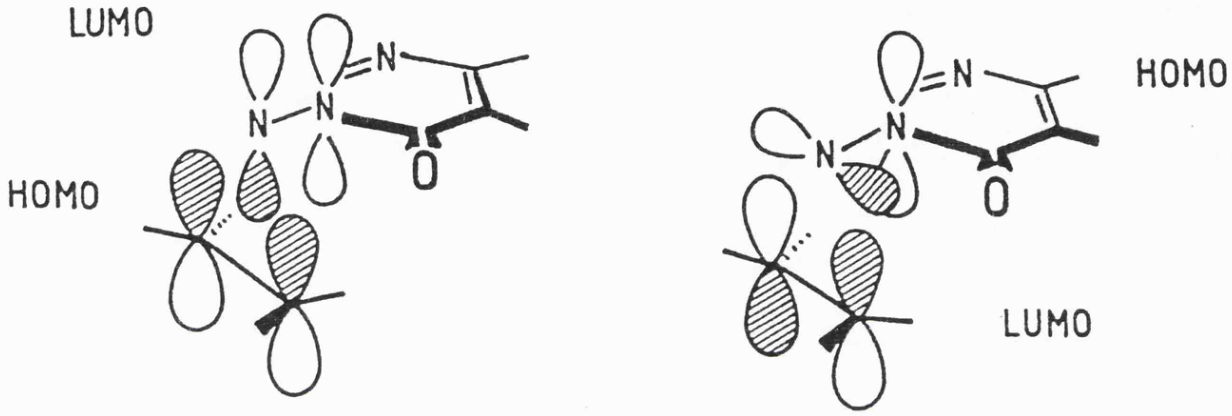


Fig.9

The nitrene nitrogen (N-2) is assumed to be sp-hybridised with the sp-hybridised orbital and the p-orbital, each containing a lone pair: this latter p-orbital is orthogonal to the filled p-orbital on N-1 (which is the arrangement that minimizes electron repulsion).

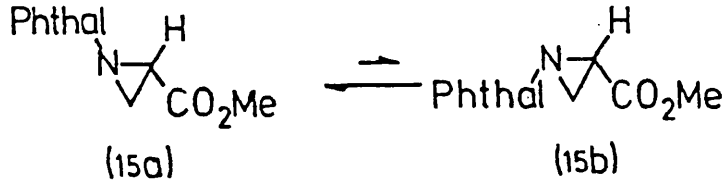
N-Nitrenes derived from (4) - (11) are ambiphilic, adding to electron-rich as well as to electron-deficient alkenes using $HOMO_{alkene}$ - $LUMO_{nitrene}$ or $HOMO_{nitrene}$ - $LUMO_{alkene}$ as the dominant interacting frontier orbitals respectively.

1.1.6. Syn-selectivity effects.

The aziridines that result from stereospecific addition of N-nitrenes to alkenes have retarded rates of inversion at nitrogen.[24] Thus,at room temperature, two invertomers of aziridine (15) are identifiable by n.m.r.

with (15a) and (15b) present in a 5:1 ratio respectively.[25] (Figure 10).

Below about -10 °C, the inversion rate is negligible. If the oxidation of NAP is carried out at temperatures less than -10 °C in the presence of methyl acrylate and the mixture is examined by n.m.r. at low temperature (less than -30 °C) without any intermediate warming of the solution, the only aziridine present is (15b). The thermodynamically more stable (15a) only makes its appearance as the temperature is raised above 0 °C, with eventual establishment of the equilibrium 5:1 ratio of (15a) and (15b). This latter ratio is unchanged on re-lowering the temperature to -30 °C.[26]



(15a) (15b)

Fig.10

It appears that the preference of the alkene substituent for a syn-relationship to the phthalimide ring in the transition state for nitrene addition leads to formation of a kinetically favoured product (15b) rather than the thermodynamically favoured (15a). This syn-selectivity is exhibited by all nitrenes derived from (4) - (11) that have been examined, and vinyl and phenyl groups show a similar propensity to alkoxycarbonyl for a syn-relationship to the heterocyclic ring in the kinetically formed product.[27]

Attempts to determine whether simple alkyl-substituted alkenes show the same syn-selectivity have been thwarted by their lack of reactivity towards the N-nitrenes at low temperatures, but there is little doubt that alkyl groups have a syn-affinity for the heterocyclic ring

that is greater than that of hydrogen (though less than substituents containing π-electrons). Thus, whereas phthalimidonitrene (16) adds to styrene at less than -20 °C to give the syn-substituted aziridine (17a) exclusively (on warming the solution above 0 °C, complete conversion to the more stable (17b) occurs), the use of β-methylstyrene under the same conditions results in a 94:6 mixture of (18a) and (18b) respectively. (Figure 11).

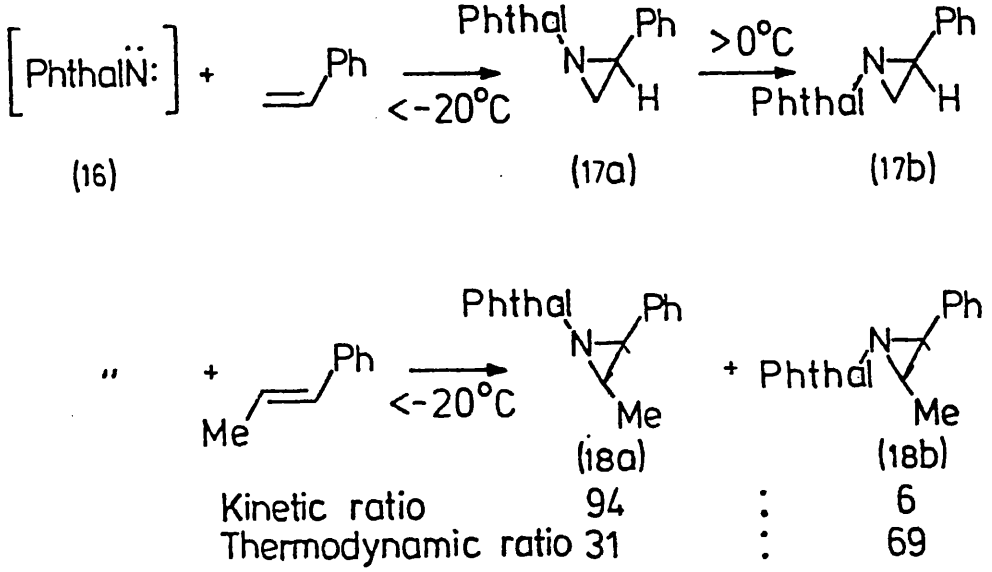
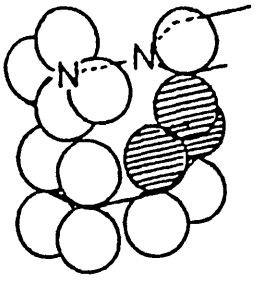


Fig.11

Although the nature of the interaction which brings about this remarkable syn-effect is unknown, Figure 12 shows a possible frontier orbital overlap which might account for it. The s-cis-conformation of the substituent (phenyl, vinyl, carbomethoxy) on the alkene has its π-electrons positioned to overlap favourably with the lobe of the p orbital in the heterocycle adjacent to N-1.

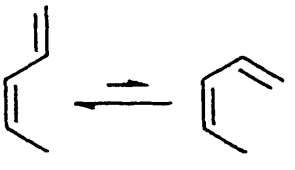
Further support for this transition-state geometry for nitrene addition comes from the superior yields of aziridines from alkenes whose substituents have orbitals that can overlap as indicated in Figure 12.[28,29]



Proposed transition state geometry
to account for Syn-selectivity effects.

Fig.12

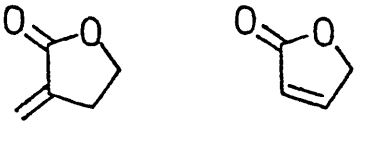
On the other hand, (Z)-penta-1,3-diene (19a ⇌ 19b), in which the concentration of the s-cis-conformation (19b) is negligible (Figure 13), fails to react with phthalimido-nitrene (16) under conditions where isoprene reacts normally.[27]



(19a) (19b)

Fig.13

Similarly, phthalimidonitrene (16) is trapped in quantitative yields by α-methylene-γ-butyrolactone (20), but not at all by 2(5H)-furanone (21).[30] (Figure 14).



(20) (21)

Fig.14

In practice, it does seem that for intermolecular reaction, an s-cis-conformation for the diene or α,β-unsaturated ester is mandatory, and the absence of reactivity of (19) and (21) suggests that the

interaction that brings about this syn-selectivity cannot be dismissed as a normal 'secondary' one if its absence results in no reactivity at all.

PART 2

INTRAMOLECULAR TRAPPING OF N-NITRENES BY ALKENES.

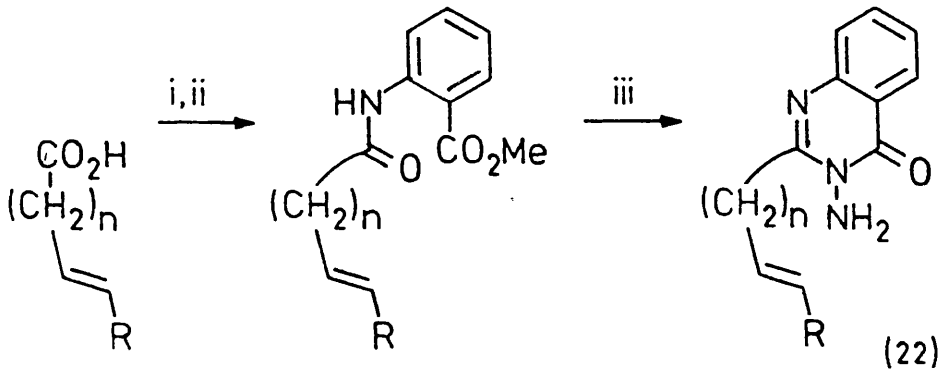
2.1. Introduction.

2.1.1.

Woodthorpe and Skinner[31-34] studied the corresponding intramolecular N-nitrene additions under conditions where 'secondary interactions' were absent.

2.1.2. N-Aminoquinazolones.

The choice of N-aminoquinazolones (22) for the study of intramolecular N-nitrene additions was based on the ready incorporation of the double bond(s) into the side-chain at position 2 when assembly of the quinazolone ring is carried out via the appropriate carboxylic acid. (Figure 15).

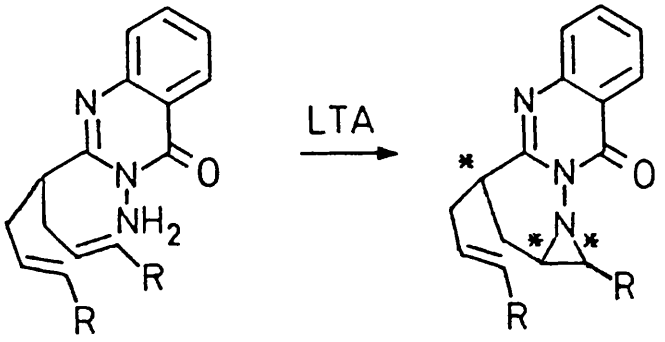


(22)

Reagents i) $SOCl_2$ or $(COCl)_2$ on Na^+ salt, ii) methyl anthranilate, iii) NH_2NH_2.

Fig.15

To avoid complications due to the secondary effects referred to earlier, nitrene additions within quinazolones with n = 2 were studied because models suggested that no interaction between the quinazolone and the alkene substituent is possible when the latter is trans- or β-substituted. At the same time it was envisaged that the intramolecularity of the reaction might offer entropic assistance.



(23) R=H (25) R=H

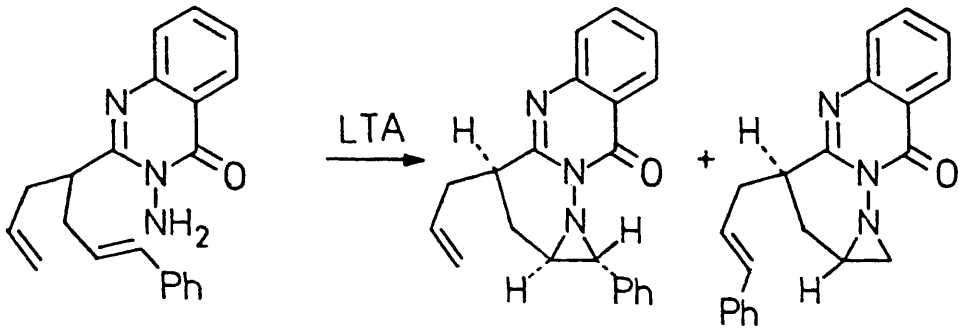
(24) R=Ph (26) R=Ph

Fig.16

Woodthorpe[32] found that oxidation of (23) and (24) gave, in each case, a single aziridine (25) (94 %) and (26) (89 %) respectively. It is noteworthy that in the case of (26), three chiral centres are created stereospecifically in the reaction. (Figure 16).

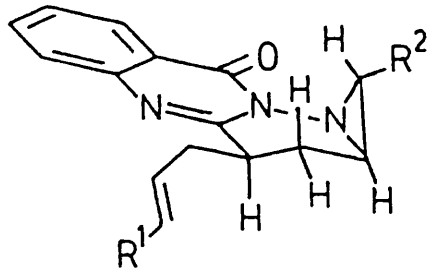
2.1.3. Competitive intramolecular additions.

Oxidation of N-aminoquinazolone (27) was carried out in order to determine the relative affinity of the nitrene towards the phenyl-substituted vs. unsubstituted double bonds. Examination of the crude reaction product by n.m.r. spectroscopy revealed the presence of both aziridines (28) and (29) in a ca 1:1 ratio. (Figure 17).



(27) (28) (29)

Fig.17



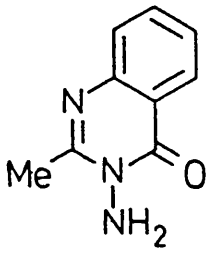
(28) R^1=H, R^2=Ph

(29) R^1=Ph, R^2=H

Fig.18

Analysis of the ^{1}H n.m.r. spectrum was simplified by the fact that both (28) and (29) adopt the same single conformation of the tetrahydropyridazine ring. (Figure 18).

This lack of discrimination by the nitrene between the two alkene traps in (27) contrasts sharply with the analogous competitive intermolecular reaction between hexene and styrene for the nitrene from oxidation of 2-methyl-N-aminoquinazolone (30) where the sole aziridine obtained was that from nitrene addition to styrene even when the concentration of hexene was five times that of styrene. (Figure 19).



(30)

LTA

$PhCH=CH_2$ (1 mol. equiv.)

$CH_3(CH_2)_3CH=CH_2$ (5 mol. equiv.)

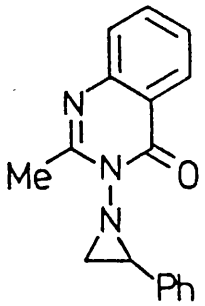


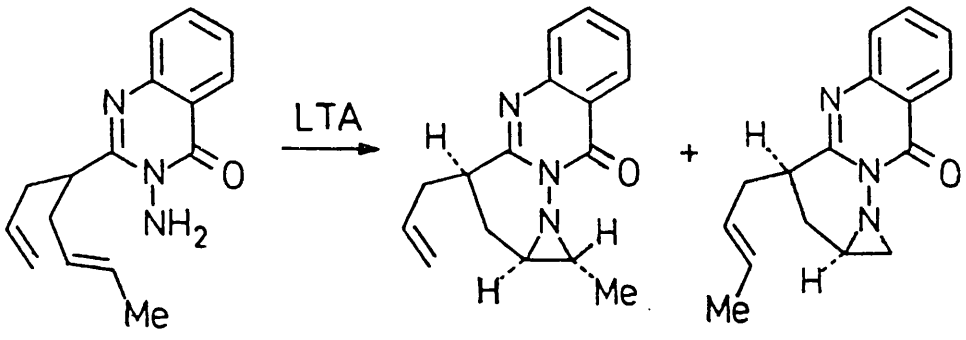
Fig.19

The intramolecular reactions can be diverted, in part, by the intermolecular reaction with styrene indicating that the same nitrene species is involved in both inter- and intramolecular trapping by alkenes.

To account for the difference in relative double bond reactivity

in inter- and intramolecular reactions requires either that a different mechanism is operating in each case or that the same mechanism (presumably concerted nitrene cycloaddition), operates and the lack of discrimination by the nitrene between the two competing double bonds is the result of a geometrically-enforced deprivation of the secondary interaction in addition of the nitrene to the styrenoid double bond.

Other competition experiments using similar bifurcated quinazolones suggest that the mechanisms of inter- and intramolecular nitrene addition are different. Skinner[32] found that the reactivity of a methyl-substituted versus an unsubstituted double bond is critically dependent upon the placement of the methyl group whereas oxidation of (31) gave a 1:1 ratio of aziridines (32) and (33), oxidation of (34) gave exclusively the aziridine (35) from addition to the β-methyl substituted double bond. (Figure 20).



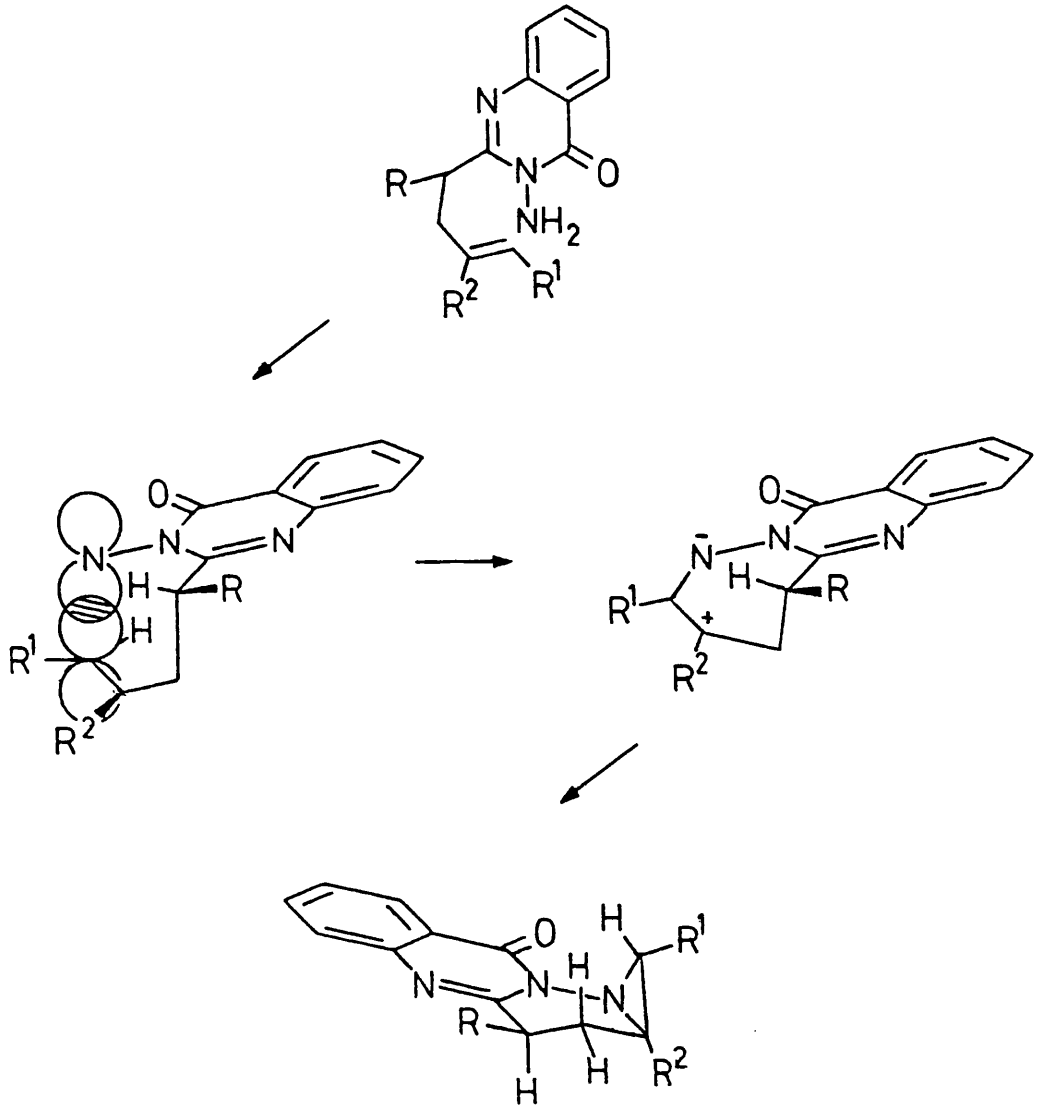
(31) (32) (33)

(34) (35)

Fig.20

2.1.4. Mechanism of intramolecular nitrene addition.

The results from these competitive intramolecular additions were rationalised by assuming that the sp-hybridised nitrene attacks the double bond as indicated in Figure 21 with overlap of the empty p-orbital of the nitrene with a p-ortbial of the π-bond leading to an intermediate having high dipolar character which undergoes ring-closure to give the aziridine.



(32) R= $CH_2CH{=}CH_2$, R^1= Me, and R^2= H

(33) R= (E)-$CH_2CH{=}CHMe$, R^1=H, and R^2=H

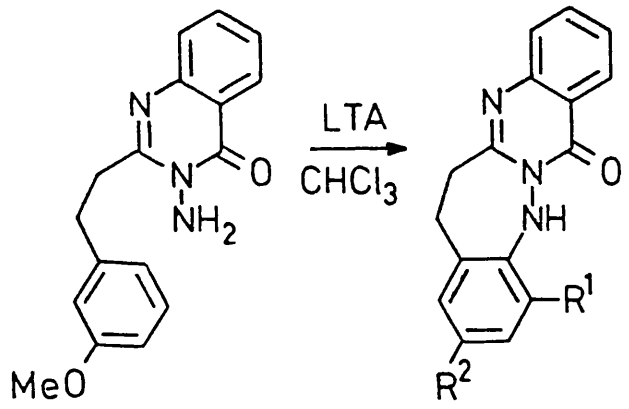
(35) R= $CH_2CH{=}CH_2$, R^1=H, and R^2=Me

Fig.21

The preferential attack on the β-methyl bearing double bond in the oxidation of (34) becomes clear since a tertiary carbocation is generated and the 1:1 ratio of attack on the two different double bonds in (27) and (31) is because similar secondary carbocations are being generated in both cases.

2.1.5. Oxidation of N-Amino-2-(arylalkyl)quinazolones.[33,34]

Other experimental evidence used to support the existence of a dipolar intermediate was that intramolecular trapping of methoxyphenylethylquinazolones is very sensitive to the location of the methoxy group. Oxidation of m-methoxyphenylethylquinazolone (36) gave two products, (37) and (38), whereas oxidation of the p-methoxyphenylethyl analogue gave only the deaminated product. (Figure 22).



(36)

(37) R^1=H, R^2=OMe (46%)

(38) R^1=OMe, R^2=H (29%)

Fig.22

The explanation given for this is that the empty orbital of the nitrene overlaps best with an aryl p(π) orbital in a 7-membered transition state with the resultant carbocation being stabilised by a m-OMe but not by a p-OMe substituent. (Figure 23). Loss of a proton and protonation on nitrogen then gives the products.

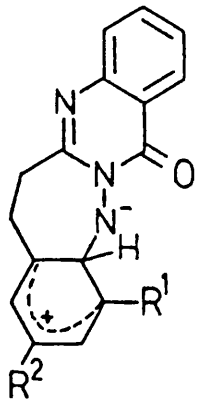


Fig.23

2.1.6. Conclusion.

The preferred transition state geometry for fully concerted intramolecular nitrene cycloaddition cannot, it appears, be accommodated in the substituted quinazolone framework when n = 2 (22). From an examination of models it seems that a transition state closely resembling that shown in Figure 9 is not accessible in this system and that the limited length of the carbon chain directs electrophilic attack of the nitrene to the terminal alkene carbon as shown in Figure 21 leading to a fully developed dipolar intermediate.

2.2. Intramolecular trapping of N-nitrenes by alkenes where n = 3.

2.2.1. Objective

Woodthorpe and Skinner[31-34] concluded that the preferred transition state geometry for fully concerted nitrene cycloaddition suggested by frontier orbital considerations (Figure 9) cannot be accommodated in the substituted quinazolone framework ((22) Figure 15) when n = 2. However, it seemed reasonable to assume that concerted nitrene addition should be preferred when quinazolones with sufficiently large values of n are used. If so, a description of the transition state geometry for concerted nitrene addition to double bonds should therefore be available (with the aid of models) from a determination of the value of n at which a changeover from non-concerted to concerted reaction takes place.

Hence, the main objective of present research was to recognise the onset of concerted cycloaddition, to determine the value of n ((22) Figure 15) at which this occurred, and hence (with the aid of models) to describe the preferred transition state geometry for this concerted cycloaddition. It was important,also, to establish the role (if any) played by the secondary effect in bringing about concerted addition.

2.2.2. Transition state geometry and pericyclic reactions.

Every reaction has a preferred transition state geometry, and pericyclic reactions have preferred transition state geometries which are those satisfying the requirements of symmetry in orbital ovelap.

Knowledge of, and confidence in a reaction's transition state geometry is invaluable for prediction of the effects (particularly stereochemical ones) likely to be brought about by variation in substituents on the component(s) taking part in the pericyclic reaction.

A study of the intramolecular version of a particular reaction can be a useful experimental tool for determination of the transition state geometry for that reaction (some pericyclic reactions, e.g. sigmatropic rearrangements are necessarily intramolecular).

However, the intramolecular reaction must involve a nice amount of conformational freedom: too little means that the geometry of the reaction under study may be that forced upon the molecule and not the preferred one (the product may in fact be formed by a different mechanism from that obtained with the preferred transition state geometry): too much conformational freedom will mean that definition of the relative geometry of the reacting components in the transition state becomes correspondingly more ambiguous.

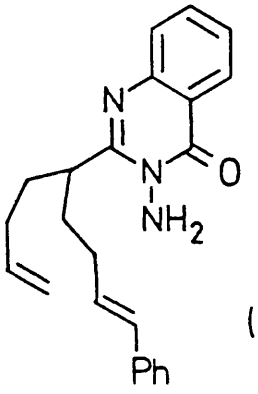
It is clear from the above that some criterion or characteristic must be sought which distinguishes the lower from the higher energy transition state (usually concerted from non-concerted in pericyclic reactions). This criterion may be recognised in intramolecular reaction by incremental increase (or decrease) in conformational freedom although the nature of the criterion may not be known with confidence a priori. Unfortunately the criterion is not always a simple stereochemical one - only when the intermediates in a non-concerted reaction have relatively long lifetimes is loss of stereo-specificity expected (e.g. addition of triplet nitrenes to alkenes).

Simulation of the various accessible transition state geometries using models will be invaluable but it must always be borne in mind that subsequent conformational changes may mean that the product isolated from the reaction may bear little resemblance to the geometry of the transition state by which it was formed.

2.2.3. Synthesis of N-Amino-2-(1-phenylhepta-1,6-dien-4-yl)-quinazolin-4(3H)-one (27) and N-Amino-2-[4(propen-3-yl)-1-phenylpent-1-en-5-yl]-quinazolin-4(3H)-one (39).

These compounds were synthesised on the assumption that the criterion, referred to above, would be a discrimination by the nitrene between two different double bonds to give ratios of aziridines which would be different in concerted and non-concerted reactions.

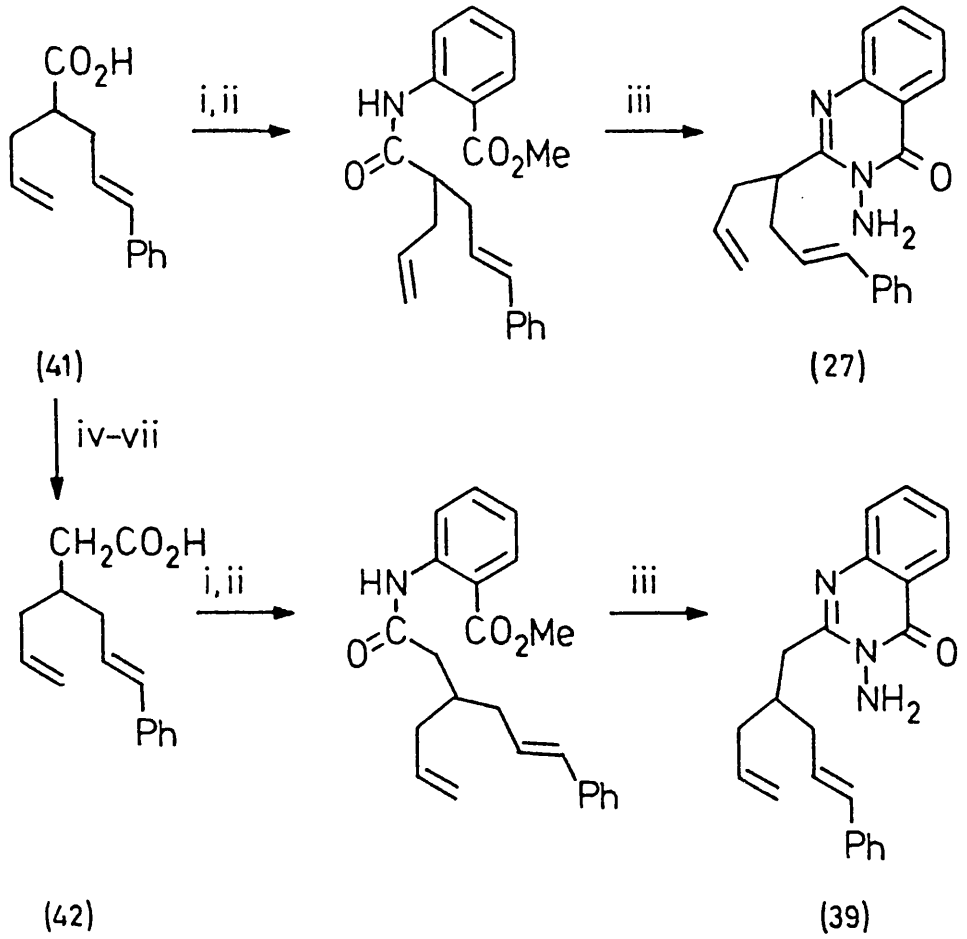
Since the reactivity of the N-nitrene towards phenyl substituted vs unsubstituted double bond in (27) was known,[22] the smallest increase in conformational freedom would require the quinazolone analogue where n = 3 (40) (Figure 24).



(40)

Fig. 24

As described earlier, oxidation of quinazolone (27) and examination of the spectrum of the crude reaction product by n.m.r. revealed the presence of both aziridines (28) and (29) in ca 1:1 ratio as measured from the integration of the signals due to alkene protons on the intact allyl side-chains in the n.m.r. spectra run at 90 MHz of these compounds. It was thought worthwhile to repeat the oxidation of quinazolone (27) in order to obtain a more accurate determination of the ratio of aziridines (28) and (29) by high field n.m.r. (400 MHz).



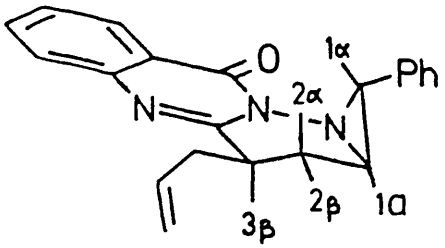
Reagents: i) NaOMe, $(COCl)_2$; ii) Methyl anthranilate; iii) NH_2NH_2, MeOH, sealed tube 120-130°C; iv) $LiAlH_4$; v) TsCl, C_6H_5N; vi) KCN, DMSO; vii) 20% aq KOH sol, reflux.

Fig. 25

Instead of synthesising (40) it was more expedient to synthesise (39) and the appropriate carboxylic acid (42) was prepared by chain-extension of (41) (Figure 25).

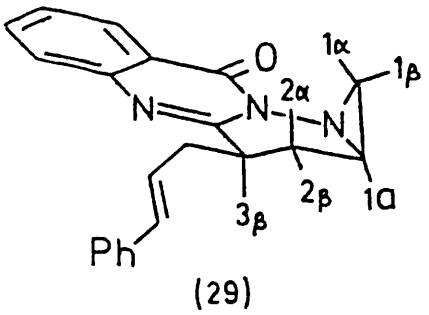
2.2.4. Oxidation of N-Amino-2-(1-phenylhepta-1,6-dien-4-yl)-quinazoline-4(3H)-one (27).

The 400 MHz ^1H n.m.r. spectrum on the crude reaction product showed signals corresponding to only the two aziridines (28) and (29), and selected n.m.r. data are given in Figure 26.



(28)

8.20 (dd, J 8.3 and 1.3 Hz, quinaz. H-1)
5.94 (dddd, J 17.2, 10, 7.9, and 6.1 Hz, -CH=CH_2)
5.15 (dq, J 17.2 and 1.5 Hz, 1 H, CH=CH_2)
5.10 (dq, J 10 and 0.6 Hz, 1 H, -CH=CH_2)
2.35 (ddd, J 14.2, 8.1, and 7.9 Hz, -CHHCH=CH_2
and 1.41 (ddd, J 13.1, 13.1, and 8.6 Hz, H-2α)



(29)

8.24 (dd, J 8.1 and 1.3 Hz, quinaz. H-1)
6.48 (d, J15.8 Hz, -CH=CHPh)
6.32 (ddd, J 15.8, 8, and 6.5 Hz, -CH=CHPh)
2.48 (ddd, J 14.4, 8, and 8 Hz, CHHCH=CHPh)
1.80 (dd, J 5.4 and 2 Hz, H-1α)
and 1.26 (ddd, J 13, 13, and 8.3 Hz, H-2α)

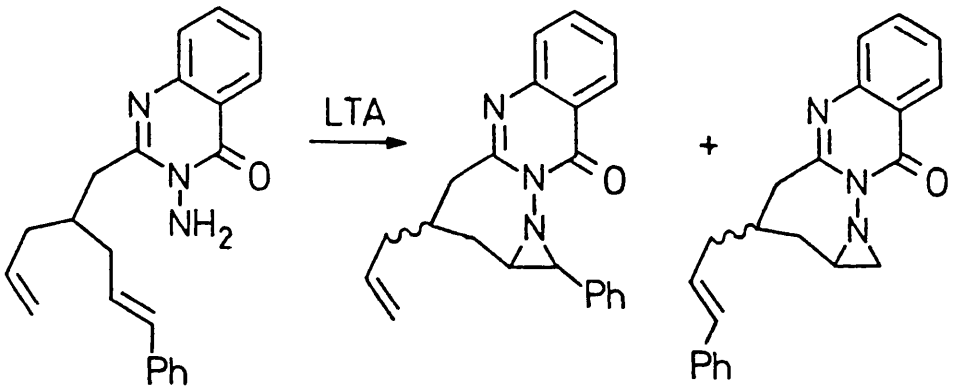
Fig. 26

By comparison of the respective integration values of quinaz H-1, olefinic protons, CHHCH=CHPh, or H-2α, the ratio of the two aziridines was found to be 1.5:1 (± 0.1) in favour of (28).

2.2.5. Oxidation of N-Amino-2-[4(propen-3-yl)-1-phenylpent-1-en-5-yl]-quinazolin-4(3H)-one (39).

Examination of the 400 MHz ^{1}H n.m.r. spectrum on the crude reaction product revealed the presence of both aziridines (43) and (44). By comparing the two sets of olefinic protons, the ratio of aziridines was calculated to be 5.8:1* with the N-nitrene preferentially adding to the phenyl substituted double bond giving (43) as the major product (Figure 27).

Aziridines (43) and (44) were separated by column chromatography. Examination of their 400 MHz ^{1}H n.m.r. spectra revealed that addition



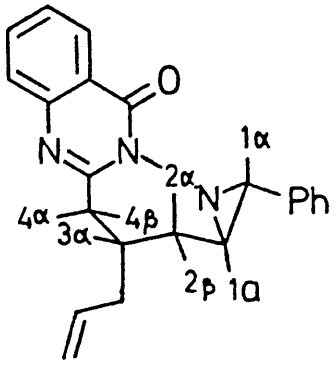
(39) (43) (44)

Fig.27

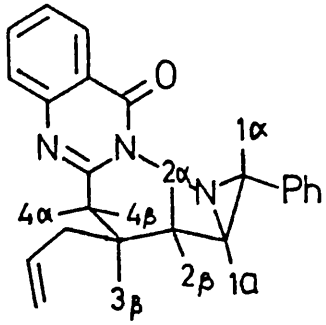
of the N-nitrene to the double bond in both cases was non-stereospecific with respect to the orientation of the alkenylmethylene side chain although addition to the double bond in (43) was stereospecific in that the aziridine ring protons were trans in both stereoisomers. Interpretation of these spectra was greatly facilitated by the single conformation of the 7-membered ring present in every case with the result that the configurations of the alkenylmethylene side chains are definable from analysis of coupling constants as shown in Figure 28.

Confirmation of these assignments came after separation of the two stereoisomers of aziridine (44), (44a) and (44b), by chromatography. All the 400 MHz ^{1}H n.m.r. data for (44a) along with assignments which were made with the help of a COSY projection are given in Figure 29.

* Unfortunately, in the communicated part of this work (J.Chem.Soc., Chem.Commun., 1985, 9, 544) this figure was incorrectly given as 8.5:1.

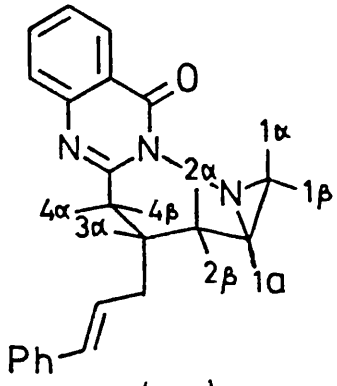


(43a)

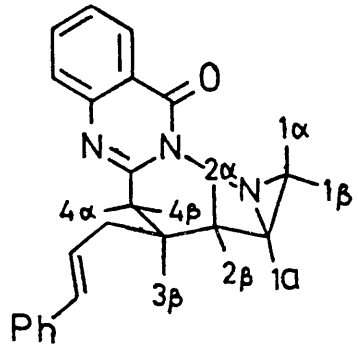


(43b)

H-4β	3.26 (dd, J 12.8 and 11.4 Hz)	3.74 (dd, J 13.2 and 7.2 Hz)
H-2α	1.51 (ddd, J 15.2, 12.2, and 6.3 Hz)	1.04 (ddd, J 15.2, 12, and 12 Hz)



(44a)

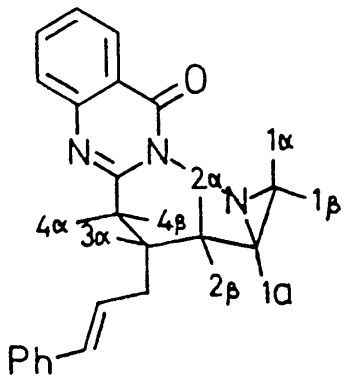


(44b)

H-4β	3.20 (dd, J 12.7 and 11.7 Hz)	3.66 (dd, J 13.1 and 7.3 Hz)

Fig. 28

Thus, on going from (27) to (39), the N-nitrene generated shows an increase in selectivity for the phenyl-substituted double bond, from 1.5:1 to 5.8:1 respectively. This change in ratio could be interpreted as indicating a change in the mechanism of nitrene addition. Alternatively, the same mechanism (non-concerted addition) could be operating in addition of the nitrene generated from (39) with competitive attack on the β-carbon atom of the phenyl-substituted double bond and on the α-carbon atom of the unsubstituted double bond with intermediates



(44a)

8.24 (dd, J 8 and 1.4 Hz, quinaz. H-1)

7.69 (ddd, J 7.9, 7, and 1.2 Hz, quinaz. H-3)

7.60 (dd, J 7.9 and 1.4 Hz, quinaz. H-4)

7.43 (ddd, J 8, 7, and 1.2 Hz, quinaz. H-2)

6.50 (d, J 15.7 Hz, -CH=CHPh)

6.23 (dt, J 15.7 and 7.3 Hz, -CH=CHPh)

3.26 (dd, J 12.1 and 12.1 Hz, H-4β)

2.98 (dd, J 6.1 and 3.2 Hz, H-1β)

2.95 (dd, J 12.1 and 6 Hz, H-4α)

2.75 (dddd, J 12.2, 6.1, 6.1, and 3 Hz, H-1a)

2.50 (m, CH_2CH=CHPh)

2.33 (m, H-2β and H-3α)

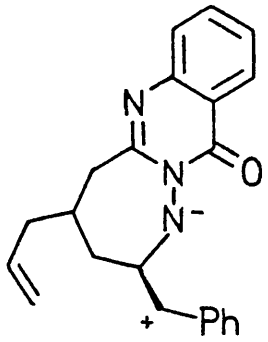
2.16 (dd, J 6.1 and 3.2 Hz, H-1α)

and 1.31 (ddd, J 15.4, 12.2, and 6.5 Hz, H-2α)

Fig. 29

having high dipolar character being generated in each case. Preferential attack on the phenyl substituted double bond would then be attributable to benzylic stabilisation of the carbonium ion in the intermediate (45) (Figure 30). However, if the later explanation was correct then one might reasonably expect the preference of the N-nitrene for the phenyl-substituted double bond to be more pronounced than 5.8:1 especially since

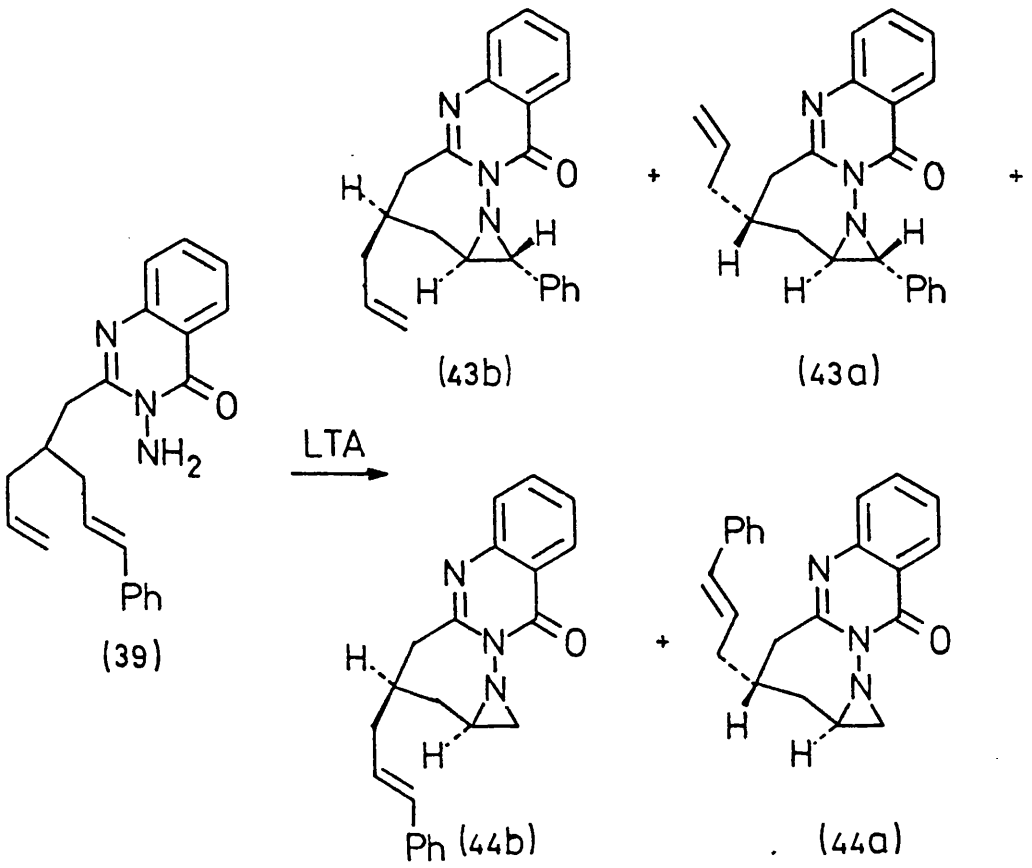
attack on the α-position is constrained to occur via a larger ring than is required for attack on the β-position. Moreover, the ratio of stereoisomers produced in addition to each of the double bonds of (39) does support this non-concerted mechanism (see below).



(45)

Fig. 30

2.2.6. Ratio of stereoisomers.



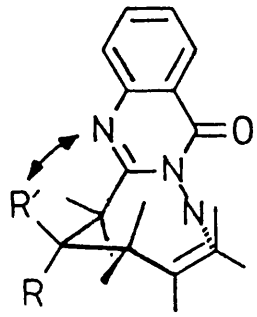
Ratio of stereoisomers (43b):(43a) or (44b):(44a)

1:2·2 (±0·1)

Fig. 31

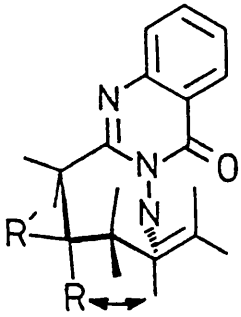
As indicated previously (Figure 28), the addition of the N-nitrene to both double bonds in (39) is non-stereospecific with both faces of both the double bonds being attacked. The ratio of stereoisomers produced in each case was the same (Figure 31).

Although the additional carbon atoms in the chains of (39) allow some increased flexibility in attack of the nitrene on either double bond (by comparison with (27)), an examination of models suggests that the chain is still sufficiently tight for identifiably different conformations to be necessary for attack on the α- and β-carbon atoms of the alkenes. Representations of these two conformations, (46) and (47), are shown in Figure 32 with the significant differences in eclipsing or steric strain elements between the two arrowed.



Attack on the α-carbon

(46)

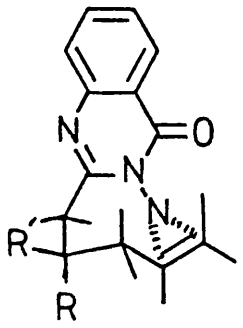


Attack on the β-carbon

(47)

Fig. 32

It is apparent that a switch from attack on the α- to the β-position would, as a result of these conformational differences between (46) and (47), be accompanied by a significant change in the stereoisomer ratio: specifically, reaction via (47) would be expected to result in more of that stereoisomer with R = H. Identity of these stereoisomer ratios, however, would be anticipated if attack of the nitrene on both double bonds in (39) was intermediate between (46) and (47), hence (48)



Concerted transition state

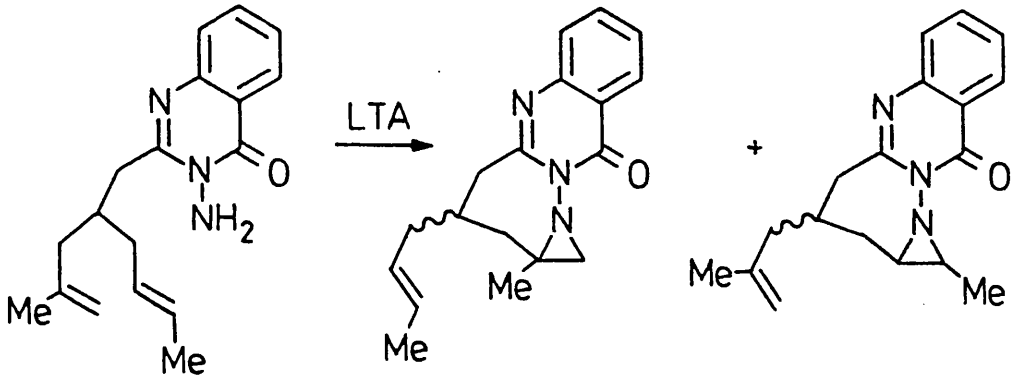
(48)

Fig. 33

(Figure 33). This proposed transition state leads directly to the conformation adopted by aziridines (43) and (44).

2.2.7. Oxidation of N-Amino-2-[5-(2-methylprop-2-enyl)-E-hex-2-en-6-yl]-quinazolin-4(3H)-one (49).

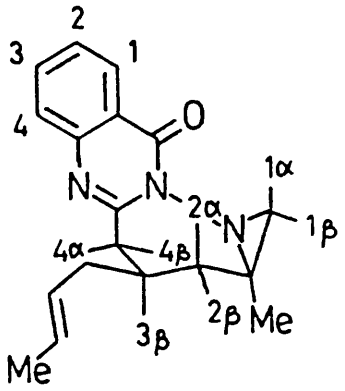
Quinazolone (49) was synthesised via a similar route to that outlined for (39) in Figure 25. Examination of the crude oxidation product revealed the presence of both aziridines (50) and (51) in a 1.05:1 (± 0.05) ratio respectively (Figure 34).



(49) (50) (51)

Ratio 1·05 : 1(±0·05)

Fig. 34



(50b)

8.25 (ddd, J 8, 1.5, and 0.6 Hz, ArH_1)

7.70 (ddd, J 8.2, 6.7, and 1.5 Hz, ArH_3)

7.65 (ddd, J 8.2, 1.5, and 0.5 Hz, ArH_4)

7.44 (ddd, J 8, 6.7, and 1.5 Hz, ArH_2)

5.50 (m, -CH=CHMe)

3.41 (dd, J 13 and 6.8 Hz, H-4β)

2.83 (dd, J 13 and 1 Hz, H-4α)

2.79 (d, J 3 Hz, H-1β)

2.20 (m, H-2β, H-3β, and CHHCH=CHMe)

2.19 (d, J 3 Hz, H-1α)

1.95 (ddd, J 13, 8.2, and 8.2 Hz, CHHCH=CHMe)

1.69 (dd, J 8.9 and 1.3 Hz, -CH=CHMe)

1.42 (s, Me)

and 0.82 (dd, J 16.2 and 13.1 Hz, H-2α)

Fig. 35

Aziridines, (50) and (51), were separated by column chromatography. In the case of aziridine (51), both stereoisomers were present and, significantly, in the same ratio as that found with aziridines (43) and (44), i.e. 1:2.2 (± 0.1). Confirmation of n.m.r. assignments was made by comparison of the spectrum of the crude reaction mixture with those of the separated stereoisomers. However, examination of the 400 MHz ^1H n.m.r. spectrum of aziridine (50) showed the ratio of stereoisomers in this case to be at least 7:1 in favour of that stereoisomer in which the alkenylmethylene side chain takes up the equatorial position (50b) (Figure 35).

Addition to one face of the β-methyl-substituted double bond in (49) is likely to be particularly favoured since attack on the other face would involve methyl-CH_2(alkenyl)-repulsion (see Figure 33). This adverse steric interaction causes the reaction to be highly stereoselective giving mostly (50b) (Figure 35).

A transition state resembling (48) (Figure 33) cannot be claimed to represent the preferred one for addition of N-nitrene to alkenes unless it can be shown that others (perhaps even more favourable) have not been excluded by adverse strain factors. In fact, nitrene attack in (39) or (49) with N-N and C=C bonds parallel (Figure 36) as opposed to orthogonal in Figure 33 is permitted (from examination of models) but can be discounted: predominant or exclusive formation of the stereoisomer having the aziridine ring Hβ and alkenylmethylene side-chain trans would involve alkenylmethylene-alkene Hα interaction (arrowed in Figure 36). Moreover, it is difficult to see why addition to the β-methyl-substituted double bond should be so much more stereoselective if the transition state did resemble this geometry.

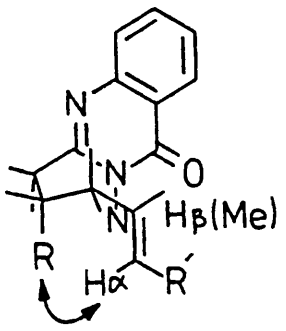
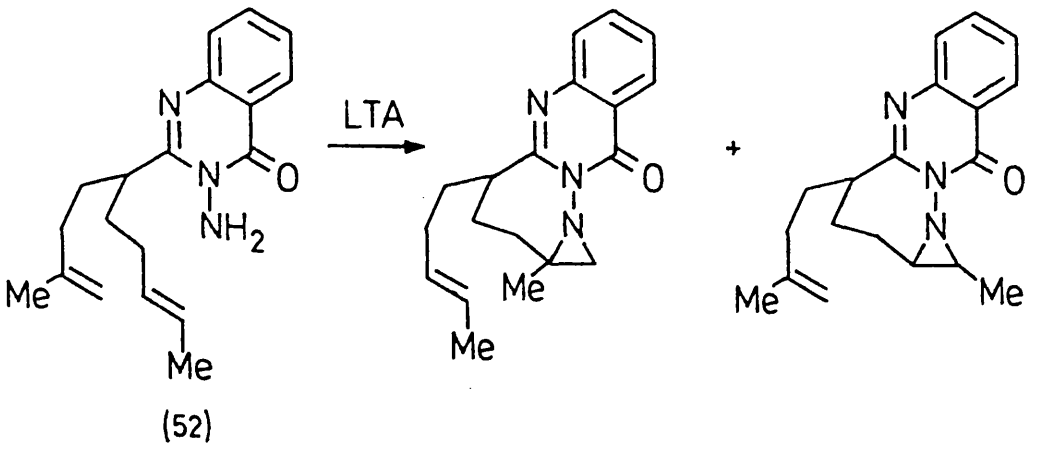


Fig. 36

It was recognised that because addition to one face of the β-methyl-substituted double bond in (49) is inhibited by adverse steric interaction, the ratio of 1:1.05 does not reflect the real relative affinities of the α-methyl and β-methyl substituted double bonds,



Ratio 3:1 (±0·3)

Fig. 37

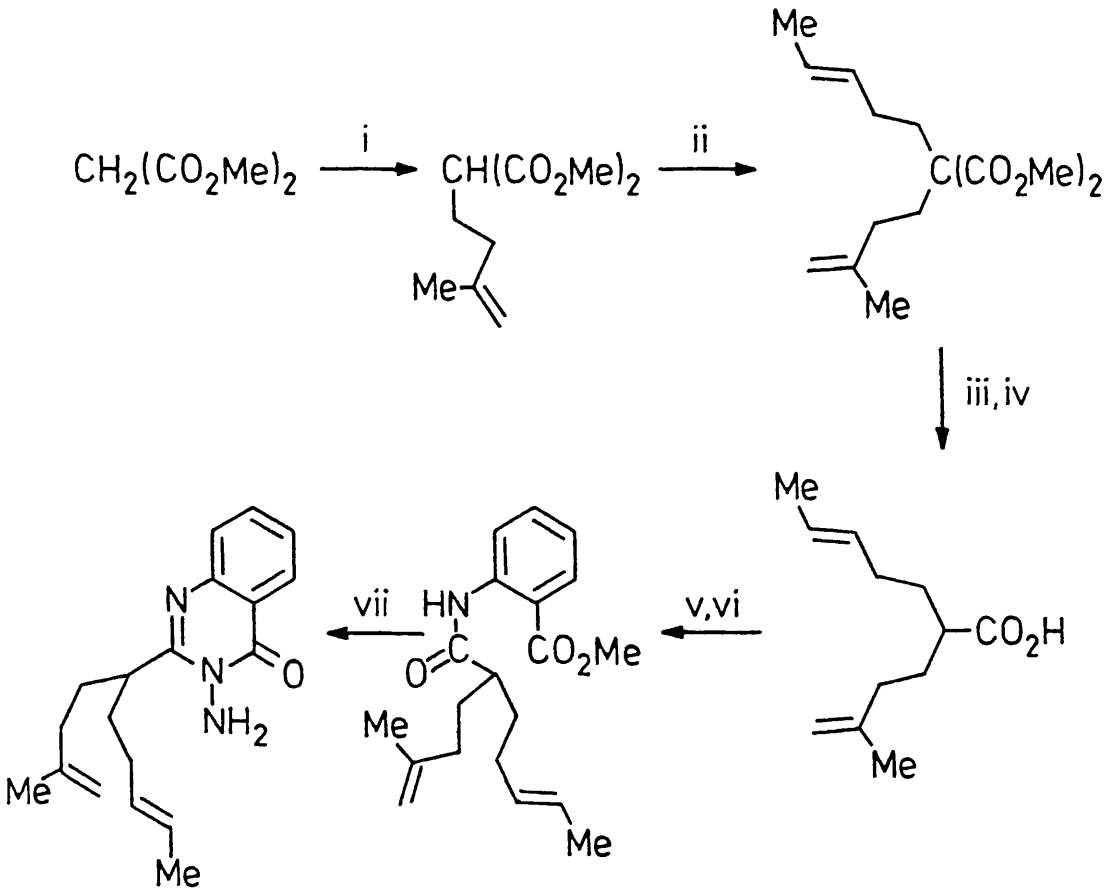
respectively, for the nitrene. Indeed, the corresponding ratio in oxidation of the α-branched analogue (52) is 3:1 (± 0.3) (Figure 37).

As in the oxidation of (23) or (24), addition of the nitrene in this case is wholly stereospecific. Synthesis of (52) was accomplished as shown in Figure 38.

A change in mechanism, therefore, is implicated in the nitrene additions to double bonds in (39) by comparison with addition to those in (27). The greater reactivity of the phenyl-substituted double bond in (39) over the unsubstituted double bond *via* transition state (48) can be ascribed to better $HOMO_{alkene}$ - $LUMO_{nitrene}$ overlap (see Appendix II. Energy of the HOMO of styrene higher than that of propene) *i.e.* the change in mechanism referred to above is a change from non-concerted to concerted addition.

2.2.8. Conformational factors.

One could argue that the preferential attack on the phenyl-substituted double bond in (39) is a consequence of obscure conformational factors which give rise to a higher (time-averaged) concentration of the phenyl-substituted double bond correctly positioned for attack



(52)

Reagents: i) $H_2C{=}CMeCH_2CH_2OTs$, NaOMe-MeOH; ii) $MeCH{=}CHCH_2CH_2OTs$, NaOMe-DMSO; iii) NaOH-H_2O; iv) Δ, 130-150°C; v) NaOMe, $(COCl)_2$; vi) Methyl anthranilate; vii) NH_2NH_2, sealed tube, 120-130°C.

Fig. 38

by the nitrene. However, these (unspecified) 'conformational factors' would have to be highly unusual since they would be required to bring about a more favourable attack on the phenyl-substituted double bond without changing the ratio of attack of the nitrene on the respective two faces of the two double bonds. A more economical explanation is that the conformational factors are identical for attack on the same faces of either double bond but that electronic/mechanistic factors as explained previously make attack on the phenyl-substituted

double bond easier.

2.2.9. Oxidation of N-Amino-2-(2-methylhepta-1,6-dien-4-yl)-quinazolin-4(3H)-one (53).

Skinner[32] found that whereas oxidation of (31) gave a 1:1 ratio of aziridines (32) and (33), oxidation of (34) gave exclusively the aziridine (35) from addition to the β-methyl-substituted double bond (Figure 20).

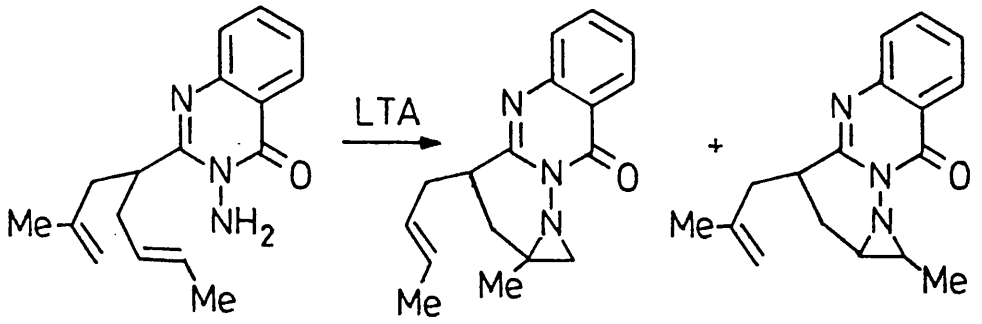


Fig. 39

By collation of those findings, one would expect oxidation of quinazolone (53) to give regiospecifically the aziridine from addition to the β-methyl-substituted double bond. Examination of the crude reaction product by n.m.r. showed the presence not only of the aziridine formed from addition of the nitrene to the β-methyl-substituted double bond (54) but also the aziridine from addition to the α-methyl-substituted double bond (55) in a 5.3:1 (± 0.4) ratio respectively (Figure 39). This ratio is particularly striking when contrasted with the ratio obtained from a competition reaction between trans-but-2-ene and isobutene for the nitrene from oxidation of N-amino-2-methylquinazolin-4(3H)-one in which trans-but-2-ene was shown to be 7.4 times more

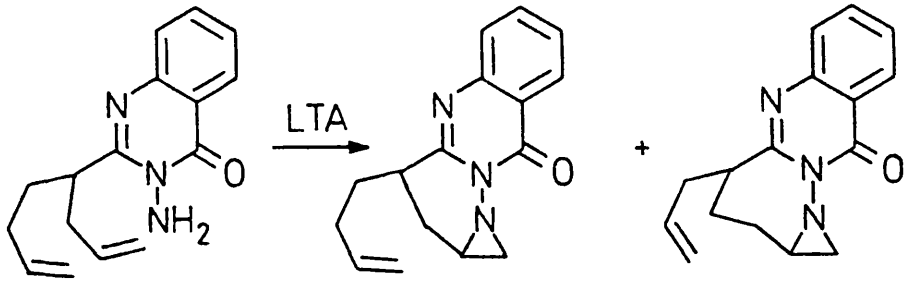
reactive than isobutene.

2.2.10. Oxidation of N-Amino-2(oct-1,7-dien-4-yl)-quinazolin-4(3H)-one (56) and solvent effects.

From oxidation of substituted quinazolones when n = 2 (22) the evidence suggests that there is some build-up of charge in the transition state leading to the aziridine with N-C_α bond formation running ahead of N-C_β bond formation.

The question as to how much charge development takes place in the transition state is a difficult one to answer but if partial charges are being developed then conceivably solvent effects may be detectable.

Quinazolone (56) (first synthesised and oxidised by Skinner[74]) was prepared bearing a bifurcated chain at position 2. Both chains have terminal unsubstituted double bonds and differ only in their length with one being n = 2 and the other n = 3. Oxidation of (56) in CH_2Cl_2 produces both aziridines (57) and (58) in a 3.4:1 ratio respectively (Figure 40).



(56) (57) (58)

Fig. 40

Now, if attack of the nitrene on the unsubstituted double bond where n = 2 is progressing through a transition state that has a greater degree of charge developemnt (i.e. non-concerted mechanism) than the corresponding attack on the double bond where n = 3 (i.e.

(56) $\xrightarrow{LTA}$ (57) + (58)

Benzene	2·8	: 1
CH_2Cl_2	3·4	: 1
CH_3CN	4·7	: 1

Fig. 41

concerted mechanism), the ratio of aziridines could be affected by changes in the solvent in which oxidation of (56) is carried out. This is found to be so: when the oxidation is carried out in benzene, the ratio of aziridines obtained is 2.8:1, whereas in acetonitrile the ratio is 4.7:1 (Figure 41).

Although the effects are small, there is a correlation between expected changes in the ratio of aziridines (57) and (58) with that of the solvent polarity: with increasing solvent polarity more of aziridine (57) is produced relative to (58) indicating that attack of the nitrene on the double bond where n = 2 is progressing through a transition state that has a greater degree of charge development than the corresponding attack on the double bond where n = 3.

2.2.11. Conclusion.

The change in selectivity of the N-nitrene for two alkene double bonds in (39) and (49) with n = 3 by comparison with the cases where n = 2 has been interpreted as the result of a changeover from non-concerted to concerted addition. Examination of models supports a description of the preferred transition state geometry for this concerted nitrene cycloaddition as shown in Figure 9.

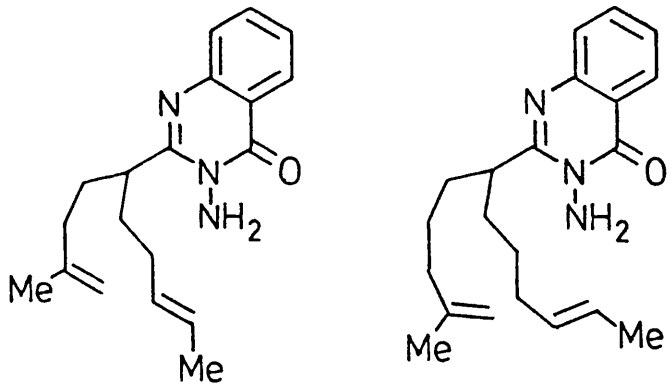
It appears that concerted addition can take place even when the secondary effect is absent which is believed to be the case in intramolecular N-nitrene additions from N-aminoquinazolones (22) (Figure 15) with n = 3 and trans or β-substituted alkenes.

2.3. Intramolecular trapping of N-nitrenes by alkenes where n = 4.

2.3.1.

It has been shown in the previous chapter that addition of the N-nitrene to double bonds with n = 3 by comparison with n = 2 can be interpreted as the result of a changeover from non-concerted to concerted reaction.

It was interesting to compare the ratio of aziridines obtained in the oxidation of (52) with the corresponding ratio obtained in the oxidation of (59) (Figure 42). A comparison of these ratios would indicate how important are conformational factors in determining the selectivity of the N-nitrene for the two double bonds, assuming, of course, that the secondary effect referred to earlier (p. 8) does not come into play.



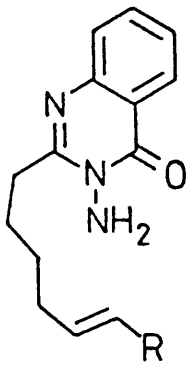
(52) (59)

Fig. 42

Before discussing the result of oxidation of quinazolone (59), oxidations of quinazolones (60), (61), and (62) (Figure 43) are described.

2.3.2. Oxidation of N-Amino-2-(1-phenylhex-1-en-6-yl)-quinazolin-4(3H)-one (60).

Woodthorpe[35] found that oxidation of (60) gave a polymeric material



(60) R=Ph
(61) R=Me
(62) R=H

Fig. 43

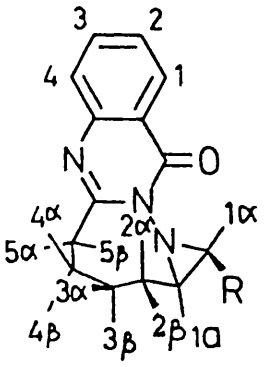
of high molecular weight which was believed to be the result of repeated addition of the nitrene of one molecule to the styrenoid d.b. of another. Skinner[36] had more success with (61) and isolated the crystalline aziridine (64) in 37 % yield.

Since the original oxidation of (60), the experimental procedure has been modified to maximise the intramolecular reaction and oxidation of (60) was therefore repeated under high dilution conditions described in the Experimental. An n.m.r. spectrum of the (crude) (crystalline) product showed only the presence of aziridine (63) (Figure 44). Crystallisation from ethanol gave (63) as colourless crystals m.p. 181 - 183 ^{o}C.

The n.m.r. data suggested that the eight membered ring in (63) is exclusively or at least heavily biased towards the twist-boat-chair conformation shown. (The same conformation as proposed by Skinner for (64)).

2.3.3. Oxidation of N-Amino-2-(E-hept-2-en-7-yl)-quinazolin-4(3H)-one (61) and N-Amino-2-(hex-1-en-6-yl)-quinazolin-4(3H)-one (62) under high dilution conditions.

Examination of the 300 MHz ^{1}H n.m.r. spectra of the crude reaction products obtained from oxidation of (61) or (62) showed the presence



(63) R=Ph
(64) R=Me
(65) R=H

(63) R = Ph 8.14 (dd, J8 and 1.6 Hz, quinaz. H-1)
7.62 (ddd, J 8.3, 7, and 1.6 Hz, quinaz. H-3)
7.55 (dd, J 8.3 and 1.2 Hz, quinaz. H-4)
7.44 (m, 2 x ArH)
7.33 (m, quinaz. H-2 and 2 x ArH)
7.25 (m, ArH)
3.44 (d, J 5.9 Hz, H-1α)
3.31 (ddd, J 13.5, 11.8, and 1 Hz, H-5β)
2.92 (ddd, J 13.5, 7.7, and 1 Hz, H-5α)
2.78 (ddd, J 10.4, 5.9, and 1.3 Hz, H-1a)
2.36 (m, H-2β and H-4β)
2.00 (ddddd, J 13.8, 6, 5.8, 1.2, and 1.2 Hz, H-3α)
1.94 (ddddd, J 13, 12.7, 11.8, 5.8, and 1 Hz. H-4α)
1.68 (ddddd, J 13.8, 12.7, 12.3, 5.3, and 1.4 Hz, H-3β)
and 1.09 (dddd, J 15.9, 12.3, 10.4, and 1.2 Hz, H-2α)

Fig. 44

of both the corresponding aziridines and de-amination products ($NNH_2 \rightarrow NH$).

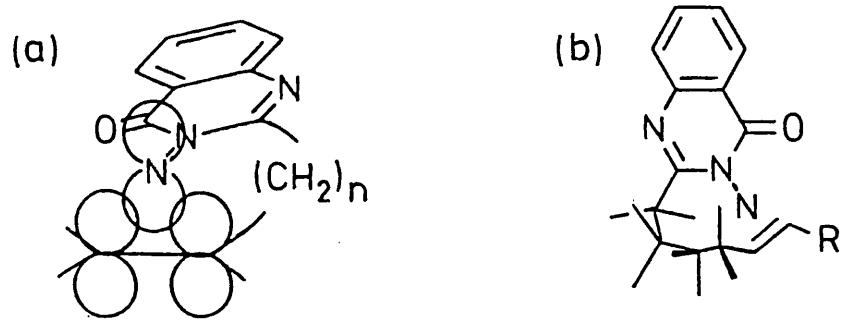
By comparison of the integration values of H-5β or H-5α and olefinic protons, the ratio of aziridine (64) to de-amination product is ca 2:1 respectively. An analogous comparison of H-5α, H-5β, H-1a, or H-1α in aziridine (62) and olefinic protons in the de-amination product reveals the ratio of these two products to be ca 1:2.5 respectively.

These results indicate that in going from R = Ph (60) through R = Me (61) to R = H (62) the double bond becomes less efficient at

trapping the nitrene.

2.3.4. Transition state geometry.

By analogy with the situation where n = 3 ((a) Figure 45), a transition state resembling (66) ((b) figure 45) could represent that involving addition of N-nitrene to alkenes where n = 4 since this conformation of the chain has a minimum of eclipsing interactions present.



(66)

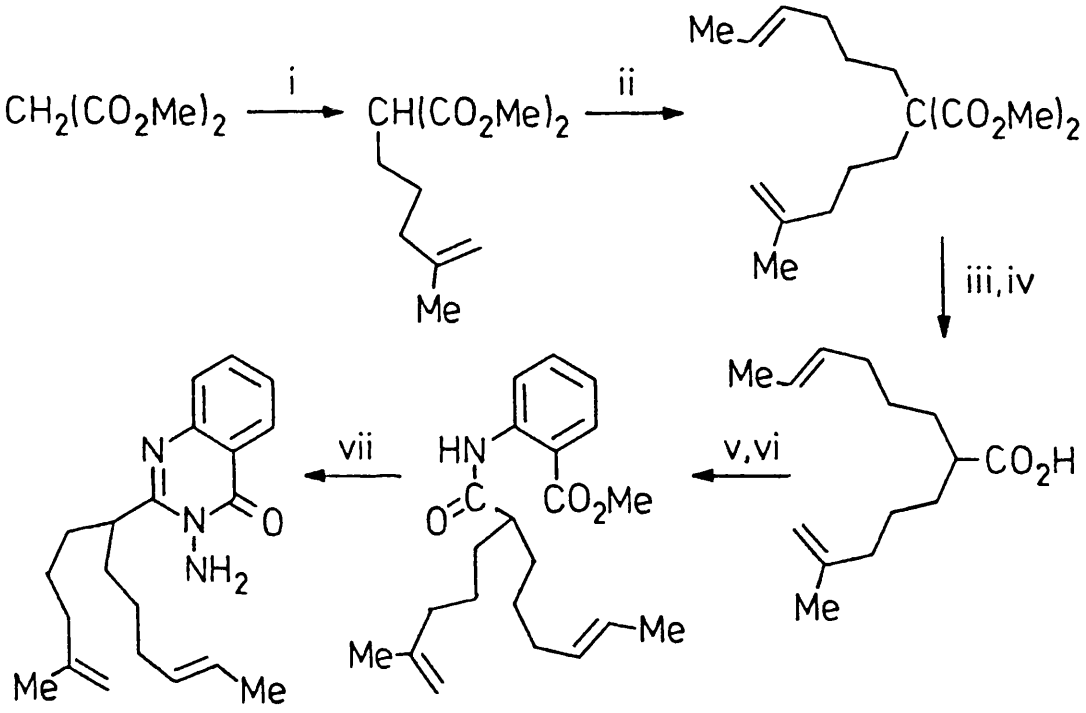
Fig. 45

The greater nitrenophilicity of the double bond in going from (62) to (60) can be ascribed to better $HOMO_{alkene}$ - $LUMO_{nitrene}$ overlap. (The ordering of the energies of the HOMO's of propene, trans-butene, and styrene support this - see Appendix II).

2.3.4. Synthesis of N-Amino-2-(2-methyldodeca-1,10-dien-6-yl)-quinazolin-4(3H)-one (59)

Quinazolone (59) was prepared by the route outlined in Figure 46. trans-Hex-4-en-1-ol tosylate was prepared by tosylation of the corresponding alcohol obtained from sodium-scission of 3-bromo-2-methyltetrahydropyran using a procedure similar to that outlined by Crombie and Harper.[37]

A 300 MHz ^1H n.m.r. spectra carried out on (59) purified by



(59)

Reagents: i) $H_2C{=}CMe(CH_2)_3OTs$, NaOMe-MeOH; ii) $MeCH{=}CH(CH_2)_3OTs$, $NaCH_2SOCH_3$-DMSO; iii) Wet DMSO, NaCl, 185°C; iv) NaOH-H_2O; v) NaOMe, $(COCl)_2$; vi) Methyl anthranilate; vii) NH_2NH_2, sealed tube, 120-130°C.

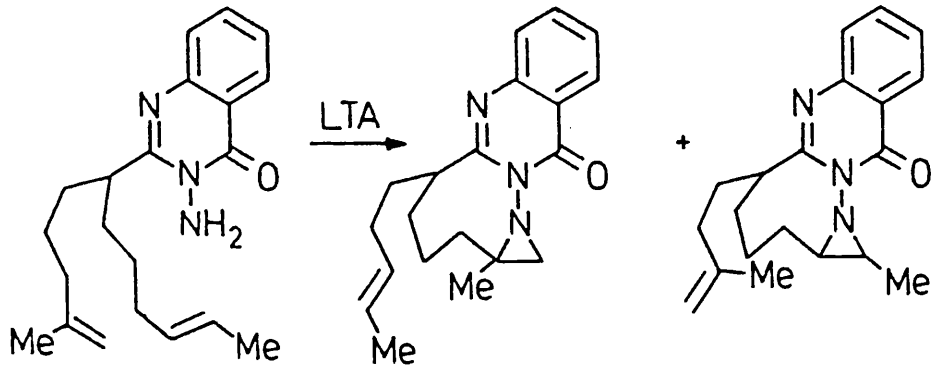
Fig. 46

chromatography, showed the olefinic protons of the two double bonds to be present in a 1:1 ratio.

2.3.5. Oxidation of N-Amino-2-(2-methyldodeca-1,10-dien-6-yl)-quinazolin-4(3H)-one (59).

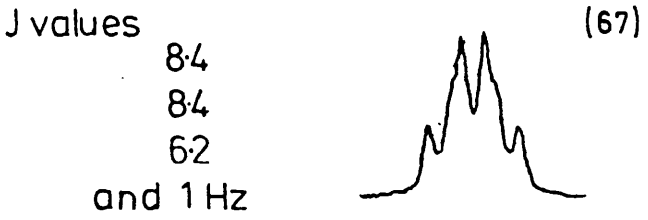
Oxidation of (59) was carried out under the usual high dilution conditions. From a 400 MHz ^1H n.m.r. spectrum on the crude reaction product, the ratio of attack of the N-nitrene on the two double bonds was determined as 2:1 (± 0.1) with preferential attack on the trans-methyl-substituted double bond.

Chromatography on alumina with light petroleum-ethyl acetate (6:1) cleanly separated the two aziridines. Examination of their 400 MHz

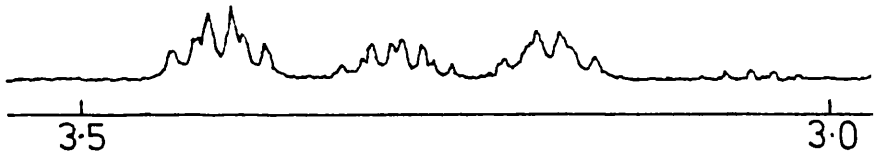


(59) (67) (68)

CH-quinaz.



Crude reaction mixture



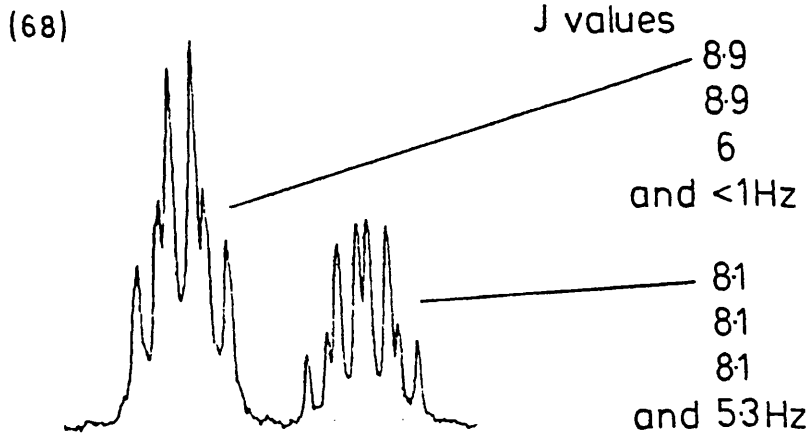


Fig. 47

^{1}H n.m.r. spectra confirmed what was suspected from the 400 MHz ^{1}H n.m.r. spectrum of the crude reaction product - that addition of the nitrene to the β-methyl-substituted double bond is stereospecific whereas addition to the trans-methyl substituted double bond is not, with respect to orientation of the side-chain (Figure 47).

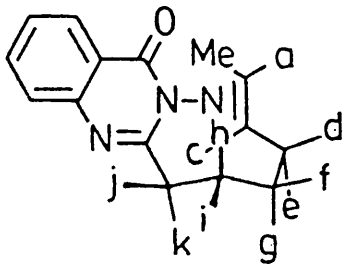
Looking at the conformation of the eight-membered ring in (63) (Figure 44), one would expect the side-chain at the 5α position if the reaction proceeds via the transition state geometry as shown in Figure 45(b); the coupling constants remaining for H-5β, therefore, would be ∿11.8 and ∿1 Hz.

The coupling constants for the same proton in the 1a-methyl-substituted aziridine (67) or in the major stereoisomer of the 1β-methyl-substituted aziridine (68) are 8.7, 8.7, 6.1, and ≦ 1 Hz (average values). None of the coupling constants are as large as 11.8 Hz. This could mean that putting a substituent on the 5α position has caused a slight distortion of the ring. Unfortunately, the spectra of (67) and (68) are too complex (even at 400 MHz) for discrete resonances to be unambiguously identified and clarify the degree of distortion which has occurred.

2.3.6. Explanation for the non-stereospecificity of N-nitrene addition to the trans-methyl-substituted double bond in (59).

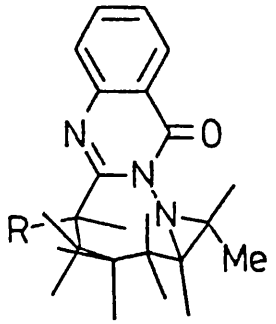
From examination of models of the transition state as shown in Figure 45(b) it is difficult to explain why, in the case of (59), addition of the nitrene to the β-methyl-substituted double bond is stereospecific whereas addition to the trans-methyl-substituted double bond is not.

(a)



(69)

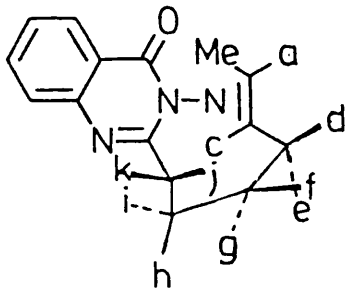
(b)



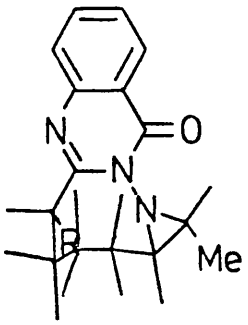
R= $(CH_2)_3CMe=CH_2$

Fig. 48

One possible explanation is that some of the nitrenes could be adding to the other face of the trans-methyl-substituted double bond via an alternative conformation. Transition state (69) could have a favourable secondary interaction between the heterocycle and the methyl group on the trans-substituted double bond. From examination of models of (69), the preferred position of the side-chain should be in position j, but after formation of the aziridine, inversion at nitrogen gives the same diastereoisomer as obtained previously as shown in Figure 48(b).



(70)



(71)

Fig. 49

However, a modification of the linking (butyl) chain conformation in (69) which still preserves the secondary interaction between the heterocycle and the methyl group on the trans-substituted double bond is that shown in (70). From examination of models of (70), the

preferred position of the side-chain should be k. After forming the aziridine and inverting at nitrogen (71) is obtained (Figure 49).

The measured coupling constants (8.1, 8.1, 8.1, and 5.3 Hz) are more consistent with stereoisomer (71).

2.3.7.

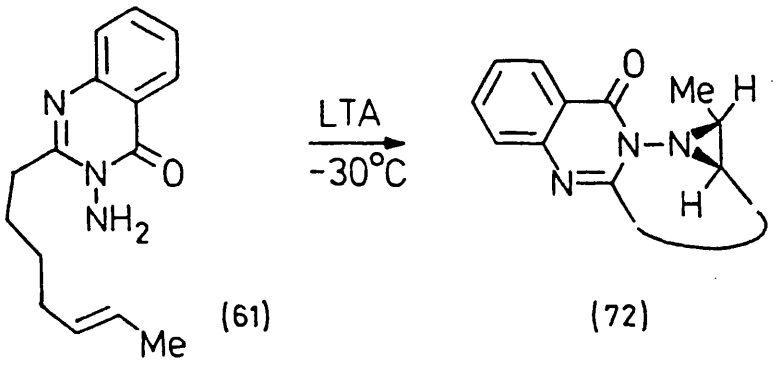
Since the ratio of attack of the nitrene on the two double bonds in (59) was different from that obtained in (52) and addition to the trans-methyl-substituted double bond in (59) is non-stereospecific, it appears that with n = 4, there are accessible conformations which allow the secondary interaction to operate.

It is conceivable that both the double bond methyls (trans or β-substituted) can interact in a secondary way with the heterocycle, but in the case of the β-substituted double bond, the methyl enounters an unfavourable steric interaction with the linking (butyl) chain and hence reacts exclusively via geometry (66) b (Figure 45).

2.4. Low-temperature oxidation of N-Amino-2-substituted quinazolones.

2.4.1.

In an attempt to provide experimental evidence for the presence of a favourable secondary interaction between the heterocycle and the methyl on the trans-substituted double bond in the transition state for nitrene addition when n = 4, oxidation of (61) was carried out at -30 °C (i.e. below the temperature at which interconversion of invertomers occurs at a measurable rate) with the expectation of observing aziridine (72) in the n.m.r. spectrum of the reaction mixture at this low temperature (Figure 50).



(61) (72)

Fig. 50

2.4.2. Low-temperature oxidation of N-Amino-2-(E-hept-2-en-yl)-quinazolin-4(3H)-one (61).

Over a period of 30 min., small portions of LTA (0.16 g, 1.15 mol. equiv.) and quinazolone (61) (0.08 g) were added alternately to magnetically stirred deuteriochloroform (2 - 3 ml) cooled at -30 °C in a dry ice-wash acetone bath. The reaction mixture was stirred for a further 20 min. and then lead di-acetate was separated off and the solution transferred into a n.m.r. tube, all operations being carried out at < -25 °C.

Examination of the 300 MHz ^{1}H n.m.r. spectrum of the resulting

crude reaction at -30 °C indicated the presence of a single product whose n.m.r. data is given below.

8.26 (dd, J 8 and 1.4 Hz, quinaz. H-1)

7.83 (ddd, J 8.3, 7, and 1.4 Hz, quinaz. H-3)

7.74 (dd, J 8.3 and 1.5 Hz, quinaz. H-4)

7.52 (ddd, J 8, 7, and 1.5 Hz, quinaz. H-2)

5.45 (m, -CH=CHMe)

3.16 ddd, J 13.5, 9, and 6.4 Hz,
} CH_2 quinaz.
2.97 ddd, J 13.5, 9, and 6.4 Hz

2.07 (q, J 6 Hz, $-CH_2CH=CHMe$)

1.85 (m, $-CH_2CH_2CH_2CH=CHMe$)

1.65 (dd, J 4.5 and 1.5 Hz, -CH=CHMe), and

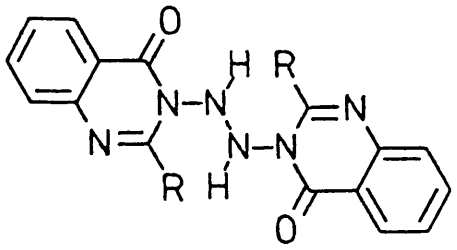
1.52 (quintet, J 7 Hz, $-CH_2CH_2CH=CHMe$)

(Acetic acid - A by-product of the oxidation when LTA used also present. 10.96 br s, CH_3CO_2H, and 2.18 s, CH_3CO_2H).

Clearly, the quinazolone ring is intact. The product is not an aziridine as shown by the presence of two olefinic protons; it is not the de-aminated product ($NNH_2 \rightarrow NH$) since the methylene protons next to the quinazolone (δ 3.16 and 2.97) are non-equivalent. One possibility is that it could be tetrazane (73) (Figure 51).

The observed n.m.r. data would fit if it was assumed that the NH protons are undergoing rapid exchange (CH_3CO_2H) and therefore not observable.

Tetrazanes have been proposed previously as intermediates in the oxidation of N-amino-lactams.



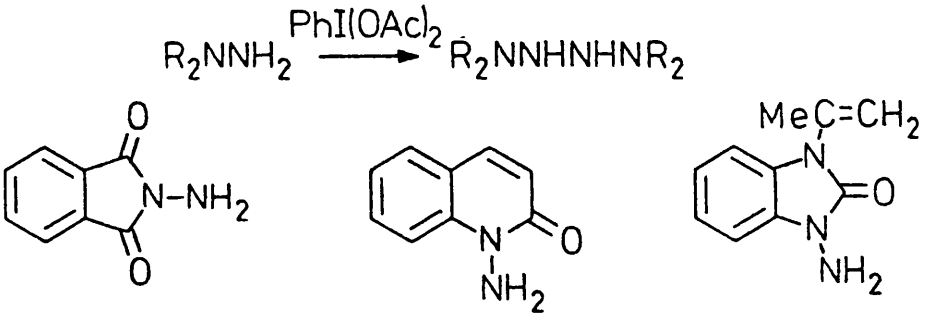
R= $(CH_2)_4CH{=}CHMe$

(73)

Fig. 51

2.4.3. Tetrazanes as intermediates in the oxidation of N-amino-lactams.

Anderson, Gilchrist, and Rees[38] obtained tetrazanes by oxidation of N-aminophthalimide (4), 1-amino-2-quinolone (7), and 1-amino-3-isopropenyl-benzimidazolin-2-one (74) with iodosobenzene diacetate (Figure 52). These tetrazanes gave the parent lactam on mild heating, and the trans-tetrazene on further oxidation.



(4) (7) (74)

Fig. 52

Hoesch and Dreiding[39] have speculated that phthalimide is formed by the fragmentation of an intermediate tetrazane (Figure 53). This mechanism could operate with other tetrazanes which have an α-carbonyl group such as (73).

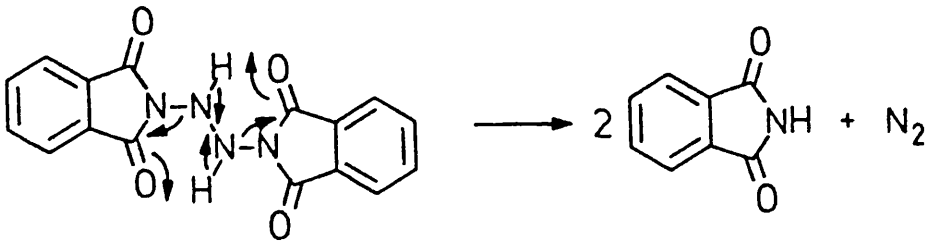


Fig. 53

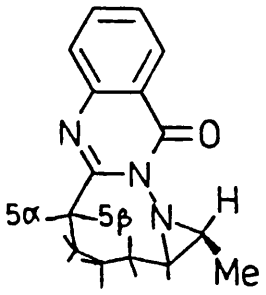
2.4.4.

On allowing the n.m.r. solution described above to warm up from -30 °C to room temperature, the signals at 3.16 and 2.97 diminish with the corresponding growth of a triplet at 2.81 (J 7.5 Hz). The rest of the spectrum becomes much more complicated but the ratio of integration values of aromatics to olefins stays at ca 2:1. Interestingly, there appears to be a small amount of aziridine (75) produced in warming from -30 °C to room temperature. The evidence for this is the observation of signals at 3.30 (J 13, 12, and 1 Hz) and 2.94 (J 13, 8, and 1 Hz), characteristic for H-5β and H-5α respectively (Figure 54).

The breakdown of the intermediate on raising the temperature of the n.m.r. solution from -30 °C to room temperature to give what was assumed to be de-aminated product suggested at the time that the intermediate could be the tetrazane (73).

However, formation of the tetrazane requires only 0.5 mol. equiv. of LTA whereas 1.15 mol. equiv. was used.

The generation of a small amount of aziridine (75) could conceivably have originated from reaction of the tetrazane with unreacted LTA on warming to give the nitrene which reacted with the double bond in the usual way.



(75)

Fig.54

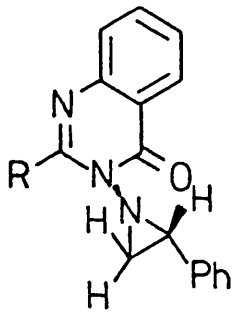
2.4.5. Low-temperature oxidation of N-Amino-2-(E-hept-2-en-7-yl)-quinazolin-4(3H)-one (61) in the presence of styrene.

The low-temperature oxidation of (61) was repeated but using only 0.55 mol. equiv. of LTA since, as indicated above, only 0.5 mol. equiv. is necessary for generation of the tetrazane. A 300 MHz ^{1}H n.m.r. spectrum on the crude reaction product at -30 ^{o}C revealed the presence of not only the 'tetrazane' intermediate but also unchanged (61) in ca 1:1 ratio. This result seems to suggest that the intermediate is not tetrazane (73).

To the above n.m.r. solution at -30 ^{o}C, an excess of styrene was added. Another spectrum was obtained which, apart from signals from the styrene, showed no change from that obtained prior to addition of styrene. On allowing the solution to warm up from -30 ^{o}C to room temperature, signals due to the intermediate disappeared with the appearance of those due to aziridine (76) (Figure 55). The yield of aziridine (76), in contrast to the small yield of (75) above, appeared to be quantitative based on the reacted N-amino-quinazolone.

Clearly, the intermediate formed at low temperature is acting as a nitrene precursor: simply raising the temperature of the solution from -30 ^{o}C to room temperature is enough to generate the nitrene.

What is the structure of this intermediate? One possibility is



R= $(CH_2)_4CH{=}CHMe$

(76)

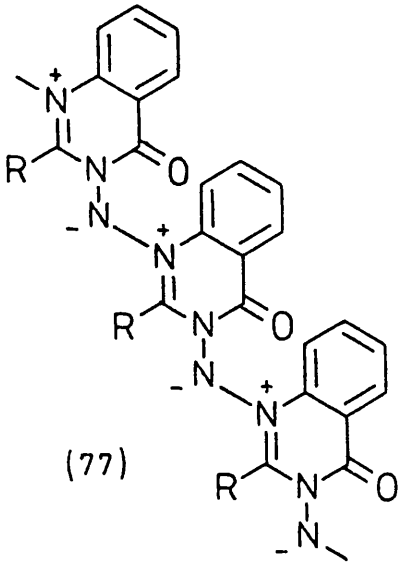
3.67 (dd, J 7.5 and 6 Hz, CHPh)

3.19 (dd, J 7.5 and 2.2 Hz, azirid. ring H trans to Ph)

and 2.88 (dd, J 6 and 2.2 Hz, azirid. ring H cis to Ph).

Fig.55

that it could be a (poly) dipolar species such as (77), formed by the attack of the nitrene on the quinazolone N-1 of another molecule (Figure 56). This 'polynitrene' would account for the stoichiometry of the oxidation. It does not obviously, however, explain why the methylene protons adjacent to the quinazolone are diastereotopic.

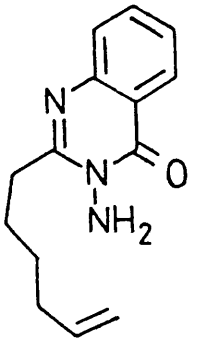


(77)

R= $(CH_2)_4CH{=}CHMe$

Fig. 56

2.4.6. Low-temperature oxidation of N-Amino-2-(hex-1-en-6-yl)-quinazolin-4(3H)-one (78) in the presence of styrene.



(78)

A low-temperature oxidation of quinazolone (78) was carried out with 0.9 mol. equiv. of LTA. The 300 MHz ^{1}H n.m.r. spectrum on the crude reaction product revealed the intermediate, whose n.m.r. data is given in Figure 57, and starting material (78) to be present in ca 9:1 ratio, respectively, as determined by the integration values of the methylene protons next to the quinazolone ring. These methylene protons in the intermediate are again diastereotopic and resonate at 3.15 and 2.99, whereas those in (78) (which are not) resonate as a triplet at 2.81.

8.23 (dd, J 8 and 1.5 Hz, quinaz. H-1)

7.82 (ddd, J 8.3, 7, and 1.5 Hz, quinaz. H-3)

7.72 (dd, J 8.3 and 1.3 Hz, quinaz. H-4)

7.51 (ddd, J 8, 7, and 1.3 Hz, quinaz. H-2)

5.84 (m, -C<u>H</u>=CH_2)

5.02 (m, -CH=<u>CH_2</u>)

3.15 m, 3.01 m } CH_2, quinaz.

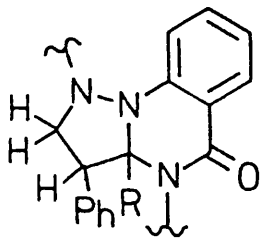
2.14 (m, <u>CH_2</u>$CH=CH_2$)

1.87 (m, <u>CH_2</u>$CH_2CH_2CH=CH_2$)

and 1.57 (quintet, J 7 Hz, -<u>CH_2</u>$CH_2CH=CH_2$)

Fig. 57

After the addition of styrene to the n.m.r. solution at -30 °C, a subsequent 300 MHz ^{1}H n.m.r. spectrum revealed the presence of a small amount of what could have been a 1,3-dipolar addition product (79) with the coupling constants shown in Figure 58.



R= $(CH_2)_4CH=CH_2$

(79)

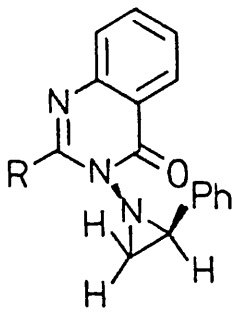
3.82 (dd, J 6 and 5.4 Hz)

3.68 (dd, J 6 and 4.5 Hz)

and 3.44 (dd, J 5.4 and 4.5 Hz)

Fig. 58

The syn-aziridine structure (80) for this minor product could be eliminated by comparison with the n.m.r. data from the analogous syn-aziridine (81)[31] (Figure 59).



(80) R= $(CH_2)_4CH=CH_2$

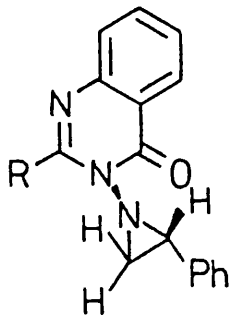
(81) R=Me

3.92 (dd, J 7.5 and 6 Hz, CHPh)

3.80 (dd, J 6 and 2 Hz, azirid. ring H cis to Ph)

and 3.52 (dd, J 7.5 and 2 Hz, azirid. ring H trans to Ph)

Fig. 59



(82) R= $(CH_2)_4CH=CH_2$

3.69 (dd, J 8 and 5.5 Hz, CHPh)

3.22 (dd, J 8 and 2.4 Hz, azirid. ring H trans to Ph)

and 2.91 (dd, J 5.5 and 2.4 Hz, azirid. ring H cis to Ph)

Fig. 60

On allowing the n.m.r. solution to warm to room temperature, the resulting spectrum showed neither the presence of the first-formed intermediate nor the minor product (79?) but only that of the anti-aziridine (82) (Figure 60).

It is not clear why the (transient) minor product (79?) should appear in this case and not in the corresponding low temperature oxidation of (61) since the spectra were both run after similar intervals after addition of the styrene.

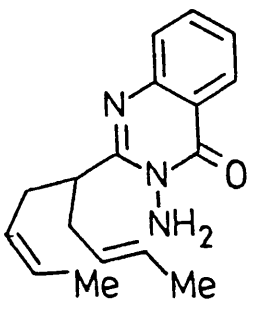
2.4.7.

Investigations into the nature of the intermediates in these low-temperature oxidations are continuing but it is possible that a method is in hand for generation of quinazolone N-nitrenes under the mildest of stimuli (raising the temperature from -30 ^{o}C to 20 ^{o}C), without the requirement that potential traps be stable to oxidising agents such as LTA, and without the formation in the trapping step of any by-products from the nitrene precursor. Extension of this method to other nitrenes may be possible and work in this area is being actively pursued.

2.5. Competitive intramolecular trapping of the N-nitrene by cis- and trans-α-methyl-substituted double bonds.

2.5.1.

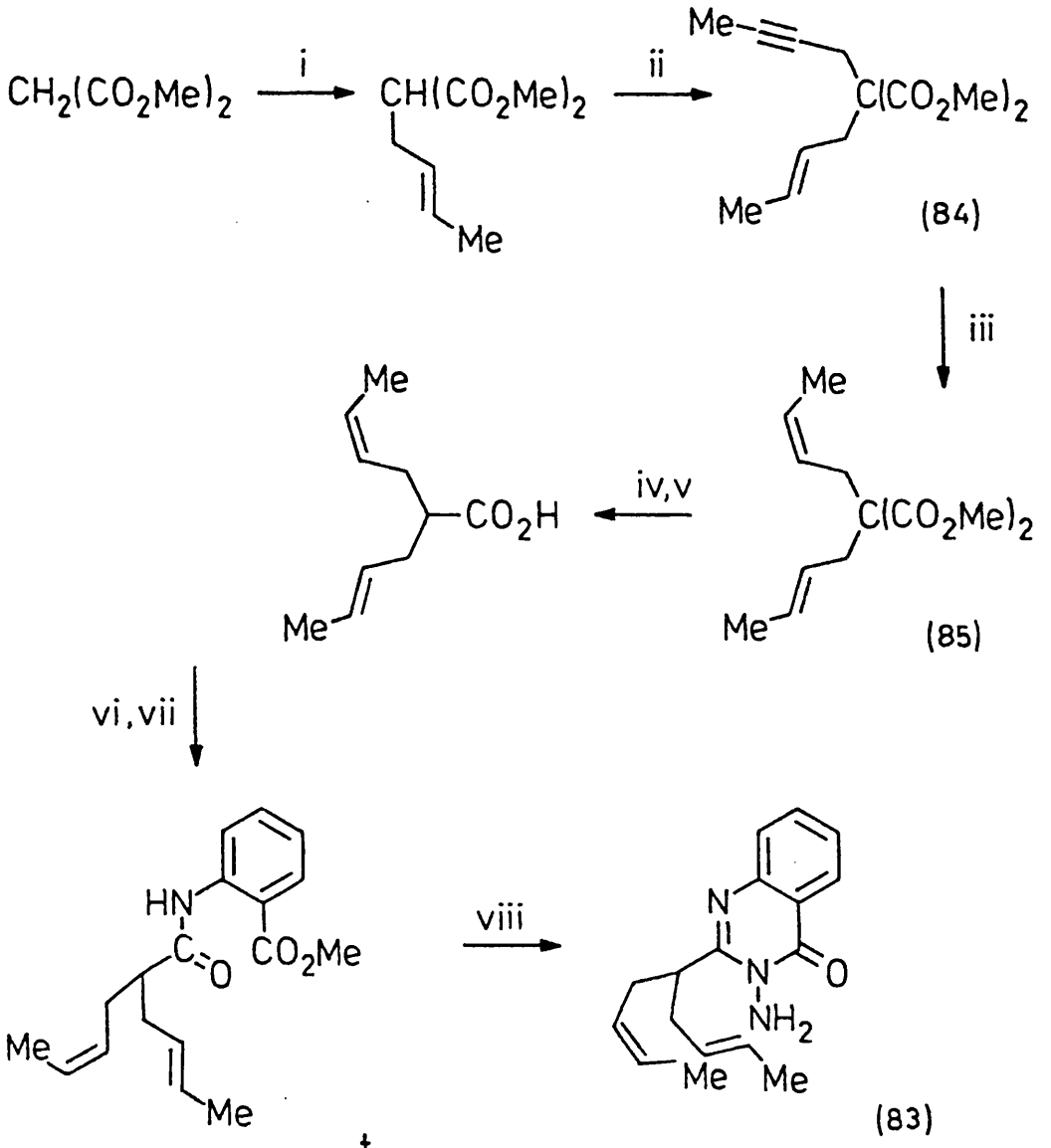
The N-amino quinazolone (83) bearing cis- and trans-substituted double bonds in the side chain was synthesised. How the nitrene derived from oxidation of quinazolone (83) behaved was of particular interest since it could indicate the importance of the secondary interaction of a methyl group in intramolecular N-nitrene additions to double bonds within the quinazolone framework which, from the previous discussion, would be expected to be non-concerted: only the methyl on the cis-substituted double bond is close enough to interact with the heterocycle and if addition to this cis-double bond proceeds via a mechanism similar to that in Figure 21, then probably the Me group is not within the range required for secondary interaction to operate. The relative reactivity of trans- and cis-butenes towards the nitrene derived from oxidation of N-amino-2-methylquinazolone was compared with the selectivity of the nitrene for the two double bonds in (83) (Figure 61).



(83)

Fig. 61

2.5.2. Synthesis of N-Amino-2-((2-E),(7-Z)nona-2,7-dien-5-yl)-quinazolin-4(3H)-one (83).



Reagents: i) $MeCH{=}^{t}CHCH_2Cl$, NaOMe-MeOH; ii) $MeC{\equiv}CCH_2Br$, NaOMe-MeOH; iii) H_2, Pd-$BaSO_4$, pyr; iv) NaOH-H_2O; v) Δ, 130-150°C; vi) $SOCl_2$; vii) Methyl anthranilate; viii) NH_2NH_2, sealed tube, 120-130°C.

Fig. 62

The route used to synthesise quinazolone (83) is given in Figure 62.

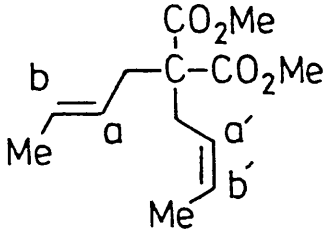
The stereochemically important steps were the alkylation of dimethyl propanedioate with commercially available trans-crotyl chloride (20 % of which is 3-chloro-1-butene), and Lindlar reduction of the but-2-ynyl)-substituted propanedioate (84) to the cis-trans-dialkenylpropanedioate (85).

Lindlar catalyst is highly effective for the selective hydrogenation of triple bonds to cis-double bonds. In the hydrogenation of dimethyl 5-decynedioate, Cram and Allinger[40] employed a palladium-on-barium sulfate catalyst poisoned by quinoline and obtained dimethyl cis-5-decenedioate in 97 % yield. Schneider[41] found an even better catalyst to be 5 % palladium-on-barium sulfate with pyridine as the solvent and these were the conditions used when the hydrogenation of (84) to (85) was attempted.

It was found that in the hydrogenation of (84), the uptake of hydrogen decreased sharply after addition of 1 mol. equiv. of hydrogen. In order to check the stereochemistry of the two double bonds in the product (85), a 400 MHz ^{1}H n.m.r. spectrum was run on the colourless liquid obtained after hydrogenation.

The cis double bond methyl resonates at a slightly higher field than the trans double bond methyl (δ 1.58 and 1.61, respectively) whereas the olefinic proton, Ha´ resonates at a lower field than the corresponding proton, Ha, on the trans-substituted double bond (δ 5.57 and 5.48, respectively) (Figure 63).

From the ratios of the two methyl signals and olefinic protons, Ha and Ha´, the ratio of trans- to cis-methyl substituted double bonds was found to be 1.01:1(± 0.01), respectively. It appeared, therefore, that both double bonds had been introduced to give a single stereoisomer (85).

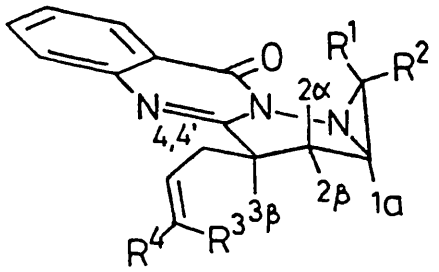


(85)

Fig. 63

2 5.3. Oxidation of N-Amino-2-((2-E),(7-Z)nona-2,7-dien-5-yl)quinazolin-4(3H)-one (83).

The remaining steps as shown in Figure 62 were carried through (with the isolation of 2-(Z-but-2-enyl)-2-(E-but-2-enyl)-1,3-propanedioic acid as a crystalline intermediate) and oxidation of the resulting quinazolone (83), which appeared to be satisfactorily pure from its t.l.c. and spectroscopic properties, was carried out. A 90 MHz ^1H n.m.r. spectrum of the crude reaction product indicated that the nitrene had added to both the cis- and trans-methyl-substituted double bonds.



(86) R^1=Me, R^2=$H_{1\beta}$, R^3=H, and R^4=Me.
(87) R^1=$H_{1\alpha}$, R^2=Me, R^3=Me, and R^4=H.
(88) R^1=Me, R^2=$H_{1\beta}$, R^3=Me, and R^4=H.
(89) R^1=$H_{1\alpha}$, R^2=Me, R^3=H, and R^4=Me.

Fig. 64

A 400 MHz ^1H n.m.r. spectrum was necessary in order to determine the exact ratio of the two aziridines formed.

On detailed analysis of the 400 MHz ^1H n.m.r. spectrum, it was found that not only were aziridines (86) and (87) present but also minor amounts of aziridines (88) and (89) (Figure 64).

The presence of aziridines (88) and (89) was particularly disturbing since it suggested that addition of the nitrene to the double bonds was

non-stereospecific, a result contrary to all experience with addition of these N-nitrenes to alkenes. Subsequently, however, a 400 MHz ^1H n.m.r. spectrum of quinazolone (83), suggested that some isomerisation of the double bonds had taken place during its synthesis and formation of (88) and (89), therefore, was not due to any non-stereospecificity in addition of the N-nitrene to the double bonds (for further evidence see Section 2.5.5).

2.5.4. Source of non-stereospecificity in the synthesis of (83).

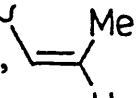
A re-examination of the 400 MHz ^1H n.m.r. spectrum of the colourless liquid obtained after the Lindlar reduction referred to earlier indicated that the two double bonds might not in fact have been introduced stereospecifically to give (85). A rationalisation which would accommodate the equal ratios of the respective double bond methyl and olefinic protons was that both the alkylation of dimethyl propanedioate with crotyl chloride and hydrogenation of the but-2-ynyl-substituted propanedioate (84) had gone with the same degree of non-stereospecificity.

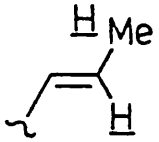
In order to test this, dialkylation of dimethyl propanedioate with commercial trans-crotyl chloride was carried out and high field ^1H (300 MHz) and ^{13}C (75 MHz) n.m.r. spectra were obtained on the distilled product (Figure 65).

^{13}C n.m.r. 171.41 ($-\underline{C}O_2Me$)
129.50 and 124.62 (trans C=C)
127.68 and 123.59 (cis C=C)
52.12 ($-CO_2\underline{Me}$)
35.63 (trans CH_2)
29.74 (cis CH_2)

17.95 (trans CH_3)

and 12.86 (cis CH_3

^{1}H n.m.r. 5.59 (m, 

5.52 (m, 

5.25 (m, -CH=CHMe)

3.70 (s, $-CO_2Me$)

For methylene protons see Figure 66.

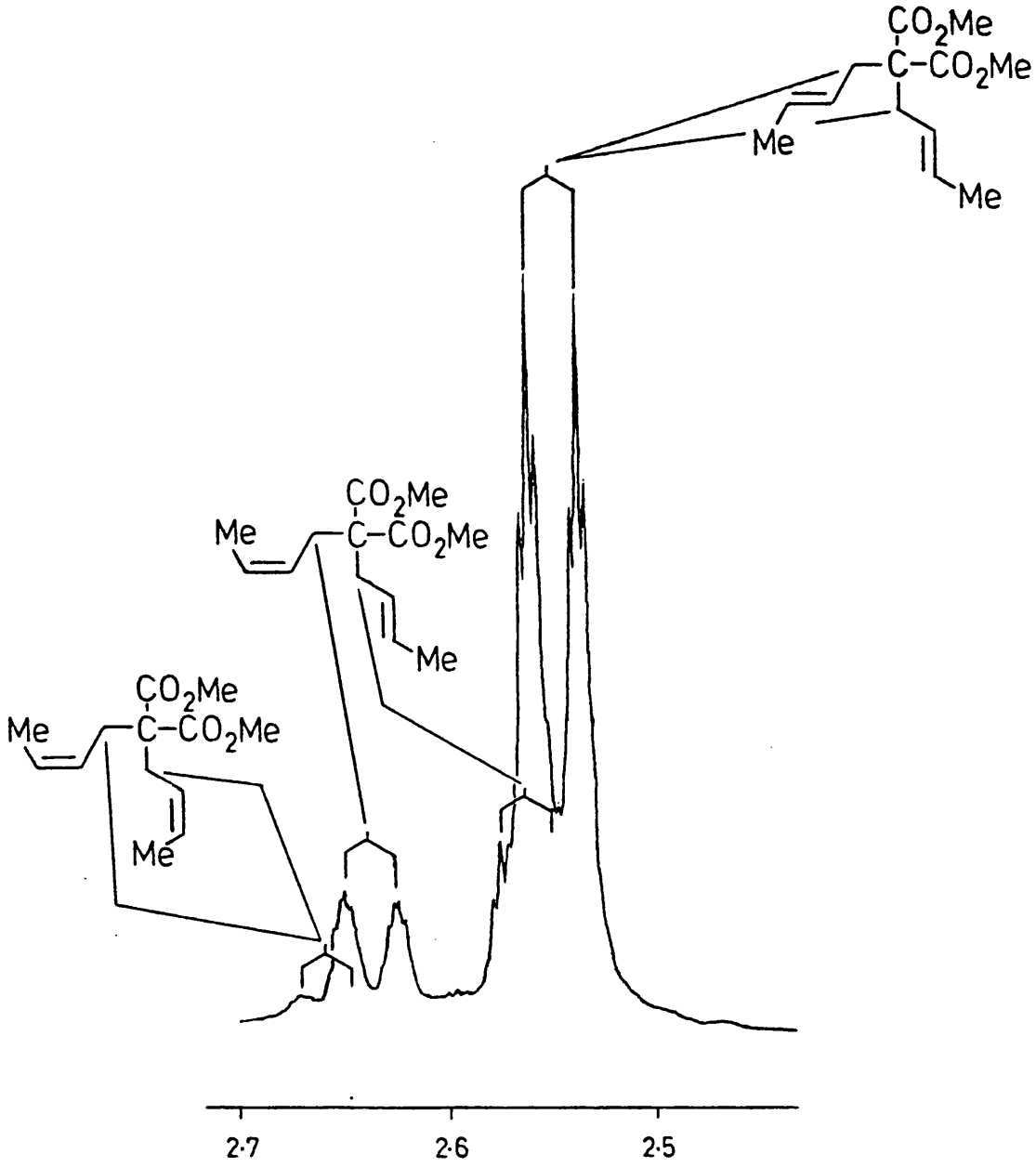
1.64 (ddt, J 6.4, 1.5, and 1.4 Hz, trans-CH=CHMe)

and 1.60 (ddt, J 7.7, 1.7, and 0.9 Hz, cis-CH=CHMe

Fig. 65

Both the ^{13}C and ^{1}H n.m.r. spectra show the presence of cis- as well as the trans-methyl-substituted double bonds. The ratio of trans- to cis-methyl-substituted double bonds as determined from the methylene proton signals (Figure 66) is 85:15, respectively.

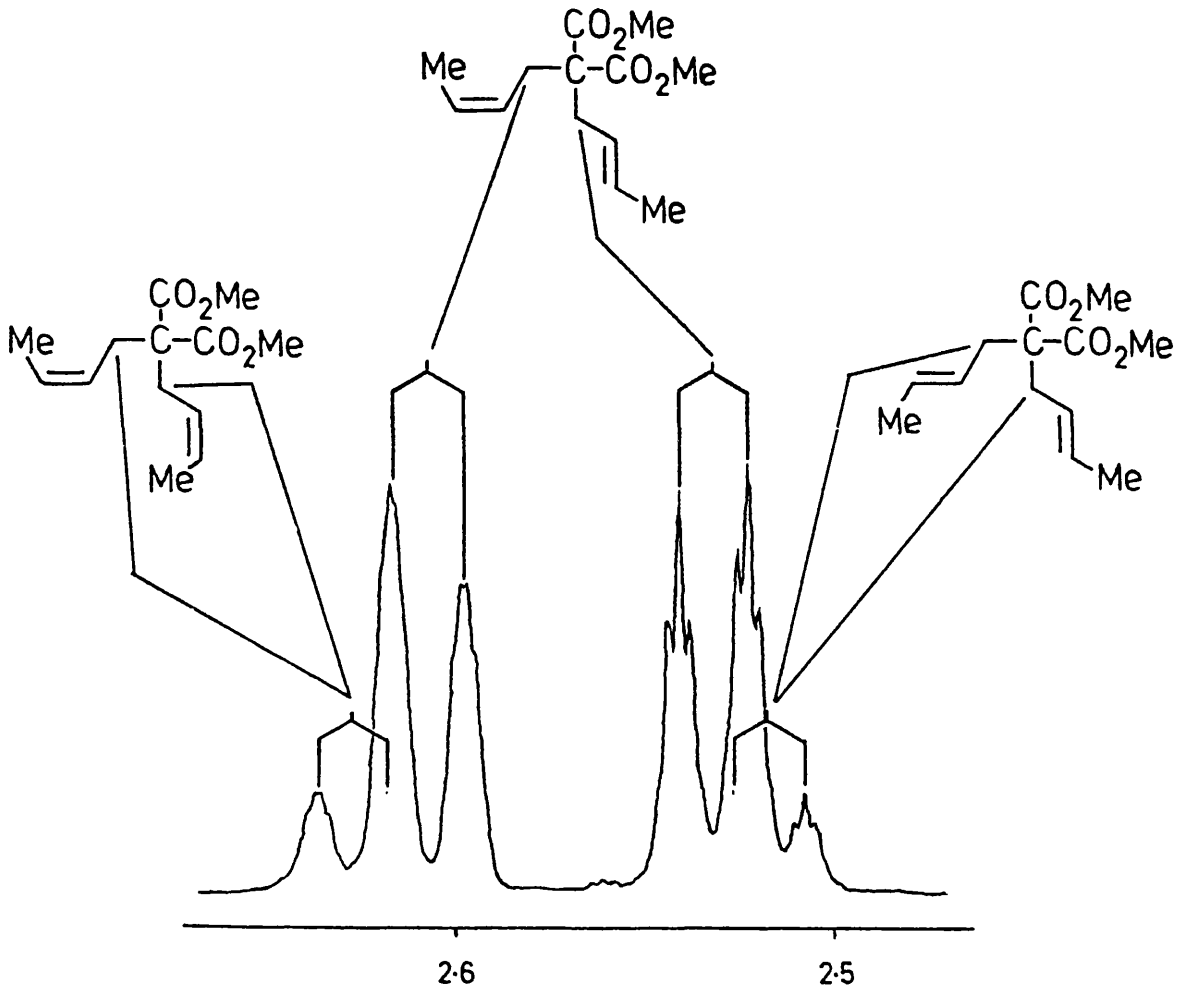
Methylene proton signals



Part of the 300 MHz ^{1}H n.m.r. spectrum showing the methylene proton signals present in dimethyl 2,2-dicrotyl-1,3-propanedioate.

Fig. 66

Methylene proton signals



Part of the 400 MHz spectrum showing the methylene proton signals present in the colourless liquid (85) obtained after the hydrogenation step.

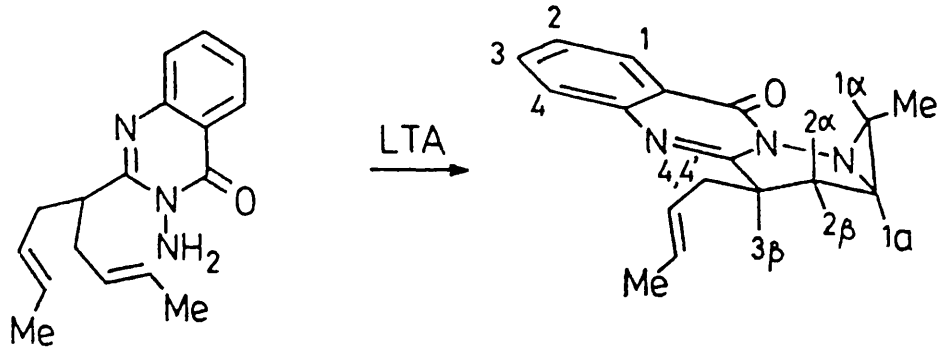
Fig. 67

By comparing the spectra of dimethyl 2,2-dicrotyl-1,3-propanedioate with that of the colourless oil obtained after hydrogenation of dimethyl 2-(but-2-ynyl)-2-(crotyl)-1,3-propanedioate it can be seen from the methylene proton signals (Figure 66 and Figure 67, respectively) that both the alkylation of dimethyl propanedioate with crotonyl chloride and hydrogenation of dimethyl 2-(but-2-ynyl)-2-(crotyl)-1,3-propanedioate have proceeded with the same degree of non-stereospecificity. The net result of this is that the dimethyl dialkenylated-1,3-propanedioate (85) obtained was in fact a mixture of dimethyl 2-(cis-but-2-enyl)-2-(trans-but-2-enyl)-1,3-propanedioate (74 %), dimethyl 2,2-di-(trans-but-2-enyl)-1,3-propanedioate (13 %), and dimethyl 2,2-di-(cis-but-2-enyl)-1,3-propanedioate (13 %).

This degree of non-stereospecificity in the hydrogenation step was unexpected. The 2-(cis-but-2-enyl)-1,3-propanedioate from which the 2,2-di-(cis-but-2-enyl)- arises is presumably formed along with the 2-(trans-but-2-enyl)-1,3-propanedioate) by alkylation of dimethyl-propanedioate with the 3-chloro-1-butene contained in the commercially available trans-crotyl chloride.

2.5.5. Oxidation of N-Amino-2-((2-E),(7-E)nona-2,7-dien-5-yl)-quinazolin-4(3H)-one (90).

Quinazolone (90) was obtained as colourless crystals and after several recrystallisations from light petroleum, the 300 MHz ^{1}H n.m.r. spectrum indicated it to be stereochemically pure. On oxidation, quinazolone (90) gave only aziridine (89) confirming that the N-nitrene adds stereospecifically to the double bond (Figure 68).



(90) (89)

8.23 (ddd, J 8.1, 1.5, and 0.5 Hz, ArH_1)

7.65 (ddd, J 8.1, 6.7, and 1.5 Hz, ArH_3)

7.61 (ddd, J 8.1, 1.5, and 0.5 Hz, ArH_4)

7.39 (ddd, J 8.1, 6.7, and 1.5 Hz, ArH_2)

5.54 (m, -CH=CHMe)

2.99 (m, $H_{4'}$)

2.89 (dddd, J 12.5, 8, 3.6, and 3.6 Hz, H-3β)

2.67 (m, H-1a, and H-2β)

2.22 (m, H_4)

2.01 (dq, J 5.7 and 5.5 Hz, H-1α)

1.66 (m, -CH=CHMe)

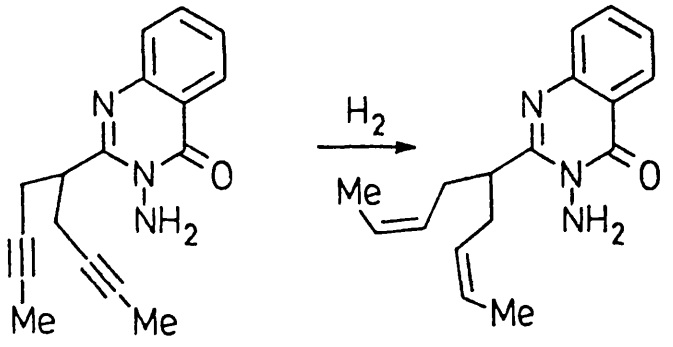
1.51 (d, J 5.5 Hz, Me)

and 1.18 (ddd, J 12.3, 12.3, and 7.5 Hz, H-2α)

Fig. 68

2.5.6. Oxidation of N-Amino-2-((2-Z),(7-Z)nona-2,7-dien-5-yl)-quinazolin-4(3H)-one (91)

Hydrogenation of N-amino-2-(nona-2,7-diyn-5-yl)-quinazolin-4(3H)-one (101) followed by column chromatography gave an oil which n.m.r. indicated was mainly quinazolone (91).



(101) (91)

Fig. 69

Oxidation of the above oil gave (88) as the major aziridine (Figure 70).

A close examination of the aziridine ring methyl doublets at 0.97 (J 6.1 Hz) and 1.49 (J 5.6 Hz) in the ^{1}H n.m.r. spectrum of crude oxidation product, showed that aziridines (86), and (87) & (89), respectively were also present. The presence of aziridines (86), (87), and (89) arises from quinazolone (83) being stereoisomerically impure.

8.21 (dd, J 8.1 and 1.4 Hz, ArH_1)

7.64 (ddd, J 8.1, 6.6, and 1.4 Hz, ArH_3)

7.60 (dd, J 8.1 and 1.6 Hz, ArH_4)

7.37 (ddd, J 8.1, 6.6, and 1.6 Hz, ArH_2)

5.55 (m, -CH=CHMe)

3.03 - 2.83 (m, H-1β, H-1a, H-3β, and H-4')

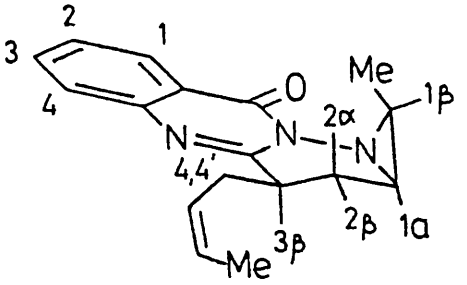
2.47 (ddd, J 13.5, 8.5, and 4.4 Hz, H-2β)

2.38 (ddd, J14.7, 8.5, and 8.5 Hz, H_4)

1.64 br (d, J 6.5 Hz, -CH=CHMe)

1.22 (ddd, J 13.5, 13.2, and 8.7 Hz, H-2α)

and 0.98 (d, J 6.1 Hz, Me)



(88)

Fig. 70

2.5.7. Oxidation of N-Amino-2-((2-E),(7-Z)nona-2,7-dien-5-yl)-quinazolin-4(3H)-one (83)

Because of the double bond stereoisomers present with (83), oxidation gives not only aziridines (86) and (87) but also aziridines (88) and (89). N.m.r. data for aziridines (86) and (87) are given in Figure 71.

The ratio of aziridines (86) and (87) measures the relative reactivity of the cis- and trans-methyl-substituted double bonds towards the N-nitrene and is independent of the amount of aziridines (88) and (89) present. In the 400 MHz ^{1}H n.m.r. spectrum of the crude reaction product, the methyl doublet belonging to R^1 of (86) (Figure 64) is separated from that in (88), but the methyl doublet belonging to R^2 of (87) coincides with that due to R^2 in (89). From the integration values, the ratio of (86):(87) and (89) was found to be 3.4:1.

Fortunately, aziridines (86) and (88) could be separated from aziridines (87) and (89) by column chromatography since it is apparently the orientation of the methyl group on the aziridine ring that determines the relative rate at which these aziridines move down the column and not whether the allyl side chain contains a cis- or trans-methyl-substituted double bond. The ratio of aziridines (87) and (89) could be extracted from the 400 MHz ^{1}H n.m.r. spectrum of the mixture of the two after chromatography and was found to be 2:1, respectively.

Hence, the relative reactivity of the cis- and trans-methyl-substituted double bonds towards the N-nitrene in (83) can be calculated to be 5.1:1 respectively. This ratio is particularly striking when contrasted with the ratio obtained from a competition reaction between trans- and cis-but-2-ene for the nitrene from oxidation of N-amino-2-methylquinazolin-4(3H)-one when trans-but-2-ene is six times more reactive than cis-but-2-ene.[42]

8.22 (ddd, J 8, 1.5, and 0.6 Hz, quinaz. H-1)

7.64 (ddd, J 8.2, 6.7, and 1.5 Hz, quinaz. H-3)

7.60 (ddd, J 8.2, 1.5, and 0.6 Hz, quinaz. H-4)

7.37 (ddd, J 8, 6.7, and 1.5 Hz, quinaz. H-2)

5.54 (m, -CH=CHMe)

3.02 (m, CHHCH=CHMe)

2.96 (ddd, J 8.7, 8.5, and 6.6 Hz, H-1a)

2.87 (dq, J 6.6 and 6.1 Hz, H-1β)

2.86 (dddd, J 12.9, 8.6, 4.4, and 4.4 Hz, H-3β)

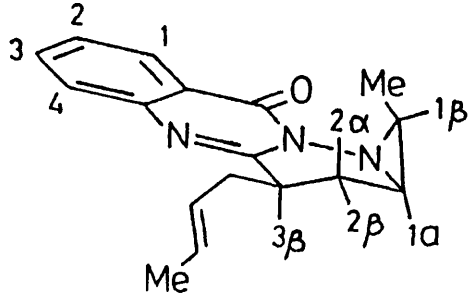
2.48 (ddd, J 13.7, 8.5, and 4.4 Hz, H-2β)

2.23 (m, CHHCH=CHMe)

1.65 br (d, J 4.4 Hz, -CH=CHMe)

1.19 (ddd, J 13.7, 12.9, and 8.7 Hz, H-2α)

and 0.98 (d, J 6.1 Hz, Me)



(86)

8.21 (dd, J 8.1 and 1.5 Hz, quinaz. H-1)

7.64 (ddd, J 8.2, 6.6, and 1.5 Hz, quinaz. H-3)

7.60 (dd, J 8.2 and 1.5 Hz, quinaz. H-4)

7.37 (ddd, J 8.1, 6.6, and 1.5 Hz, quinaz. H-2)

5.55 (m, -CH=CHMe)

2.97 (m, CHHCH=CHMe)

2.88 (m, H-3β)

2.70-2.61 (m, H-1a and H-2β)

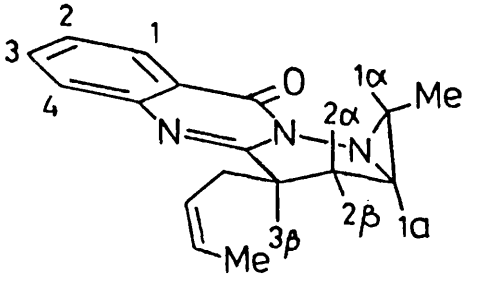
2.33 (ddd, J 14.6, 8.6, and 8.6 Hz, CHHCH=CHMe)

2.00 (dq, J 5.5 and 5.6 Hz, H-1α)

1.63 br (d, J 6.5 Hz, -CH=CHMe)

1.49 (d, J 5.6 Hz, Me)

and 1.21 (ddd, J 12.4, 12.4, and 7.4 Hz, H-2α)



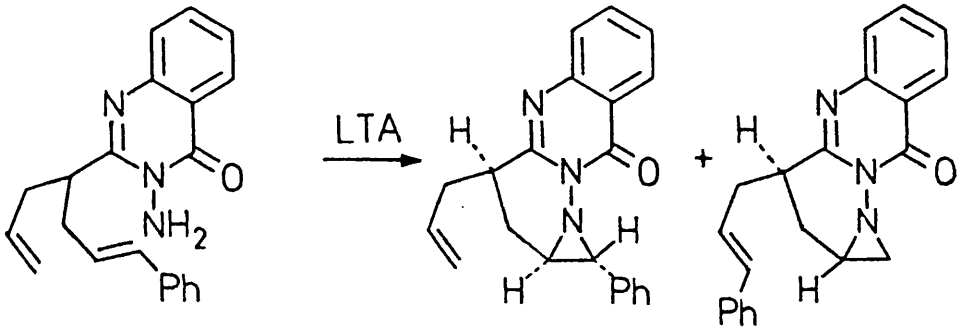
(87)

Fig. 71

2.5.8. Conclusion

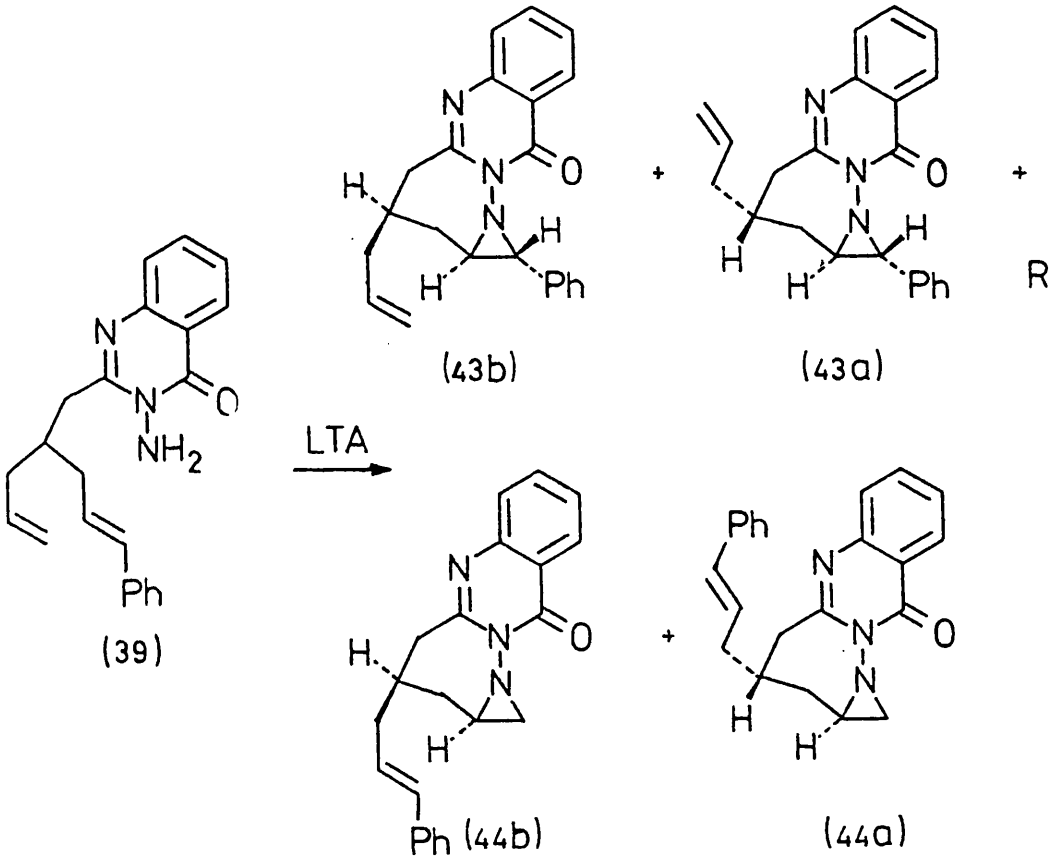
The above result might seem to indicate that in the intramolecular N-nitrene addition to double bonds within the quinazolone framework when n = 2, that the methyl on the cis-substituted double bond can interact with the heterocycle even in what presumably is a non-concerted addition.

Summary of Results from Competitive Trapping Experiments.



(27) (28) (29)

Ratio 1·5:1 (±0·1)

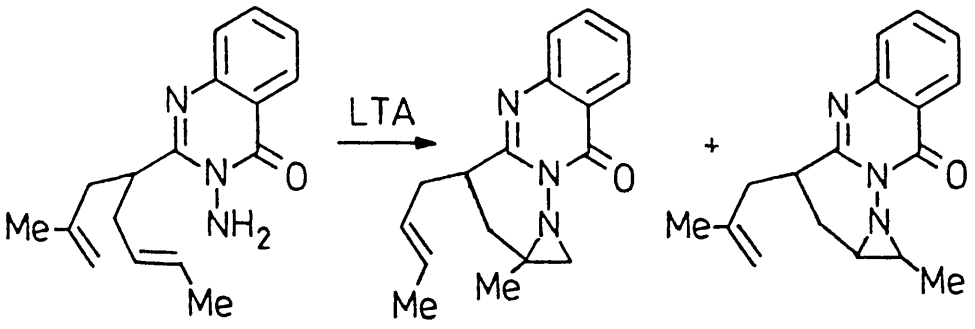


(39) (43b) (43a) (44b) (44a)

Ratio 5·8 : (±1) : 1

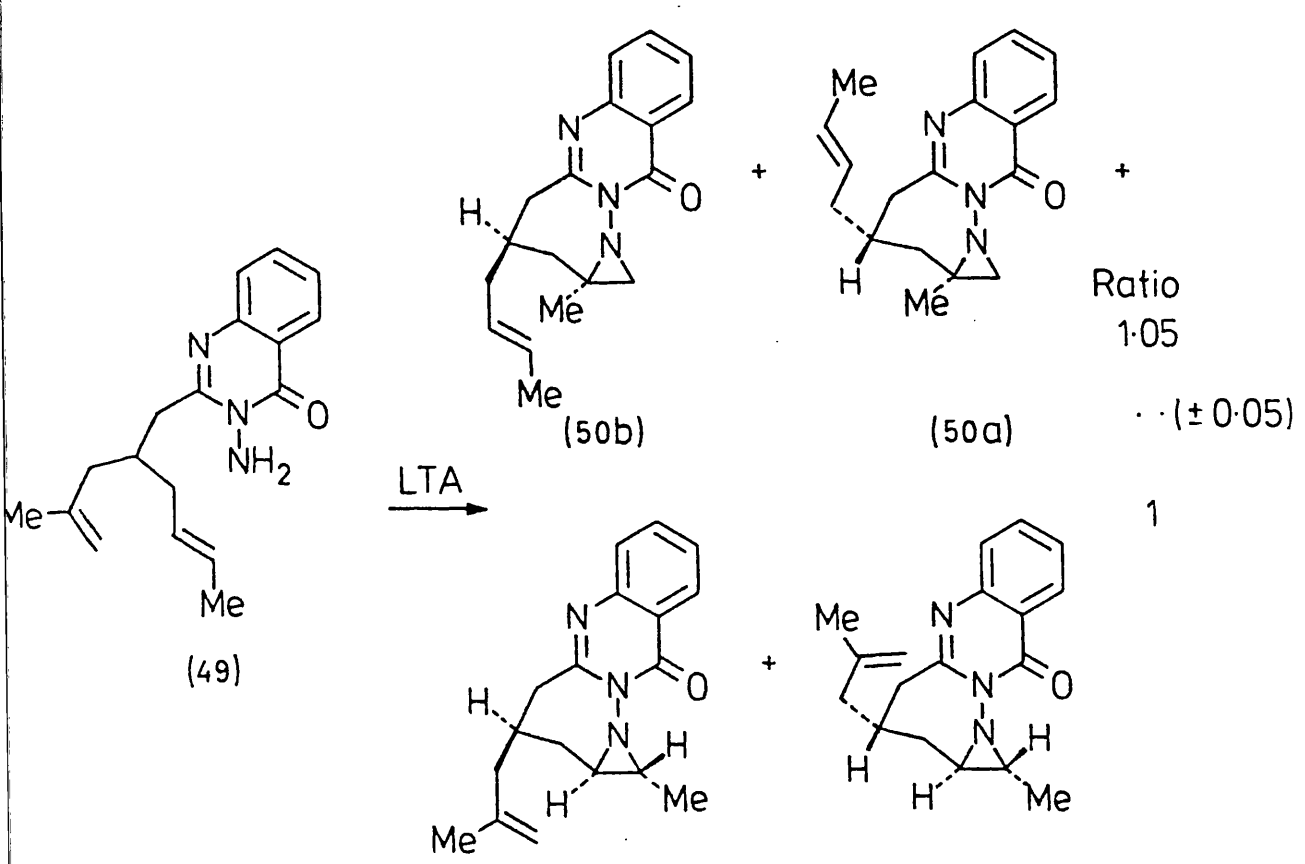
Ratio of stereoisomers (43b):(43a) or (44b):(44a)

1:2·2 (±0·1)



(53) (54) (55)

Ratio 5·3:1 (±0·4)

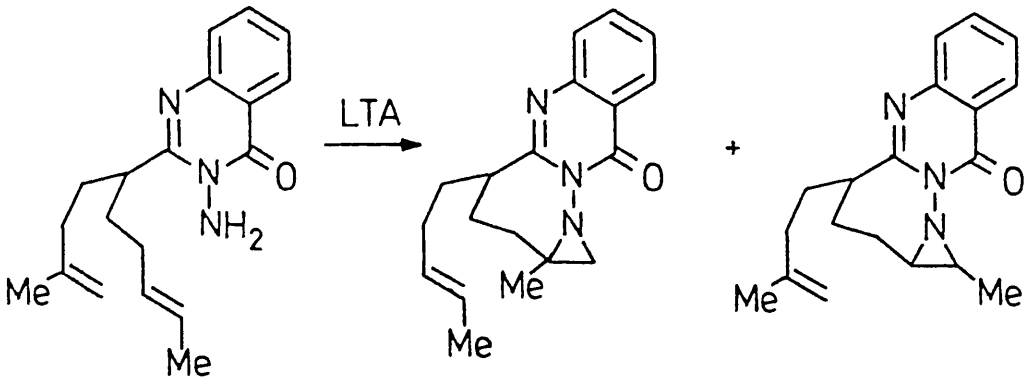


(49) (50b) (50a) (51b) (51a)

Ratio 1·05 ··(±0·05) 1

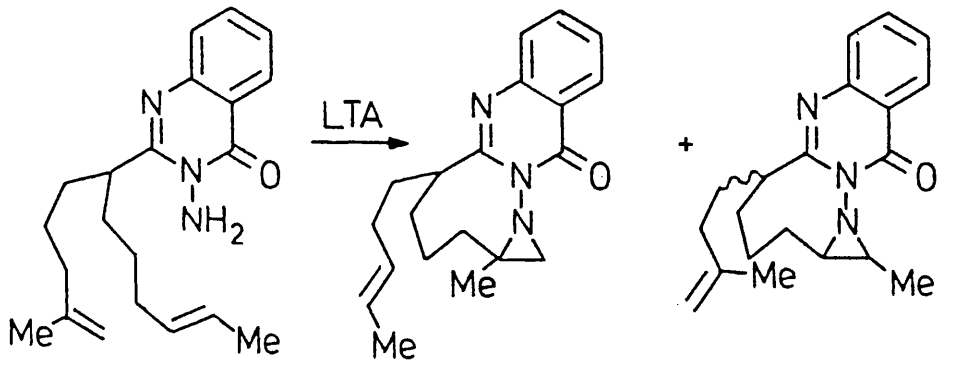
Ratio of stereoisomers (50b):(50a) >7:1

(51b):(51a) 1:2·2(±0·1)



(52)

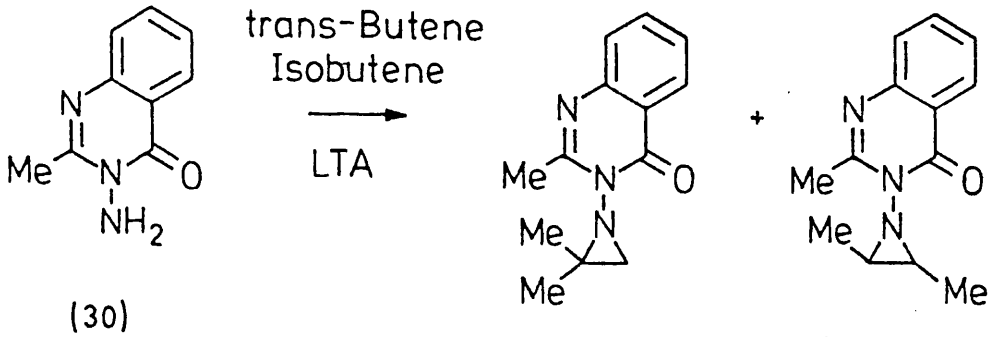
Ratio 3 : 1 (±0·3)



(59) (67) (68)

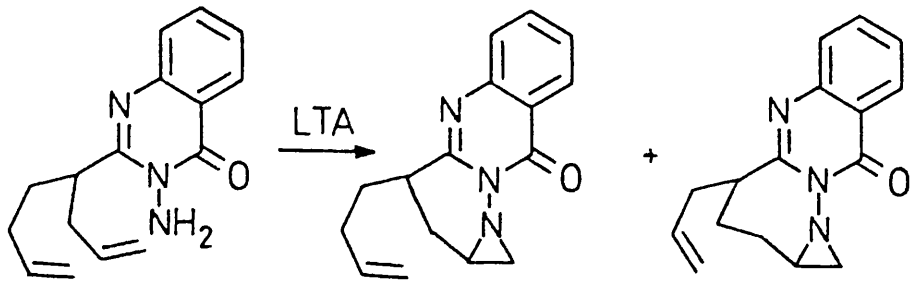
Ratio 1 : 2 (±0·1)

Addition to <u>trans</u>-substituted double bond non-stereospecific 1·6 : 1 (±0·1)



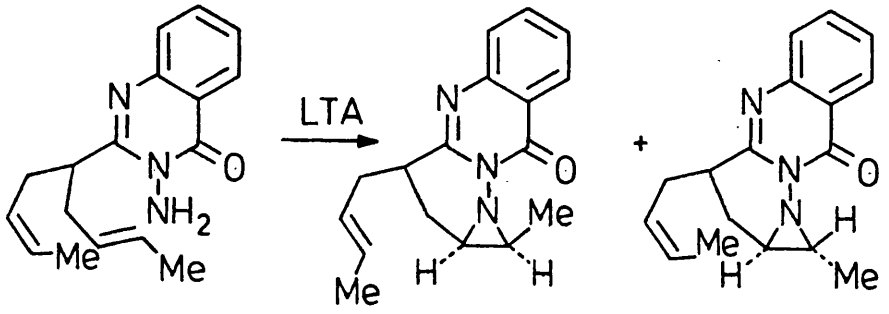
(30)

Ratio 1 : 7·4 (±1)



(56) (57) (58)

Benzene	2·8	:	1
CH_2Cl_2	3·4	:	1
CH_3CN	4·7	:	1



(83) (86) (87)

Ratio 5·1:1

Conclusion

From the different selectivity of the N-nitrenes for the two double bonds in (39) and (49) (or (52)) by comparison with (27) and (53), respectively, and from a consideration of the stereoisomer ratios it is concluded that extending the chain length between the quinazolone and the alkene trap from n = 2 to n = 3 (Figure 15 (22)) results in a changeover from non-concerted to concerted reaction. This determination of the value of n at which the onset of concerted cycloaddition occurred allowed a description of the likely transition state geometry (Figure 33).

In the above mentioned intramolecular reactions, only terminal trans-substituted or β-methyl substituted double bonds were used, specifically to eliminate any secondary interaction of the double bond substitutents with the quinazolone ring. This secondary interaction is known to be important in intermolecular reactions and presumably accounts for the selectivity of the N-nitrene derived from oxidation of N-amino-2-methylquinazolin-4(3H)-one between trans-but-2-ene and isobutene with trans-but-2-ene 7.4 times more reactive than isobutene, a result to be contrasted with the corresponding ratio of 1:3 for the nitrene addition to the two analogously substituted double bonds in (52).

That the ratio of attack of the nitrene on the two double bonds in (59) is different from that obtained in (52) together with the fact that addition to the trans-methyl-substituted double bond is non-stereospecific, suggests that with n = 4, there are accessible conformations which allow this secondary interaction to operate.

Preliminary studies on the low-temperature oxidation of N-amino-2-substituted quinazolones raises the possibility that a method might be available for generation of quinazolone N-nitrenes under the mildest of

stimuli (raising the temperature from -30 ^{o}C to 20 ^{o}C). The exact nature of the intermediate involved is unknown, but it is thought to be a (poly)dipolar species such as (77).

PART 3

INTRAMOLECULAR TRAPPING OF N-NITRENES BY ALKYNES.

3.1. Introduction.

3.1.1. Nomenclature.

Azirines are azacyclopropenes and two isomeric forms are possible, namely 1H-azirine (93) and 2H-azirine (94). (Figure 72).

(93) (94)

Fig. 72

3.1.2. Intermolecular trapping of N-nitrenes by alkynes.

Rees and co-workers[43] studied the oxidation of N-aminophthalimide by lead tetra-acetate (LTA) in the presence of alkynes. With propyne, but-2-yne, pent-1-yne, and hex-3-yne, 2H-azirines were isolated in low yields. (Figure 73).

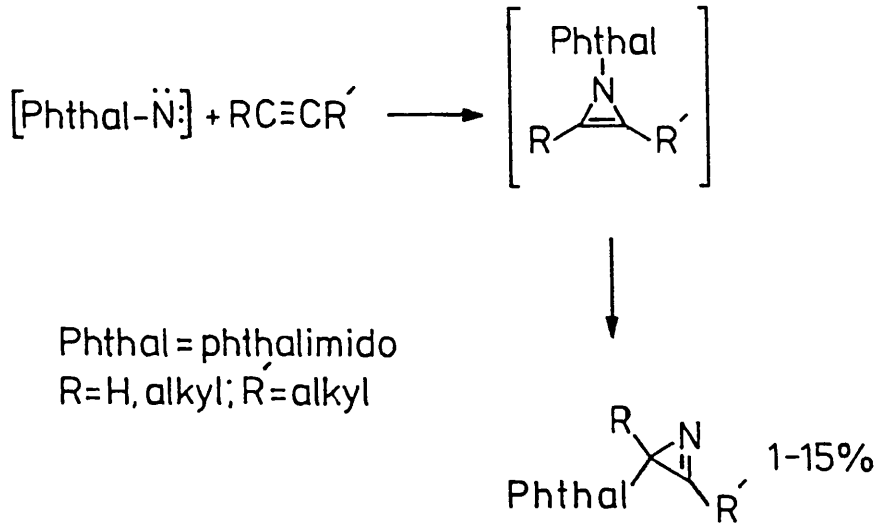
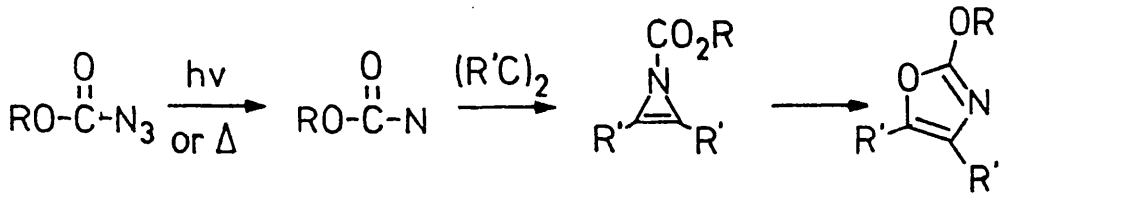


Fig. 73

Several other alkynes were also tried unsuccessfully, phthalimide being the only product isolated, so the reaction appears to be limited in scope to simple alkyl substituted alkynes.

The mechanism proposed for the reaction involves the formation and rapid rearrangement of the 1H-azirine. No 1H-azirine has yet been isolated and their instability can be attributed to their antiaromatic character. Molecular orbital calculations[44] show that there is a destabilising interaction between the electrons of the π-bond and the nitrogen lone pair. Clark[44] has also calculated the inversion barrier in 1H-azirine to be 147 kJ mol^{-1}, some 84 kJ mol^{-1} higher than the inversion barrier in aziridines, thus supporting the idea of the instability of the planar antiaromatic form.

Huisgen and Blaschke,[45] and Meinwald and Ave[46] showed the addition of carboethoxy or carbomethoxy nitrene, generated thermally or photochemically from the corresponding azidoformate, to alkynes gave oxazoles, which could be formed by rearrangement of intermediate 1H-azirines (Figure 74a) rather than by direct 1,3-dipolar addition of the nitrenes to the alkynes.



R=CH_3, C_2H_5
R'=CH_3, C_2H_5, Ph

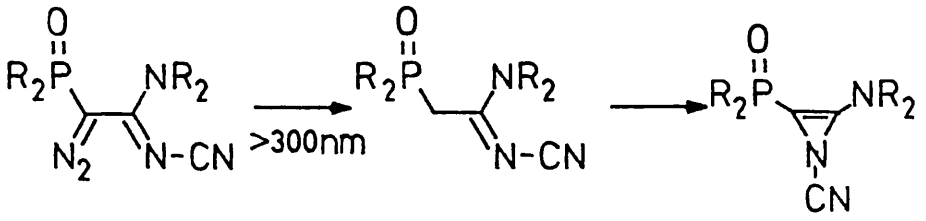
Fig. 74a

3.1.3. Other experimental evidence to support the intermediacy of 1H-azirines.

Rees and co-workers[47] examined the pyrolysis of 4-methyl-5-phenyl-1-phthalimido-1,2,3-triazole and 5-methyl-4-phenyl-1-phthalmido-1,2,3-triazole. Both triazoles gave identical mixtures of 2H-azirines and

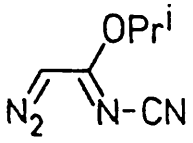
their pyrolysis products, indicating that the products are formed from a common intermediate (i.e. 2-methyl-3-phenyl-1-phthalimido-1H-azirine). Subsequent pyrolysis studies on substituted [5-^{13}C]-labelled 1,2,3-triazoles have confirmed these results.[48]

Taking advantage of donor-acceptor substituent stabilisation, Regitz and co-workers[49] claim to have detected the presence of 1H-azirine (96) by the photoirradiation of α-diazoimine (95) in a CH_2Cl_2-glass at 77 °K (Figure 74b), the evidence being the 1867 cm^{-1} infrared absorption. Similar frequencies (1880 - 1890 cm^{-1}) were observed on photolysis of α-diazoiminoester (97) in an argon matrix at 8 °K.



(95) (96)

R=Ph

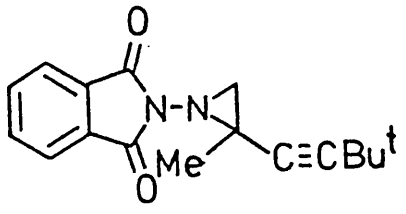


(97)

Fig. 74b

3.1.4. Competition for the N-nitrene between alkenes and alkynes.

Rees et al[43] found that the attempted cycloaddition of phthalido-nitrene to di-t-butylacetylene gave only adduct (136) formed by addition to the double bond of 2,5,5-trimethylhex-1-en-3-yne, an impurity in the acetylene (ca. 2 %) (Figure 74c). Reaction at the double bond of the enyne is evidently much more favourable than attack on the triple bond



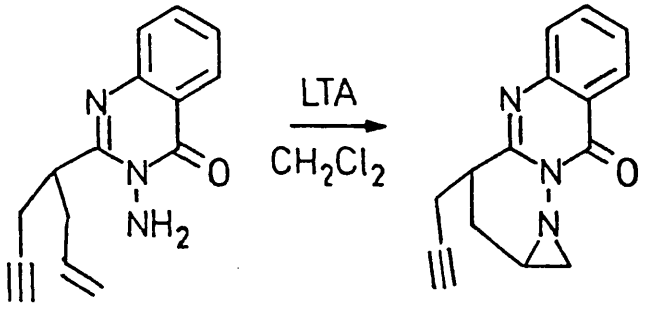
(136)

Fig. 74c

in the same enyne or attack at the triple bond of di-t-butylacetylene.

The nitrene generated on oxidation of 2-methyl-3-aminoquinazolone with lead tetra-acetate can be trapped in 11 % yield by hex-1-ene, whereas our attempts to trap it with hex-1-yne were unsuccessful.

The greater reactivity of the double bond over the triple bond for the N-nitrene is found in both intermolecular and intramolecular reactions.



(137) (138)

Fig.74d

Thus, in the oxidation of (137) (first carried out by Brown[68]), only the aziridine (138) from addition of the N-nitrene to the alkene was isolated (84 %) (Figure 74d). In the oxidation of 2-butenyl-3-amino-quinazolones, intramolecular addition of the nitrene is believed to take place via a transition state having dipolar character (Figure 21), so the preference for attack on the double bond by the nitrene in (137) could be rationalised in terms of the lesser stability of the vinyl cation which would result from electrophilic attack of the nitrene on the triple bond.

3.2. Intramolecular trapping of N-nitrenes by alkynes where n = 2.

3.2.1. The Objective.

The intramolecular trapping of N-nitrenes by alkynes was examined with the expectation of increasing the efficiency of trapping. It was hoped also that the intramolecular reaction might permit observation or identification of the transitory 1H-azirine.

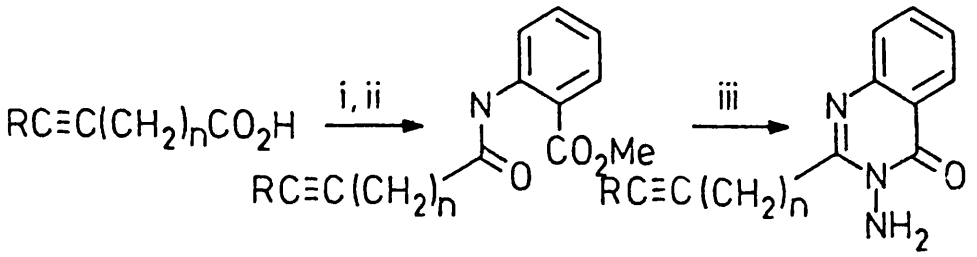
3.2.2. Synthesis of N-Amino-2-(alkynylalkyl)-quinazolones.

The choice of N-aminoquinazolones for the study of intramolecular N-nitrene additions was based on the ready incorporation of the alkyne(s) into the side-chain at position 2 when assembly of the quinazolone ring is carried out *via* the appropriate carboxylic acid. Hence quinazolones (98) - (102) were synthesised from the corresponding acids (103) - (107) (Figure 75).

Acids (103) - (107) were obtained by mono- or dialkylation of malonate esters with the appropriate alkynyl bromide or tosylate followed by hydrolysis and decarboxylation. Acid (105) was obtained by chain extension of (104) (Figure 76).

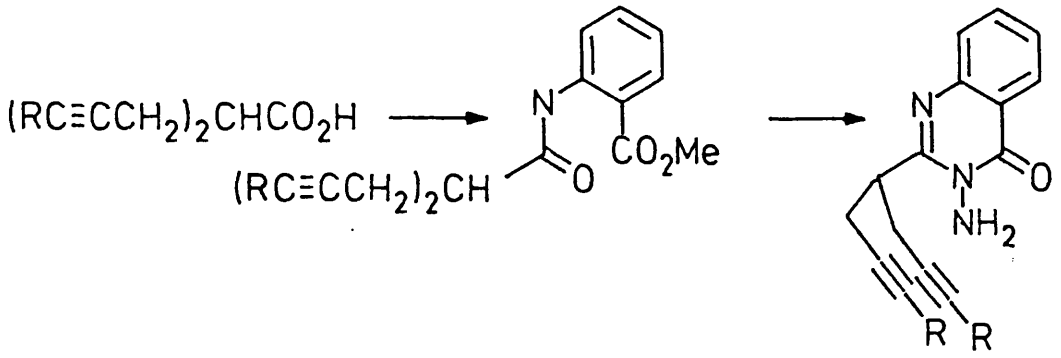
3.2.3. Oxidation of N-Amino-2-(pent-2-yn-5-yl)quinazolin-4(3H)-one (98)

In the oxidation of (98) with LTA, a crystalline product was obtained in quantitative yield after separating the lead di-acetate, washing the dichloromethane solution with sodium hydrogen carbonate solution and then evaporating the dried solution. The ^{13}C n.m.r. data for this oxidation product is summarised in Figure 77. Assignment of signals was helped by the fact that the ^{13}C n.m.r. spectra of several quinazolones had already been reported by S.P. Singh.[50] A striking difference in chemical shift exists between the heterocyclic ring carbons 2 and 3 of 2H-azirines.



(103) R=Me, n=2
(104) R= H , n=2
(105) R=H, n=3

(98) R=Me, n=2
(99) R= H, n=2
(100) R=H, n=3

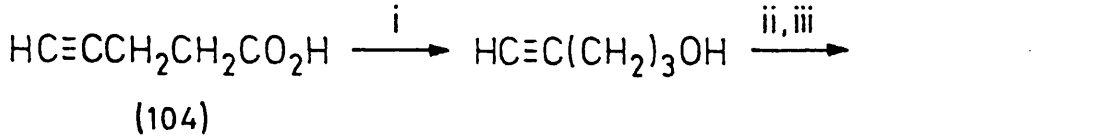


(106) R=Me
(107) R=H

(101) R=Me
(102) R=H

Reagents: i) $SOCl_2$; ii) Methyl anthranilate; iii) NH_2NH_2, MeOH (reflux); iv) NH_2NH_2, sealed tube, 120-130°C.

Fig.75



(104)

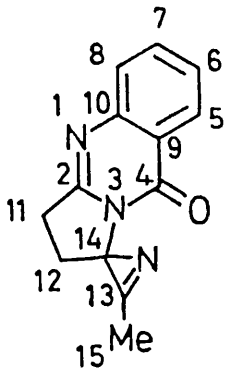
(105)

Reagents: i) $LiAlH_4$; ii) TsCl, KOH; iii) KCN, DMSO; iv) $NaOH-H_2O$.

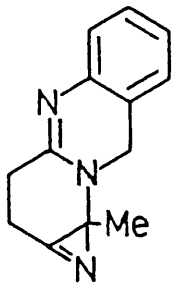
Fig. 76

Carbon-3 appears in the imino region of the ^{13}C spectrum (171.5 p.p.m.) whereas carbon-2 comes at 55.9 p.p.m.

^{13}C n.m.r. (100 MHz)	δ		Assignments	
	171.50	(s)		C_{13}
	160.81	(s)		C_4
	158.48	(s)		C_2
	148.70	(s)		C_{10}
	134.30	(d)		C_7
	126.92	(d)	May be interchanged	C_5
	126.34	(d)		C_6, C_8
	126.16	(d)		
	120.92	(s)		C_9
	55.1	(s)		C_{14}
	29.42	(dd)	could be reversed	C_{11}
	28.15	(dd)		C_{12}
	14.96	(q)		C_{15}



(109)



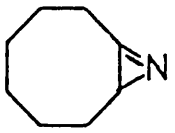
(110)

Fig. 77

The ^{13}C n.m.r. spectrum along with ^{1}H n.m.r. data for this oxidation product were in agreement with its formulation as the spiro-fused azirine

(109). Although the alternative isomer (110) was compatible with this data, bicyclo[n.1.0] ring-fused azirines have been isolable only with n = 6 or greater[51] e.g. (111) (Figure 78).

Confirmation of the structure of this oxidation product as (109) was eventually obtained by carrying out an X-ray crystal structure determination which will be discussed in detail later.



(111)

Fig. 78

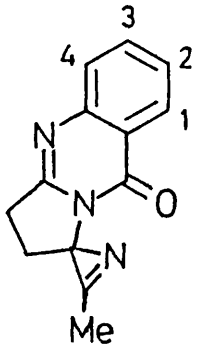
3.2.4. Oxidation of N-Amino-2-(but-1-yn-4-yl)quinazolin-4(3H)-one (99).

A similar oxidation of (99) gave a product whose ^{1}H n.m.r. data (given in Figure 79 along with that for (109)) unambiguously supported (112) as its structure.

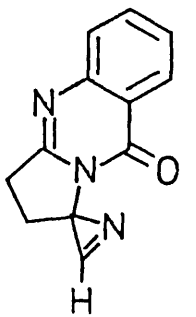
Thus (112) shows a characteristic low-field resonance at 10.41 p.p.m. (J 2.8 and 0.6 Hz) for the azirine ring proton signal. Comparing the chemical shift of the aldimine proton with that of an open chain one, e.g. $CH_3\underline{CH}{=}NCH_2CH_2CH_3$ (7.63 p.p.m.[52]), deshielding is observed and this can be ascribed to anisotropy of the azirine ring. Coupling of azirine ring protons at C-3 over four bonds has been previously reported by Taniguchi,[53] but it is clear that only one of the methylene protons adjacent to the spiro-centre in (112) is significantly coupled in this way, i.e. the magnitude of the coupling is dependent on geometrical factors.

The infrared spectra of (109) (and (115)) show a weak absorption at 1760 - 1780 cm^{-1} which compares well with the value of 1775 cm^{-1} given

Azirine ring proton		10.41 (dd, J 2.8 and 0.6 Hz)
quinaz. H-1	8.05 (ddd, J 8, 1.5, and 0.5 Hz)	8.02 (dd, J 8 and 1.5 Hz)
quinaz. H-3	7.64 (ddd, J 8, 7, and 1.5 Hz)	7.63 (ddd, J 8.1,6.9, and 1.5 Hz)
quinaz. H-4	7.56 (ddd, J 8, 1.5, and 0.5 Hz)	7.54 (dd, J 8.1 and 1.7 Hz)
quinaz. H-2	7.34 (ddd, J 8, 7, and 1.5 Hz)	7.32 (ddd, J 8, 6.9, and 1.7 Hz)
	3.48 (ddd, J 17.5, 10.9, and 9.3 Hz)	3.47 (ddd, J 17.5, 10.9, and 9.3 Hz)
	3.03 (ddd, J 17.5, 9.7, and 1.5 Hz)	3.03 (ddd, J 17.5, 9.6, and 1.3 Hz)
CH_3	2.71 (s)	
	2.61 (ddd, J 13.9, 10.9, and 9.7 Hz)	2.65 (dddd, J 13.9, 10.9, 9.6, and 2.8 Hz)
	and 1.73 (ddd, J 13.9, 9.3, and 1.5 Hz)	and 1.75 (dddd, J 13.9, 9.3, 1.3, and 0.6 Hz)



(109)



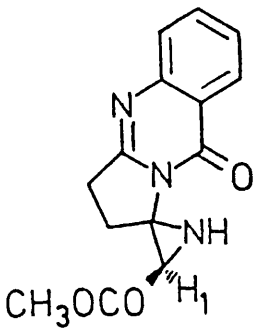
(112)

Fig. 79

for the C=N stretching absorption of 3-alkyl substituted 2H-azirines. No band is observed in this position in the i.r. spectra of (112) (and (116)) (or other azirines bearing a hydrogen at C-3).

3.2.5. Reactivity of azirines (109) and (112) towards acetic (or formic) acid.

Azirine (112) is much more reactive than (109) towards acetic acid (a by-product of the oxidation using LTA) and the yield was maximised when its contact with acetic acid in the reaction medium was minimised. If work-up was carried out after setting the reaction mixture aside overnight, the only product isolated was the acetic acid addition product (113) (Figure 80).



(113)

δ (90 MHz) 8.00 (d, J 8 Hz, quinaz. H-1).
7.68 - 7.24 (m, 3 x ArH)
6.10 (d, J 8 Hz, on D_2O shake, collapses to s, H_1)
3.88 (br d, J 8 Hz, on D_2O shake, collapses to s, NH)
3.08 (t, J 9 Hz, CH_2-quinaz.)
2.31 (t, J 9 Hz, CH_2-C(spiro))
and 2.09 (s, $OCOCH_3$).

Fig. 80

Formation of the acetic acid addition product (113) was very rapid and could be readily monitored by n.m.r. by gradual addition of acetic acid in small quantities (as a solution in deuteriochloroform) to a deuteriochloroform solution of the azirine (112).

This was found to be the case with formic acid also; a spectrum of the crude oxidation product typically showed (112) and (113) in a ca 2:1 ratio respectively (Figure 81:A). When one drop of formic acid (as a solution in deuteriochloroform) was added to the n.m.r. solution, the

A: Initial spectrum

B: After addition of 4 drops of HCO_2H (in $CDCl_3$)

C: Spectrum 6 minutes later.

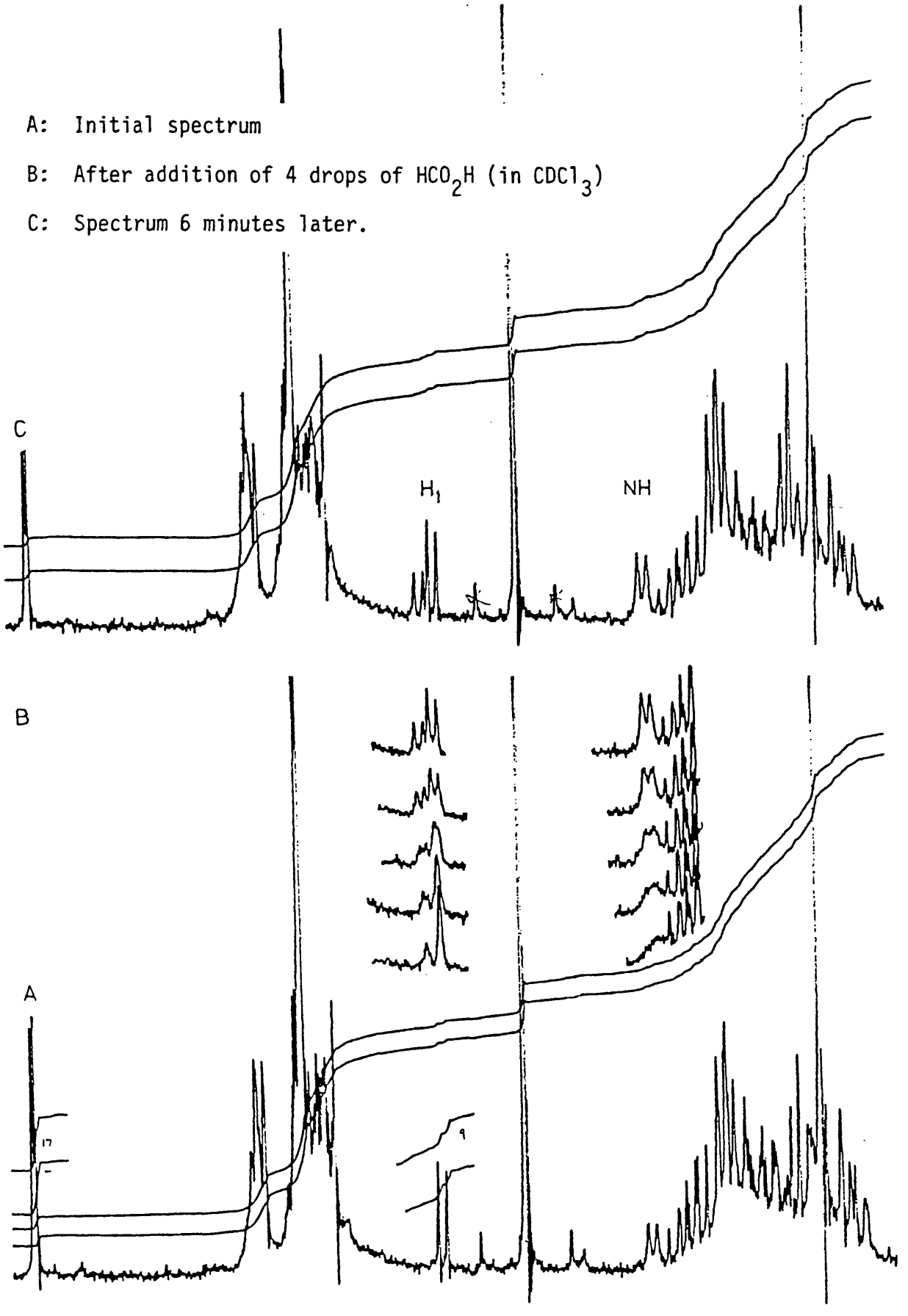


Fig. 81

A: Spectrum after 11 drops

B: After addition of 12 drops of HCO_2H (in $CDCl_3$)

C: Spectrum 16 minutes later

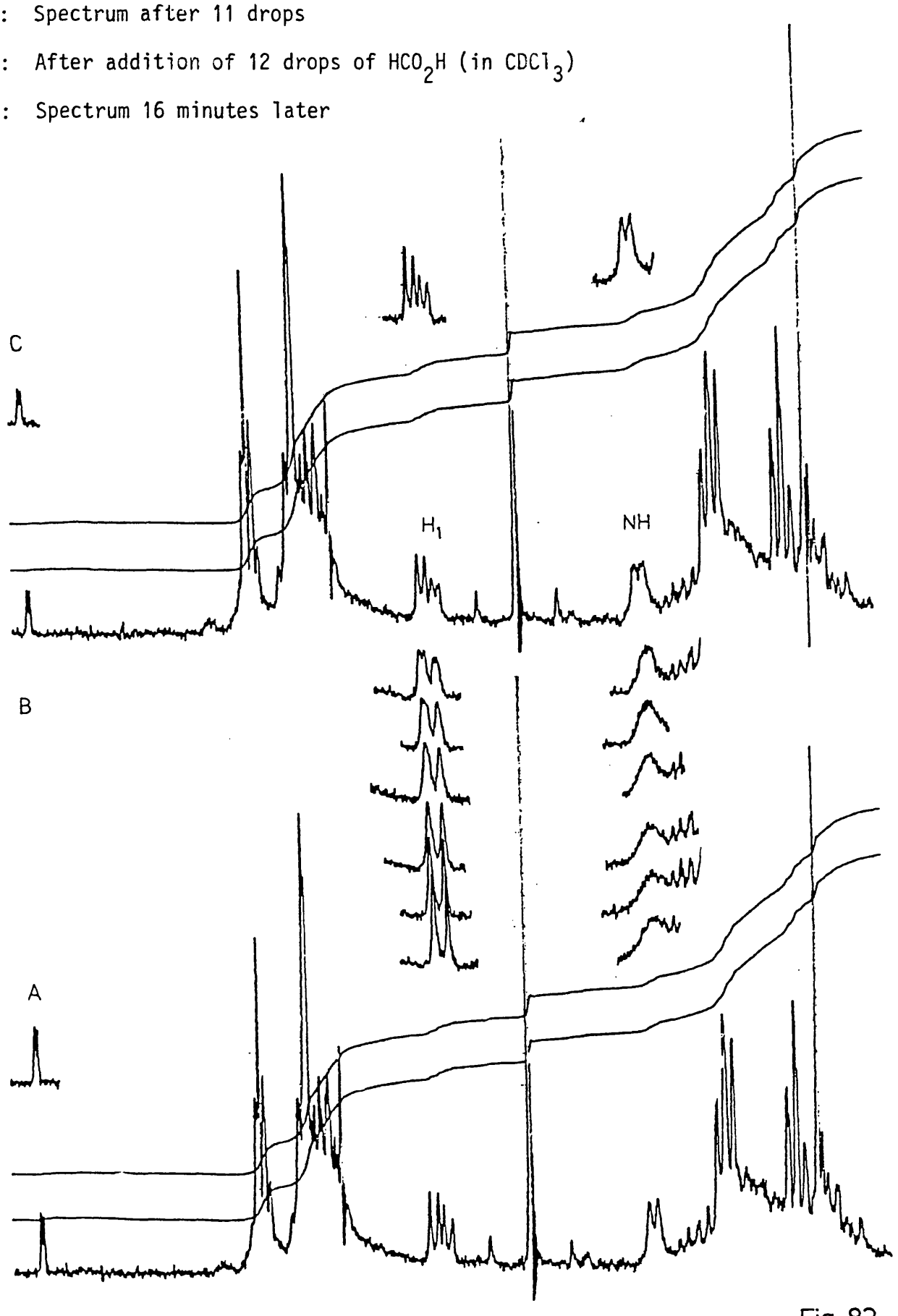


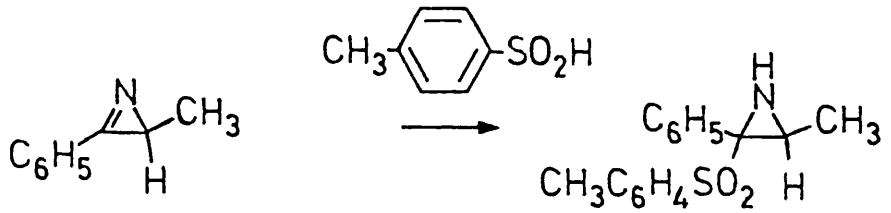
Fig. 82

doublet at δ 6.10 due to the H_1 on the acetoxy-aziridine (see Figure 80) collapses to a sharp singlet, and the NH signal becomes much broader and loses its doublet character. As the formic acid is scavenged by the azirine, the singlet due to H_1 broadens and eventually reverts to a sharp doublet. Conveniently, the doublet due to H_1 in the formyloxy-aziridine resonates at slightly lower field compared with that in the acetoxy-aziridine. Figure 81:B and Figure 82:B shows this process diagramatically, with Figure 81:C showing the appearance of the spectrum 6 minutes after addition of 4 drops and Figure 82:C 16 minutes after addition of 12 drops of formic acid (diluted with deuteriochloroform).

By contrast, azirine (109) was markedly less reactive to acetic acid and no measurable loss of signals from this azirine in its n.m.r. spectrum was apparent after several hours in contact with two molecular equivalents of acetic acid in deuteriochloroform solution at comparable dilution.

In reactions of acids with 2H-azirines, the proposed overall mechanism of the reaction generally involves initial protonation on nitrogen followed by addition of nucleophile to the azirinium ion and usually subsequent ring opening. Interestingly, Meek and Fowler[54] observed that the addition of toluene p-sulphinic acid to 2-methyl-3-phenyl-2H-azirine gave sulfonyl-aziridine (114) (Figure 83).

If protonation was the first and rate determining step, then azirine (109) should be more reactive towards acetic acid than (112). As the reverse is the case, this suggests that the rate determining step in addition of acetic acid to azirine is not protonation of the azirine ring nitrogen with the generation of a carbonium ion as an intermediate. Incidentally, the basicity of 2H-azirines does not appear to be as low as that of nitriles, yet 2-methyl-3-phenyl-2H-azirine is insoluble in 10 % hydrochloric acid solution.[55]

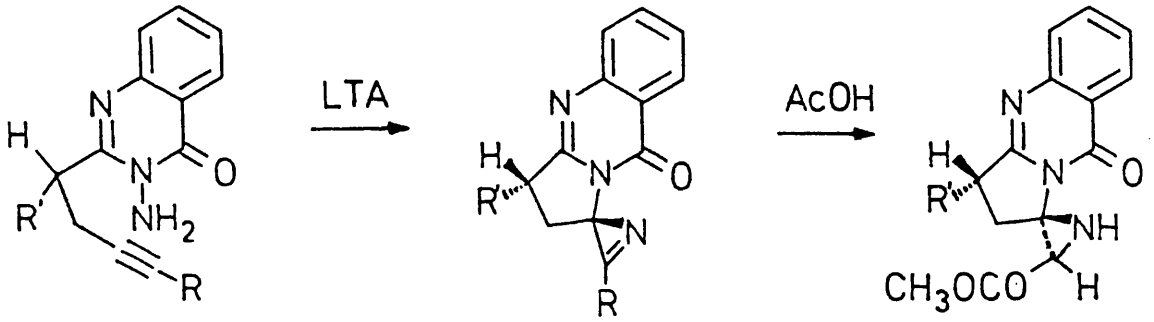


(114)

Fig. 83

3.2.6. Oxidation of N-Amino-2-(nona-2,7-diyn-5-yl)-quinazolin-4(3H)-one (101) and N-Amino-2-(hepta-1,6-diyn-4-yl)-quinazolin-4(3H)-one (102).

Oxidation of quinazolones (101) and (102) bearing bifurcated chains also proceeded in excellent yield to give the corresponding azirines (115) and (116), respectively (Figure 84).



(101) R=Me, R'=$CH_2C{\equiv}CMe$ (115) R=Me, R'=$CH_2C{\equiv}CMe$

(102) R=H, R'=$CH_2C{\equiv}CH$ (116) R=H, R'=$CH_2C{\equiv}CH$

(117)

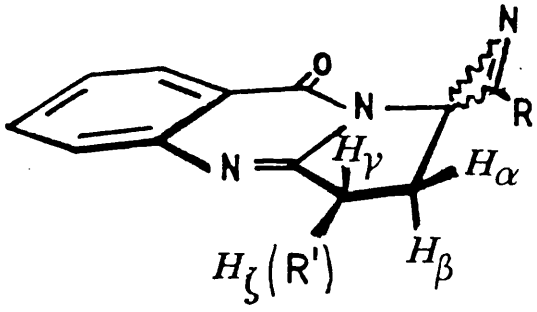
Fig. 84

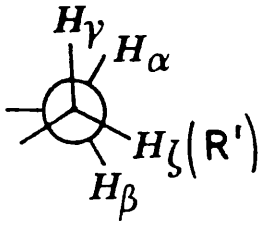
Woodthorpe[35] first synthesised and carried out the oxidation of (102). Like the C-3 unsubstituted azirine (112), (116) is also very reactive towards the acetic acid generated in its formation. Acetoxyaziridine (117) is assigned the configuration shown at the acetoxy-bearing carbon

atom with the assumption of attack of acetate anion on the azirine C=N from the side of the azirine ring opposite to the quinazolone (assignment in (113) is believed to be as shown in Figure 80 for the same reason).

3.2.7. Conformational analysis of azirines (109), (112), (115), and (116).

Since four atoms of the five-membered ring are fixed in a plane, the five-membered ring in the title azirines adopts an envelope as its stable conformation. Comparison of the ^1H n.m.r. spectra of azirines (109), (112), (115) and (116) showed clearly that they all adopt a single conformation for the five-membered ring whose envelope shape accorded with the magnitude of the vicinal coupling constants between the five-membered ring protons as shown in the Newman projection along the CH_2-CH_2 (CH(R)-CH_2) bond (Figure 85).





	$J_{\alpha\gamma}$	$J_{\alpha\zeta}$	$J_{\beta\gamma}$	$J_{\beta\zeta}$
R = R' = H	9·3	1·3	10·9	9·6
R = H, R' = $CH_2C{\equiv}CH$	8·1	-	10·6	-
R = Me, R' = H	9·3	1·5	10·9	9·7
R = Me, R' = $CH_2C{\equiv}CMe$	8·3	-	10·5	-

Fig. 85

Nuclear Overhauser effect (N.O.e.) studies on (112) showed that on irradiation of the azirine proton at 10.41 p.p.m., none of the other protons were affected whereas irradiation of proton at 1.75 p.p.m. (H_α) showed a strong interaction with proton at 2.65 p.p.m. (23 %) and weak

interaction with proton at 3.47 p.p.m. (4 %). This latter proton is, therefore, cis to that at 1.75 p.p.m., and is known to be H_γ (see Figure 85).

The orientation of the azirine ring with respect to the envelope flap was, at this stage, unknown. However, it was clear from these assignments and especially from the magnitude of $J\alpha\delta$ (1.3 - 1.5 Hz) that the five-membered ring has a conformational preference for the envelope flap to be located on one side rather than the other of the plane containing the quinazalone ring but it was not obvious why this should be.

The two sides of the quinazolone in azirines (109) and (112) are defined by the orientation of the azirine ring and it seemed logical to assume that the origin of the conformational preference of the five-membered ring was to be found in a corresponding preference of the C-N (or C-C) bond of the azirine ring for one of the two differentiated positions on the five-membered ring at the spiro centre.

3.2.8. X-Ray crystal structure of azirine (109).

In order to define the orientation of the azirine ring with respect to the envelope flap of the five-membered ring, an X-ray crystal structure determination was carried out on azirine (109) and gave the result shown in Figure 86(a).[+] Figure 86(b) is part of this structure viewed perpendicular to the azirine ring with the quinazolone ring residue removed for clarity.

Figure 86(b) clearly shows that the conformation adopted is the one where the nitrogen of the azirine ring is on the opposite side to the flap of the five-membered envelope.

Also, Figure 86(b) shows a remarkable deformation of bond angles at the spiro-centre in that the C-C bond of the azirine ring is nearly

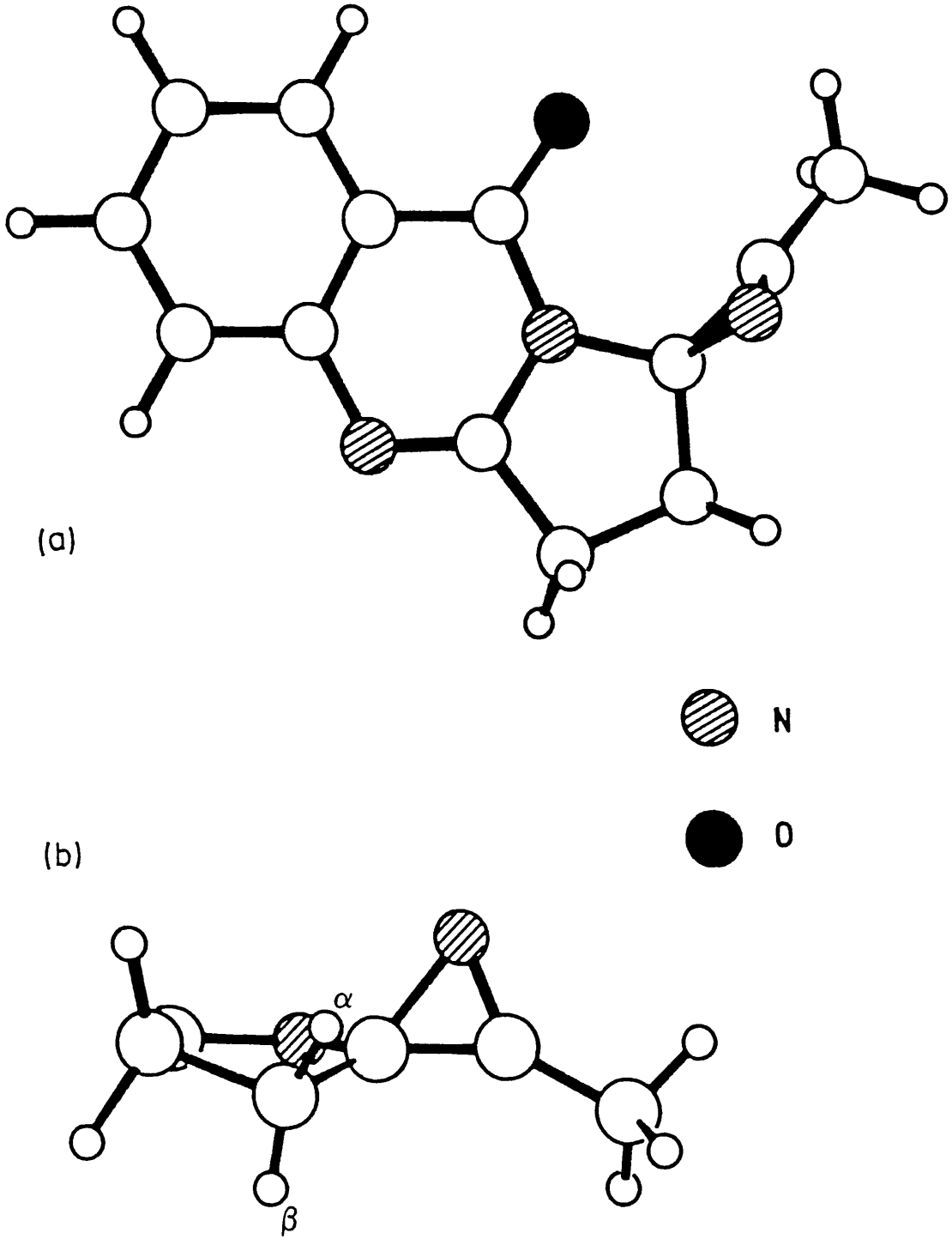


Fig.86

+ Figure 86(a) differs from the same figure in J.C.S.Chem.Commun., (1985, 9, 544) in that a hydrogen atom in the latter on the carbon atom of the 5-membered ring adjacent to the spiro-centre was inadvertently drawn in when in fact it is not visible from the perspective drawn.

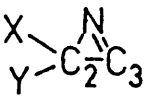
coplanar with the two bonds of the five-membered ring to the spiro-centre: the C-C bond of the azirine ring is only 5.9° out of the plane defined by the C-N and C-C five-membered ring bonds to the spiro-centre whereas the C-N bond of the azirine ring is at an angle of 44.5° to this plane. Alternatively, the near-coplanarity of C-N and C-C bonds of the five-membered ring and the C-C bond of the azirine ring can be quantified by summation of the angles between them which gives a value of 358 ± 1.2°: a perfect plane would, of course, require a value of 360°.

This unexpected feature of the azirine ring geometry in (109) was the more surprising when it was found to be also present, but unremarked upon, in the four azirine ring containing crystal structures available from the Cambridge Data File. These four structures along with the appropriate angle summations are shown in Figure 87, and it is clear that the substantial deformation towards coplanarity at C-2 as in (109) has taken place in all cases.

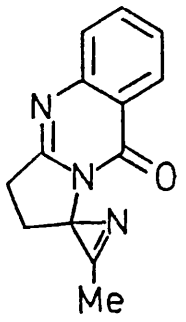
3.2.9. Hybridisation in three-membered rings.

The orbitals used for forming the endocyclic bonds of three-membered rings have a greater amount of p-character in order to better accommodate the small ring bond angles and this results in an increase in s character in the orbitals used for forming the exocyclic bonds.

Measurement of ^{13}C-^{1}H coupling constants has been used to determine the percentage s character in the exocyclic orbitals of small heterocyclic and carbocyclic rings. The value of the ^{13}C-^{1}H coupling constant of 166 Hz for the methylene protons of cyclopropene corresponds to 33.2 % s character[60] and the ^{13}C- ^{1}H coupling constant of 176 Hz indicates 35.6 % s character for the carbon-hydrogen orbitals at position 2 in 3-phenyl-2H-azirine.[55]

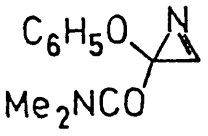


Sum of XC_2C_3, XC_2Y, YC_2C_3



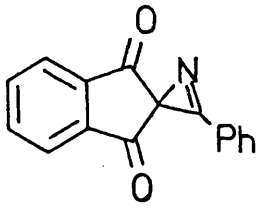
358°

3-Phenoxy-3-Dimethylcarbamoyldimethylamino-2-Azirine[56]



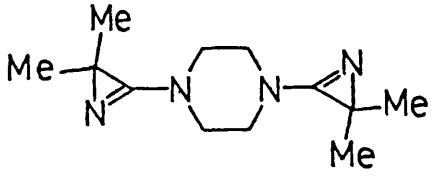
357.2°

Spiro(Indan-1,3-Dione)-2,3'-(2'-Phenylazirine)[57]



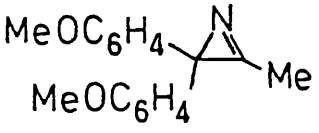
357°

1,4-Bis(3,3-Dimethylazirinyl)-Piperazine[58]



356.7°

2,2-Bis(p-Methoxyphenyl)-3-Methyl-2H-Azirine[59]



358.1°

Fig.87

Our examination of crystal structures of cyclopropenes available on the Cambridge Data File suggests that they are symmetrical with respect to the spiro-centre; one such example, 3,3-bis(methoxycarbonyl)-1-methyl-2-phenyl-cyclopropene[61] (Figure 88).

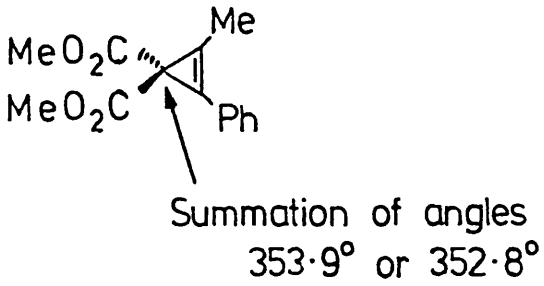


Fig. 88

Given in Figure 89 are the bond angles and lengths associated with the azirine ring in (109). The C-N bond does seem unusually long and indeed this feature has already been noted.[59]

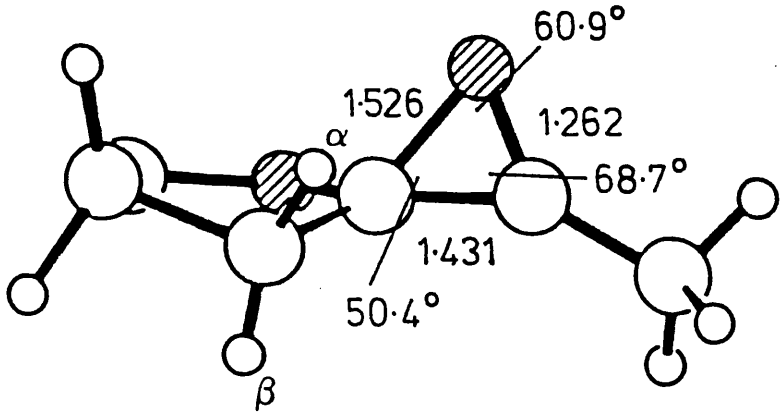


Fig. 89

The deformation of C-2 in (109), in the four azirine ring containing crystal structures available from the Cambridge Data File, and presumably in all other azirines, can be accommodated by assuming hybridisation for the carbon atom at this position which is close to sp^2-with the C-N bond of the azirine formed by overlap of the p-orbital at C-2 with an orbital

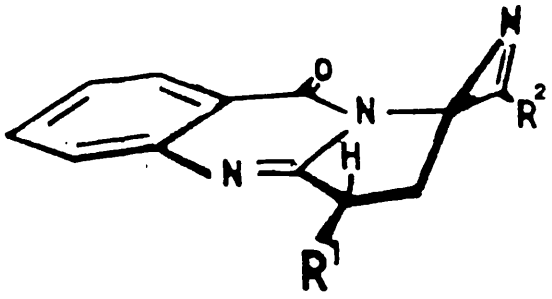
on the nitrogen. This could be necessary in order to best accommodate the C(3)=N bond (which is shorter than a C=C bond) into the three-membered ring.

Interestingly, in 2-phenyl-2H-azirine, the C_3-H coupling constant is 242.5 Hz, which corresponds to about 49 % s character of the C-H bond, indicating sp-like hybridisation of carbon-3.[55]

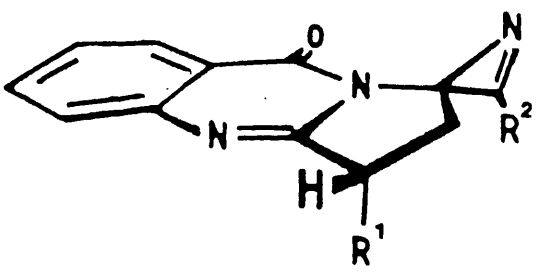
3.2.10. Further conformational analysis.

Analysis of the ^{1}H n.m.r. spectra of (109) (together with (112), (115), and (116)), is in agreement with the same geometry at the spiro-centre in solution as in the crystal structure. In particular, the chemical shift upfield of the signal from H_α (Figure 86(b)) by comparison with H_β can be ascribed to shielding of H_α by the adjacent azirine ring.

However, there remains the problem of why conformation (118) is preferred over (119) for these five-membered ring spiro-fused azirines (Figure 90).



(118)



(119)

Fig. 90

Both these conformations have the azirine C-C bond nearly co-planar with the two five-membered ring bonds to the spiro-centre and they are interconverted by movement of the envelope flap from one side of the quinazolone plane to the other. Of course, in the ring-substituted compounds (115) and (116) there may be a contribution to the stabilisation of (118) over (119) from the preferred siting of the side-chain R in an 'equatorial' rather than an 'axial' position (although these are not cyclohexane-like equatorial or axial bonds because they are free from 1,3-diaxial interactions). However, (109) and (112) are free from this complication and yet still have the same preferred conformation indicated for the five-memebred ring.

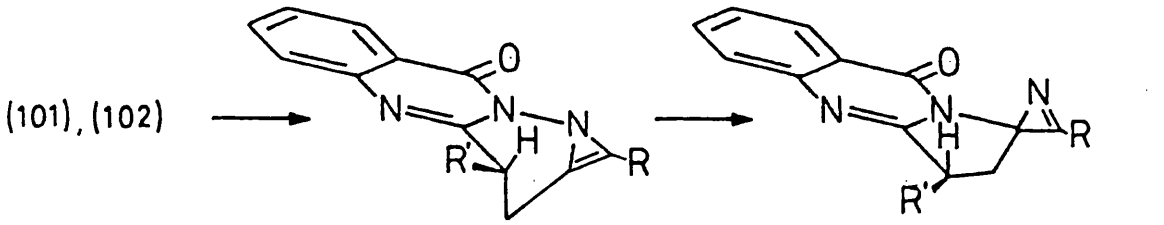
Examination of models of (118) and (119) suggests that the origin of the greater stability of (118) may be the result of an alignment of the (bonded) p-orbital at the spiro-centre in the latter with the filled p-orbital of the quinazolone ring nitrogen. The tilting of the p-orbital at the spiro-centre which is anticipated because the three bonds to the spiro-centre are not completely co-planar would serve to improve this alignment in (118) but reduce it in (119).

3.2.11. Stereospecific formation of (115) and (116).

Both (115) and (116) are formed stereospecifically with the side-chain and C-N bond of the azirine ring trans. If intramolecular N-nitrene addition to the triple bond proceeds analogously to the recently proposed pathway for intramolecular addition to alkenes[31] then the rigid boat-shaped 1H-azirine (120) in Figure 91 would result, where 1,2-migration delivers (115) and (116) directly in their stable conformations for the five-membered rings.

Although the envelope conformation (118) of azirines (109), (112),

(115), and (116) would, therefore, be the kinetically favoured products of rearrangement, it is likely that they are also the thermodynamically favoured conformations since the ^1H n.m.r. spectrum of (109) in chlorobenzene was unchanged when recorded at 120 ^oC.



(120)

(115) R=Me, R'= $CH_2C{\equiv}CMe$

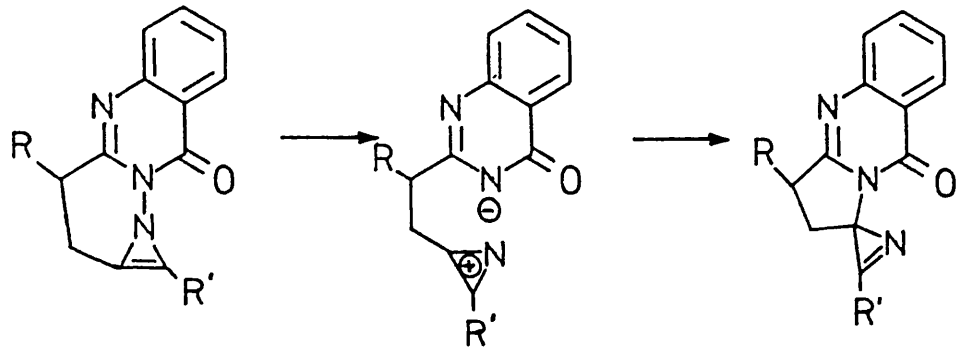
(116) R=H, R'= $CH_2C{\equiv}CH$

Fig. 91

3.2.12. Mechanism of 1H to 2H-azirine rearrangement.

The mechanism of the 1H-to 2H-azirine rearrangement has not been established. A simple concerted 1,3-sigmatropic rearrangement is not orbital symmetry allowed. The 1,3-sigmatropic shift would have to be suprafacial and to be allowed this must occur with inversion in the migrating group. It is difficult to see how this process can occur since the nitrogen is sp^2 hybridised. Rees et al[43] suggest that the mechanism may involve heterolytic cleavage of the N-N bond to give an azirinium cation and the heterocyclic anion, followed by recombination at a ring carbon (Figure 92).

Applying this mechanism to the case of (98), recombination at the spiro-centre after the heterocyclic cleavage of the N-N bond would need to be very rapid, since no rotation of the azirinium ion with respect to the heterocyclic anion has taken place. If rotation had taken place it is unlikely that a single stereoisomer of the azirine would have been produced.

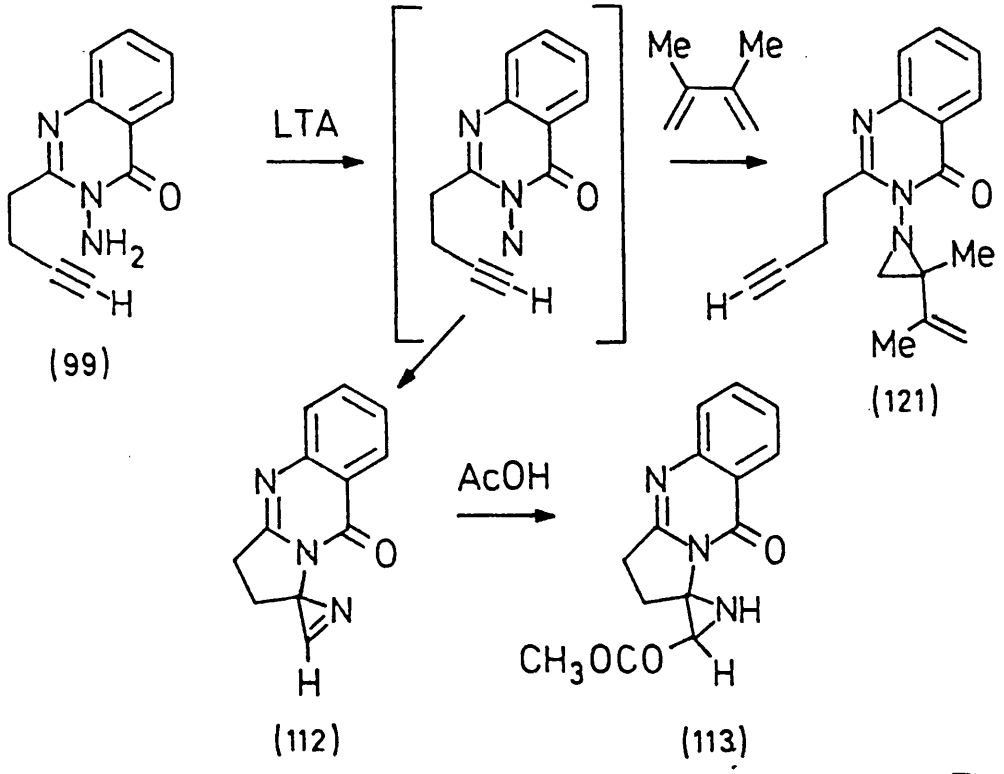


1H-Azirine 2H-Azirine

Fig. 92

3.2.13. Attempted trapping of the 1H-azirine.

The fact that migration of the N-N bond in the 1H-azirine delivers 2H-azirines (109), (112), (115), and (116) directly in their most stable conformations does not augur well for the prospect of trapping the 1H-azirine in these systems. Indeed, attempts to trap the 1H-azirine with 2,3-dimethylbutadiene have not been successful.



(99) (121) (112) (113)

Fig. 93

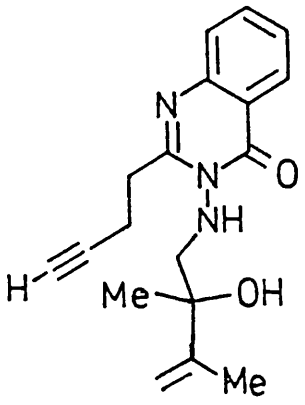
Thus,separate dichloromethane solutions containing quinazolone (99) and LTA were added together at -78 ^{o}C (High Dilution Method) and the reaction flask was subsequently charged with a large excess of 2,3-dimethylbutadiene. After allowing the solution to warm to ambient temperature and work-up in the normal way, the n.m.r. spectrum of the crude reaction mixture showed the presence of aziridine (121) and, significantly, some of the azirine (112) together with its acetic acid addition product (113) (Figure 93).

Clearly, the nitrene is intercepted by the diene but formation of azirine (112) in the same reaction mixture indicates that either the 1H- to 2H-azirine rearrangement is very fast or that the 1H-azirine is not particularly reactive towards 2,3-dimethylbutadiene.

Later it was found that oxidation of (99) under the conditions used in the above experiment proceeds very slowly if at all (at -78 ^{o}C) (see 2.4). Thus, even after 8 hr very little lead diacetate precipitate was present and testing with starch-iodide paper indicated unreacted LTA. To this reaction mixture, 2,3-dimethylbutadiene was added as before and the solution was then allowed to warm up gradually from -78 ^{o}C to room temperature overnight. Examination of the crude reaction product by n.m.r. showed the presence of only the acetoxy compound (113) and aziridine (121) in 3:2 ratio, respectively. So it seems that in the initial experiment, the actual oxidation of (99) took place during the warming up of the solution to room temperature prior to work-up.

Subsequently, oxidation of (99) was carried out under conditions to maximise intermolecular trapping of the N-nitrene by 2,3-dimethylbutadiene and indeed the n.m.r. spectrum of the crude reaction product showed aziridine (121) only. Chromatography on alumina gave aziridine (121)

in 51 % yield as a crystalline solid. Like other vinyl aziridines,[13] aziridine (121) was particularly sensitive to ring opening and further elution of the column in the chromatography above also gave alcohol (122) in 13 % yield (Figure 94).



(122)

Fig. 94

3.3. Intramolecular trapping of N-nitrenes by alkynes where n = 3.

3.3.1. Oxidation of N-Amino-2-(pent-1-yn-5-yl)quinazolin-4(3H)-one (100).

Oxidation of quinazolone (100) gave a mixture of azirines (123) and (124) in a ratio of 9:4 respectively (Figure 95).

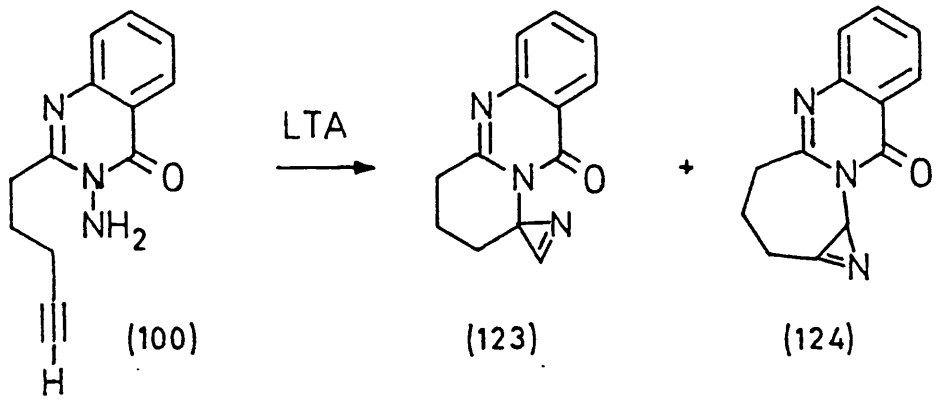


Fig. 95

Azirine (123) was separated by crystallisation from ethanol and comparison of the n.m.r. spectrum of the crystalline material with that of the crude reaction product (which contained (123) and (124) only) showed no loss or modification of signals assignable to (123).

Interestingly, azirine (123) was significantly more resistant towards attack by acetic acid than its spiro-fused five-membered ring analogues (112) and (116), and none of the acetic acid addition product (analogous to (113) or (117) respectively) was isolated. N.m.r. monitoring of the solution showed that the mixture of (123) and (124) was stable to two mol. equivalents of acetic acid in deuteriochloroform over several hours.

3.3.2. Conformational analysis of azirine (123).

The conformation of (123), which can be deduced from the vicinal coupling constants in its n.m.r. spectrum of protons in the trimethylene chain, is a twist-boat as shown in Figure 96.

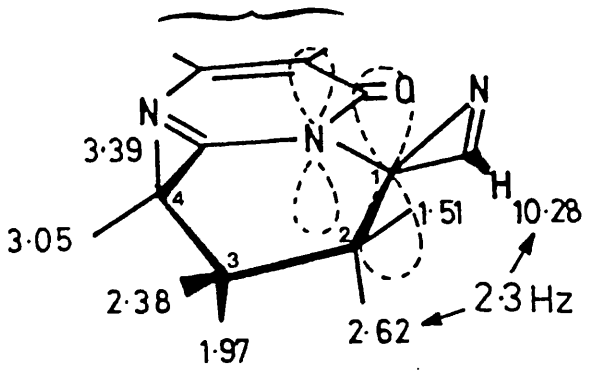


Fig. 96

Newman projections looking along the C_3-C_2 and C_3-C_4 bonds are represented in Figure 97 along with the vicinal coupling constants.

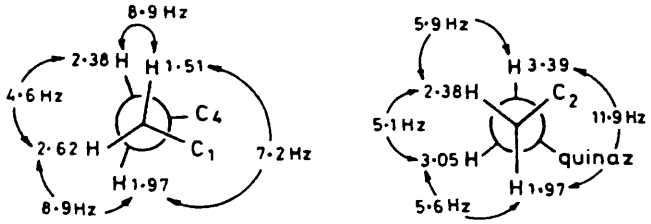


Fig. 97

The magnitude of these vicinal coupling constants for C_2H-C_3H excludes both half-chair conformations for (123), one of which is illustrated in Figure 98(a), since none of the C_3H-C_2H coupling constants is large enough for an axial-axial coupling ($\sim$ 12 Hz). But they are compatible with the alternative twist-boat (Figure 98(b)).

Fortunately, the conformations of the two possible twist-boats have different Newman projections along the C_2-C(spiro) bond (Figure 99).

Because of the similarity of the protons on the methylene group adjacent to the spiro-centre to those in (112) both in chemical shift (δ 1.52 v 1.75 and 2.62 v 2.65, respectively) and coupling constant to the azirine ring H (J 2.3 v 2.8 Hz to the lower-field resonance in each case), the twist-boat represented in Figure 96 is the conformation adopted by (123).

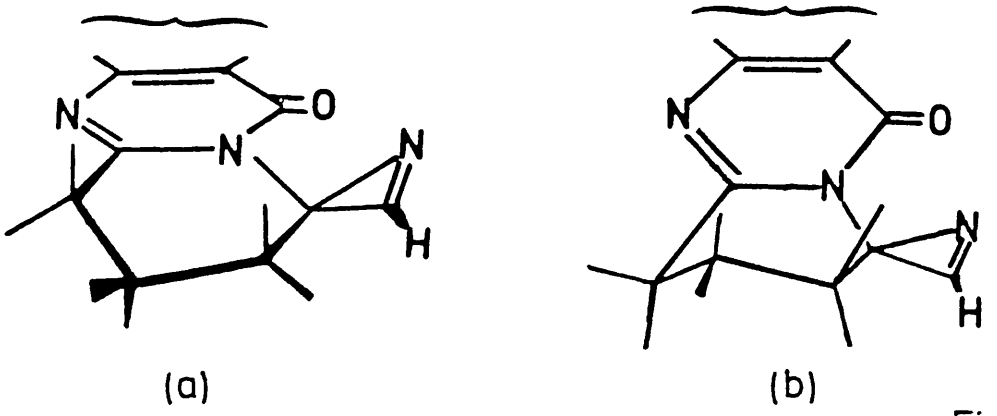
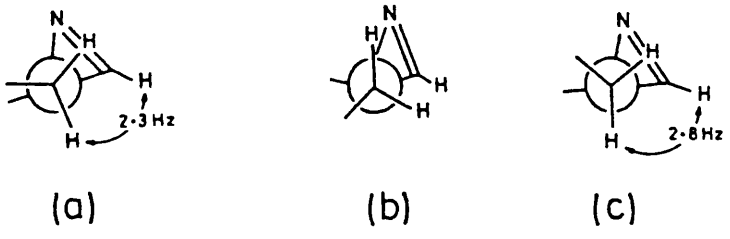


Fig. 98

Why should this twist-boat be favoured to the exclusion of other conformations? Examination of models suggest that as in the case previously (3.2.10), this is the conformation where there is the best alignment of the (bonded) p-orbital at the spiro-centre with the p-orbital of the quinazolone ring nitrogen and thus results in a lowering of energy and a stabilisation of this conformation over the others. Also as previously, the slight tilting of the p-orbital at the spiro-centre would serve to increase this alignment in the preferred conformation in Figure 96 but to decrease it in other possible conformations.



Newman projections along the C_2-C(spiro) bonds in

(a) Azirine (123) in the twist-boat represented in Figure 96

(b) Azirine (123) in the alternative twist-boat (Figure 98(b))

(c) Azirine (112)

Fig. 99

3.3.3. Conformational analysis of azirine (124).

The ring fused azirine (124) has not been separated from (123) but in the 400 MHz n.m.r. spectrum of the mixture, signals from (124) are sufficiently separated from those for (123) for its structure to be assigned. Thus, the azirine ring proton signal is a singlet at δ 4.42 and the vicinal coupling constants within the trimethylene chain show the ring to have the conformation shown in Figure 100.

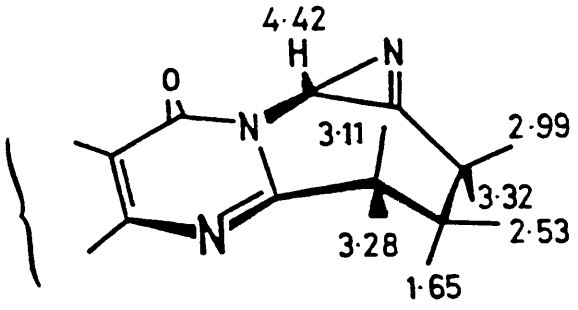


Fig. 100

Figure 101 shows Newman projections along the (azirine) CH_2-CH_2 and CH_2CH_2(quinaz) C-C bonds with the measured vicinal coupling constants.

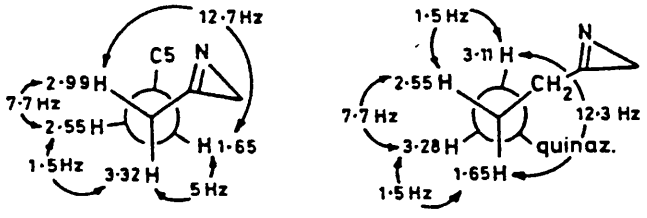


Fig. 101

Examination of models suggests that there is an accessible alternative conformation (Figure 102) for this ring-fused azirine in which there is better staggering of bonds in the trimethylene chain but which, nevertheless, can be excluded from the size of the coupling constants referred to above.

Again, the preference of the ring-fused azirine (124) for the conformation shown in Figure 100 is probably due to the same reason

outlined previously for azirine (123) - because it gives rise to the best alignment of the (bonded) p-orbital at the spiro-centre with the p-orbital of the quinazolone ring nitrogen.

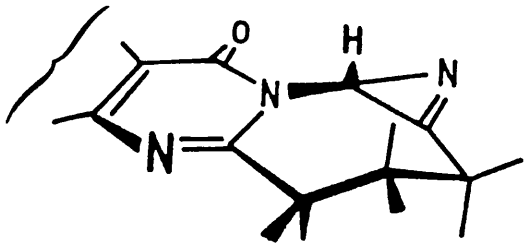


Fig. 102

3.3.4. Stereochemistry of 1H to 2H-azirine rearrangement.

Oxidation of quinazolone (100) with LTA generates the corresponding N-nitrene which adds to the alkyne bond, and (123) and (124) are formed by rearrangement of the unstable 1H-azirine intermediate (Figure 103). By analogy with the corresponding intramolecular addition of N-nitrenes to alkenes,[62] nitrene addition to the alkyne bond would be expected to take place as shown and would lead to the conformation of 1H-azirine indicated. It is noteworthy that migration of the N-N-bond in the two modes a and b shown deliver (123) and (124) directly in their most stable conformations.

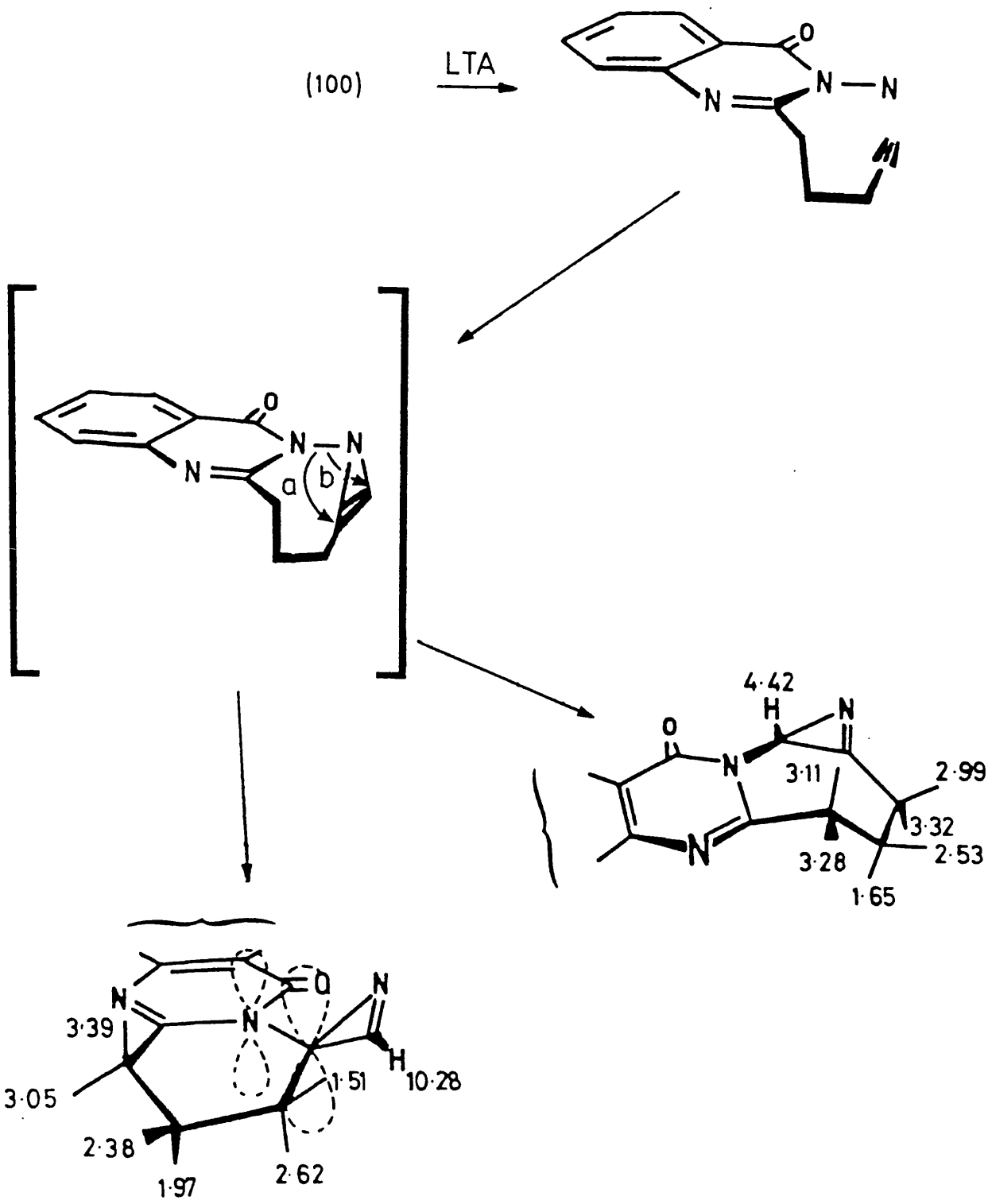

(100)
LTA
O
N
N
a
b
4·42
H
3·11
2·99
3·32
3·28
2·53
1·65
3·39
3·05
2·38
1·97
2·62
1·51
10·28

Fig.103

Conclusion

2H-Azirines are obtained in greatly improved yields on going from inter- to intra-molecular trapping of N-nitrenes by alkynes.

Analysis of the n.m.r. spectra of azirines (109), (112), (115), and (116) together with the X-ray crystal structure of (109) reveals that a requirement for near-coplanarity of three bonds at the spiro-centre results in conformational anchoring of the five-membered ring.

Similarly, azirines (123) and (124) are shown to be anchored in solution in the conformations shown (Figures 96 and 100, respectively). It is suggested that these and the envelope conformations in (109), (112), (115), and (116) are stabilised by an interaction between the quinazolone nitrogen (N-3) p-orbital and a (bonded) p-orbital on the adjacent azirine carbon atom (the spiro-centre in (109), (112), (115), (116), and (123).

Examination of the four azirine ring containing structures in the Cambridge crystallographic data file (Figure 87) shows that all of these show the same near-coplanarity of azirine C-C bond and substituent bonds at the 3-position.

Attempts to trap the 1H-azirine were unsuccessful, most probably due to the fact that migration of the N-N bond in the 1H-azirine delivers the 2H-azirine, in the cases studied, directly in their most stable conformations.

3.4. Conformational studies on 3-Phenyl-2,2-pentamethylene azirine (126).

3.4.1.

Since the near co-planarity at the spiro-centre in (109) is also present at C-2 in all other published crystal structures of azirines and is therefore, presumably, common to all azirines, further conformational manifestation of this effect was anticipated in other spiro- or ring-fused azirines. In an attempt to provide experimental evidence that this was the case, n.m.r. studies were carried out on 3-phenyl-2,2-pentamethylene azirine (126).

3.4.2. Synthesis of 3-Phenyl-2,2-pentamethylene azirine (126).

Azirine (126) was prepared by reaction of dimethylhydrazone methiodide (125) with sodium isoproxide in isopropanol (a modified Neber reaction) as outlined by Sato[63] but the reaction did not go cleanly in our hands due to formation of isopropoxyaziridine (127) (Figure 104).

Azirine (126) and isopropoxyaziridine (127) were produced in a 3:1 ratio respectively but chromatography yielded pure (126) as a pale yellow oil.

3-Phenyl-2,2-pentamethylene azirine (126) shows a medium intensity C=N stretching absorption in the i.r. spectrum at 1726 cm^{-1}.

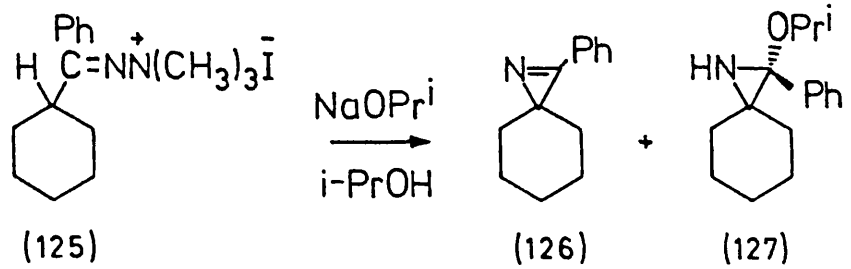


Fig.104

3.4.3. Conformational analysis of 3-Phenyl-2,2-pentamethylene azirine (126).

The conformations and conformational energy changes in cyclohexane

are given in Figure 105.[64]

Conformational inversion in cyclohexane occurs rapidly at room temperature. However, when cyclohexane is cooled, the rate of chair-chair interconversion is reduced and at low temperatures (< -100 ^{o}C) it is possible to identify two sets of signals in the ^{1}H n.m.r. spectrum, corresponding to the axial and equatorial hydrogen atoms. As the temperature is raised the two sets of signals coalesce, producing a single sharp signal at room temperature.

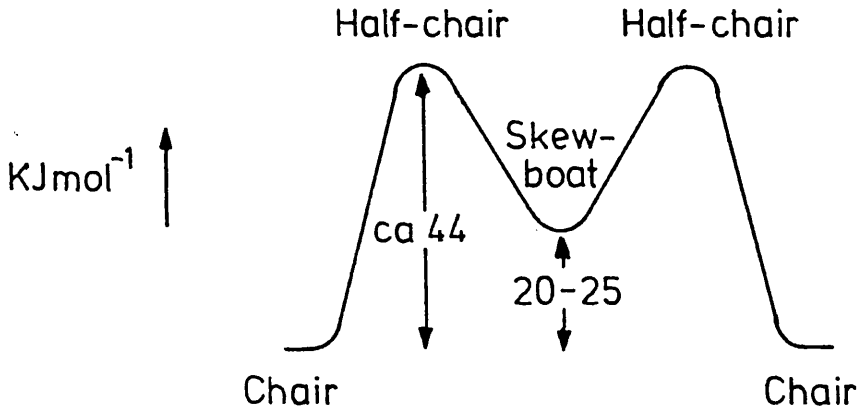
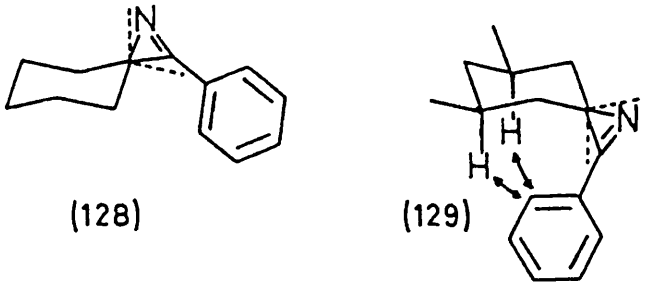


Fig. 105

Simple substitution on a cyclohexane ring does not significantly affect the rate of conformational inversion, but it does affect the equilibrium position between alternative chair forms which are no longer identical. For example, with the phenylcyclohexane, the free-energy difference (ΔG^{o}) between the equatorial and axial phenyl group on a cyclohexane ring is $\sim$ 3 Kcal mol^{-1},[65] or put another way, the ratio of two chairs is 172:1.

If it is assumed that the azirine ring is symmetrical (as is the case with a cyclopropene ring), the two alternative chair forms that

3-phenyl-2,2-pentamethylene azirine (126) could adopt are shown in Figure 106.

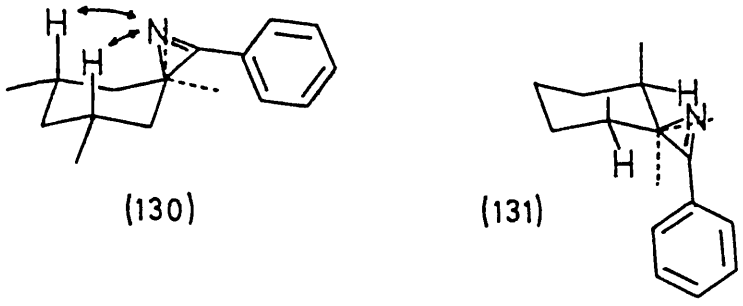


(128) (129)

Fig.106

Conformation (128) should be marginally preferred over (129), due to the absence of the destabilising interactions between the phenyl group and the axial cyclohexyl ring protons.

However, if the near co-planarity at the spiro-centre found in (109) is also present at C-2 in 3-phenyl-2,2-pentamethylene azirine (126), the two alternative chair forms are not (128) and (129), but (130) and (131) (Figure 107).



(130) (131)

Fig.107

Examination of models reveals that deformation at C-2 substantially reduces the destabilising interactions between the phenyl group and the axial cyclohexyl ring protons (compared with (129)) in one chair form, but it also brings the azirine ring nitrogen into closer proximity with the axial cyclohexyl ring protons in the alternative chair form and

possibly gives rise to an aggravated destabilising 1,3-diaxial interaction. The net effect of deformation at C-2 therefore would be expected to cause conformation (131) to be preferred over (130). This analysis neglects the eclipsing between the azirine C-C bond and equatorial C-H bonds at the α positions which are present in both (130) and (131) (and which, to a first approximation, will cancel out).

3.4.4. ^{1}H n.m.r. of 3-Phenyl-2,2-pentamethylene azirine (126).

The 400 MHz ^{1}H n.m.r. spectrum of azirine (126) shows that two of the cyclohexyl ring protons come at slightly lower field compared with the other cyclohexyl ring protons and appear as a structured multiplet (Figure 108).

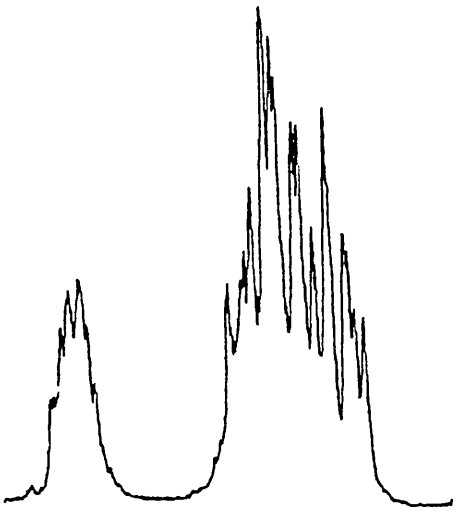
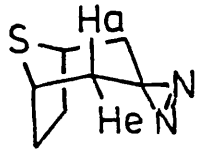


Fig.108

In substituted cyclohexanes, the width of the multiplet at half height ($W_{\frac{1}{2}}$) is characteristic and permits configurational assignment of the cyclohexyl ring proton with an axial proton generally having $W_{\frac{1}{2}}$

larger than 15 Hz while $W_{\frac{1}{2}}$ of an equatorial proton is generally below 12 Hz.[66] $W_{\frac{1}{2}}$ of the structured multiplet at 1.9 p.p.m. (Figure 108) is 21.5 Hz indicating that the two cyclohexyl ring protons involved are axial protons - possibly the ax-H at positions 2 and 6.

Normally axial protons in the cyclohexane ring give rise to resonances upfield from their equatorial counterparts (typically 1.12 and 1.60 p.p.m. respectively). However, it is known that some substituents are capable of inverting the usual order, and indeed this same inversion has been observed by Uebel and Martin[67] for spiro-compound (132) (Figure 109).



(132) Ha 2·25ppm
He 0·68ppm

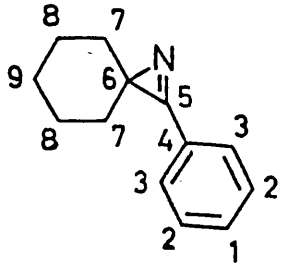
Fig. 109

Attempts to separate out the resonances of the cyclohexyl ring protons with a shift reagent such as $Eu(dpm)_3$ though successful, were accompanied by substantial line-broadening.

The 400 MHz ^1H n.m.r. spectrum of (126) shows the aromatic protons to be split into two multiplets - a three proton multiplet at 7.54 p.p.m. and a two proton multiplet (presumably the ortho protons) at 7.84 p.p.m. N.O e's on irradiating the two ortho aromatic protons at 7.84 p.p.m. were δ 7.54 (4.7 %), 1.9 (0 %), and 1.65 - 1.52 (1.6 %).

With both conformations, (130) and (131), no N.O.e. on irradiating ortho-ArH is expected at the two proton multiplet at 1.9 p.p.m., (assuming this is the signal from ax-H at C-2 and C-6) and this was found to be

the case. N.O.e. effects are found with one or more resonances in the 8 proton multiplet (1.70 - 1.52 p.p.m.) but this was not helpful in determining which of (130) or (131) was the preferred conformation. Low temperature ^{13}C- n.m.r. was then used in order to determine what exactly was the ratio of the two conformers assuming of course, that there were two.



Assignment		$CFCl_3$ + ∿ 20 % CD_2Cl_2 (75 MHz) RT	(100 MHz) -128 °C Major conformer	$CFCl_3$ (100 MHz) -128 °C Minor conformer
5		179.46 (s)	178.82	178.08
		133.28 (d)	132.72	132.72
1,2,3		130.23 (d) 130.09 (d)	129.02(2)	129.02(2)
4		128.13 (s)	125.03	125.03
6		41.48 (s)	40.13	39.39
7		37.02 (t)	35.38	34.38
8		27.89 (t)	27.83	24.30
9	and	27.65 (t)	25.49	25.85

Fig.110

3.4.5. ^{13}C n.m.r. of 3-Phenyl-2,2-pentamethylene azirine (126).

A 100 MHz ^{13}C n.m.r. spectrum carried out at -128 °C in $CFCl_3$ + ∿ 20 % CD_2Cl_2 did indeed reveal the presence of two conformers, and in a 3:1 ratio (Figure 110).

To check that these signals were due to two conformers, a spectrum was subsequently run at room temperature which showed the presence of only one set of signals. From integration of their respective signals the free-energy difference between the conformers can be calculated and is found to be 0.3 Kcal mol^{-1}.

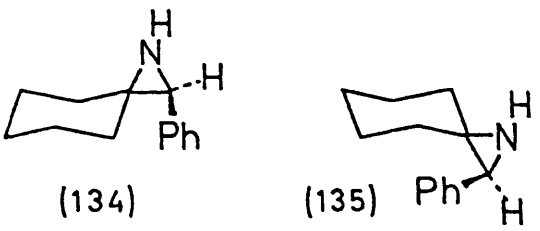
Curiously, the ratio of conformers changed from 2:1 to 3:1 on going from $CFCl_3$ to $CFCl_3$ + ∿ 20 % CD_2Cl_2. Although the solution in $CFCl_3$ froze at -128 °C, enough data was accumulated for a spectrum to be obtained before this occurred.

3.4.6. 3-Phenyl-2,2-pentamethylene aziridine (133) - A comparison.

3-Phenyl-2,2-pentamethylene aziridine (133) was prepared by lithium aluminium hydride reduction of azirine (126) as a colourless oil in quantitative yield. The i.r. spectrum shows a NH stretching absorption at 3,250 cm^{-1} and a 300 MHz ^1H n.m.r. spectrum shows that all the cyclohexyl ring protons came together as a broad multiplet over the 1.75 - 1.05 region.

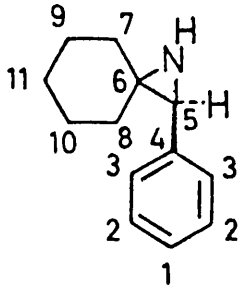
The two alternative chair forms that aziridine (133) could adopt are shown in Figure 111, with (134) probably the preferred one.

A 100 MHz ^{13}C n.m.r. spectrum carried out at -112 °C also showed the presence of two conformers in 3:1 ratio (Figure 112). In contrast to (126), there was no change in the ratio of conformers of (133) on changing from $CFCl_3$ to $CFCl_3$ + ∿ 20 % CD_2Cl_2.



(134) (135)

Fig. 111



$CFCl_3$ + ~ 20 % CD_2Cl_2 (-112 °C)	$CFCl_3$ (-112 °C)
Major conformer	Minor conformer
138.05	137.87
127.73	127.73
127.35	127.35
126.28	126.28
44.68	44.56
44.00	44.00
38.06	37.91
28.90	28.56
26.55	25.83
24.99	24.69
and 24.08	and 24.26

Fig. 112

3.4.7. Conclusion

The main problem encountered in the conformational studies on 3-phenyl-2,2-pentamethylene azirine (126) was that n.m.r. investigations were unable to establish the major conformation adopted by the azirine (126), but low temperature 100 MHz ^{13}C n.m.r. was successful in showing that there were only two conformers and in a 3:1 ratio.

The significance (if any) of the identity of conformer ratios in

both the spiro azirine (126) and aziridine (133) remains to be established. From the discussion above, the two spiro-centres would be expected to have different geometries. Introduction of an oxygen into the 4-position of the six-membered ring of (126) could help to resolve this question by increasing the chemical shift differences between the protons on this ring in its n.m.r.

PART 4

EXPERIMENTAL

Experimental

Melting points were determined on a Kofler block and are uncorrected.

Infrared spectra were run as thin films or Nujol mulls on a Perkin-Elmer 298 spectrophotometer, and reported by denoting the position of significant peaks in cm^{-1} (suffix: v = very; br = broad; s = strong; m = medium; w = weak).

Routine ^{1}H n.m.r. spectra were recorded on Varian EM 390 spectrometer. Chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ 0.00) as an internal standard. Multiplicities are reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

Elemental microanalyses were carried out by C.H.N. Analysis Ltd., Leicester.

Chromatographic technique, that as described by W. Clark Still.[81]

Lead tetra-acetate was freed from acetic acid prior to use by placing in a vacuum desiccator and evacuating using a water pump for 5 min. Dichloromethane was distilled prior to use from calcium hydride.

4.1. Experimental work appertaining to Part 2, intramolecular trapping of N-nitrenes by alkenes.

4.1.1. Preparation of alkylating agents.

Allyl chloride, crotyl chloride, and 3-chloro-2-methylpropene were commercially available (Aldrich) and were used as received. Cinnamyl bromide and 1-bromobut-2-yne prepared from the corresponding alcohols by treatment with hydrobromic acid and phosphorus tribromide, respectively.

3-Methylbut-3-en-1-ol tosylate: To an ice-cooled mixture of 3-methylbut-3-en-1-ol (Aldrich, 5 g, 1 mol. equiv.) and tosyl chloride (12.7 g, 1.2 mol. equiv.) in dry ether was added freshly powdered KOH (9.8 g, 3 mol. equiv.) with stirring. After stirring with cooling for a further 2 hr., the mixture was poured into ice-water, the ether layer separated and the aqueous layer extracted twice more with ether. The combined ether layers were dried and evaporated to leave the tosylate as an oil, (12.2 g, 87 %) δ 7.72 (d, J 8 Hz, 2 ArH ortho to SO_2O), 7.28 (d, J 8 Hz, 2 ArH orhto to Me), 4.67 (m, -CMe=CH_2), 4.06 (t, J 7 Hz, CH_2OTs), 2.39 (s, Me), 2.29 (t, J 7 Hz, -CH_2CMe=CH_2), and 1.62 (s, -CMe=CH_2).

Similarly, But-3-en-1-ol tosylate was prepared from the corresponding alcohol as outlined above and was obtained as an oil (15.9 g, 99 %). δ 7.78 (d, J 8 Hz, 2 ArH ortho to SO_2O), 7.32 (d, J 8 Hz, 2 ArH ortho to Me), 5.68 (m, -CH=CH_2), 5.06 (m, -CH=CH_2), 4.06 (t, J 7 Hz, CH_2OTs), 2.43 (s, Me), and 2.40 (q, J 7 Hz, -CH_2CH=CH_2).

E-Pent-3-en-1-ol was prepared in four steps from crotyl chloride. 1) Pent-3-enyl nitrile was prepared by treating crotyl chloride with cuprous cyanide as described in the literature,[69] as a pale yellow liquid, yield 66.7 g (75 %), b.p. 70 - 92 °C/80 mmHg; δ 5.82 (m, -CH=CH), 5.32 (m, CH=CH), 3.03br (d, J 5 Hz, CH_2) and 1.70br (d, J 5 Hz, Me);

ν_{max} 2250(m) and 968(s) cm^{-1}. 2) Pent-3-enyl nitrile (63.8 g) was treated with concentrated hydrochloric acid (79 ml) in the manner described by Falaise and Frognier[70] for conversion of but-3-enyl nitrile to 3-butenoic acid. However, after continuous shaking for 30 min. whilst occasionally heating with a small flame the two layers were still apparent miscible and no ammonium chloride was produced. The reaction mixture was diluted with water, saturated with salt and extracted four times with ether. The combined ether layers were extracted three times with 100 ml portions of 10 % sodium carbonate solution and the combined sodium carbonate extracts were washed with ether, acidified with concentrated hydrochloric acid, and saturated with salt, and extracted four times with ether. After drying, removal of ether by evaporation gave 3-pentenoic acid (3.9 g). Repeating the same treatment on the recovered but-3-enyl nitrile (35.4 g) gave more 3-pentenoic acid (3.9 g, combined yield 10 %); δ 9.08br (s, CO_2H), 5.54 (m, -CH=CH-), 3.03 (m, CH_2), and 1.69 (m, Me). 3) E-Pent-3-en-1-ol was prepared by reducing 3-pentenoic acid with lithium aluminium hydride as described for the reduction of 2-propenyl-5-phenyl pent-4-enoic acid to the corresponding alcohol (4.1.5) and obtained as a colourless liquid (2.8 g, 42 %), b.p. 140 ^{o}C/150 mmHg; δ 5.48 (m, -CH=CHMe), 3.58 (t, J 7 Hz, CH_2OH), 2.19 (m, CH_2CH=CHMe), 1.94br (s, OH), and 1.66 (m, -CH=CHMe). 4) E-Pent-3-en-1-ol tosylate was prepared by the method described previously and was obtained as an oil (7.2 g, 92 %); δ 7.87 (d, J 8 Hz, 2 ArH ortho to SO_2O), 7.31 (d, J 8 Hz, 2 ArH ortho to Me), 5.39 (m, -CH=CHMe), 4.00 (t, J 7 Hz, $-CH_2OTs$), 2.44 (s, Me), 2.32 (m, CH_2CH=CHMe), and 1.61br (d, J 5 Hz, -CH=CHMe).

4-Methylpent-4-en-1-ol tosylate: Dimethyl 2(2-methylprop-2-enyl)-1,3-propanedioate, was first decarbomethoxylated (for experimental procedure

see 4.1.4) to give methyl 4-methylpent-4-enoate as a pale yellow liquid (53.2 g, 58 %), δ 4.66 (m, -CMe=$\underline{CH_2}$), 3.61 (s, -CO_2Me), 2.35 (m, $\underline{CH_2CH_2}$), and 1.70 (s, -$\underline{CMe}$=CH_2). Methyl 4-methylpent-4-enoate was reduced with lithium aluminium hydride to give 4-methylpent-4-en-1-ol (31.7 g, 65 %), b.p. 60 - 64 °C/19 mmHg; δ 4.68br (s, -CMe=$\underline{CH_2}$), 3.60 (t, J 7 Hz, $\underline{CH_2}$OH), 2.46br (s, OH), 2.08 (t, J 7 Hz, $\underline{CH_2}$CMe=CH_2), and 1.71 (m, $\underline{CH_2CH_2CMe}$=CH_2); ν_{max} 3340(br,s), 1650(m), 1440(m), 1375(m), 1060(s), and 890(s) cm^{-1}. 4-Methylpent-4-en-1-ol tosylate was obtained as an oil (31.2 g, 98 %); δ 7.76 (d, J 8 Hz, 2 ArH ortho to SO_2O), 7.30 (d, J 8 Hz, 2 ArH ortho to Me), 4.63 (m, -CMe=$\underline{CH_2}$), 4.00 (t, J 7 Hz, $\underline{CH_2}$OTs), 2.40 (s, Me), 1.98 (m, -$\underline{CH_2}$CMe=CH_2), 1.77 (m, $CH_2\underline{CH_2}CH_2$), and 1.63 (s, -$\underline{CMe}$=CH_2).

E-Hex-4-en-1-ol tosylate: 2,3-Dibromotetrahydropyran and methyl magnesium iodide were reacted to give 3-bromo-2-methyltetrahydropyran, which was converted by ring scission with sodium into E-hex-4-en-1-ol using a procedure similar to that used by Crombie and Harper;[71] δ 5.41 (m, -$\underline{CH}$=$\underline{CH}$Me), 3.59 (t, J 6 Hz, -$\underline{CH_2}$OH), 2.07 (m, -$\underline{CH_2}CH_2CH_2\underline{OH}$), and 1.62 (m, $CH_2\underline{CH_2}CH_2CH$=$\underline{CHMe}$). E-Hex-4-en-1-ol tosylate was obtained as an oil (14 g, 99 %); δ 7.74 (d, J 8 Hz, 2 ArH ortho to SO_2O), 7.31 (d, J 8 Hz, 2 ArH ortho to Me), 5.31 (m, -$\underline{CH}$=$\underline{CH}$Me), 4.00 (t, J 7 Hz, $\underline{CH_2}$OTs), 2.42 (s, Me), 2.00 (m, $\underline{CH_2}$CH=CHMe), and 1.65 (m, $\underline{CH_2CH_2}$CH=CHMe).

4.1.2. Synthesis of dimethyl monosubstituted propane-1,3-dioates. General procedure.

Dimethyl monosubstituted propane-1,3-dioates were obtained by addition of dimethyl propanedioate (1.1 mol. equiv.) to a solution of sodium methoxide (1 mol. equiv.) in methanol followed by dropwise addition of the alkylating agent indicated (1.05 mol. equiv.) with stirring. When an allyl or substituted allyl group was used as the alkylating agent the

solution was left stirring overnight, otherwise, the solution was heated under reflux over 1-2 days. After cooling and separation of the sodium chloride or tosylate, the methanol was evaporated under reduced pressure, the residue dissolved in ether and the ether washed twice with water, dried and evaporated. Distillation gave the required propanedioates as colourless liquids. The following were obtained in this way:

Dimethyl 2-(E-but-2-enyl)-1,3-propanedioate — using crotyl chloride; yield 58.5 g (67 %), b.p. 69 - 76 ^{o}C/0.7 mmHg; δ 5.42 (m, -CH=CHMe), 3.67 (s, 2 x CO_2Me), 3.35 (t, J 7 Hz, CH), 2.52 (t, J 7 Hz, CH_2) and 1.60 (d, J 6 Hz, -CH=CHMe); dimethyl 2-(2-methylprop-2-enyl)-1,3-propanedioate — using 3-chloro-2-methylpropene; yield 82.5 g (58 %), b.p. 97 - 108 ^{o}C/15 mmHg; δ 4.72 (m, -CMe=CH_2), 3.70 (s, 2 x CO_2Me), 3.59 (t, J 7 Hz, CH), 2.60 (d, J 7 Hz, CH_2), and 1.72 (s, -CMe=CH_2); dimethyl 2-(propenyl)-1,3-propanedioate — using allyl chloride; yield 40.1 g (56 %), b.p. 60 - 61 ^{o}C/0.6 mmHg; δ 5.84 (m, -CH=CH_2), 5.19 (m, -CH=CH_2), 3.82 (s, 2 x CO_2Me), 3.54 (t, J 7 Hz, CH), and 2.68 (m, CH_2); dimethyl 2-(3-methylbut-3-enyl)-1,3-propanedioate — using 3-methylbut-3-en-1-ol tosylate; yield 10.6 g (35 %), b.p. 82 - 85 ^{o}C/0.4 mmHg; δ 4.71 (m, -CMe=CH_2), 3.70 (s, 2 x CO_2Me), 3.37 (m, CH), 2.04 (m, CH_2CH_2), and 1.71 (s, -CMe=CH_2); dimethyl 2-(4-methylpent-4-enyl)-1,3-propanedioate — using 4-methylpent-4-en-1-ol tosylate; yield 11.9 g (35 %), b.p. 85 - 90 ^{o}C/0.15 mmHg; δ 4.67 (m, -CMe=CH_2), 3.71 (s, 2 x CO_2Me), 3.36 (t, J 7 Hz, CH), 1.98 (m, $CH_2CH_2CH_2$), 1.78 (s, -CMe=CH_2), and 1.46 (m, $CH_2CH_2CH_2$). Dimethyl 2-(but-3-enyl)-1,3-propanedioate was obtained similarly but dimethyl sulphoxide was used as the solvent and alkylation using sodium methoxide and but-3-en-1-ol tosylate carried out by heating the solution at 90 - 100 ^{o}C (oil bath temp.) for 2 days. After cooling,

the solution was poured into water, extracted twice with ether, the combined ether extracts worked up as described above to give a colourless oil; yield 16.4 g (25 %), b.p. 73 - 78 ^{o}C/0.4 mmHg; δ 5.73 (m, -CH=CH_2), 5.02 (m, -CH=CH_2), 3.70 (s, 2 x CO_2Me), 3.37 (t, J 7 Hz, CH), and 2.01 (m, CH_2CH_2).

4.1.3. Synthesis of dimethyl disubstituted propane-1,3-dioates

General procedure

With an allyl or substituted allyl group as the alkylating agent, dimethyl disubstituted propane-1,3-dioates were obtained by addition of dimethyl monosubstituted propane-1,3-dioate (1 mol. equiv.) to a solution of sodium methoxide (1.05 mol. equiv.) in methanol followed by addition of the alkylating agent (1.1 mol. equiv.) as described above. The following were prepared using this method:

Dimethyl-2,2-di-(E-but-2-enyl)-1,3-propanedioate —— prepared from dimethyl 2-(E-but-2-enyl)-1,3-propanedioate and crotyl bromide, yield 16.4 g (60 %), b.p. 90 - 92 ^{o}C/0.35 mmHg; δ 5.49 (m, -CH=CHMe), 3.74 (s, CO_2Me), 2.60 (m, CH_2), and 1.66 (m, -CH=CHMe); ν_{max} 2950, 1735(s), 1438(s), 1275, 1205(m), 1132, 1038, and 968(s) cm^{-1}; dimethyl 2-(2-methylprop-2-enyl)-2-(E-but-2-enyl)-1,3-propanedioate —— prepared from dimethyl 2-(E-but-2-enyl)-1,3-propanedioate and 3-chloro-2-methylpropene, yield 24.4 g (29 %), b.p. 104 - 110 ^{o}C/1.5 mmHg; δ 5.40 (m, -CH=CHMe), 4.77 (m, -CMe=CH_2), 3.66 (s, 2 x CO_2Me), 2.65 (s, CH_2CMe=CH_2), 2.57 (d, J 7 Hz, CH_2CH=CHMe), and 1.62 (m, -CMe=CH_2, and -CH=CHMe); dimethyl 2-(but-2-ynyl)-2-(E-but-2-enyl)-1,3-propanedioate —— prepared from dimethyl 2-(E-but-2-enyl)-1,3-propanedioate and 1-bromobut-2-yne, yield 6 g (64 %), b.p. 100 - 107 ^{o}C/0.4 mmHg; δ 5.41 (m, -CH=CHMe), 3.69 (s, 2 x CO_2Me); 2.68 (m, 2 x CH_2), 1.74 (t, J 2 Hz, -C≡CMe), and 1.66 (d, J 6 Hz, -CH=CHMe); ν_{max} 2973, 1732(s),

1432(s), 1279, 1200(m), 1128, 1049, and 966(s) cm^{-1}; dimethyl 2-(3-phenylprop-2-enyl)-2-(prop-2-enyl)-1,3-propanedioate —— prepared from dimethyl 2-(propenyl)-1,3-propanedioate and cinnamyl bromide, yield 50.1 g (75 %), b.p. 153 - 158 ^{o}/0.6 mmHg; δ 7.39 (s, 5 x ArH), 6.53 - 5.03 (m, -CH=CH_2 and -CH=CHPh), 3.80 (s, 2 x CO_2Me), and 2.80 (two overlapping doublets, J 6 Hz, 2 x CH_2); dimethyl 2-(prop-2-enyl)-2-(but-3-enyl)-1,3-propanedioate: —— prepared from dimethyl 2-(but-3-enyl)-1,3-propanedioate and allyl chloride, yield 5.8 g (29 %), b.p. 87 - 91 ^{o}C/0.4 mmHg; δ 5.65 (m, 2 x CH=CH_2), 5.00 (m, 2 x -CH=CH_2), 3.68 (s, 2 x CO_2Me), 2.62 (d, J 7 Hz, -CH_2CH=CH_2) and 1.98 (m, CH_2CH_2CH=CH_2).

For other alkylations, the solvent used was dimethyl sulphoxide with heating at 55 ^{o}C (bath temp.) overnight. After the work up described above, distillation gave the dimethyl disubstituted propane-1,3-dioates as colourless oils. The following were prepared in this way:

dimethyl 2-(E-pent-3-enyl)-2-(3-methylbut-3-enyl)-1,3-propanedioate —— prepared from dimethyl 2-(3-methylbut-3-enyl)-1,3-propanedioate and E-pent-3-en-1-ol tosylate, yield 2.1 g (25 %), b.p. 140 - 150 ^{o}C/5 x 10^{-6} mmHg; δ 5.40 (m, -CH=CHMe), 4.67 (m, -CMe=CH_2), 3.66 (s, 2 x CO_2Me), 1.90 (m, 2 x CH_2CH_2), 1.69 (s, CMe=CH_2), and 1.61 (d, J 4 Hz, -CH=CHMe); dimethyl 2-(E-hex-4-enyl)-2-(4-methylpent-4-enyl)-1,3-propanedioate —— prepared from dimethyl 2-(4-methylpent-4-enyl)-1,3-propanedioate and E-hex-4-en-1-ol tosylate, yield 5.1 g (31 %), b.p. 145 - 155 ^{o}C/1.7 x 10^{-5} mmHg; δ 5.38 (m, -CH=CHMe), 4.66 (m, -CMe=CH_2), 3.68 (s, 2 x CO_2Me), 1.92 (m, 2 x $CH_2CH_2CH_2$), 1.64 (m, -CH=CHMe and -CMe=CH_2), and 1.27 (m, 2 x $CH_2CH_2CH_2$); for dimethyl 2-(Z-but-2-enyl)-2-(E-but-2-enyl)-1,3-propanedioate the following method was used: dimethyl 2-(but-2-ynyl)-2-(E-but-2-enyl)-1,3-propanedioate (6 g) was dissolved in dry pyridine (60 ml) and 5 % palladium-on-barium sulfate

(1.6 g) added. The solution was left rapidly stirring under hydrogen. After an induction period (10 - 15 min.) the solution absorbed hydrogen at a steady rate (ca 20 cm^3 H_2 per min.) which decreased sharply after addition of 1 mol. equiv. of hydrogen. The solution was filtered to remove catalyst and ether added. The ethereal layer was washed with hydrochloric acid (2 M), then water, dried and evaporated to leave a colourless liquid, yield 6 g. δ (400 MHz) 5.57 (dqt, J 10.9, 6.8, and 1.6 Hz, Z -CH=CHMe), 5.48 (dqt, J 14.9, 6.8 and 1.1 Hz, E -CH=CHMe), 5.20 (m, Z -CH=CHMe) & E -CH=CHMe), 3.68 (s, 2 x CO_2Me), 2.62 (m, 2 H), 2.52 (m, 2 H), 1.61 (ddt, J 6.8, 1.2, and 1.2 Hz, trans-d.b. methyl), and 1.58 (ddt, J 6.8, 1.7, and 0.8 Hz, cis-d.b. methyl). The composition of this colourless liquid is, however, believed to be a mixture of dimethyl 2-(Z-but-2-enyl)-2-(E-but-2-enyl)-1,3-propanedioate (74 %), dimethyl 2,2-di(E-but-2-enyl)-1,3-propanedioate (13 %), and dimethyl 2,2-di(Z-but-2-enyl)-1,3-propanedioate (13 %) (see Section 2.5, Competitive intramolecular trapping of the N-nitrene by cis- and trans- α-methyl-substituted double bonds).

4.1.4. Preparation of the mono-acids.

General procedure.

Method (a) involved the hydrolysis of dimethyl disubstituted propane-1,3-dioate followed by decarboxylation. Method (b) involved decarbomethoxylation followed by hydrolysis to give the mono-acid.

Method (a)

The appropriate propanedioate and sodium hydroxide solution (2 M, 4 - 10 mol. equiv.) were heated to boiling under reflux . Ethanol was added until reaction mixture became homogeneous then the solution was heated under reflux for a further 2 hr. or overnight. Ethanol was removed

under reduced pressure using a rotatory evaporator and the residual solution was extracted twice with ether and then cooled by addition of ice before being acidified down to pH 1 with conc. hydrochloric acid. The mixture was then extracted twice with ether and the ether layers combined, dried, and evaporated to leave the required propanedioic acid. The following were obtained in this way:

2,2-Di(E-but-2-enyl)-1,3-propanedioic acid as colourless crystals (from CCl_4), yield 5.9 g (80 %); δ 11.3br (s, CO_2H), 5.58 (m, -CH=CHMe), 2.66 (d, J 6 Hz, CH_2), and 1.68 (d, J 5 Hz, -CH=CHMe); 2-(Z-but-2-enyl)-2-(E-but-2-enyl)-1,3-propanedioic acid as colourless crystals (from CCl_4/light petroleum), yield 2.5 g (49 %); δ 11.59br (s, 2 x CO_2H), 5.48 (m, 4 olefinic H), 2.64 (overlapping doublets, J 7 Hz, 2 x CH_2), and 1.67 (m, 2 x CH_3); 2-(3-phenyl-prop-2-enyl)-2-(prop-2-enyl)-1,3-propanedioic acid as a pale yellow oil, yield 32.6 g (72 %); δ 11.4br (s, 2 x CO_2H), 7.37 (s, 5 x ArH), 6.68 - 5.13 (5 olefinic H), and 2.93 (overlapping doublets, J 6 Hz, 2 x CH_2).

Decarboxylation: The appropriate propanedioic acid was heated in an oil bath at 130 - 150 °C until gas evoluton ceased (usually 90 - 120 min.). Kugelrohr distillation gave the following mono acids:

2-(E-but-2-enyl)-E-hex-4-enoic acid as a colourless oil, b.p. 130 - 150 °C/0.7 mmHg, yield 4.5 g (96 %); δ 11.3br (s, CO_2H), 5.53 (m, 2 x -CH=CHMe), 2.33 (m, CH and 2 x CH_2), and 1.65 (d, J 5 Hz, 2 x -CH=CHMe); 2-(Z-but-2-enyl)-E-hex-4-enoic acid as a colourless oil, b.p. 150 - 160 °C/0.17 mmHg, yield 0.7 g (81 %); δ 11.3br (s, CO_2H), 5.46 (m, 4 olefinic H), 2.38 (m, CH and 2 x CH_2), and 1.63 (m, 2 x CH_3); 2-(propenyl)-5-phenyl pent-4-enoic acid as an oil, yield 26.1 g (97 %); δ 9.28br (s, CO_2H), 7.31 (s, 5 x ArH), 6.66 - 4.96 (m, 5 olefinic H), and 2.59 (m, CH and 2 x CH_2).

Method (b)

The appropriate propanedioate (1 mol. equiv.), sodium chloride (2 - 4 mol. equiv.) and water (3 - 6 mol. equiv) in dimethyl sulphoxide were heated in an oil bath at 185 ^{o}C overnight. The solution was cooled, poured into water and extracted twice with ether, the combined ether extracts washed twice with water, dried and evaporated and the residual ester distilled under reduced pressure. The following were obtained in this way.

methyl 2-(2-methylprop-2-enyl)-E-hex-4-enoate as a liquid, b.p. 44 - 66 ^{o}C/0.35 mmHg, yield 13.7 g (69 %); δ 5.28 (m, -CH=CHMe), 4.60 (m, -CMe=CH_2), 3.52 (s, CO_2Me), 2.46 (m, CH), 2.16 (m, 2 x CH_2), 1.64 (s, -CMe=CH_2), and 1.58 (d, J 4 Hz, -CH=CHMe); methyl 2-(prop-2-enyl)-hex-5-enoate as a liquid, yield 3.3 g (77 %); δ 5.70 (m, 2 x -CH=CH_2), 4.97 (m, 2 x -CH=CH_2), 3.62 (s, $-CO_2Me$), and 2.46 - 1.52 (m, $-CH_2CH_2CH=CH_2$, $-CH_2CH=CH_2$, and CH); methyl 2-(3-methylbut-3-enyl)-E-hept-5-enoate as a liquid, yield 1.3 g (83 %); δ 5.36 (m, -CH=CHMe), 4.64 (m, -CMe=CH_2), 3.62 (s, CO_2Me), and 2.39 - 1.50 (m, CH, 2 x CH_2CH_2 and 2 x Me); methyl 2-(4-methylpent-4-enyl)-E-oct-6-enoate as an oil, yield 3.5 g (87 %); δ 5.38 (m, -CH=CHMe), 4.64 (m, -CMe=CH_2), 3.62 (s, CO_2Me), and 2.42 - 1.26 (m, CH, 2 x $CH_2CH_2CH_2$ and 2 x Me).

Hydrolysis of the esters above was carried out by heating under reflux with sodium hydroxide solution (2 M) containing ethanol in the usual way to give the following acids:

2-(2-methylprop-2-enyl)-E-hex-4-enoic acid as an oil, yield 1.76 g (95 %); δ 11.24br (s, CO_2H), 5.42 (m, -CH=CHMe), 4.73 (m, -CMe=CH_2), 2.57 (m, CH), 2.22 (m, 2 x CH_2), 1.70 (s, -CMe=CH_2), and 1.63 (d, J 4 Hz, -CH=CHMe); 2-(prop-2-enyl)-hex-5-enoic acid as a liquid, yield 2.9 g

(96 %); δ 10.56br (s, CO_2H), 5.78 (m, 2 x $C\underline{H}=CH_2$), 5.04 (m, 2 x $-CH=C\underline{H}_2$), and 2.57 - 1.51 (m, 7 H); 2-(3-methylbut-3-enyl)-E-hept-5-enoic acid as a liquid, yield 1.1 g (90 %); δ 9.75br (s, CO_2H), 5.38 (m, $-C\underline{H}=CHMe$), 4.64 (m, $-CMe=C\underline{H}_2$), and 2.40 - 1.52 (m, CH, 2 x $CH_2\underline{CH}_2$ and 2 x Me).

2-(4-Methylpent-4-enyl)-E-oct-6-enoic acid. After removal of ethanol as described in the procedure above, the insoluble organic material present was removed by extracting twice with ether, the ether layers combined, dried and evaporated to leave the sodium salt of the title acid as an oil; δ 5.36 (m, $-C\underline{H}=C\underline{H}Me$), 4.62 (m, $-CMe=C\underline{H}_2$), 2.16 - 1.14 (m, CH, 2 x $CH_2\underline{CH}_2CH_2$ and 2 x Me); ν_{max} 2938(s), 1580(s), 1440(s), 1305, 1150, 967(m) and 888(m) cm^{-1}. The sodium salt was dissolved in ether, the ether solution washed twice with hydrochloric acid (2 M), dried and evaporated to leave the title acid as an oil (2.2 g) (66 %); δ 11.53br (s, CO_2H), 5.36 (m, $-C\underline{H}=C\underline{H}Me$), 4.68 (m, $-CMe=C\underline{H}_2$), and 2.40 - 1.26 (m, CH, 2 x $\underline{CH}_2\underline{CH}_2\underline{CH}_2$ and 2 x Me); ν_{max} 3060 (s & very br), 2920(s), 1700(s), 1450(m), 1290, 1230, 1148, 962(m) and 886(m) cm^{-1}.

4.1.5. Acid Homologation $RCO_2H \rightarrow RCH_2CO_2H$

3-(prop-2-enyl)-6-phenylhex-5-enoic acid

2-Propenyl-5-phenylpent-4-enoic acid was homologated by 1) reduction with lithium aluminium hydride in ether to the corresponding alcohol (20.2 g, 80 %), b.p. 145 - 148 °C/0.35 mmHg; δ 7.21 (s, 5 x ArH), 6.48 - 5.86 (m, $C\underline{H}=C\underline{H}Ph$ and $-C\underline{H}=CH_2$), 5.00 (m, $-CH=C\underline{H}_2$), 3.53 (d, J 5 Hz, $\underline{CH}_2OH$), 2.16 (m, 2 x CH_2), and 1.73 (m, CH and OH); ν_{max} 3400(s) cm^{-1}, 2) converted to the tosylate (31.7 g, 89 %) as described previously, 3) reacted with potassium cyanide in dimethyl sulphoxide to form the nitrile (17.6 g, 93 %), b.p. 148 - 155 °C/0.35 mmHg; δ 7.21 (s, 5 x ArH), 6.50 - 5.48 (m, $C\underline{H}=C\underline{H}Ph$ and $-C\underline{H}=CH_2$), 5.06 (m, $-CH=C\underline{H}_2$), 2.24 (m, 3 x CH_2),

and 1.90 (m, CH); ν_{max} 2250(w) cm^{-1}, and 4) hydrolysis of the foregoing nitrile by heating in aqueous alcoholic potassium hydroxide solution. 3-(Prop-2-enyl)-6-phenylhex-5-enoic acid was obtained as an oil (9.4 g, 49 %); δ 10.12br (s, CO_2H), 7.21 (s, 5 x ArH), 6.45 - 5.48 (m, -CH=CHPh and -CH=CH_2), 5.03 (m, CH=CH_2), and 2.20 (m, CH and 3 x CH_2); ν_{max} 3000br(s) and 1705(s) cm^{-1}. Similarly, 3-(2-methylprop-2-enyl)-E-hept-5-enoic acid was converted to the corresponding alcohol (6.7 g, 96 %); δ 5.45 (m, -CH=CHMe), 4.72 (m, -CMe=CH_2), 3.50 (d, J 5 Hz, CH_2OH), 2.20br (s, OH), 2.00 (m, CH and 2 x CH_2), 1.71 (s, -CMe=CH_2), and 1.64 (d, J 3 Hz, -CH=CHMe), and then via the tosylate into the corresponding nitrile (5.9 g, 84 %); δ 5.39 (m, CH=CHMe), 4.75 (m, -CMe=CH_2), 2.27 (d, J 5 Hz, CH_2CN), 2.05 (m, 2 x CH_2), and 1.64 (m, -CMe=CH_2 and -CH=CHMe). Hydrolysis of this nitrile gave 3-(2-methylprop-2-enyl)-E-hept-5-enoic acid as an oil (4.4 g, 66 %); δ 11.43br (s, CO_2H), 5.40 (m, -CH=CHMe), 4.79 (m, -CMe=CH_2), 2.29 - 1.98 (m, CH and 3 x CH_2), 1.71 (s, -CMe=CH_2), and 1.64 (d, J 5 Hz, -CH=CHMe).

4.1.6. Synthesis of Hept-6-enoic acid from 1,6-hexanediol

6-Chlorohexan-1-ol was prepared from 1,6-hexanediol by treatment with hydrochloric acid as described by Campbell and Sommers,[72] yield 18.3 g (59 %), b.p. 107 - 112 °C/15.5 mmHg (lit.[72] 100 - 104 °C/9 mmHg); δ 3.58 (m, $-CH_2Cl$ and $-CH_2OH$) and 1.84 - 1.31 (m, 4 x CH_2 and OH); ν_{max} 3340br(s) cm^{-1}. 6-Chlorohexan-1-ol (35 g) and potassium cyanide (25 g, 1.5 mol. equiv.) dissolved in dimethyl sulphoxide (140 ml) were heated in an oil-bath at 105 °C for 5 hr., then at room temperature overnight. The mixture was poured into water and extracted four times with benzene, the benzene layers combined, washed with water, dried and evaporated. Since the n.m.r. spectrum of the residual liquid indicated that the

reaction had only gone half-way to completion, the mixture was dissolved in dimethyl sulphoxide (70 ml), potassium cyanide (16.4 g, 1 mol. equiv. compared with starting 6-chlorohexan-1-ol) was added and solution heated at 105 ^{o}C overnight. The same work-up as above gave 6-cyanohexanol as a liquid (15.3 g, 47 %); δ 3.53 (t, J 6 Hz, $\underline{CH_2}OH$), 2.26 (t, J 6 Hz, $\underline{CH_2}CN$), 1.97br (s, exchangeable D_2O, OH), and 1.73 - 1.32 (m, 4 x CH_2); ν_{max} 3400br(s) and 2240(m) cm^{-1}. To 6-cyanohexanol (14.3 g) in pyridine, phosphorus oxychloride (10.3 ml) was slowly added over 20 min. After heating to 50 ^{o}C for 1 hr., the mixture was poured into water and extracted three times with ether, the ether layers combined, washed with water, dried and evaporated to leave 6-cyanohexanylchloride (12.2 g, 75 %) as a liquid; δ 3.48 (t, J 6 Hz, $\underline{CH_2}Cl$), 2.33 (t, J 6 Hz, -$\underline{CH_2}CN$), and 1.84 - 1.36 (m, 4 x CH_2); ν_{max} 2240(m) cm^{-1}. 6-Cyanohexanylchloride (11.9 g) and 1,5-diazabicyclo[5.4.0]undecane (DBU) (12.5 g, 1 mol. equiv.) were heated at 90 ^{o}C with stirring for 2 hr., then at room temperature for 3 - 4 hr. The reaction mixture was transferred to a separating funnel and the flask washed out successively with dilute hydrochloric acid (0.2 M) and ether. The ether layer was separated off, and the aqueous layer washed twice more with ether before being neutralised with sodium hydroxide solution. Water was evaporated under reduced pressure and distillation of the residue gave 6-cyanohexene (6.6 g, 74 %); δ 5.70 (m, -$\underline{CH}$=CH_2), 4.92 (m, -CH=$\underline{CH_2}$), 2.27 (t, J 6 Hz, -$\underline{CH_2}CN$), 2.03 (q, J 7 Hz, -$\underline{CH_2}CH$=CH_2), and 1.54 (m, $\underline{CH_2CH_2}$). 6-Cyanohexene (6.9 g) and aqueous potassium hydroxide solution (20 %, 30 ml) were heated under reflux overnight. The cooled solution, after washing with ether, was acidified with conc. hydrochloric acid. The mixture was extracted four times with ether and the ether layers combined, dried, and evaporated. A subsequent distillation of the residue gave hept-6-enoic acid as a colourless liquid, b.p. 108 - 112 ^{o}C/11 mmHg

(lit.[73] 100 - 103 °C/5 mmHg) (5.4 g, 66 %); δ 11.29br (s, CO_2H), 5.72 (m, -C<u>H</u>=CH_2), 4.91 (m, -CH=C<u>H</u>$_2$), 2.28 (t, J 7 Hz, <u>CH_2</u>CN), 2.00 (q, J 7 Hz, -<u>CH_2</u>CH=CH_2), and 1.49 (m, <u>CH_2CH_2</u>); ν_{max} 1710(s), 990(w), and 912(m) cm^{-1}.

4.1.7. <u>Synthesis of methyl N-substituted anthranilates</u>

<u>General procedure</u>

<u>Method (a)</u>

The mono-acid and thionyl chloride (1.3 mol. equiv.) were heated to 40 - 50 °C for 1 - 3 hr. by which time bubbles had ceased to be observable. Excess of thionyl chloride was removed by evaporation under reduced pressure (an i.r. spectrum on the residual showed ν_{max} C=O at 1795 - 1800 cm^{-1} only) and the residual acid chloride diluted with dry ether and added dropwise but briskly with stirring to methyl anthranilate (2 - 4 mol. equiv.) in dry ether. The mixture was set aside overnight after which the insoluble hydrochloride was separated off and the ether solution washed several times with dilute hydrochloric acid (2 M) and once with water, dried and evaporated. The following amides, each an oil, were obtained in this manner:

<u>methyl N-(hept-6-enoyl) anthranilate</u> —— yield 9.9 g (90 %); δ 10.95br (s, NH), 8.66 (dd, J 8 and 1 Hz, ArH <u>ortho</u> to NH), 7.95 (dd, J 8 and 2 Hz, ArH <u>ortho</u> to C=O), 7.47 (ddd, J 8, 8, and 2 Hz, ArH <u>meta</u> to NH), 7.00 (ddd, J 8, 8, and 1 Hz, ArH <u>meta</u> to C=O), 5.78 (m, -C<u>H</u>=CH_2), 4.96 (m, -CH=C<u>H</u>$_2$), 3.86 (s, CO_2Me), 2.41 (t, J 7 Hz, -<u>CH_2</u>CO-), 2.08 (q, J 7 Hz, <u>CH_2</u>CH=CH_2), and 1.85 - 1.34 (m, <u>CH_2CH_2</u>); <u>methyl N-(2-(E-but-2-enyl)-E-hex-4-enoyl) anthranilate</u> —— yield 6.3 g (78 %); δ 11.22br (s, NH), 8.92 (dd, J 8 and 1 Hz, ArH <u>ortho</u> to NH), 8.17 (dd, J 8 and 2 Hz, ArH <u>ortho</u> to C=O), 7.63 (ddd, J 8, 8, and 2 Hz, ArH <u>meta</u> to NH), 7.17 (ddd, J 8, 8,

and 1 Hz, ArH meta to C=O), 5.61 (m,2 x -CH=CHMe), 3.99 (s, CO_2Me), 2.40 (m, CH and 2 x CH_2) and 1.64 (d, H 4 Hz, 2 x -CH=CHMe); methyl N-(2-(Z-but-2-enyl)-E-hex-4-enoyl) anthranilate — yield 1.1 g (91 %); δ 10.94br (s, NH), 8.67 (dd, J 8 and 1 Hz, ArH ortho to NH), 7.92 (dd, J 8 and 2 Hz, ArH ortho to C=O), 7.43 (ddd, J 8, 8, and 2 Hz, ArH meta to NH), 6.95 (ddd, J 8, 8, and 1 Hz, ArH meta to C=O), 5.44 (m, 2 x CH=CHMe), 3.86 (s, CO_2Me), 2.35 (m, CH and 2 x CH_2), and 1.58 (d, J 4 Hz, 2 x -CH=CHMe).

Method (b).

The mono-acid was added to a solution of sodium (1-1.1 mol. equiv.) in methanol. After 10 - 30 min. the solution was evaporated under reduced pressure to give an oil which solidified on trituration with ether. This sodium salt was separated, dried in an oven (100 °C) for 30 min. then suspended in dry benzene and treated with 4 drops of dry pyridine. Oxalyl chloride (6 mol. equiv.) was added to the ice-cooled reaction mixture and after 30 min. the solution was evaporated under reduced pressure. The residual acid chloride was added in ether to methyl anthranilate and the amide isolated as described above as an oil. The following amides were obtained in this manner:

methyl N-(2-(2-methylprop-2-enyl)-E-hex-4-enoyl) anthranilate — yield 2 g (71 %); δ 10.89br (s, NH), 8.58 (dd, J 8 and 1 Hz, ArH ortho to NH), 7.87 (dd, J 8 and 2 Hz, ArH ortho to C=O), 7.39 (ddd, J 8, 8, and 2 Hz, ArH meta to NH), 6.91 (ddd, J 8, 8, and 1 Hz, ArH meta to C=O), 5.39 (m, -CH=CHMe), 4.64 (s, -CMe=CH_2), 3.80 (s, CO_2Me), 2.48 - 2.10 (m, CH and 2 x CH_2), 1.66 (s, -CMe=CH_2), and 1.50 (d, J 5 Hz, -CH=CHMe); methyl N-(2-(2-methylprop-2-enyl)-E-hept-5-enoyl) anthranilate — yield 2.3 g (67 %), δ 10.96br (s, NH), 8.69 (dd, J 8 and 1 Hz, ArH ortho to NH), 7.94 (dd, J 8 and 2 Hz, ArH ortho to C=O), 7.48 (ddd, J 8, 8, and 2 Hz,

ArH meta to NH), 7.00 (ddd, J 8, 8, and 1 Hz, ArH meta to C=O), 5.40 (m, -CH=CHMe), 4.73 (m, -CMe=CH_2), 3.88 (s, CO_2Me), 2.36 - 1.98 (m, CH and 3 x CH_2), 1.72 (s, -CMe=CH_2), and 1.60 (d, J 3 Hz, -CH=CHMe); methyl N-(2-(prop-2-enyl)-5-phenylpent-4-enoyl) anthranilate — yield 1.1 g (65 %); δ 10.95br (s, NH), 8.68 (dd, J 8 and 1 Hz, ArH ortho to NH), 7.89 (dd, J 8 and 2 Hz, ArH ortho to C=O), 7.43 (ddd, J 8, 8, and 2 Hz, ArH meta to NH), 7.30 (s, 5 x ArH), 6.96 (ddd, J 8, 8, and 1 Hz, ArH meta to C=O), 6.53 - 5.38 (m, -CH=CHPh and -CH=CH_2), 5.07 (m, -CH=CH_2), 3.88 (s, CO_2Me) and 2.62 (m, CH and 2 x CH_2); methyl N-(2-(prop-2-enyl)-6-phenylhex-5-enoyl) anthranilate — yield 1.3 g (80 %); δ 11.00br (s, NH), 8.66 (dd, J 8 and 1 Hz, ArH ortho to NH), 7.93 (dd, J 8 and 2 Hz, ArH ortho to C=O), 7.45 (ddd, J 8, 8, and 2 Hz, ArH meta to NH), 6.98 (ddd, J 8, 8, and 1 Hz, ArH meta to C=O), 6.66 - 5.60 (m, -CH=CHPh and -CH=CH_2), 5.03 (m, -CH=CH_2), 3.83 (s, CO_2Me), and 2.30 (m, CH and 3 x CH_2).

Method (c).

This was the same as that given in method (b) except that the sodium salt did not solidify and hence, after methanol was evporated off, benzene was added to the residual oil followed by 4 drops of dry pyridine and oxalyl chloride as above. The following amides were obtained as oils in this way:

methyl N-(2-(prop-2-enyl)hex-5-enoyl) anthranilate — yield 2.95 g, (55 %); δ 11.09br (s, NH), 8.74 (dd, J 8 and 1 Hz, ArH ortho to NH), 7.98 (dd, J 8 and 2 Hz, ArH ortho to C=O), 7.50 (ddd, J 8, 8 and 2 Hz, ArH meta to NH), 7.02 (ddd, J 8, 8, and 1 Hz, ArH meta to C=O), 5.82 (m, 2 x CH=CH_2), 5.04 (m, 2 x -CH=CH_2), 3.89 (s, CO_2Me), and 2.60 - 1.60 (m, 7 H); methyl N-(2-(3-methylbut-3-enyl)-E-hept-5-enoyl) anthranilate — yield 1.8 g (96 %); δ 10.9br (s, NH), 8.74 (dd, J 8 and 1 Hz, ArH ortho to NH),

7.95 (dd, J 8 and 2 Hz, ArH ortho to C=O), 7.48 (ddd, J 8, 8, and 2 Hz, ArH meta to NH), 7.02 (ddd, J 8, 8, and 1 Hz, ArH meta to C=O), 5.38 (m, -CH=CHMe), 4.66 (m, -CMe=CH_2), 3.89 (s, CO_2Me), and 2.47 - 1.53 (m, CH, 2 x CH_2CH_2, -CH=CHMe and -CMe=CH_2); methyl N-(2-4-methylpent-4-enyl)E-oct-6-enoyl) anthanilate — yield 0.15 g, (77 %); δ 11.40br (s, NH), -8.75 (dd, J 8 and 1 Hz, ArH ortho to NH), 7.98 (dd, J 8 and 2 Hz, ArH ortho to C=O), 7.50 (ddd, J 8, 8, and 2 Hz, ArH meta to NH), 7.02 (ddd, J 8, 8, and 1 Hz, ArH meta to C=O), 5.35 (m, -CH=CHMe), 4.64 (m, -CMe=CH_2), 3.88 (s, CO_2Me), and 2.45 - 1.36 (m, CH, 2 x $CH_2CH_2CH_2$, -CH=CHMe and -CMe=CH_2).

4.1.8. Synthesis of N-Amino-2-substituted quinazolin-4(3H)-ones

General procedure.

The amide (1 mol. equiv.) and hydrazine hydrate (95 %, 5 mol. equiv.) were dissolved in methanol (25 ml) and after 2 - 3 freeze-thaw cycles to eliminate oxygen the mixture was sealed in vacuo in a Carius tube. After being heated at 120 - 130 °C overnight in an oven and then allowed to cool down, the tube was opened and the bulk of the methanol evaporated under reduced pressure. The residue was dissolved in ether, the ether solution washed once with water, dried, and evaporated to give the following quinazolones:

N-amino-2-(1-phenylhept-1,6-dien-4-yl)quinazolin-4(3H)-one (27) — (in this case the seal broke while the Carius tube was being heated overnight). Chromatography on the residual oil on alumina using light petroleum-ethyl acetate (3:1) as the elutant gave (27) as a colourless oil, yield 54 mg (5 %); δ 8.15 (d, J 8 Hz, ArH ortho to C=O), 7.68 - 7.07 (m, 8 x ArH), 6.50 - 5.61 (m, -CH=CHPh and -CH=CH_2), 5.00 (m, -CH=CH_2), 4.76br (s, NH_2). 3.90 (quintet, J 8 Hz, CH), and 2.83 - 2.41

(m, 2 x CH_2). This compound was prepared previously by Skinner[31]; N-amino-2-(4-(prop-2-enyl)-1-phenylpent-1-en-5-yl)-quinazolin-4(3H)-one (39) — chromatography on alumina using light petroleum-ethyl acetate (4:1) as the elutant gave (39) as a colourless oil, yield 0.5 g (41 %); δ 8.12 (d, J 8 Hz, quinaz. H ortho to C=O), 7.67 - 7.11 (m, 8 x ArH), 6.40 - 5.60 (m, -CH=CHPh and -CH=CH_2), 5.00 (m, -CH=CH_2), 4.78br (s, NH_2), 3.01 (d, J 6 Hz, CH_2 quinaz.), and 2.50 - 2.10 (m, CH and 2 x CH_2); N-amino-2-(5-(2-methylprop-2-enyl)-E-hex-2-en-6-yl)-quinazolin-4(3H)-one (49) — obtained as an oil, yield 2 g (90 %); δ 8.15 (d, J 8 Hz, ArH ortho to C=O), 7.70 - 7.17 (m, 3 x ArH), 5.39 (m, -CH=CHMe), 4.84br (s, -CMe=CH_2), 4.62br (s, NH_2), 2.94 (d, J 6 Hz, -CH_2 quinaz.), 2.50 (m, CH), 2.11 (m, 2 x CH_2), 1.70 (s, -CMe=CH_2), and 1.58 (m, -CH=CHMe); N-amino-2-(2-methyldeca-1,8-dien-5-yl)-quinazolin-4(3H)-one (52) — chromatography on alumina using light petroleum - ethyl acetate (5:1) as the elutant gave (52) as an oil, yield 0.74 g (47 %); δ 8.2 (d, J 8 Hz, ArH ortho to C=O), 7.68 - 7.27 (m, 3 x ArH), 5.36 (m, -CH=CHMe), 4.84br (s, NH_2), 4.60 (m, -CMe=CH_2), 3.71 (m, CH), 2.17 - 1.82 (m, 2 x CH_2CH_2), 1.68 (s, -CMe=CH_2), and 1.56 (m, -CH=CHMe). A 300 MHz ^{1}H n.m.r. spectrum showed -CMe=CH_2 and -CH=CHMe to be present in a 1:1 ratio; N-amino-2(2-methylhepta-1,6-dien-4-yl)-quinazolin-4(3H)-one (53) — obtained as colourless crystals, yield 1.8 g (90 %), m.p. 67 - 69 °C (from light petroleum); (Found: C, 72.0; H, 7.5; N, 14.9; $C_{17}H_{21}N_3O$ requires C, 72.0; H, 7.5; N, 14.8 %); δ 8.15 (d, J 8 Hz, ArH ortho to C=O), 7.68 - 7.20 (m, 3 x ArH), 5.30 (m, -CH=CHMe), 4.81br (s, -CMe=CH_2), 4.62br (s, NH_2), 3.94 (quintet, J 8 Hz, CH), 2.74 - 2.13 (m, 2 x CH_2), 1.71 (s, -CMe=CH_2) and 1.53 (d, J 4 Hz, -CH=CHMe); N-amino-2-(oct-1,7-dien-4-yl)-quinazolin-4(3H)-one (56) — chromatography on alumina using light petroleum - ethyl acetate (4:1) as

the elutant gave (56) as an oil, yield 1.6 g, (56 %); δ 8.16 (d, J 8 Hz, ArH ortho to C=O), 7.70 - 7.25 (m, 3 x ArH), 5.74 (m, 2 x C<u>H</u>=CH_2), 4.9 (m, 2 x CH=C<u>H_2</u> and NH_2), 3.80 (quintet, J 7 Hz, CH), and 2.62 - 1.70 (m, 6 H); N-amino-2-(2-methyldodeca-1,10-dien-6-yl)-quinazolin-4(3H)-one (59) — chromatography on alumina using light petroleum - ethyl acetate (7:2) as the elutant gave (59) as an oil, yield 0.07 g (60 %); δ 8.15 (d, J 8 Hz, ArH ortho to C=O), 7.68 - 7.23 (m, 3 x ArH), 5.32 (m, -C<u>H</u>=C<u>H</u>Me), 4.79br (s, NH_2), 4.60 (m, -CMe=C<u>H_2</u>), 3.65 (quintet, J 6 Hz, CH), and 2.06 - 1.14 (m, 2 x $CH_2CH_2CH_2$ and 2 x Me). A 300 MHz ^1H n.m.r. spectrum showed -CMe=CH_2 and -CH=CHMe to be present in a 1:1 ratio; High resolution mass spectrum for $C_{21}H_{29}N_3O$ M^+ 339.231050; found 339.2311.

The N-amino-2-(1-phenyl-E-hex-1-en-6-yl)-quinazolin-4(3H)-one (60) used, was a sample prepared by Atkinson[35] and the N-amino-2-(E-hept-2-en-7-yl)-quinazolin-4(3H)-one (61) used, was a sample prepared by Skinner.[36]

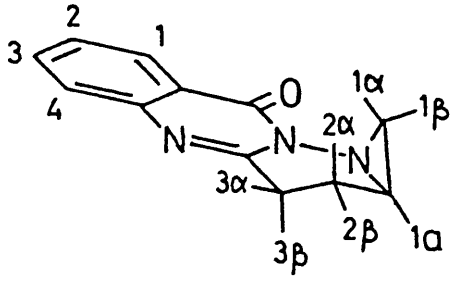
N-amino-2-(hex-1-en-6-yl)-quinazolin-4(3H)-one (62) — The corresponding amide (1 mol. equiv.) and hydrazine hydrate (95 %; 5 mol. equiv.) were dissolved in methanol and heated under nitrogen and under reflux for 1 h. Cooling the solution in ice gave (62) as colourless crystals, yield 3.3 g (63 %), m.p. 57.5 - 59.5 °C (from ethanol); (found: C, 69.0; H, 7.0; N, 17.3; $C_{14}H_{17}N_3O$ requires C, 69.1; H, 7.0; N, 17.3 %); δ 8.21 (d, J 8 Hz, ArH ortho to C=O), 7.79 - 7.30 (m, 3 x ArH), 5.85 (m, -C<u>H</u>=CH_2), 5.14 - 4.85 (m, -CH=C<u>H_2</u> and NH_2), 3.04 (t, J 8 Hz, CH_2 next to quinaz.), 2.18 (q, J 7 Hz, -C<u>H_2</u>CH=CH_2), and 1.99 - 1.39 (m, C<u>H_2CH_2</u>); ν_{max} (Nujol) 3284(m), 3195(m), 990(w), and 910(m) cm^{-1}. The following were prepared by the general procedure given above.

N-amino-2-((2-E)(7-Z)nona-2,7-dien-5-yl)-quinazolin-4(3H)-one (83) as a colourless oil, yield 0.75 g (73 %), which was chroamtographed on alumina and eluted with light petroleum - ethyl acetate (7:1); δ (400 MHz) 8.21 (ddd, J 8.1, 1.5, and 0.6 Hz, ArH ortho to C=O), 7.71 (ddd, J 8.2, 6.7, and 1.5 Hz, ArH meta to NH), 7.67 (ddd, J 8.2, 1.6, and 0.6 Hz, ArH

ortho to NH), 7.42 (ddd, J 8.1, 6.7, and 1.6 Hz, ArH meta to C=O), 5.42 (m, 2 x CH=CHMe), 4.83br (s, NH_2), 3.79 (tt, J 8.3 and 6 Hz, CH), 2.59 (m, 2 H), 2.41 (m, 2 H), 1.57br (d, J 4.8 Hz, E-CH=CHMe), and 1.52br (d, J 6.5 Hz, Z-CH=CHMe); N-amino-2-((2-E),(7-E)nona-2,7-dien-5-yl)-quinazolin-4(3H)-one (90) as colourless crystals, yield 3.9 g (67 %), m.p. 81 - 85 °C (from light petroleum); (Found: C, 72.0; H, 7.5; N, 14.8; $C_{17}H_{21}N_3O$ requires C, 72.0; H, 7.5; N, 14.8 %); δ (400 MHz) 8.23 (ddd, J 8.1, 1.5, and 0.7 Hz, ArH ortho to C=O), 7.72 (ddd, J 8.2, 6.7, and 1.5 Hz, ArH meta to NH), 7.68 (ddd, J 8.2, 1.5, and 0.7 Hz, ArH ortho to NH), 7.43 (ddd, J 8.1, 6.7, and 1.5 Hz, ArH meta to C=O), 5.42 (m, 2 x -CH=CHMe), 4.82br (s, NH_2), 3.75 (tt, J 8.2 and 6.1 Hz, CH), 2.52 (m, 2 H), 2.37 (m, 2 H), and 1.57br (d, J 5 Hz, 2 x -CH=CHMe); ν_{max} (Nujol) 3340(m), 3295(m), 1673(s), 1610(s), 1597(s), 967(s), 772(s), and 694(s) cm^{-1}; N-amino-2-((2-Z),(7-Z)nona-2,7-dien-5-yl)quinazolin-4(3H)-one (91) —— chromatography on alumina with light petroleum - ethyl acetate (6:1) gave (91) as an oil, yield 0.15 g (74 %); δ (400 MHz) 8.15 (dd, J 8 and 1.4 Hz. ArH ortho to C=O), 7.65 (ddd, J 8.1, 6.6, and 1.4 Hz, ArH meta to NH), 7.60 (dd, J 8.1 and 1.4 Hz, ArH ortho to NH), 7.35 (ddd, J 8, 6.6, and 1.4 Hz, ArH meta to C=O), 5.37 (m, 2 x -CH=CHMe), 4.77br (s, NH_2), 3.77 (tt, J 8.6 and 5.9 Hz, CH), 2.59 (m, 2 H), 2.39 (m, 2 H), and 1.48 (d, J 5.9 Hz, 2 x -CH=CHMe).

4.1.9. Oxidation of N-Amino-2-substituted quinazolin-4(3H)-ones.

The numbering system for the aziridines produced in these oxidations.



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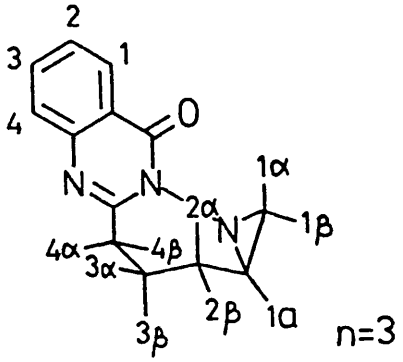
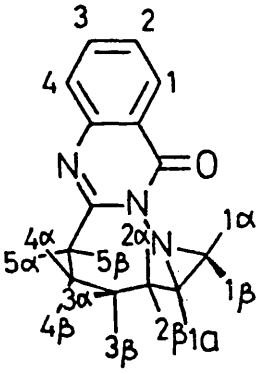


n=3



n=4

General procedure.

The apparatus was flame dried. The foregoing quinazolone (100 mg, 1 mol.equiv.) was dissolved in dry dichloromethane (≅ 30 ml) and lead tetra-acetate (1.15 mol. equiv.) was also dissolved in an equal volume of dry dichloromethane. Both solutions were added simultaneously at the same rate over 15 - 30 min. to rapidly stirred dry dichloromethane (≅ 40 ml). The reaction mixture stirred for a further 10 - 30 min., precipitated lead di-acetate was separated off and the solution washed with aqueous sodium hydrogen carbonate, dried, and evaporated to give the products in quantitative yield (n.m.r.) except where indicated.

N-Amino-2-(1-phenylhepta-1,6-dien-4-yl)quinazolin-4(3H)-one (27).

Examination of the crude reaction product by n.m.r. showed aziridines (28) and (29) in 1.5:1 (± 0.1) ratio respectively as determined from the ratio of the respective signals from quinaz H-1, olefinics, -CHHCH=C, and H-2α in the respective aziridines. Aziridine (28); δ (400 MHz) 8.20 (dd, J 8.3 and 1.3 Hz, quinaz. H-1), 7.68 - 7.10 (m, 8 x ArH), 5.94 (dddd, J 17.2, 10, 7.9, and 6.1 Hz, -CH=CH_2), 5.15 (dq, J 17.2 and 1.5 Hz, Z-CH=CHH), 5.10 (dq, J 10 and 0.6 Hz, E-CH=CHH), 3.22 - 2.70 (m, H-1a, H-2β, H-3β, and -CHHCH=CH_2). Also doublet at 3.01 (J 5.2 Hz) due to H-1α), 2.35 (ddd, J 14.2, 8.1, and 7.9 Hz, -CHHCH=CH_2), and 1.41 (ddd, J 13.1, 13.1, and 8.6 Hz, H-2α): Aziridine (29); δ (400 MHz) 8.24 (dd, J 8.1 and 1.3 Hz, quinaz. H-1), 7.68 - 7.10 (m, 8 x ArH), 6.48 (d, J 15.8 Hz, -CH=CHPh), 6.32 (ddd, J 15.8, 8, and 6.5 Hz, -CH=CHPh), 3.22 - 2.70 (m, H-1β, H-1a, H-2β, H-3β, and -CHHCH=CHPh), 2.48 (ddd, J 14.4, 8, and 8 Hz, -CHHCH=CHPh), 1.8 (dd, J 5.4 and 2 Hz, H-1α), and 1.26 (ddd, J 13, 13, and 8.3 Hz, H-2α).

N-Amino-2-(4-(prop-2-enyl)-1-phenylpent-1-en-5-yl)-quinazolin-4(3H)-one (39) — Oxidation of (39) (100 mg) gave a mixture of aziridines (43a), (43b) and (44a), (44b). Chromatography on alumina and elution with light petroleum - ethyl acetate (3:1) gave a mixture of (43a) and (43b) (53 mg). Aziridine (43a) has inter alia δ (400 MHz) 3.37 (d, J 5.4 Hz, H-1α), 3.26 (dd, J 12.8 and 11.4 Hz, H-4β), and 1.51 (ddd, J 15.2, 12.2, and 6.3 Hz, H-2α). Aziridine (43b) has inter alia δ 3.74 (dd, J 13.2 and 7.2 Hz, H-4β), 3.38 (d, J 5.4 Hz, H-1α), and 1.04 (ddd, J 15.2, 12, and 12 Hz, H-2α). From the ratio of peak areas at 3.26 and 3.74 (H-4β) the ratio of (43a):(43b) was 2.1:1. Further elution with ethyl acetate gave (44a) and (44b) (31 mg). Re-chromatography on alumina and elution with light petroleum - ethyl acetate (1:1) gave aziridine (44a) as an

oil (16 mg); δ (400 MHz) 8.24 (dd, J 8 and 1.3 Hz, quinaz. H-1), 7.69 (ddd, J 7.9, 7, and 1.3 Hz, quinaz. H-3), 7.60 (dd, J 7.9 and 1.4 Hz, quinaz. H-4), 7.43 (ddd, J 8, 7, and 1.4 Hz, quinaz. H-2), 6.50 (d, J 15.7 Hz, CH=CHPh), 6.23 (dt, J 15.7 and 7.3 Hz, -CH=CHPh), 3.26 (dd, J 12.1 and 12.1 Hz, H-4β), 2.98 (dd, J 6.1 and 3.2 Hz, H-1β), 2.95 (dd, J 12.1 and 6 Hz, H-4α), 2.75 (dddd, J 12.2, 6.1, 6.1, and 3 Hz, H-1a), 2.50 (m, CH_2CH=CHPh), 2.33 (m, H-2β and H-3α), 2.16 (dd, J 6.1 and 3.2 Hz, H-1α), and 1.31 (ddd, J 15.4, 12.2, and 6.5 Hz, H-2α). (These assignments were consistent with a COSY projection). Further elution gave aziridine (44b) (1.5 mg) as an oil. In the mixture of (44a) and (44b), signals from (44b) are visible at 3.66 (dd, J 13.1 and 7.3 Hz, H-4β) and 2.11 (dd, J 7.4 and 3.3 Hz, H-1α). From the ratio of peak areas at 2.11 and 2.10 (H-1α) or 3.66 and 3.26 (H-4β) the ratio of (44a):(44b) was 2.2:1. The ratio of (44a) + (44b) to (43a) + (43b) was found to be 5.8:1 from the olefin proton signals at 6.50 and 6.23 to those at 5.75 and 5.10 in the n.m.r. spectrum of the total reaction product.

N-Amino-2-(5-(2-methylprop-2-enyl)-E-hex-2-en-6-yl)-quinazolin-4(3H)-one (49). Oxidation of (49) (500 mg) and chromatography on alumina eluting with light petroleum - ethyl acetate (2:1) gave aziridine (51a) as an oil (53 mg); δ (400 MHz) 8.24 (dd, J 8 and 1.4 Hz, quinaz. H-1), 7.69 (ddd, J 8.2, 6.9, and 1.4 Hz, quinaz. H-3), 7.62 (dd, J 8.2 and 1.1 Hz, quinaz. H-4), 7.44 (ddd, J 8, 6.9, and 1.1 Hz, quinaz. H-2), 4.85 (m, -CMe=CH_2), 3.17 (dd, J 12.5 and 10.9 Hz, H-4β), 2.86 (dd, J 12.5 and 4.7 Hz, H-4α), 2.50 (ddd, J 12.2, 5.5, and 3.1 Hz, H-1a), 2.30 (m, H-1α, H-2β, H-3α, CH_2CMe=CH_2), 1.76 (s, -CMe=CH_2), 1.58 (d, H 5.7 Hz, azir. Me), and 1.26 (ddd, J 14.4, 12.2, and 6.1 Hz, H-2α). Further elution gave aziridine (51b) as an oil (12 mg); δ (400 MHz) 8.24 (dd, J 8 and 1.5 Hz, quinaz. H-1), 7.70 (ddd, J 8.2, 6.8, and 1.5 Hz, quinaz. H-3), 7.65 (dd, J 8.2 and

1.5 Hz, quinaz. H-4), 7.44 (ddd, J 8, 6.8, and 1.5 Hz, quinaz. H-2), 4.85 (m, -CMe=$\underline{CH_2}$), 3.67 (dd, J 13.1 and 7.3 Hz, H-4β), 2.79 (dd, J 13.1 and 1.5 Hz, H-4α), 2.48 (ddd, J 11.9, 5.8, and 2.8 Hz, H-1a), 2.40 (m, H-2β and H-3β), 2.33 (dq, J 5.8 and 5.7 Hz, H-1α), 2.25 (dd, J 13.9 and 7.6 Hz, C$\underline{H}$HCMe=CH_2), 2.01 (dd, J 13.9 and 7 Hz, CH$\underline{H}$CMe=CH_2), 1.76 (s, -C$\underline{Me}$=CH_2), 1.57 (d, J 5.7 Hz, azir. Me), and 0.8 (ddd, J 16.4, 13, and 11.9 Hz, H-2α). Further elution gave aziridine (50b) (55 mg) as colourless crystals, m.p. 161 - 165 °C (from ethanol), (Found: C, 72.9; H, 7.3; N, 14.0; $C_{18}H_{21}N_3O$ requires C, 73.2; H, 7.2; N, 14.2 %); δ (400 MHz) 8.25 (dd, J 8 and 1.5 Hz, quinaz. H-1), 7.70 (ddd, J 8.2, 6.7, and 1.5 Hz, quinaz. H-3), 7.65 (dd, J 8.2 and 1.5 Hz, quinaz. H-4), 7.44 (ddd, J 8, 6.7, and 1.5 Hz, quinaz. H-2), 5.50 (m, -C$\underline{H}$=C$\underline{H}$Me), 3.41 (dd, J 13 and 6.8 Hz, H-4β), 2.83 (dd, J 13 and 1 Hz, H-4α), 2.79 (d, J 3 Hz, H-1β), 2.20 (m, H-2β, H-3β, and C$\underline{H}$HCH=CHMe), 2.19 (d, J 3 Hz, H-1α), 1.95 (ddd, J 13, 8.2, and 8.2 Hz, CH$\underline{H}$CH=CHMe), 1.69 (dd, J 6.2 and 1.3 Hz, -CH=CH$\underline{Me}$), 1.42 (s, azir. Me), and 0.82 (dd, J 16.2 and 13.1 Hz, H-2α). Examination of the mother liquor after crystallisation of (50b) by n.m.r. revealed the presence of (50a) with $\underline{inter\ alia}$ δ 3.13 (dd, J 13 and 12.2 Hz, H-4β), 2.91 (dd, J 13 and 4.8 Hz, H-4α), 2.75 (d, J 3 Hz, H-1β), 2.16 (d, J 3 Hz, H-1α), 1.71 (dd, J 7 and 1.5 Hz, -CH=CH$\underline{Me}$) and 1.50 (s, azir. Me).

The ratio of (51a) + (51b):(50a) + (50b) was measured from the methyl and olefinic signals in the n.m.r. spectrum of the crude reaction product and found to be 1.05:1 (± 0.05). From the peak areas of signals at 1.50 and 1.42 (azir. Me) the ratio of (50a):(50b) was estimated to be 7:1. The ratio of (51a):(51b) was calculated from the respective H-4β signals to be 2.3:1.

N-Amino-2-(2-methyldeca-1,8-dien-5-yl)-quinazolin-4(3H)-one (52).

Oxidation of (52) (310 mg) and chromatography of the product on alumina eluting with light petroleum - ethyl acetate (4:1) gave the 1-β methyl substituted aziridine (addition to the trans-methyl-substituted double bond) as an oil (62 mg); δ (400 MHz) 8.17 (dd, J 8.1 and 1.5 Hz, quinaz. H-1), 7.61 (ddd, J 8.2, 6.6, and 1.5 Hz, quinaz. H-3), 7.58 (dd, J 8.2, and 1.6 Hz, quinaz. H-4), 7.36 (ddd, J 8.1, 6.6, and 1.6 Hz, quinaz. H-2), 4.64 (m, -CMe=CH_2), 3.49 (dddd, J 12, 7.9, 6.3, and 6.3 Hz, H-4β), 2.38 (ddd, J 11.9, 5.5, and 3.1 Hz, H-1a), 2.26 (m, 3 H), 1.98 (m, 3 H), 1.69 (m, 4 H), 1.50 (m, 4 H), and 1.1 (m, 1 H). Further elution gave the 1α-methyl substituted aziridine (addition to the β-methyl substituted double bond) as an oil (193 mg); δ (400 MHz) 8.17 (dd, J 8.2 and 1.5 Hz, quinaz. H-1), 7.61 (ddd, J 8.2, 6.5, and 1.5 Hz, quinaz. H-3), 7.57 (dd, J 8.2 and 1.7 Hz, quinaz. H-4), 7.35 (ddd, J 8.2, 6.5, and 1.7 Hz, quinaz. H-2), 5.40 (m, -CH=CHMe), 3.24 (dddd, J 11.8, 6.6, 6.6, and 6.6 Hz, H-4β), 2.72 (d, J 3.1 Hz, H-1β), 2.1 (m, 6 H), 1.70 (m, 1 H), 1.57 (dd, J 3.7 and 0.9 Hz, -CH=CHMe), 1.40 (m, 1 H), 1. 32 (s, Me), and 1.09 (ddd, J 14.2, 12.0, and 6.3 Hz, H-2α). From comparison of the peak areas of the respective signals from olefinic,H-4β, and 2.38 (H-1a):2.72 (H-1β), the ratio of the two aziridines is 1:3 (± 0.3).

N-Amino-2-(2-methylhepta-1,6-dien-4-yl)-quinazolin-4(3H)-one (53).

Oxidation of (53) and chromatrography on alumina with light petroleum - ethyl acetate (2:1) gave aziridine (55), m.p. 97 - 100 °C (from ethanol); δ (400 MHz) 8.21 (dd, J 8 and 1.3 Hz, quinaz. H-1), 7.64 (ddd, J 8.1, 6.8, and 1.3 Hz, quinaz. H-3), 7.58 (dd, J 8.1 and 1.1 Hz, quinaz. H-4), 7.37 (ddd, J 8, 6.8, and 1.1 Hz, quinaz. H-2), 4.80 (m, -CMe=CH_2), 3.18 (dd, J 14.4 and 3.1 Hz, CHHCMe=CH_2), 3.03 (dddd, J 12.6, 10.7, 3.6, and 3.1 Hz, H-3β), 2.71 (ddd, J 13, 8, and 3.6 Hz, H-2β), 2.63 (ddd, J 8.3, 8, and

5.3 Hz, H-1a), 2.05 (dd, J 14.4 and 10.7 Hz, CHHCMe=CH_2), 2.0 (dq, J 5.3 and 5.6 Hz, H-1α), 1.78 (s, -CMe=CH_2), 1.50 (d, J 5.6 Hz, Me), and 1.1 (ddd, J 13, 12.6, and 8.3 Hz, H-2α). Further elution gave aziridine (54), m.p. 159 - 164 °C (from ether-chloroform); (Found C, 72.6; H, 6.9; N, 14.9. $C_{17}H_{19}N_3O$ requires C, 72.6; H, 6.8; N, 14.8 %); δ (400 MHz) 8.30 (dd, J 8 amd 1.5 Hz, quinaz. H-1), 7.70 (ddd, J 8.2, 6.6, and 1.5 Hz, quinaz. H-3), 7.66 (dd, J 8.2 and 1.5 Hz, quinaz. H-4), 7.43 (ddd, J 8, 6.6, and 1.5 Hz, quinaz. H-2), 5.60 (m, -CH=CHMe), 3.05 (m, CHHCH=CHMe), 2.89 (dddd, J 12.8, 8.6, 4.1, and 3.9 Hz, H-3β), 2.81 (d, J 2.2 Hz, H-1β), 2.41 (dd, J 13.3 and 3.9 Hz, H-2β), 2.31 (m, CHHCH=CHMe), 1.97 (d, J 2.2 Hz, H-1α), 1.72 (d, J 4.5 Hz, -CH=CHMe), 1.47 (s, Me), and 1.33 (dd, J 13.3 and 12.8 Hz, H-2α). The ratio of (54):(55) was 5.3 (± 0.4) and was obtained form the ratio of the respective olefinic, CHHC=C, methyl, and H-2α proton signals.

N-Amino-2-(oct-1,7-dien-4-yl)-quinazolin-4(3H)-one (56). An n.m.r. spectrum of the crude product showed the presence of both aziridines (57) and (58). For (57), δ (300 MHz) inter alia 8.27 (dd, J 8 and 1.5 Hz, quinaz. H-1), 2.89 (dd, J 5.5 and 2.1 Hz, H-1β), 2.75 (ddd, J 13.1, 7.6, and 3.8 Hz, H-2β), 1.87 (dd, J 5.5 and 1.7 Hz, H-1α), 1.63 (dddd, J 13.3, 8, 8, and 5.3 Hz, CHHCH_2CH=CH_2), and 1.30 (ddd, J 13.1, 12.9, and 8.2 Hz, H-2α). For (58), δ (300 MHz) inter alia 8.22 (dd, J 8 and 1.4 Hz, quinaz. H-1), 3.66 (dddd, J 11.6, 7.1, 7.1, and 7.1 Hz, H-3β), 2.64 (dddd, J 12, 6, 6, and 3.1 Hz, H-1a), 2.15 (dd, J 6 and 3.3 Hz, H-1α), and 1.12 (dddd, J 14.7, 12.1, 12, and 6.1 Hz, H-2α). These assignments agree with those found by Skinner.[74] From composition of the peak areas of signals at 1.87 (H-1α) and 3.66 (H-3β), the ratio of aziridines (57):(58) was 3.4:1. This ratio is dependent on the solvent in which oxidation

of (56) is carried out. A repeat of the oxidation in benzene gave a ratio of 2.8:1 and in acetonitrile gave a ratio of 4.7:1.

N-Amino-2-(2-methyldodeca-1,10-dien-6-yl)-quinazolin-4(3H)-one (59).

Oxidation of (59) (50 mg) and chromatography on alumina eluting with light petroleum - ethyl acetate (6:1) gave aziridine (67) (21 mg) ; δ 8.22 (dd, J 8.1 and 1.5 Hz, quinaz. H-1), 7.77 (ddd, J 8.3, 6.8, and 1.5 Hz, quinaz. H-3), 7.63 (dd, J 8.3 and 1.3 Hz, quinaz. H-4), 7.40 (ddd, J 8.1, 6.8, and 1.3 Hz, quinaz. H-2), 5.37 (m, -CH=CHMe), 3.26 (dddd, J 8.4, 8.4, 6.2, and 1 Hz, H-5β), 2.88 (d, J 3.1 Hz, H-1β), 2.18 (d, J 3.1 Hz, H-1α), 2.14 - 1.91 (m, 6 H), 1.66 (m, 2 H), 1.61 (d, J 5 Hz, -CH=CHMe), 1.5 (s, azir. Me), 1.35 - 1.20 (m, 3 H), and 1.06 (ddd, J 15.6, 11.8, and 1.5 Hz, H-2α). Further elution gave aziridine (68) (two stereoisomers) (15 mg); δ (400 MHz) signals due to major stereoisomer: 8.22 (dd, J 8 and 1.5 Hz, quinaz. H-1), 7.68 (ddd, J 8, 7, and 1.5 Hz, quinaz. H-3), 7.63 (dd, J 8 and 1.5 Hz, quinaz. H-4), 7.41 (ddd, J 8, 7, and 1.5 Hz, quinaz. H-2), 3.48 (dddd, J 8.9, 8.9, 6.0, and 1 Hz, H-5β), 1.64 (s, -CMe=CH_2), and 1.59 (d, J 5.9 Hz, azir. Me); signals due to minor stereoisomer: 8.20 (dd, J 8 and 1.5 Hz, quinaz. H-1), 7.69 (ddd, J 8, 7, and 1.5 Hz, quinaz. H-3), 7.60 (dd, J 8 and 1.5 Hz, quinaz. H-4), 7.40 (ddd, J 8, 7, and 1.5 Hz, quinaz. H-2), 3.35 (ddd, J 8.1, 8.1, 5.3, and 1 Hz, H-5β), 1.66 (s, -CMe=CH_2), and 1.60 (d, J 5.9 Hz, azir. Me); signals common to both: 4.65 (m, -CMe=CH_2), and 0.84 (dddd, J 16, 12, 11, and 1 Hz, H-2α). The ratio of aziridines (67):(68) obtained from the ratio of olefinic proton signals in the n.m.r. spectrum of the crude product was found to be 1:1.8 (± 0.1). From the peak areas of signals at 3.48 and 3.35 (H-5β), the two stereoisomers of aziridine (68) are present in a 1.6:1 ratio respectively.

N-Amino-2-(1-phenyl-E-hex-1-en-6-yl)-quinazolin-4(3H)-one (60).

An n.m.r. spectrum of the crude (crystalline) product showed only the presence of aziridine (63). Crystallisation from ethanol gave (63) as colourless crystals, m.p. 181 - 183 ^{o}C; δ (400 MHz) 8.14 (dd, J 8 and 1.6 Hz, quinaz. H-1), 7.62 (ddd, J 8.3, 7, and 1.6 Hz, quinaz. H-3), 7.55 (dd, J 8.3 and 1.2 Hz, quinaz. H-4), 7.44 (m, 2 x ArH), 7.33 (m, quinaz. H-2 and 2 x ArH), 7.25 (m, ArH), 3.44 (d, J 5.9 Hz, H-1α), 3.31 (ddd, J 13.5, 11.8, and 1 Hz, H-5β), 2.92 (ddd, J 13.5, 7.7, and 1 Hz, H-5α), 2.78 (ddd, J 10.4, 5.9, and 1.3 Hz, H-1a), 2.36 (m, H-2β and H-4β), 2.0 (ddddd, J 13.8, 6, 5.8, 1.2, and 1.2 Hz, H-3α), 1.94 (ddddd, J 13, 12.7, 11.8, 5.8, and 1 Hz, H-4α), 1.68 (ddddd, J 13.8, 12.7, 12.3, 5.3, and 1.4 Hz, H-3β), and 1.09 (dddd, J 15.9, 12.3, 10.4, and 1.2 Hz, H-2α). The assignments are in agreement with a COSY projection.

N-Amino-2-(E-hept-2-en-7-yl)-quinazolin-4(3H)-one (61). An n.m.r. spectrum of the crude crystalline product shows the presence of aziridine (64) as the major product along with product(s) retaining olefinic protons (de-amination?); (300 MHz). Signals due to (64) inter alia, δ 8.20 (dd, J 8.1 and 1.5 Hz, quinaz. H-1), 7.69 (ddd, J 8.2, 6.8, and 1.5 Hz, quinaz. H-3), 7.62 (dd, J 8.2 and 1.4 Hz, quinaz. H-4), 7.41 (ddd, J 8.1, 6.8, and 1.4 Hz, quinaz. H-2), 3.29 (ddd, J 13, 11.8, and 1.1 Hz, H-5β), 2.93 (ddd, J 13, 8.1, and 1.1 Hz, H-5α), 1.59 (d, J 5.3 Hz, Me), and 0.92 (dddd, J 16.4, 12.6, 9.9, and 1.4 Hz, H-2α). By comparison of integration values of H-5α or H-5β to the residual olefinic protons, the ratio of aziridine (64) to other products is 2:1 respectively.

N-Amino-2-(hex-1-en-6-yl)-quinazolin-4(3H)-one (62). An n.m.r. spectrum of the crude product is complex but the following signals confirm

the presence of aziridine (65); δ (300 MHz) 3.32 (ddd, J 13, 12, and 1 Hz, H-5β), 3.08 (dd, J 6 and 3.5 Hz, H-1β), 3.00 (ddd, J 13, 8, and 1 Hz, H-5α), 2.67 (dddd, J 11, 7, 7, and 1 Hz, H-1a), and 2.27 (dd, J 6 and 3.5 Hz, H-1α). Signals from products retaining olefinic protons (including de-amination product) have inter alia δ 2.84 (t, J 7.5 Hz, CH_2, quinaz.), 5.78 (m, -CH=CH_2), and 4.94 (m, -CH=CH_2). By comparison of integration values of H-5α or H-5β to the olefinic protons, the ratio of aziridine (65) to other products is 1:2.5 respectively.

N-Amino-2-((2-E),(7-Z)nona-2,7-dien-5-yl)-quinazolin-4(3H)-one (83).

Chromatography of crude product on alumina and eluting with light petroleum - ethyl acetate (2:1) gave aziridines (87) and (89) together. Crystallisation from light petroleum gave (87), m.p. 105 - 108 °C; δ (400 MHz) 8.21 (dd, J 8.1 and 1.5 Hz, quinaz. H-1), 7.64 (ddd, J 8.2, 6.6. and 1.5 Hz, quinaz. H-3), 7.60 (dd, J 8.2 and 1.5 Hz, quinaz. H-4), 7.37 (ddd, J 8.1, 6.6, and 1.5 Hz, quinaz. H-2), 5.55 (m, -CH=CHMe), 2.97 (m, CHHCH=CHMe), 2.88 (m, H-3β), 2.70 - 2.61 (m, H-1a and H-2β), 2.33 (ddd, J 14.6, 8.6, and 8.6 Hz, CHHCH=CHMe), 2.00 (dq, J 5.5 and 5.6 Hz, H-1α), 1.63br (d, J 6.5 Hz, -CH=CHMe), 1.49 (d, J 5.6 Hz, azir. Me), and 1.21 (ddd, J 12.4, 12.4, and 7.4 Hz, H-2α). Further elution gave (86) and (88) together. Crystallisation from light petroleum - ethyl acetate gave (86), m.p. 71 - 74 °C; δ (400 MHz) 8.22 (dd, J 8 and 0.6 Hz, quinaz. H-1), 7.64 (ddd, J 8.2, 6.7, and 1.5 Hz, quinaz. H-3), 7.60 (dd, J 8.2, and 1.5 Hz, quinaz. H-4), 7.37 (ddd, J 8, 6.7, and 1.5 Hz, quinaz. H-2), 5.54 (m, -CH=CHMe), 3.02 (m, CHHCH=CHMe), 2.96 (ddd, J 8.7, 8.5, and 6.6 Hz, H-1a), 2.87 (dq, J 6.6 and 6.1 Hz, H-1β), 2.86 (dddd, J 12.9, 8.6, 4.4, and 4.4 Hz, H-3β), 2.48 (ddd, J 13.7, 8.5, and 4.4 Hz, H-2β), 2.23 (m, CHHCH=CHMe), 1.65br (d, J 4.4 Hz, -CH=CHMe), 1.19 (ddd, J 13.7, 12.9, and 8.7 Hz, H-2α), and 0.98 (d, J 6.1 Hz, azir. Me). Assignments for

(86) and (87) agree with COSY projections. The presence of aziridines (88) and (89) arises from quinazolone (83) being stereoisomerically impure - See Section 2.5.

N-Amino-2-((2-E),(7-E)nona-2,7-dien-5-yl)-quinazolin-4(3H)-one (90).

An n.m.r. spectrum of the crude (crystalline) product showed the presence of only aziridine (89). Crystallisation from CCl_4 - light petroleum gave (89) as colourless crystals, m.p. 83 - 86 °C; (Found: C, 72.5; H, 6.8; N, 14.9; $C_{17}H_{19}N_3O$ requires C, 72.6; H, 6.8; N, 14.9 %); ν_{max} (Nujol) 1675(s), 1590(s), 1560(m), 965(m), 778(s), and 688(m) cm^{-1}; δ (400 MHz) 8.23 (dd, J 8.1 and 1.5 Hz, quinaz. H-1), 7.65 (ddd, J 8.1, 6.7, and 1.5 Hz, quinaz. H-3), 7.61 (dd, J 8.1 and 1.5 Hz, quinaz. H-4), 7.39 (ddd, J 8.1, 6.7, and 1.5 Hz, quinaz. H-2), 5.54 (m, -CH=CHMe), 2.99 (m, CHHCH=CHMe), 2.89 (dddd, J 12.5, 8, 3.6, and 3.6 Hz, H-3β), 2.67 (m, H-1a and H-2β), 2.22 (m, CHHCH=CHMe), 2.01 (dq, J 5.7 and 5.5 Hz, H-1α), 1.66 (m, -CH=CHMe), 1.51 (d, J 5.5 Hz, azir. Me), and 1.18 (ddd, J 12.3, 12.3, and 7.5 Hz, H-2α).

N-Amino-2-((2-Z),(7-Z)nona-2,7-dien-5-yl)-quinazolin-4(3H)-one (91).

An n.m.r, spectrum of the crude product showed (88) as the major aziridine; δ (400 MHz) 8.21 (dd, J 8.1 and 1.4 Hz, quinaz. H-1), 7.64 (ddd, J 8.1, 6.6, and 1.4 Hz, quinaz. H-3), 7.60 (dd, J 8.1 and 1.6 Hz, quinaz. H-4), 7.37 (ddd, J 8.1, 6.6, and 1.6 Hz, quinaz. H-2), 5.55 (m, -CH=CHMe), 3.03 - 2.83 (m, H-1β, H-1a, H-3β, and CHHCH=CHMe), 2.47 (ddd, J 13.5, 8.5, and 4.4 Hz, H-2β), 2.38 (ddd, J 14.7, 8.5, and 8.5 Hz, CHHCH=CHMe), 1.64br (d, J 6.5 Hz, -CH=CHMe), 1.22 (ddd, J 13.5, 13.2, and 8.7 Hz, H-2α), and 0.98 (d, J 6.1 Hz, azir. Me), along with aziridines (86), (87), and (89) which arise from quinazolone (91) being stereoisomerically impure - See Section 2.5).

4.1.10. Low-temperature oxidation of N-Amino-2-(E-hept-2-en-7-yl)-quinazolin-4(3H)-one (61).

Quinazolone (61) (80 mg) and lead tetra-acetate (160 mg) were added alternately to deuteriochloroform (2 ml) and magnetically stirred at ca -30 °C over 30 min. After a further 20 min. lead di-acetate was separated off and solution transferred into a n.m.r. tube, all operations being carried out at < -25 °C. The initial n.m.r. spectrum was run at -30 °C with no intermediate warming of the solution; δ (300 MHz) 10.96br (s, CH_3CO_2H), 8.26 (dd, J 8 and 1.4 Hz, quinaz. H-1), 7.83 (ddd, J 8.3, 7, and 1.4 Hz, quinaz. H-3), 7.74 (dd, J 8.3 and 1.5 Hz, quinaz. H-4), 7.52 (ddd, J 8, 7, and 1.5 Hz, quinaz. H-2), 5.45 (m, -CH=CHMe), 3.16 (ddd, J 13.5, 9, and 6.4 Hz, CHH quinaz.), 2.97 (ddd, J 13.5, 9, and 6.4 Hz, CHH quinaz.), 2.18 (s, CH_3CO_2H), 2.07 (q, J 6 Hz, CH_2CH=CHMe), 1.85 (m, $CH_2CH_2CH_2CH$=CHMe), 1.65 (dd, J 4.5 and 1.5 Hz, -CH=CHMe), and 1.52 (quintet, CH_2CH_2CH=CHMe). This and subsequent work is described in Section 2.4.

4.1.11. Oxidation of N-Amino-2-methylquinazolin-4(3H)-one in the presence of 2-methylpropene and (E)-butene.

(E)-But-2-ene (0.49 g) and 2-methylpropene (6.39 g) were condensed into ice cold dichloromethane (15 ml). To this magnetically stirred solution, small portions of lead tetra-acetate (0.75 g) and the amino-quinazolone (0.25 g) were added alternately in equivalent amounts over 15 min. After stirring for a further 30 min. at 0 °C, the precipitated lead salts were separated, the solution washed with sodium hydrogen carbonate solution, dried and evaporated. Examination of the 300 MHz n.m.r. spectrum of this total oxidation product showed the presence of both

aziridines in a 1.76:1 ratio from the ratio of the aziridine methyl signals. Taking into account the ratio of the two alkenes used, the ratio of attack on the two double bonds is 7.4:1 with preferential attack of the nitrene on 2-methylpropene.

An authentic sample of the major aziridine was obtained by oxidation of the aminoquinazolone in the presence of only 2-methylpropene as above. The product was purified by chromatography on alumina, eluting with light petroleum - ethyl acetate (5:2) followed by distillation to give the aziridine in 40 % yield, b.p. 130 ^{o}C/0.3 mmHg; (Found: C, 68.1; H, 6.6; N, 18.2. $C_{13}H_{15}N_3O$ requires C, 68.1; H, 6.6; N, 18.3 %); δ (90 MHz) 8.17 (d, J 8 Hz, quinaz. H ortho to C=O), 7.70 - 7.28 (m, 3 x quinaz. H), 2.75 (m, CH_2), 2.71 (s, quinaz. Me), 1.52 (s, Me), and 1.22 (s, Me).

5.1. Experimental work appertaining to Part 3, intramolecular trapping of N-nitrenes by alkynes.

5.1.1.

Propargyl bromide was purchased as an 80 % solution in toluene (Aldrich) and was used as received. But-2-yn-1-yl toluene p-sulphonate was prepared from but-2-yn-1-ol (Aldrich) and toluene p-sulphonyl chloride using the method of Brandsma[75]. 1-Bromobut-2-yne was obtained by treating the corresponding alcohol with phosphorus tribromide[76].

5.1.2. Synthesis of dimethyl disubstituted propane-1,3-dioates.

Dimethyl disubstituted propanedioates were prepared by reaction of the sodium salt of dimethyl malonate with propargyl bromide or 1-bromobut-2-yne in dry methanol followed by successive addition of a further mol. equivalent of sodium methoxide in methanol and an additional mol. equivalent of alkylating agent. The following esters were prepared in this way:

dimethyl 2,2-dibut-2-ynyl-1,3-propanedioate as a colourless solid (81 %), m.p. 53 - 55 ^{o}C (from ethyl acetate - light petroleum); (Found: C, 66.0; H, 6.8; $C_{13}H_{16}O_4$ requires C, 66.1; H, 6.8 %); δ 3.68 (s, CO_2Me), 2.84 (q, J 2 Hz, CH_2), and 1.70 (t, J 2 Hz, CH_3); dimethyl 2,2-diprop-2-ynyl-1,3-propanedioate as a colourless solid (81 %), m.p. 85 - 87 ^{o}C (from ethyl acetate - light petroleum); δ 3.70 (s, CO_2Me), 2.92 (d, J 3 Hz, CH_2), and 2.06 (t, J 3 Hz, -C≡CH); dimethyl 2-(prop-2-enyl)-2-(prop-2-ynyl)-1,3-propanedioate was prepared similarly by reaction of dimethyl 2-(prop-2-enyl)-1,3-propanedioate with propargyl bromide and was obtained as a colourless liquid (67 %), b.p. 120 - 123 ^{o}C/14 mmHg; ν_{max} 3345(w), 3000(w), 1760(s), 1450(m), 1305(m), 1240(s), and 940(w) cm^{-1};

δ 5.58 (m, -CH=CH_2), 5.16 (m, -CH=CH_2), 3.78 (s, 2 x CO_2Me), 2.62 (m, 2 x CH_2), and 2.02 (t, J 2.5 Hz, -C≡CH).

5.1.3. Synthesis of dimethyl monosubstituted propane-1,3-dioates

Dimethyl monosubstituted propanedioates were prepared as above by reaction of the sodium salt of dimethyl malonate with propargyl bromide or but-2-yn-1-yl tosylate (1 mol. equiv.) in dry methanol, but in both cases substantial di-substitution occurred. The mixture for the case of R = $CH_2C{\equiv}CH$ (ratio mono:disubstitution 2.3:1) was partially separated in the following way: to its solution in methanol was added sodium methoxide (1 mol. equiv. based on quantity of mono- and di-substitution product present) in methanol and, after stirring briefly, the methanol was removed under reduced pressure. The residue was extracted between ether and water, the aqueous layer re-extracted with ether and the combined ether layers dried and evaporated to yield a mixture of the starting mono- and disubstituted esters (ratio 1:3, respectively). After acidification of the aqueous layer above to pH 1, it was extracted twice with ether and the combined ether layers dried and evaporated to yield a mixture of acids of the starting esters (ratio mono- to disubstitution; 11:1). Approximately equal amounts of material were recovered from the original aqueous and ether layers in extraction of the residue above.

The mixture for the case of R = $CH_2C{\equiv}CCH_3$ (ratio mono:disubstitution, 6:1) was separated as described above to give the dioic acid $CH_3C{\equiv}CCH_2CH(CO_2H)_2$ (35 %) after recovery from the aqueous layer. The combined ether layers on evaporation gave a mixture of mono and disubstituted esters (ratio 2.8:1). Repetition of this separation procedure using more sodium methoxide (1 mol. equiv.) gave a further quantity (16 %) of the same dioic acid (total 51 %). Both the monosubstituted dioic acids above were used directly as described below.

5.1.4. Hydrolysis and decarboxylation of substituted dimethyl propan-1,3-dioates.

Disubstituted 1,3-propanedioic acids were obtained by heating the corresponding ester in alcoholic aqueous sodium hydroxide solution as described on p. 128 in 80 - 90 % yields.

2,2-Diprop-2-ynyl-1,3-propanedioic acid[77] was obtained as colourless crystals, m.p. 125 - 137 °C (from 5 M hydrochloric acid); δ 8.92br (s, CO_2H), 2.99 (d, J 3 Hz, CH_2), and 2.08 (t, J 3 Hz, -C≡CH).

Decarboxylation of the crude disubstituted dioic acids, prepared as above, or the corresponding monosubstituted dioic acids, isolated by the separation procedure described earlier, was carried out by heating in an oil bath at 140 - 175 °C until gas evolution ceased (∿ 1 hr). Distillation of the residue (Kugelrohr) gave the following acids in 76 -90 % yields.

pen-4-ynoic acid (104) b.p. 90 - 110 °C/0.1 mm Hg, solidified on standing (lit.[78] m.p. 53 - 55 °C); δ 10.42br (s, CO_2H), 2.53 (m, CH_2CH_2), and 1.96 (t, J 3 Hz, -C≡CH); hex-4-ynoic acid (103) b.p. 130 - 150 °C/0.1 mmHg, solidified on standing (lit.[79] m.p. 100 - 101 °C); δ 10.42br (s, CO_2H), 2.47 (m, CH_2CH_2), and 1.72 (t, J 2 Hz, CH_3); 2-(prop-2-ynyl)-pent-4-ynoic acid (107) (not distilled); δ 10.91br (s, CO_2H), 2.69 (m, 2 x CH_2, CH), and 2.02 (t, J 3 Hz, 2 x C≡CH); 2-(but-2-ynyl)-hex-4-ynoic acid (106), b.p. 130 - 150 °C/1.5 mmHg, solidified on standing; δ 11.44br (s, CO_2H), 2.53 (m, 2 x CH_2, CH), and 1.71 (t, J 2 Hz, 2 x CH_3); 2-(prop-2-ynyl)-pent-4-enoic acid, b.p. 130 - 132 °C/19 mmHg; δ 11.02br (s, CO_2H), 5.50 (m, CH=CH_2), 2.40 (m, 2 x CH_2, CH), and 2.02 (t, J 2.5 Hz, -C≡CH).

5.1.5. Conversion of pent-4-ynoic acid (104) to hex-5-ynoic acid (105).

Pent-4-ynoic acid (104) (12.8 g) was reduced with lithium aluminium hydride to pent-4-ynol, b.p. 78 - 82 ^{o}C/29 mmHg; δ 3.67 (t, J 7 Hz, $\underline{CH_2}OH$), 2.71br (s, OH), 2.27 (td, J 7 and 2 Hz, $\underline{CH_2}C{\equiv}CH$), 1.95 (t, J 2 Hz, -C≡$\underline{CH}$), and 1.74 (quint. J 7 Hz, $CH_2\underline{CH_2}CH_2$). Pent-4-ynol was converted to the tosylate and reacted with potassium cyanide in dimethyl sulphoxide to form 5-cyanopentyne; δ 2.48 (t, J 7 Hz, CH_2CN), 2.34 (td, J 7 and 2 Hz, $\underline{CH_2}C{\equiv}CH$), 2.01 (t, J 2 Hz, C≡$\underline{CH}$), and 1.84 (quint. J 7 Hz, $CH_2\underline{CH_2}CH_2$); ν_{max} 2260 and 2160 cm^{-1}, followed by hydrolysis with alcoholic aqueous potassium hydroxide solution to give hex-5-ynoic acid (105) (lit.[78] m.p. 41 - 43.5 ^{o}C); δ 8.30br (s, CO_2H), 2.48 (t, J 8 Hz, $\underline{CH_2}CO_2H$), 2.26 (td, J 8 and 3 Hz, $\underline{CH_2}C{\equiv}CH$), 1.96 (t, J 3 Hz, C≡$\underline{CH}$), and 1.83 (quint. J 8 Hz, $CH_2\underline{CH_2}CH_2$); ν_{max} 2120 and 1700 cm^{-1} (overall yield 45 %).

5.1.6. Synthesis of Methyl N-substituted anthranilates.

Methyl N-substituted anthranilates of the above carboxylic acids were obtained in 77 - 81 % yields by successive treatment with thionyl chloride and methyl anthranilate as described previously (p. 134). The following compounds were obtained in this way:

methyl N-(pent-4-ynoyl) anthanilate as colourless crystals, m.p. 48 - 51 ^{o}C (from ethanol); δ 11.04br (s, NH), 8.65 (dd, J 8 and 1 Hz, ArH ortho to NH), 7.96 (dd, J 8 and 2 Hz, ArH ortho to C=O), 7.49 (ddd, J 8, 8, and 2 Hz, ArH meta to NH), 7.02 (ddd, J 8, 8, and 1 Hz, ArH meta to C=O), 3.86 (s, OMe), 2.62 (m, 2 x CH_2), and 1.95 (t, J 2 Hz, C≡$\underline{CH}$); methyl N-(hex-4-ynoyl) anthranilate as an oil; δ 10.93br (s, NH), 8.68 (dd, J 8 and 1 Hz, ArH ortho to NH), 7.94 (dd, J 8 and 2 Hz, ArH ortho to C=O), 7.48 (ddd, J 8, 8, and 2 Hz, ArH meta to NH), 7.02 (ddd, J 8, 8 and 1 Hz, ArH meta to C=O), 3.86 (s, OMe), 2.56 (m, 2 x CH_2), and 1.72 (t,

J 2 Hz, C≡CCH$_3$); Methyl N-(hex-5-ynoyl) anthranilate as an oil; δ 11.3br (s, NH), 8.90 (dd, J 8 and 1 Hz, ArH ortho to NH), 8.15 (dd, J 8 and 2 Hz, ArH ortho to C=O), 7.65 (ddd, J 8, 8, and 2 Hz, ArH meta to NH), 7.15 (ddd, J 8, 8, and 1 Hz, ArH meta to C=O), 3.96 (s, OMe), and 2.75 - 1.90 (m, CH$_2$CH$_2$CH$_2$, and C≡CH); methyl N-(hepta-1,6-diyn-4-oyl) anthranilate as colourless crystals, m.p. 90.5 - 92 °C (from ethanol): δ 11.18br (s, NH), 8.66 (dd, J 8 and 1 Hz, ArH ortho to NH), 7.97 (dd, J 8 and 2 Hz, ArH ortho to C=O), 7.48 (ddd, J 8, 8, and 2 Hz, ArH meta to NH), 7.03 (ddd, J 8, 8, and 1 Hz, ArH meta to C=O), 3.88 (s, OMe), 2.64 (m, 2 x CH$_2$ and CH), and 1.99 (t, J 2 Hz, 2 x C≡CH); methyl N-(nona-2,7-diyn-5-oyl) anthranilate as colourless crystals, m.p. 65 - 68 °C (from ethanol); δ11.11br (s, NH), 8.70 (dd, J 8 and 1 Hz, ArH ortho to NH), 7.96 (dd, J 8 and 2 Hz, ArH ortho to C=O), 7.47 (ddd, J 8, 8, and 2 Hz, ArH meta to NH), 7.02 (ddd, J 8, 8, and 1 Hz, ArH meta to C=O), 3.88 (s, OMe), 2.64 (m, 2 x CH$_2$ and CH), and 1.70 (m, 2 x C≡CCH$_3$); methyl N-(hept-6-en-1-yn-4-oyl) anthranilate as an oil; δ (60 MHz) 11.02br (s, NH), 8.76 (d, J 8 Hz, ArH ortho to NH), 7.96 (d, J 8 Hz, ArH ortho to C=O), 7.51 (dd, J 8 and 8 Hz, ArH meta to NH), 7.01 (dd, J 8 and 8 Hz, ArH meta to C=O), 5.66 (m, CH=CH$_2$), 5.08 (m, CH=CH$_2$), 3.91 (s, OMe), 2.56 (m, 2 x CH$_2$), and 2.00 (m, C≡CH).

5.1.7. Synthesis of N-Amino-2-substituted quinazolin-4(3H)-ones.

The above amides in which the acid part was unbranched were heated under reflux overnight with hydrazine hydrate in methanol or ethanol and the following compounds were obtained as colourless crystals:

N-amino-2-(but-1-yn-4-yl)quinazolin-4(3H)-one (99): yield 46 %; m.p. 157 - 159 °C (from methanol); (Found: C, 67.5; H, 5.3; N, 19.7. $C_{12}H_{11}N_3O$ requires C, 67.6; H, 5.2; N, 19.7 %); δ 8.18 (d, J 8 Hz,

ArH ortho to C=O), 7.63 - 7.29 (m, 3 x ArH), 4.88br (s, NH_2), 3.28 (t, J 7 Hz, quinaz. CH_2), 2.75 (td, J 7 and 2 Hz, $CH_2C{\equiv}CH$), and 1.96 (t, J 2 Hz, $C{\equiv}CH$); ν_{max} (Nujol) 3290(m), 3230(m), 1665(s), 1620(s), 770(s), and 690(s) cm^{-1}; N-amino-2-(pent-2-yn-5-yl)quinazolin-4(3H)-one (98): yield 90 %; m.p. 147 - 150 °C (from ethanol); (Found: C, 68.7; H, 5.8; N, 18.5. $C_{13}H_{13}N_3O$ requires C, 68.7; H, 5.8; N, 18.5 %); δ 8.15 (d, J 8 Hz, ArH ortho to C=O), 7.60 - 7.26 (m, 3 x ArH), 4.94br (s, NH_2), 3.20 (t, J 7 Hz, quinaz. CH_2), 2.70 (m, $CH_2C{\equiv}CCH_3$), and 1.70 (t, J 2 Hz, $C{\equiv}CCH_3$); ν_{max} (Nujol) 3300(m), 3205(w), 1640(s), 1595(s), 760(m), and 690(s) cm^{-1}; N-amino-2-(pent-1-yn-5-yl)quinazolin-4(3H)-one (100): yield 70 %; m.p. 106 - 107 °C (from ethanol); (Found: C, 68.5; H, 5.9; N, 18.5; $C_{13}H_{13}N_3O$ requires C, 68.7; H, 5.8; N, 18.5 %); δ 8.15 (d, J 8 Hz, ArH ortho to C=O), 7.60 - 7.10 (m, 3 x ArH), 4.84br (s, NH_2), 3.10 (t, J 7 Hz, quinaz. CH_2), 2.35 (td, J 7 and 2 Hz, $CH_2C{\equiv}CH$), 2.05 (quint. J 7 Hz, $CH_2CH_2CH_2$), and 1.96 (t, J 2 Hz, $C{\equiv}CH$); ν_{max} (Nujol) 3315(m), 3240(m), 1672(s), 1596(s), 781(m), and 696(m) cm^{-1}.

The methyl N-substituted anthranilates above in which the acid part contained a branched chain were heated with hydrazine hydrate in methanol or ethanol in a sealed tube in the absence of oxygen as described previously (p. 137) and the following compounds obtained as colourless crystals:

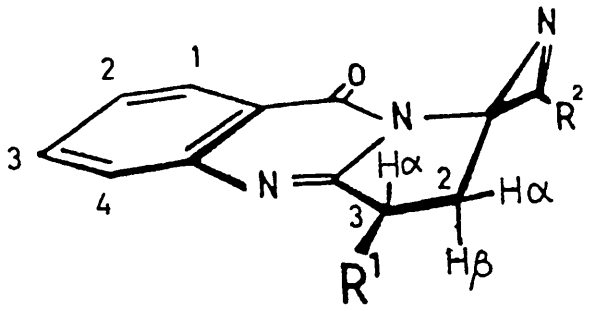
N-amino-2-(hepta-1,6-diyn-4-yl)quinazolin-4(3H)-one (102): yield 63 %; m.p. 124 - 125.5 °C (from ethanol); δ 8.20 (d, J 8 Hz, ArH ortho to C=O), 7.64 - 7.31 (m, 3 x ArH), 4.96 (s, NH_2), 4.20 (quint. J 7 Hz, CH), 2.76 (dd, J 7 and 2 Hz, 2 x CH_2), and 1.92 (t, J 2 Hz, 2 x $C{\equiv}CH$). This compound was first prepared and characterised by K.L. Woodthorpe[35]; N-amino-2-(nona-2,7-diyn-5-yl)quinazolin-4(3H)-one (101)*; yield 59 %,

m.p. 104 - 105 °C (from ethanol); (Found: C, 72.8; H, 6.2; N, 15.0. $C_{17}H_{17}N_3O$ requires C, 73.1; H, 6.1; N, 15.0 %); δ 8.22 (d, J 8 Hz, ArH ortho to C=O), 7.72 - 7.30 (m, 3 x ArH), 5.10br (s, NH_2); 4.09 (quint. J 7 Hz, CH), 2.67 (m, 2 x CH_2), and 1.69 (t, J 2 Hz, 2 x $C{\equiv}CCH_3$); ν_{max} (Nujol) 3310(m), 1680(s), 1600(s), 1583(s), 768(s), and 691(s) cm^{-1};

*One hour after the Carius tube was placed in the oven (120 - 130 °C) a leak was discovered in the seal and the tube was removed from the oven and set aside overnight at room temperature. After the normal work-up procedure, an n.m.r. spectrum revealed the product to be neither starting material nor the desired quinazolone but was consistent with its formulation as the intermediate, hydrazide (139); δ 10.87br (s, exchangeable D_2O, NH), 8.46 (dd, J 8 and 1 Hz, ArH ortho to NH), 8.21br (s, exchangeable D_2O, $-CONHNH_2$), 7.44 (dd, J 8 and 2 Hz, ArH ortho C=O), 7.38 (ddd, J 8, 8, and 2 Hz, ArH meta to NH), 6.97 (ddd, J 8, 8, and 1 Hz, ArH meta to C=O), 4.11br (s, exchangeable D_2O, $-CONHNH_2$), 2.55 (m, 2 x CH_2 and CH), and 1.70 (m, 2 x $C{\equiv}CCH_3$). After re-heating in a Carius tube as described previously (p. 137) the desired N-amino-2-(hept-6-en-1-yn-4-yl)quinazolin-4(3H)-one (137) was obtained: (yield 53 %); m.p. 60 - 62 °C (from ethanol) (Found: C, 71.1; H, 5.9; N, 16.5. $C_{15}H_{15}N_3O$ requires C, 71.1; H, 6.0; N, 16.6 %); δ 8.18 (d, J 8 Hz, ArH ortho to C=O), 7.63 - 7.29 (m, 3 x ArH), 5.73 (m, $CH{=}CH_2$), 5.07 (m, $CH{=}CH_2$), 4.89br (s, NH_2), 4.06 (quint. J 7 Hz, CH), 2.65 (dd, J 7 and 2 Hz, $CH_2C{\equiv}CH$), 2.57 (m, $CH_2CH{=}CH_2$), and 1.88 (t, J 2 Hz, $C{\equiv}CH$); ν_{max} (Nujol) 3320(m), 3260(s), 1660(s), 1590(s), 925(m), 780(s), and 700(s) cm^{-1}.

5.1.8. Oxidation of N-Amino-2-substituted quinazolin-4(3H)-ones.

Oxidations were carried out with lead tetra-acetate uisng the high dilution method as described previously (p.141) at 0 °C.



(109) R = Me, R′ = H-3β

(115) R = Me, R′ = $CH_2C{\equiv}CMe$

(112) R = H, R′ = H-3β

(116) R = H, R′ = $CH_2C{\equiv}CH$

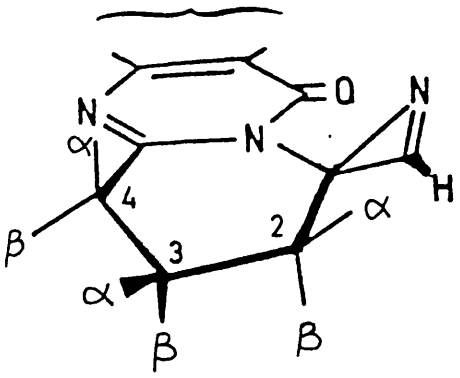
N-Amino-2-(pent-2-yn-5-yl)quinazolin-4(3H)-one (98): Oxidation of (98) in this way gave a solid product in quantitative yield. Crystallisation from ethyl acetate - light petroleum gave azirine (109) as colourless prisms (78 %), m.p. 135 - 136 °C; (Found: C, 69.2; H, 5.0; N, 18.6. $C_{13}H_{11}N_3O$ requires C, 69.3; H, 4.9; N, 18.7 %); δ, ^1H (400 MHz) 8.05 (ddd, J 8, 1.5, and 0.5 Hz, quinaz. H-1), 7.64 (ddd, J 8, 7, and 1.5 Hz, quinaz. H-3), 7.56 (ddd, J 8, 1.5, and 0.5 Hz, quinaz. H-4), 7.34 (ddd, J 8, 7, and 1.5 Hz, quinaz. H-2), 3.48 (ddd, J 17.5, 10.9, and 9.3 Hz, H-3α), 3.03 (ddd, J 17.5, 9.7, and 1.5 Hz, H-3β), 2.71 (s, CH_3), 2.61 (ddd, J 13.9, 10.9, and 9.7 Hz, H-2β), and 1.73 (ddd, J 13.9, 9.3, and 1.5 Hz, H-2α); δ, ^{13}C (100 MHz) 171.50 s, 160.80 s, 158.48 s,148.70s, 134.30d, 126.92 d, 126.34 d, 126.16 d, 120.92 s, 55.91 s, 29.42 dd, 28.15 dd, and 14.96 q; ν_{max} (Nujol) 1780(w), 1675(s), 1630(s), 1610(s), 780(s), and 700(m) cm^{-1}. N-amino-2-(nona-2,7-diyn-5-yl)-quinazolin-4(3H)-one (101): Oxidation of (101) (1 g) as described above gave a solid (950 mg) whose n.m.r. spectrum indicated it was pure. Crystallisation from ethanol gave azirine (115) as colourless needles, m.p. 140.5 - 141.5 °C; (Found:

C, 73.7; H, 5.5; N, 15.2. $C_{17}H_{15}N_3O$ requires C, 73.6; H, 5.5; N, 15.2 %); δ (400 MHz) 8.13 (ddd, J 8, 1.5, and 0.6 Hz, quinaz. H-1), 7.72 (ddd, J 8.2, 6.5, and 1.5 Hz, quinaz. H-3), 7.68 (ddd, J 8.2, 1.7, and 0.6 Hz, quinaz. H-4), 7.42 (ddd, J 8, 6.5, and 1.7 Hz, quinaz. H-2), 3.79 (dddd, J 10.5, 8.3, 7.4, and 4.4 Hz, H-3α), 2.94 (ddq, J 16.8, 4.4, and 2.5 Hz, CHHC≡CMe), 2.79 (s, azirine CH_3), 2.76 (ddq, J 16.8, 7.4, and 2.5 Hz, CHHC CMe), 2.65 (dd, J 13.7, and 10.5 Hz, H-2β), 1.97 (dd, 13.7 and 8.3 Hz, H-2α), and 1.74 (t, J 2.5 Hz, C≡CCH_3); ν_{max} (Nujol) 1760(w), 1690(s), 1628(m), 1610(m), 1330(m), and 780(s) cm^{-1}.

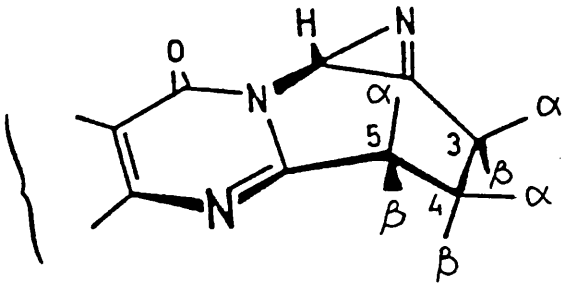
N-Amino-2-(but-1-yn-4-yl)quinazolin-4(3H)-one (99). Examination of the crude product by n.m.r. showed the presence of azirine (112) and the acetic acid addition product (113) in the ratio 79:21, respectively. Signals assigned to azirine (112) δ (400 MHz) 10.41 (dd, J 2.8 and 0.6 Hz, azirine C-H) 8.02 (dd, J 8 and 1.5 Hz, quinaz. H-1), 7.63 (ddd, J 8.1, 6.9, and 1.5 Hz, quinaz. H-3), 7.54 (dd, J 8.1, and 1.7 Hz, quinaz. H-4), 7.32 (ddd, J 8, 6.9, and 1.7 Hz, quinaz. H-2), 3.47 (ddd, J 17.5, 10.9, and 9.3 Hz, H-3α), 3.03 (ddd, J 17.5, 9.6, and 1.3 Hz, H-3β), 2.65 (dddd, J 13.9, 10.9, 9.6, and 2.8 Hz, H-2β), and 1.75 (dddd, J 13.9, 9.3, 1.3, and 0.6 Hz, H-2α). When the reaction mixture above was set aside overnight before work-up, an n.m.r. spectrum of the crude product showed the presence of aziridine (113) only which was isolated as an unstable (non-distillable) oil; δ 8.00 (d, J 8 Hz, quinaz. H-1), 7.68 - 7.24 (m, 3 x quinaz. H), 6.10 (d, J 8 Hz, CH_2OAc), 3.88br (d, J 8 Hz, (exch. D_2O), NH), 3.08 (t, J 9 Hz, H_2C-quinaz.), 2.31 (t, J 9 Hz, CH_2-C (spiro)), and 2.09 (s, $OCOCH_3$). On shaking with D_2O, δ 6.10 (d) collapsed to δ 6.10 (s). N-Amino-2-(hepta-1,6-diyn-4-yl)quinazolin-4(3H)-one (102). Oxidation of (102) as described above and work-up after only 10 min. stirring of the solution (after addition of (102) and lead tetra-acetate

complete) gave only the azirine (116), m.p. 163 - 168 °C as a colourless solid (from ether - dichloromethane). A satisfactory analysis of this material was not obtained. δ (400 MHz) 10.48 (dd, J 2.8 and 0.6 Hz, azirine C-H), 8.13 (dd, J 8 and 1.4 Hz, quinaz. H-1), 7.73 (ddd, J 8.2, 6.8, and 1.4 Hz, quinaz. H-3), 7.69 (dd, J 8.2 and 1.3 Hz, quinaz. H-4), 7.43 (ddd, J 8, 6.8, and 1.3 Hz, quinaz. H-2), 3.88 (dddd, J 10.6, 8.1, 7.3, and 4.4 Hz, H-3α), 2.99 (ddd, J 17, 4.4, and 2.6 Hz, CHHC≡CH), 2.86 (ddd, J 17, 7.3, and 2.6 Hz, CHHC≡CH), 2.75 (ddd, J 13.7, 10.6, and 2.8 Hz, H-2β), 2.04 (dd, J 13.7 and 8.1 Hz, H-2α), and 1.99 (t, J 2.6 Hz, C≡CH). When the reaction mixture above was set aside overnight before work-up, an n.m.r. spectrum on the crude product showed the presence of the acetic acid addition product (117) only. Crystallisation from ether - dichloromethane gave the aziridine (117), m.p. 128 - 131 °C (decomp.); (Found: C, 66.1; H, 5.0; N, 13.6. $C_{17}H_{15}N_3O_3$ requires C, 66.0; H, 4.9; N, 13.6 %); δ (400 MHz) 8.18 (ddd, J 8, 1.5, and 0.5 Hz, quinaz. H-1), 7.75 (ddd, J 8.2, 7, and 1.5 Hz, quinaz. H-3), 7.66 (ddd, J 8.2, 1.1, and 0.5 Hz, quinaz. H-4), 7.46 (ddd, J 8, 7, and 1.1 Hz, quinaz H-2), 6.35 (d, J 8.5 Hz, CHOAc), 3.69br (d, J 8.5 Hz, NH), 3.54 (dddd, J 9.4, 7.9, 5.5, and 4.4 Hz, HC-quinaz.), 2.85 (ddd, J 16.9, 4.4, and 2.6 Hz, CHHC≡CH), 2.75 (ddd, J 16.9, 7.9, and 2.6 Hz, CHHC≡CH), 2.57 (dd, J 14.3 and 9.4 Hz, HHC-C(spiro)), 2.45 (dd, J 14.3 and 5.5 Hz, HHC-C(spiro)), 2.16 (s, $OCOCH_3$), and 1.98 (t, J 2.6 Hz, C≡CH); ν_{max} 3230(br s), 1745(s), 1670(s), 1615(s), 1225(s), 1140(s), 995(m), 775(s), and 695(m) cm^{-1}.

N-Amino-2-(pent-1-yn-5-yl)quinazolin-4(3H)-one (100)



(123)

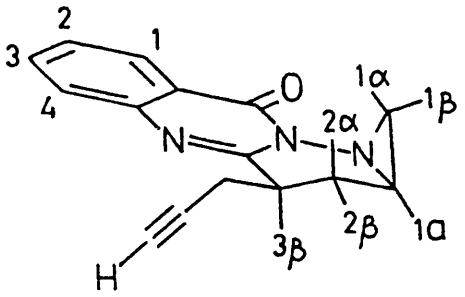


(124)

Oxidation of (100) (1 g) as described above and examination of the crude product by n.m.r. showed the presence of azirines (123) and (124) in a 9:4 ratio, respectively. Crystallisation from methanol gave a pure sample of the azirine (123) (250 mg), m.p. 120 - 124 °C, but an analytical sample could not be obtained since the (colourless) azirine produced an orange polymeric substance on standing overnight; δ (400 MHz) 10.28 (d, J 2.3 Hz, azirine H), 8.14 (dd, J 7.9 and 1.5 Hz, quinaz. H-1), 7.73 (ddd, J 8.1, 7.1, and 1.5 Hz, quinaz. H-3), 7.62 (dd, J 8.1 and 1.3 Hz, quinaz. H-4), 7.42 (ddd, J 7.9, 7.1, and 1.3 Hz, quinaz. H-2), 3.39 (ddd, J 15.4, 11.9, and 5.9 Hz, H-4α), 3.05 (ddd, J 15.4, 5.6, and 5.1 Hz, H-4β), 2.62 (dddd, J 14.9, 8.9, 4.6, and 2.3 Hz, H-2β), 2.38 (ddddd, J 13.6, 8.9, 5.9, 5.1, and 4.6 Hz, H-3α), 1.97 (ddddd, J 13.6, 11.9, 8.9, 7.2, and 5.6 Hz, H-3β), and 1.51 (ddd, J 14.9, 8.9, and 7.2 Hz, H-2α); ν_{max} (Nujol) 1668(s), 1610(s), 790(m), and 720 (m) cm^{-1}. The n.m.r. spectrum of azirine (124) was obtained from that of the crude reaction product above by subtraction of those signals belonging to azirine (123) and showed

δ (400 MHz) 8.29 (dd, J 7.9 and 1.5 Hz, quinaz. H-1), 7.71 (ddd, J 8.1, 7.1, and 1.5 Hz, quinaz. H-3), 7.56 (dd, J 8.1 and 1.3 Hz, quinaz. H-4), 7.46 (ddd, J 7.9, 7.1, and 1.3 Hz, quinaz. H-2), 4.42 (s, NCHN), 3.32 (ddd, J 13, 5, and 1.5 Hz, H-3β), 3.28 (ddd, J 15, 7.7, and 1.5 Hz, H-5β), 3.11 (ddd, J 15, 12.3, and 1.5 Hz, H-5α), 2.99 (ddd, J 13, 12.7, and 7.7 Hz, H-3α), 2.55 (ddddd, J 13.5, 7.7, 7.7, 1.5, and 1.5 Hz, H-4α), and 1.65 (ddddd, J 13.5, 12.7, 12.3, 5, and 1.5 Hz, H-4β).

N-Amino-2-(hept-6-en-1-yn-4-yl)quinazolin-4(3H)-one (137). An n.m.r. spectrum of the crude (crystalline) oxidation product showed the presence of only one product. Crystallisation from ethanol gave aziridine (138) as colourless crystals, m.p. 178 - 182 °C; (Found: C, 71.8; H, 5.3; N, 16.7. $C_{15}H_{13}N_3O$ requires C, 71.7; H, 5.2; N, 16.7 %);



(138)

δ (400 MHz) 8.30 (dd, J 8 and 1.2 Hz, quinaz. H-1), 7.71 (ddd, J 8, 6.9, and 1.2 Hz, quinaz. H-3), 7.65 (dd, J 8 and 0.9 Hz, quinaz. H-4), 7.45 (ddd, J 8, 6.9, and 0.9 Hz, quinaz. H-2), 3.28 (ddd, J 16.9, 3.8, and 2.6 Hz, CHHC≡CH), 3.21 (dddd, J 12.8, 9.2, 3.8, and 3.8 Hz, H-3β), 3.09 (ddd, J 12.8, 8, and 3.8 Hz, H-2β), 3.00 (dddd, J 8.4, 8, 5.6, and 5.6 Hz, H-1a), 2.94 (dd, J 5.6 and

2.2 Hz, H-1β), 2.55 (ddd, J 16.9, 9.2, and 2.6 Hz, CHHC≡CH), 2.08 (t, J 2.6 Hz, C≡CH), 1.92 (dd, J 5.6 and 2.2 Hz, H-1α), and 1.43 (ddd, J 12.8, 12.8, and 8.4 Hz, H-2α); ν_{max} (Nujol) 3230(w), 1660(s), 1595(s), 780(m), and 700(m) cm^{-1}.

5.1.9. Attempted Trapping of a 1H-Azirine Intermediate.

N-Amino-2-(but-1-yn-4-yl)quinazolin-4(3H)-one (99) (200 mg, 1 mol. equiv.) was dissolved in dry dichloromethane (50 ml) and lead tetra-acetate (0.9 mol. equiv.) was also dissolved in an equal volume of dry dichloromethane. Both solutions were added simultaneously at the same rate over 20 min. to rapidly stirred dry dichloromethane (100 ml) which was cooled in a dry ice-acetone bath at -78 °C. After addition was complete the solution was stirred for a further 8 hr. No precipitated lead di-acetate was visible in the solution after this time, and testing with starch-iodide paper suggested that unreacted lead tetra-acetate was still present. 2,3-Dimethylbutadiene (1.3 g, 16 mol. equiv.) was then added to the reaction mixture and the temperature of the solution allowed to rise slowly to ambient, stirring throughout. The solution was washed twice with aqueous sodium hydrogen carbonate, dried and evaporated. An n.m.r. spectrum of the crude reaction product showed the presence of acetoxyaziridine (113) and aziridine (121) in a ratio of 3:2, respectively. Rapid chromatography on alumina and elution with light petroleum - ethyl acetate (4:1) gave aziridine (121) (18 mg) as colourless laths, m.p. 96 - 97 °C (from ethanol); (Found: C, 73.7; H, 6.5; N, 14.4. $C_{18}H_{19}N_3O$ requires C, 73.7; H, 6.5; N, 14.3 %); δ (400 MHz) 8.11 (dd, J 8 and 1.5 Hz, quinaz. H-1), 7.63 (ddd, H 8.2, 6.9, and 1.5 Hz, quinaz. H-3), 7.57 (dd, J 8.2 and 1.4 Hz, quinaz. H-4), 7.36 (ddd, J 8, 6.9, and 1.4 Hz, quinaz. H-2), 5.16br (s, C=CHH), 5.10 (m, C=CHH), 3.13 (ddd, J 16.2, 8.3, and

6.4 Hz, CHH-quinaz.), 3.02 (m, 2 x azir. ring H), 2.90 (ddd, J 16.2, 7.9, and 7.9 Hz, CHH-quinaz.), 2.71 (m, $CH_2C{\equiv}CH$), 1.89 (t, J 2.6 Hz, C≡CH), 1.76br (s, $-CMe{=}CH_2$), and 1.22 (s, azir. ring Me). Minor invertomer, 1.59 (s, azir. ring Me), and 1.43 (s, $CMe{=}CH_2$). Ratio of two invertomers, ca 17:1. ν_{max} (Nujol) 3250(m), 1660(s), 1590(s), 1300(w), 1230(w), 1120(w), 900(m), and 780(m) cm^{-1}.

Oxidation of (99) (300 mg) with lead tetra-acetate (650 mg, 1.15 mol. equiv.) in dichloromethane (5 ml) and 2,3-dimethylbutadiene (5 ml) at 0 °C in the usual way[14] gave aziridine (121) only. Rapid chromatography on alumina on elution with light petroleum - ethyl acetate gave the aziridine (51 %). Further elution with ethyl acetate gave the amino-alcohol (122) as an oil (13 %); δ 8.15 (d, J 8 Hz, quinaz. H-1), 7.70 - 7.30 (m, 3 x quinaz. H), 5.55 (dd, J 8 and 5 Hz, (exchange D_2O), NH), 5.21br (s, C=CHH), 4.95br (s, C=CHH), 3.56 - 3.13 (m, CH_2-quinaz. and CHHNH), 2.91 - 2.68 (m, 4 H (→ 3 H after D_2O exchange.), $CH_2C{\equiv}CH$, CHHNH, and OH), 1.95 (t, J 2 Hz, C≡CH), 1.87 (s, $-CMe{=}CH_2$), and 1.36 (s, $C(OH)CH_3$); ν_{max} 3440br(m), 3290br(m), 2950(m), 2120(w), 1670(s), 1590(s), 1470(m), and 780(m) cm^{-1}.

5.1.10. N.m.r. Studies on 2-Phenyl-3,3-pentamethyleneazirine (126).

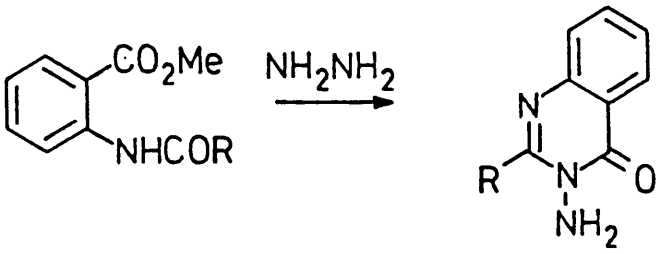
2-Phenyl-3,3-pentamethyleneazirine (126) was prepared by the method of Sato.[63] Cyclohexylphenylketonedimethylhydrazone was obtained as a yellow oil; δ 7.35 - 7.05 (m, 5 x ArH), 2.30 (s, $-NMe_2$), and 1.96 - 1.06 (m, cyclohexyl ring protons); ν_{max} 1615(w) cm^{-1}, and cyclohexylphenylketonedimethylhydrazone methiodide (125) was obtained as colourless crystals, m.p. 142 - 144 °C (lit.[63] 148 - 149 °C); δ 7.51 (m, 3 x ArH), 7.29 (m, 2 x ArH, ortho), 3.54 (s, $\overset{+}{N}Me_3$), 2.51 (m, cyclohexyl C-H), and 2.04 - 1.10 (5 x cyclohexyl CH_2); ν_{max} (Nujol) 1625(w) cm^{-1}.

Addition of (125) (2.23 g) to a solution of sodium (0.13 g, 0.9 mol. equiv.) in isopropanol (20 ml) at 40 °C gave a 3:1 mixture of azirine (126) and 2-phenyl-2-isopropoxy-3,3-pentamethyleneazirine (from the appearance of signals due to isopropoxy group in the n.m.r. spectrum of the product at δ 3.73 (septet, J 6 Hz, CH), 1.11 (d, J 6 Hz, $\underline{CH_3}CCH_3$), and 0.91 (d, J 6 Hz, $CH_3CH\underline{CH_3}$). Chromatography on silica and elution with light petroleum - ethyl acetate (9:1) gave (126) as a pale yellow oil (0.33 g); ν_{max} 1726(m) cm^{-1}. δ (400 MHz) 7.84 (m, 2 x ArH, ortho), 7.54 (m, 3 x ArH), 1.90 (structured multiplet; total width 21.5 Hz, 2 H), and 1.70 - 1.52 (m, 8H).

2-Phenyl-3,3-pentamethylene aziridine (133) was prepared by lithium aluminium hydride reduction of (126).[79] The product was obtained as a colourless oil; ν_{max} 3250 cm^{-1}. δ (300 MHz) 7.36 - 7.14 (m, 5 x ArH), 2.93 (s, azir. ring -CH), and 1.75 - 1.05 (m, cyclohexyl ring protons and NH).

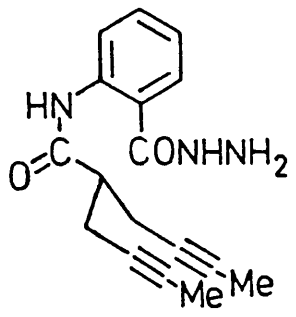
APPENDIX

I. Synthesis of N-Amino-2-substituted quinazolin-4(3H)-ones.



Amides in which R was a single chain were simply heated under reflux overnight in ethanol with hydrazine hydrate (under nitrogen), whereas those amides with bifurcated sidechains needed to be heated at 120 - 130 °C overnight in a sealed tube with hydrazine hydrate in degassed ethanol. The slower rate of reaction for the bifurcated species is due to steric hindrance.

Previously, it has been thought that the initial attack of the hydrazine was on the amide carbonyl.[35] The following result suggests otherwise. With methyl N-(nona-2,7-diyn-5-oyl)anthanilate, one hour after the Carius tube was placed in the oven a leak was discovered in the seal and the tube was removed from the oven and set aside overnight at room temperature. After the normal work-up procedure, an n.m.r. spectrum revealed the product to be neither starting material nor the desired quinazolone but was consistent with its formulation as the intermediate hydrazide (139) (for n.m.r. data see p. 158).



(139)

After reheating hydrazine (139) in a Carius tube as previously described (p. 137), N-Amino-2-(nona-2,7-diyn-5-yl)quinazolin-4(3H)-one (101) was obtained.

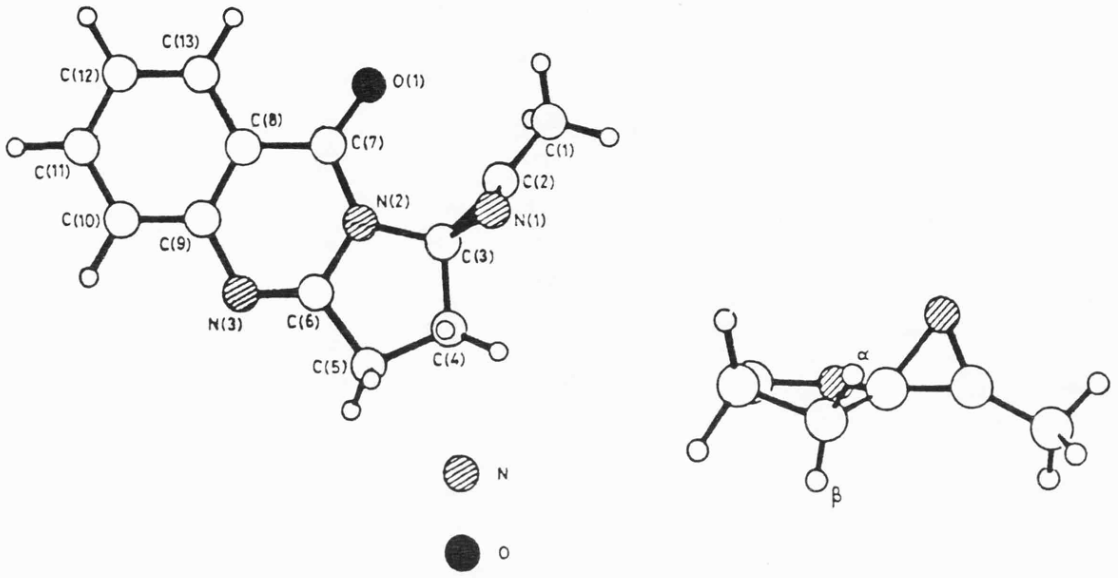
This finding suggests as one would normally assume that the intial attack of the hydrazine is on the ester and not the amide carbonyl. However, the possibility has not yet been excluded that attack of hydrazine on the anthranilate without α-branching in acid portion may first take place on the amide carbonyl group since hydrazide corresponding to (139) has not been isolated or identified from the reaction of such an anthranilate with hydrazine which has not proceeded to completion to the quinazolone.

II. The energies of the HOMO of some simple molecules.

Photoelectron spectroscopy measures the energy levels of filled orbitals. Below are listed the values obtained by this technique for the energies of the HOMO of some simple molecules.[80]

Alkene	Vertical Ionization Energy (I_r (eV))	MO Energy -E (eV)
Ethylene	10.51	12.12
Propene	10.03	9.59
cis-Butene	9.36	9.07
trans-Butene	9.37	9.08
Isobutene	9.45	9.14
Styrene	8.47	
Acetylene	11.40	11.02
Methyl Acetylene	10.37	10.23

III Azirine(109)- X-Ray Crystal Structure Data.



Bond distances (Å) with estimated standard deviations in parentheses.

C(1)-H(11)	1.080	C(6)-N(3)	1.268(8)
C(1)-H(12)	1.080	C(7)-C(8)	1.458(10)
C(1)-H(13)	1.080	C(7)-O(1)	1.221(7)
C(1)-C(2)	1.475(10)	C(7)-N(2)	1.387(8)
C(2)-C(3)	1.341(10)	C(8)-C(9)	1.399(9)
C(2)-N(1)	1.262(9)	C(8)-C(13)	1.390(10)
C(3)-C(4)	1.497(10)	C(9)-C(10)	1.398(10)
C(3)-N(1)	1.526(9)	C(9)-N(3)	1.395(8)
C(3)-N(2)	1.463(9)	C(10)-H(101)	1.080
C(4)-H(41)	0.91(5)	C(10)-H(11)	1.378(10)
C(4)-H(42)	1.12(8)	C(11)-H(111)	1.080
C(4)-C(5)	1.526(12)	C(11)-C(12)	1.391(10)
C(5)-H(51)	1.12(8)	C(12)-H(121)	1.080
C(5)-H(52)	1.07(8)	C(12)-C(13)	1.387(10)
C(5)-C(6)	1.519(10)	C(13)-H(131)	1.080
C(6)-N(2)	1.385(8)		

Bond angles (°) with estimated standard deviations in parentheses.

H(12)-C(1)-H(11)	109.5	N(3)-C(6)-C(5)	126.1(0.7)
H(13)-C(1)-H(11)	109.5	N(3)-C(6)-N(2)	125.9(0.7)
H(13)-C(1)-H(12)	109.5	O(1)-C(7)-C(8)	127.1(0.7)
C(2)-C(1)-H(11)	109.4(0.4)	N(2)-C(7)-C(8)	112.1(0.7)
C(2)-C(1)-H(12)	109.0(0.5)	N(2)-C(7)-O(1)	120.8(0.7)
C(2)-C(1)-H(13)	110.0(0.4)	C(9)-C(8)-C(7)	120.3(0.7)
C(3)-C(2)-C(1)	152.2(0.8)	C813)-C(8)-C(7)	119.2(0.7)
N(1)-C(2)-C(1)	139.0(0.7)	C(13)-C(8)-C(9)	120.5(0.7)
N(1)-C(2)-C(3)	68.7(0.6)	C(10)-C(9)-C(8)	118.8(0.7)
C(4)-C(3)-C(2)	129.9(0.8)	N(3)-C(9)-C(8)	122.9(0.6)
N(1)-C(3)-C(2)	50.4(0.4)	N(3)-C(9)-C(10)	118.3(0.7)
N(1)-C(3)-C(4)	119.9(0.7)	H(101)-C(10)-C(9)	119.4(0.5)
N(2)-C(3)-C(2)	122.3(0.6)	C(11)-C(10)-C(9)	120.8(0.8)
N(2)-C(3)-C(4)	105.8(0.6)	C(11)-C(10)-H(101)	119.8(0.5)
N(2)-C(3)-N(1)	116.7(0.6)	H(111)-C(11)-C(10)	120.2(0.5)
H(41)-C(4)-C(3)	106.2(3.3)	C(12)-C(11)-C(10)	119.8(0.8)
H(42)-C(4)-C(3)	101.4(4.1)	C(12)-C(11)-H(111)	119.9(0.5)
H(42)-C(4)-H(41)	125.0(5.7)	H(121)-C(12)-C(11)	119.9(0.5)
C(5)-C(4)-C(3)	103.8(0.7)	C(13)-C(12)-C(11)	120.4(0.8)
C(5)-C(4)-H(41)	104.4(3.3)	C(13)-C(12)-H(121)	119.7(0.5)
C(5)-C(4)-H(42)	113.8(4.0)	C(12)-C(13)-C(8)	119.6(0.8)
H(51)-C(5)-C(4)	110.1(4.2)	H(131)-C(13)-C(8)	120.0(0.5)
H(52)-C(5)-C(4)	110.0(3.6)	H(131)-C(13)-C(12)	120.4(0.5)
H(52)-C(5)-H(51)	118.3(5.6)	C(3)-N(1)-C(2)	60.9(0.5)
C(6)-C(5)-C(4)	104.1(0.7)	C(6)-N(2)-C(3)	110.9(0.6)
C(6)-C(5)-H(51)	111.8(4.0)	C(7)-N(2)-C(3)	125.8(0.6)
C(6)-C(5)-H(52)	101.3(4.0)	C(7)-H(2)-C(6)	123.3(0.6)
N(2)-C(6)-C(5)	108.0(0.6)	C(9)-N(3)-C(6)	115.6(0.6)

Interatomic non-bond distances (Å).

C(1)...C(3)	2.820	C(6)...C(7)	2.440
C(1)...N(1)	2.565	C(6)...C(8)	2.703
H(11)...H(12)	1.764	C(6)...C(9)	2.255
H(11)...H(13)	1.764	C(7)...C(9)	2.478
H(11)...C(2)	2.097	C(7)...C(13)	2.457
H(12)...H(13)	1.764	C(8)...C(10)	2.407
H(12)...C(2)	2.093	C(8)...C(11)	2.778
H(12)...N(1)	2.412	C(8)...C(12)	2.400
H(13)...C(2)	2.105	C(8)...H(131)	2.145
C(2)...C(4)	2.653	C(8)...O(1)	2.401
C(2)...O(1)	2.759	C(8)...N(2)	2.361
C(2)...N(2)	2.535	C(8)...N(3)	2.454
C(3)...H(41)	1.959	C(9)...H(101)	2.146
C(3)...H(42)	2.041	C(9)...C(11)	2.413
C(3)...C(5)	2.379	C(9)...C(12)	2.786
C(3)...C(6)	2.346	C(9)...C(13)	2.421
C(3)...C(7)	2.537	C(9)...N(2)	2.686
C(4)...H(51)	2.180	C(10)...H(111)	2.136
C(4)...H(52)	2.140	C(10)...C(12)	2.396
C(4)...C(6)	2.402	C(10)...C(13)	2.779
C(4)...N(1)	2.617	C(10)...N(3)	2.398
C(4)...N(2)	2.360	H(101)...C(11)	2.131
H(41)...H(42)	1.809	C(11)...H(121)	2.144
H(41)...C(5)	1.965	C(11)...C(13)	2.411
H(42)...C(5)	2.230	H(111)...C(12)	2.145
C(5)...N(2)	2.351	C(12)...H(131)	2.146
C(5)...N(3)	2.487	H(121)...C(13)	2.139
H(51)...H(52)	1.877	O(1)...N(2)	2.270
H(51)...C(6)	2.196	N(1)...N(2)	2.544
H(52)...C(6)	2.020	N(2)...N(3)	2.363

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PUBLICATIONS

Intramolecular Addition of *N*-Nitrenes to Alkenes: Transition from Non-concerted to Concerted Addition

Robert S. Atkinson* and Michael J. Grimshire

Department of Chemistry, Leicester University, Leicester LE1 7RH, U.K.

The nitrenes generated by oxidation of the *N*-amino compounds (**6**) and (**7**) are trapped competitively by the phenyl-substituted and unsubstituted double bonds: the grossly different selectivity of the nitrenes for the two double bonds in each case has been interpreted in terms of a change in mechanism from non-concerted to concerted and has allowed a description of the likely transition state geometry in the latter case.

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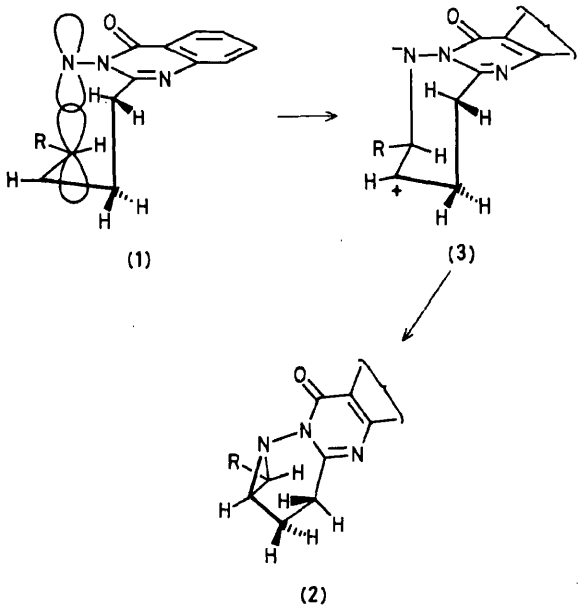
Intramolecular addition of the quinazolone *N*-nitrene to the alkene in (**1**) giving aziridine (**2**) has been interpreted as proceeding *via* an intermediate having high dipolar character (**3**),[1] Scheme 1. The non-concertedness of this addition was rationalised by assuming that the sp-hybridised nitrene attacks the double bond as indicated in (**1**) with overlap of the empty p-orbital of the nitrene with the terminal p-orbital of the double bond. The tight belt of atoms connecting nitrene and alkene even in (**1**) made the further deformation required for overlap as in (**4**) seem unlikely.



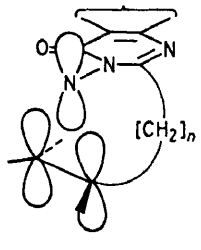
(1) (3) (2)

R = Ph, H

Scheme 1

We now present evidence that extension of this belt of atoms in (**1**) by one carbon atom brings about a change in mechanism for attack of the nitrene on the alkene to one with a transition state resembling (**5**).

Whereas oxidation of (**6**) results in little selectivity of the derived nitrene for the phenyl-substituted *vs.* unsubstituted double bonds (ratio 1.5 : 1,† respectively), the corresponding selectivity of the nitrene derived from oxidation of (**7**) is high (ratio 8.5 : 1, respectively). This change in ratio signals either a change in mechanism of nitrene addition, or conceivably,



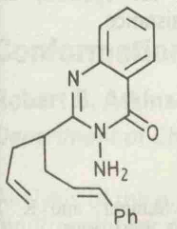
(4) $n = 2$

(5) $n = 3$

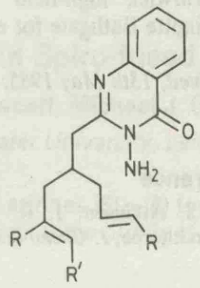
† This value was earlier given as *ca.* 1 : 1 from examination of the 90 MHz spectrum of the crude product (ref. 1): re-measurement at 400 MHz gives this revised ratio.

competitive attack on the β-carbon atom of the phenyl-substituted double bond and on the α-carbon atom of the unsubstituted double bond with intermediates having high dipolar character being generated in each case: preferential attack on the phenyl-substituted double bond would then be attributable to benzylic stabilisation of the carbonium ion in the intermediate (**8**).

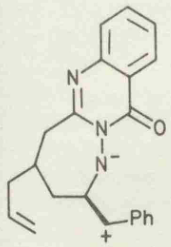
Attack of the nitrene generated by oxidation of (**9**) takes place on both α-methyl- and β-methyl-substituted double bonds with almost equal facility (ratio 1:1.05, respectively) but we recognise that this ratio does not reflect the real relative affinities of these double bonds for the nitrene since the corresponding ratio in oxidation of the α-branched analogue (**10**) is 1:3. Addition to one face of the β-methyl-substituted double bond in (**9**) is inhibited by adverse steric interaction (see below) and the reaction is stereoselective giving mostly (**11**) (Scheme 2). In contrast, addition of the nitrene to the α-methyl-substituted double bond in (**9**) and to the two double bonds in (**7**) is non-stereospecific with both faces of the double bonds being attacked in each case: *the ratio of stereoisomers produced in all three cases is the same* (Scheme 2).



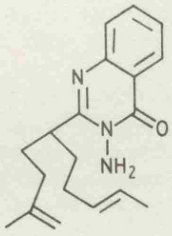
(**6**)



(**7**) R = H, R′ = Ph
(**9**) R = Me, R′ = H



(**8**)

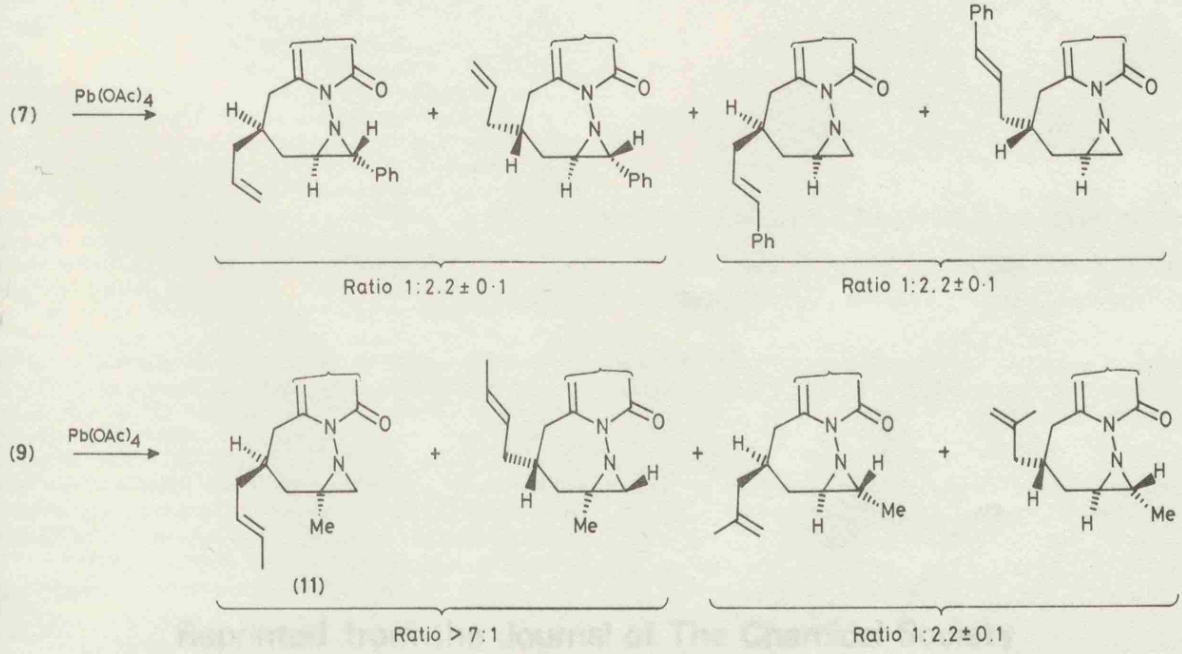


(**10**)

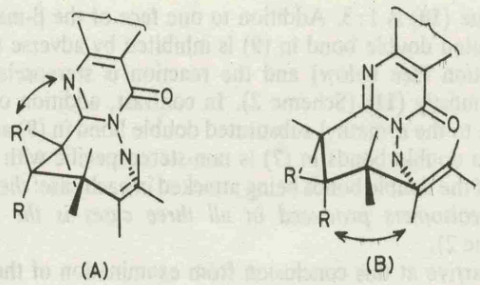
We arrive at this conclusion from examination of the 400 MHz spectra on the crude oxidation products of (**7**) and (**9**). Interpretation of these spectra is facilitated by the quantitative yields (n.m.r.) of aziridines obtained and by the single conformation of the seven-membered ring in each case with the result that the configurations of the alkenylmethyl side chains are definable from analysis of coupling constants. Confirmation of assignments was made by comparison of these spectra of the crude products with those of the separated isomers and, in some cases, stereoisomers.

Although the additional carbon in the side chains of (**7**) and (**9**) allows some increased flexibility in attack of the nitrene on either double bond [by comparison with (**6**)], an examination of Dreiding models suggests that the chain is still sufficiently tight for identifiably different conformations to be necessary for attack on the α- and β-carbon atoms of the alkenes. Representations of these two conformations are shown in structures (A) and (B), respectively, with the significant differences in eclipsing or steric strain elements shown by arrows.

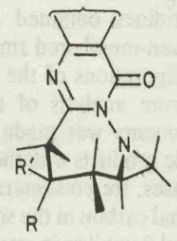
We believe that a switch from attack on the α- to the β-position would, as a result of those conformational differences between (A) and (B), be accompanied by a significant change in stereoisomer ratio: specifically, reaction *via* (B) would be expected to result in more of the stereoisomer with R=H. Identical stereoisomer ratios, however, would be anticipated if attack of the nitrene on both double bonds in (**7**) and on the α-methyl-substituted double bond in (**9**) was intermediate between (A) and (B) [*cf.* (**5**)]. This proposed transition state leads directly to what our n.m.r. interpretation



Scheme 2



(A) (B)



(C)

R, R′ = H, alkenylmethyl (phenyl-, α- and β-methyl- and unsubstituted) side chain.

shows is the only conformation (C) present in the aziridines in Scheme 2. It is clear also why attack on one face of the double bond bearing a β-methyl is particularly favoured since attack on the other face would involve methyl–CH_2 (alkenyl) repulsion.

A change in mechanism is, therefore, implicated in the nitrene additions to double bonds in (**7**) and (**9**) by comparison with those in (**6**). The greater reactivity of the phenyl-substituted double bond in (**7**) over the unsubstituted double bond *via* a transition state (**5**) can be ascribed to better HOMO (alkene)–LUMO (nitrene) overlap in the former case *i.e.* the change in mechanism referred to above is a change from non-concerted to concerted addition.

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Conformational Effects in Spiro-fused Azirines

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Department of Chemistry, Leicester University, Leicester LE1 7RH, U.K.

Analysis of the n.m.r. spectra of azirines (**5**)—(**8**) together with the *X*-ray crystal structure of (**7**) reveals that a requirement for near-coplanarity of three bonds at the spiro centre results in conformational anchoring of the five-membered ring.

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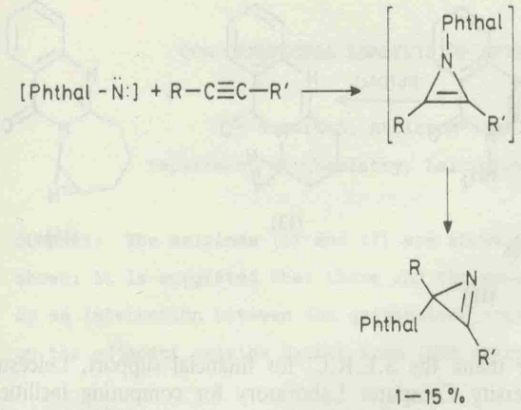
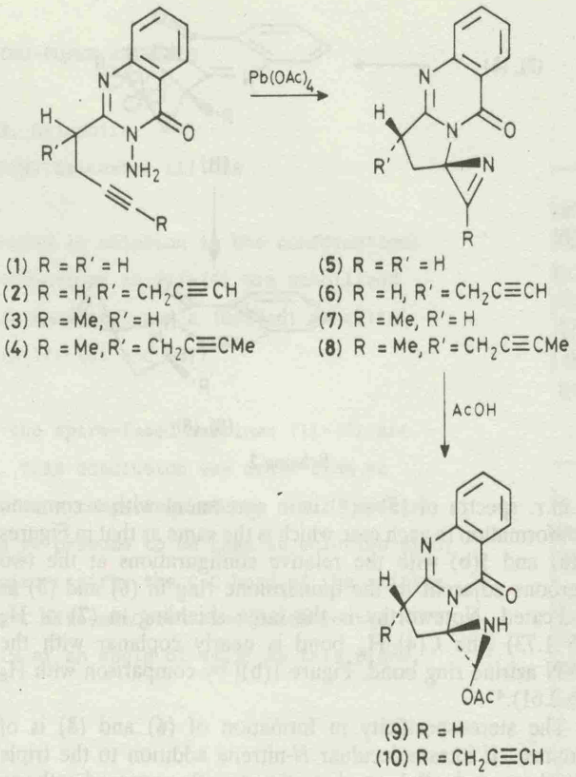
Intermolecular addition of *N*-nitrenes to alkynes has been shown to give 2*H*-azirines by rearrangement, it is thought, of the initially formed 1*H*-azirines (Scheme 1).[1] We have examined the intramolecular version of this reaction by oxidation of (**1**)—(**4**) and find the corresponding spiro-azirines (**5**)—(**8**) are produced as crystalline solids. The yields of (**7**) and (**8**) are quantitative but (**5**) (79%) and (**6**) (90%) are more reactive and are accompanied by acetic acid addition products (**9**) and (**10**), respectively. There are striking and unexpected differences in chemical shifts of the protons on the five-membered ring in *e.g.* azirine (**5**) by comparison with the corresponding protons in the acetoxyaziridine (**9**): in (**5**) these protons resonate at δ 1.75 (*J* 13.9, 9.3, and 1.3 Hz), 2.65 (*J* 13.9, 10.9, 9.6, and 2.8† Hz), 3.03 (*J* 17.5, 9.6, and 1.3 Hz),

† This coupling constant is a long-range one with the azirine ring H δ 10.41 (*J* 2.8 Hz): see K. Isomura, M. Okada, and H. Taniguchi, *Tetrahedron Lett.*, 1969, 4073.



Phthal = phthalimido
R = H, alkyl; R' = alkyl

Scheme 1



and 3.47 (J 17.5, 10.9, and 9.3 Hz) whereas in (**9**) these protons resonate (at 90 MHz) as two triplets (each two protons) at δ 2.31 and 3.08 (a 400 MHz spectrum shows that these four protons are non-equivalent).

The results of an X-ray crystallographic determination on the structure of (**7**)‡ are shown in Figure 1(a): Figure 1(b) is part of this structure viewed perpendicular to the azirine ring with the quinazolone ring residue removed for clarity. It is clear from Figure 1(b) that the C–C bond of the azirine ring is nearly coplanar with the two bonds of the five-membered ring to the spiro-centre [summation of the angles between these bonds gives a value of 358(1.2)°]. Examination of the four azirine ring containing structures in the Cambridge crystallographic data file[2] shows that all of these exhibit the same effect with a similar near-coplanarity of azirine C–C bond and substituent bonds at the 3-position.§ In azirines, the abnormal length of the C–N bond [2a] together with the magnitude of

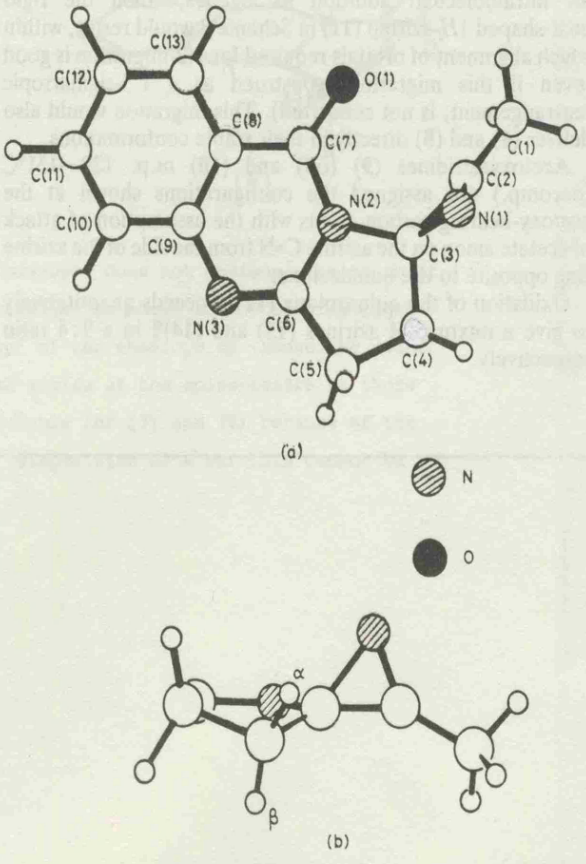


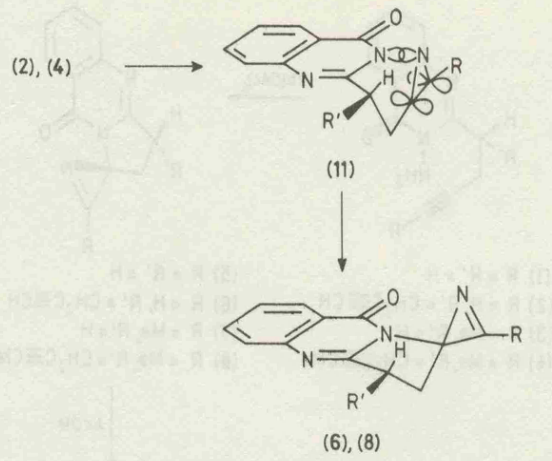
Figure 1

J(^{13}C–H) at C(3)[3] have been interpreted as evidence for increased p-character in the C–N bond and increased sp^2-character at C(3). The near-coplanarity at C(3) in the azirine crystal structures available is consistent with this conclusion.

Analysis of chemical shifts and coupling constants in the

‡ *Crystal data:* $C_{13}H_{11}N_3O$, M = 225.25, monoclinic, a = 8.345(2), b = 13.354(3), c = 10.405(6) Å, β = 106.9(1)°, U = 1109.4 Å^3 [cell determined by least squares refinement of diffractometer measurements of zero and upper layer reflections and from oscillation photographs (*c*)], space group $P2_1/n$ (alt. $P2_1/c$ No. 14), Z = 4, D_x = 1.348 g cm^{-3}. The crystals were colourless prisms, λ(Mo-K_α) = 0.7107 Å, μ(Mo-K_α) = 0.52 cm^{-1}. The intensities of 2314 unique reflections ($7 \leq 2\theta \leq 50°$, $+h$ $+k$ $\pm l$) were measured on a Stoe STADI-2 Weissenberg diffractometer with graphite monochromated Mo-K_α radiation using an ω-scan technique. The data were corrected for Lorentz and polarisation effects, to yield 795 reflections with $I \geq 2.5\sigma(I)$. The structure was solved using the TREF direct methods option of SHELXS 84.[6] All subsequent calculations were carried out using the computer program SHELX.[7] The number of variables refined by full matrix least squares was restricted owing to the limited amount of intensity data available. The methyl hydrogen atoms and the atoms of the phenyl groups were refined as rigid groups but the hydrogen atoms on C(4) and C(5) were allowed to refine for position and isotropic motion. Final cycles employed a weighting parameter g(0.00052) $\{w = [1/\sigma^2(F) + g(F)^2]\}$ and gave the final residual indices $R\{= \Sigma(|F_o| - |F_c|)/\Sigma|Fo|\}$ 0.0748 and $R_w\{= [\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2]^{\frac{1}{2}}\}$ 0.0694. The final difference Fourier map was featureless, and an analysis of the weighting scheme over F_o and sinθ/λ was satisfactory. The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

§ It is not surprising that this effect was overlooked since the deformation required to achieve this near-coplanarity is not large and only by viewing the crystal structures perpendicular to the azirine ring is the effect visible.



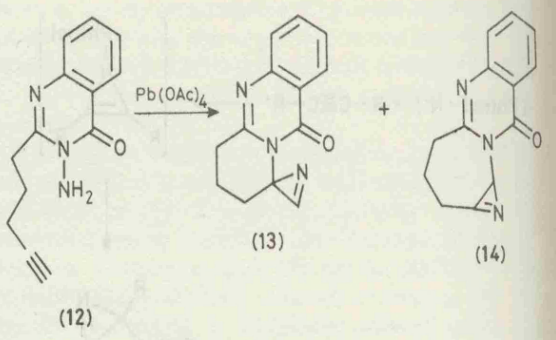
Scheme 2

n.m.r. spectra of (**5**)—(**8**) is in agreement with a common conformation in each case which is the same as that in Figures 1(a) and 1(b) with the relative configurations at the two carbons adjacent to the quinazolone ring in (**6**) and (**8**) as indicated. Noteworthy is the large shielding in (**7**) of H_α (δ 1.73) [the C(4)–H_α bond is nearly coplanar with the C–N azirine ring bond, Figure 1(b)] by comparison with H_β (δ 2.61).[4]

The stereospecificity in formation of (**6**) and (**8**) is of interest. If intramoleculuar *N*-nitrene addition to the triple bond proceeds analogously to the recently proposed pathway for intramolecular addition to alkenes,[5] then the rigid boat-shaped 1*H*-azirine (**11**) in Scheme 2 would result, within which alignment of orbitals required for 1,2-migration is good (even if this migration, construed as a 1,3-sigmatropic rearrangement, is not concerted). This migration would also deliver (**6**) and (**8**) directly in their stable conformations.

Acetoxyaziridines (**9**) (oil) and (**10**) m.p. 128—131°C (decomp.) are assigned the configurations shown at the acetoxy-bearing carbon atoms with the assumption of attack of acetate anion on the azirine C=N from the side of the azirine ring opposite to the quinazolone.

Oxidation of the quinazolone (**12**) proceeds quantitatively to give a mixture of azirines (**13**) and (**14**)¶ in a 9:4 ratio respectively.



We thank the S.E.R.C. for financial support, Leicester University Computer Laboratory for computing facilities, Professor G. M. Sheldrick for the use of SHELXS-84, the University of Warwick high-field n.m.r. service for spectra, and Dr. K. L. Woodthorpe who first prepared compounds (**2**) and (**10**).

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6 G. M. Sheldrick, SHELXS 84, personal communication.
7 G. M. Sheldrick, SHELXS 76 Program for Crystal Structure Determination, University of Cambridge, 1976.

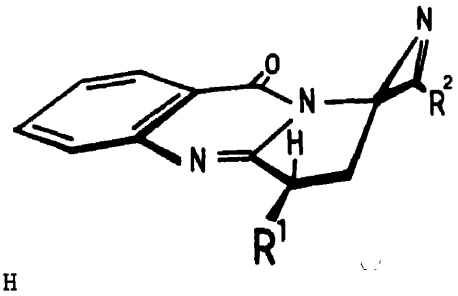
¶ Both (**13**) and (**14**) have definable conformations which will be described in due course.

CONFORMATIONAL ANALYSIS OF SPIRO- AND RING-FUSED AZIRINES

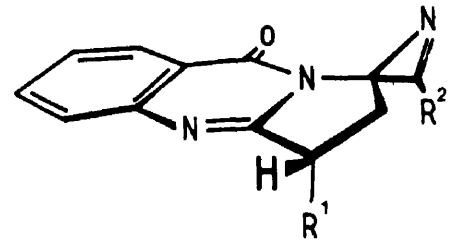
Robert S. Atkinson* and Michael J. Grimshire
Department of Chemistry, Leicester University, Leicester LE1 7RH

SUMMARY: The azirines (6) and (7) are shown to be anchored in solution in the conformations shown: it is suggested that these and the envelope conformations in (1)-(4) are stabilised by an interaction between the quinazolone nitrogen (N-3) p-orbital and a (bonded) p-orbital on the adjacent azirine carbon atom (the spiro-centre in (1)-(4) and (6)).

We recently reported that the 5-membered rings of the spiro-fused azirines (1)-(4) are apparently locked in the envelope conformation shown.[1] This conclusion was drawn from an X-ray crystal structure determination on (2) together with a comparison of the n.m.r. spectra of (1)-(4). The structure in the crystal of (2), which we presume to be that in solution also, shows a remarkable deformation of bond angles at the spiro-centre: the C-C bond of the azirine ring is only 5.9° out of plane defined by the C-N and C-C five-membered ring bonds to the spiro-centre whereas the C-N bond of the azirine ring is at an angle of 44.5° to this plane.



(1) $R^1 = R^2 = H$
(2) $R^1 = H$, $R^2 = Me$
(3) $R^1 = CH_2C{\equiv}CH$, $R^2 = H$
(4) $R^1 = CH_2C{\equiv}CMe$, $R^2 = Me$

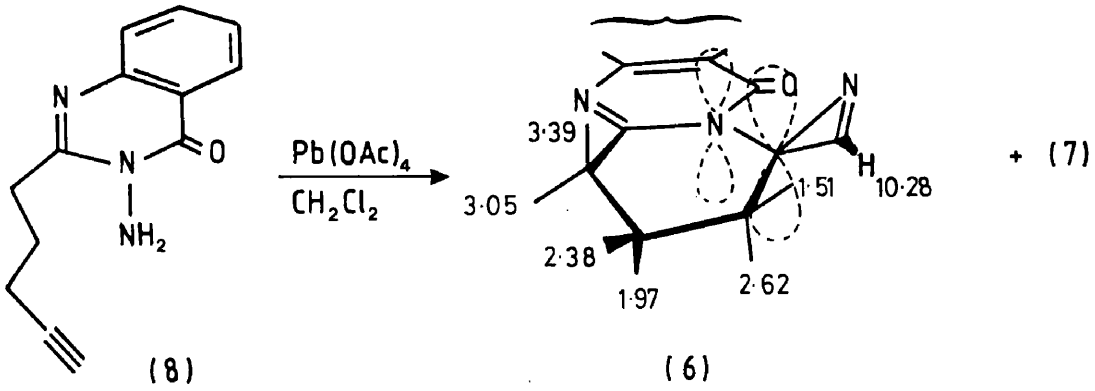


(5)

This deformation at the spiro-centre in (1)-(4), however, does not obviously bring about the anchoring of the five-membered ring envelope conformation as shown in the diagram since there is an alternative conformation (5) with the 'flap' of the envelope up (above the plane defined by the quinazolone ring) which has similar bond angles at the spiro-centre to those in (1)-(4). Conceivably conformation (5) is less favourable for (3) and (4) because of the requirement for an 'axial' rather than an 'equatorial' disposition of R^1 but this cannot be

the case for (1) and (2).

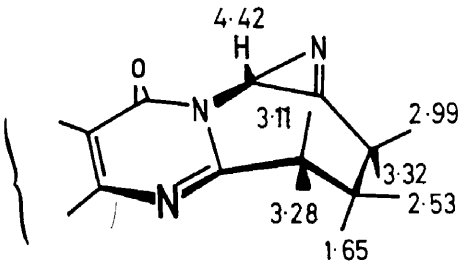
In this letter we describe the conformations of two closely related azirines (6) and (7) and suggest an explanation for the anchoring present in (1)-(4), (6) and probably (7) also. Oxidation of the N-aminoquinazolone (8) in dichloromethane gave a mixture of (6) and (7) in a ratio of 9:4, respectively. Azirine (6) was separated by crystallisation from ethanol and comparison of the n.m.r. spectrum of the crystalline material with that of the crude reaction product (which contained (6) and (7) only) showed no loss or modification of signals assignable to (6).



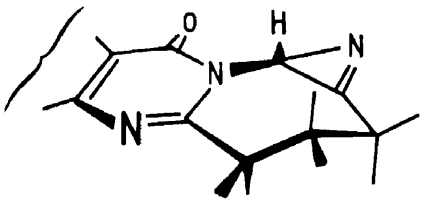
(8) (6)

The conformation of (6), which can be deduced from the vicinal coupling constants in its n.m.r. spectrum of protons in the trimethylene chain (δ3.39 J 11.9 and 5.9; 3.05 J 5.6 and 5.1; 2.62 J 8.9, 4.6 and 2.3; 2.38 J 8.9, 5.9, 5.1 and 4.6; 1.97 J 11.9, 8.9, 7.2 and 5.6; 1.51 J 8.9 and 7.2 Hz) is a twist-boat as shown. Both half-chair conformations and the alternative twist-boat can be eliminated; the former because of the absence of axial-axial coupling and the latter because of the similarity of the protons on the methylene group adjacent to the spiro-centre to those in (2) both in chemical shift (δ1.52 v. 1.75 and 2.62 v. 2.65, respectively) and coupling constant to the azirine ring H (J 2.3 v. 2.8 Hz to the lower field resonance in each case).

The ring-fused azirine (7) has not been separated from (6) but in the 400 MHz spectrum of the mixture, signals from (7) are sufficiently separated from those of (6) for its structure to be assigned. Again the vicinal coupling contants in the trimethylene unit define the conformation of the molecule as shown in (7) (δ3.32 J 5 and 1.5; 3.28 J 7.7 and 1.5; 3.11 J 12.3 and 1.5; 2.99 J 12.7 and 7.7; 2.55 J 7.7, 7.7, 1.5, and 1.5; 1.65 J 12.7, 12.3, 5 and 1.5 Hz). Examination of models suggests that there is an accessible alternative conformation (9) for this ring-fused azirine in which there is better staggering of bonds in this trimethylene chain but which, nevertheless, can be excluded from the size of the coupling contants referred to above.

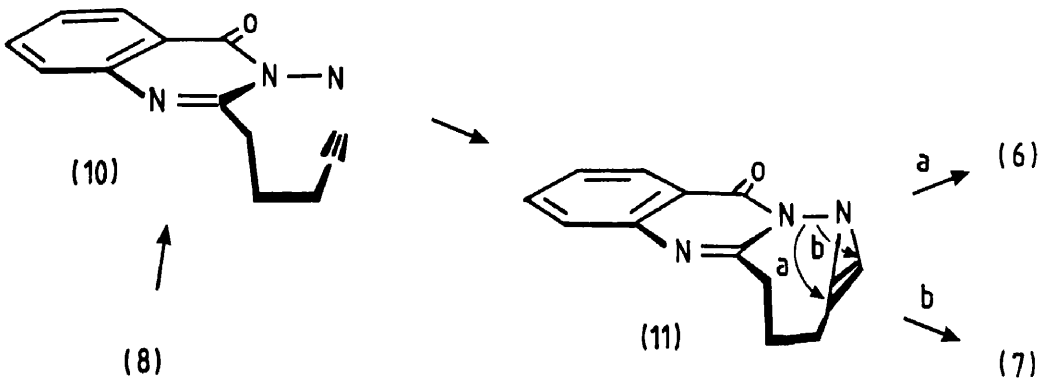


(7)



(9)

What is the origin of the conformational anchoring effect in (1)-(4) and why are the azirines derived by oxidation of (8) anchored in what appear to be their less stable conformations (6) and (7)? The near planarity at the spiro-centre in (2) referred to earlier is believed to be the result of a hybridisation at this centre which is close to sp^2 with the p-orbital utilised in C-N (azirine) bond formation. We suggest that in the preferred conformations shown for (1)-(4), (6) and probably also (7), there is an alignment of this (bonded) p-orbital with the p-orbital of the quinazolone ring nitrogen (see (6)) and the interaction which results leads to a lowering of energy and a stabilisation of these conformations over others. It is clear from examination of (1)-(4) and (6) that the slight tilting of the p-orbital at the spiro-centre which is anticipated (the three bonds at this centre referred to earlier are not completely planar) would serve to increase this alignment in the preferred conformations of the azirines shown but to decrease it in other possible conformations.



Scheme

Oxidation of N-aminoquinazolone (8) generates the corresponding N-nitrene (10) which adds to the acetylenic bond and (6) and (7) are believed to be formed by rearrangement of the unstable 1H-azirine intermediate (11) (Scheme).[2] By analogy with the corresponding intramolecular addition of N-nitrenes to alkenes,[3] nitrene addition to the alkyne bond would be expected to take place as shown and would lead to the conformation of 1H-azirine indicated. It is noteworthy that migration of the N-N bond in the two modes a and b as shown delivers (6) and (7) directly in their most stable conformations. We do not think this augurs well for the prospect of trapping the 1H-azirines in this system.

Since the near-planarity at the spiro-centre in (2) is also present at C-3 in all other published crystal structures of azirines[1] and is therefore, presumably, common to all azirines, further conformational manifestations of this effect can be anticipated in spiro- or ring-fused azirines.

We thank the University of Warwick 400 MHz n.m.r. service (S.E.R.C.) for spectra and S.E.R.C. for support to M.J.G.

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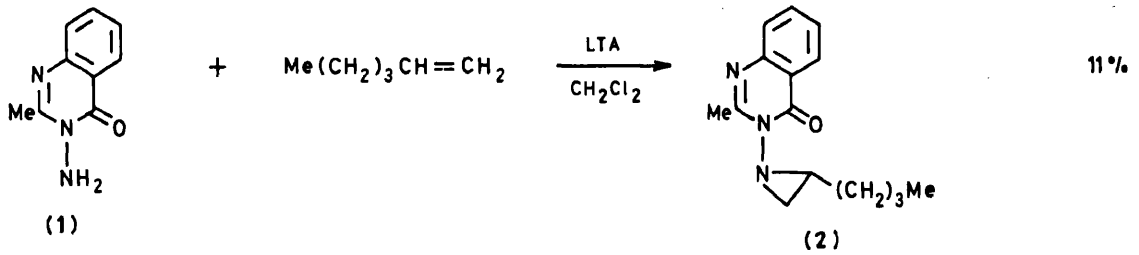
Intramolecular Reactions of *N*-Nitrenes with Alkynes: Conformational Anchoring in Spiro-fused 2*H*-Azirines

Robert S. Atkinson * and Michael J. Grimshire
Department of Chemistry, University of Leicester, Leicester LE1 7RH

Oxidation of *N*-aminoquinazolin-4(3*H*)-ones (**7**)—(**11**) with lead tetra-acetate in dichloromethane results in the intramolecular addition of the *N*-nitrene to the triple bond in each case and azirines (**20**), (**22**), (**17**), (**23**), and (**30**), respectively, are isolated with (**31**) identified as a by-product in the oxidation of compound (**11**). An *X*-ray crystal structure determination on compound (**17**) reveals a remarkable deformation of bond angles at the spiro centre and this feature appears to be common to all azirines. The five membered ring in the azirines (**17**), (**20**), (**22**), and (**23**) has the envelope conformation (**26**) and the six-membered ring in azirine (**30**) has the twist-boat conformation (**32**): a possible explanation for this conformational anchoring is offered.

Our studies of the reactions of *N*-nitrenes have shown that poor traps for these species can be much improved by carrying out the trapping intramolecularly.[1,2] Thus oxidation of the 3-amino-2-methyl quinazolone (**1**) in the presence of a terminal alkene *e.g.* hex-1-ene, gave the aziridine (**2**) in only 11% yield whereas oxidation of the *N*-aminoquinazolone (**3**) gave the corresponding aziridine (**4**) in 94% isolated yield.

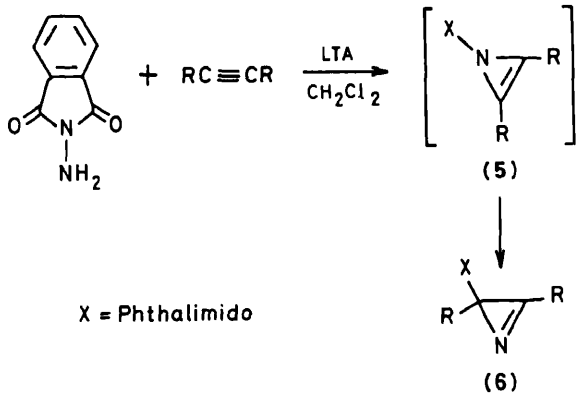


Alkynes are also poor traps in intermolecular reactions with *N*-nitrenes and low yields of the (rearrangement) products (**6**) (Scheme 1) are isolated from the oxidation of *N*-amino-phthalimide in the presence of dialkylalkynes.[3] Our attempts to trap the *N*-nitrene from oxidation of the *N*-aminoquinazolone (**1**) by hex-1-yne were unsuccessful and no product analogous to compound (**6**) was isolated. We have examined the intramolecular version of this reaction with the expectation of increasing the efficiency of trapping. It was hoped also that the intramolecular reaction might permit observation or identification of the proposed transitory 1*H*-azirines (**5**) (Scheme 1) which are believed to rearrange rapidly to the isolated 2*H*-azirines (**6**).[3]

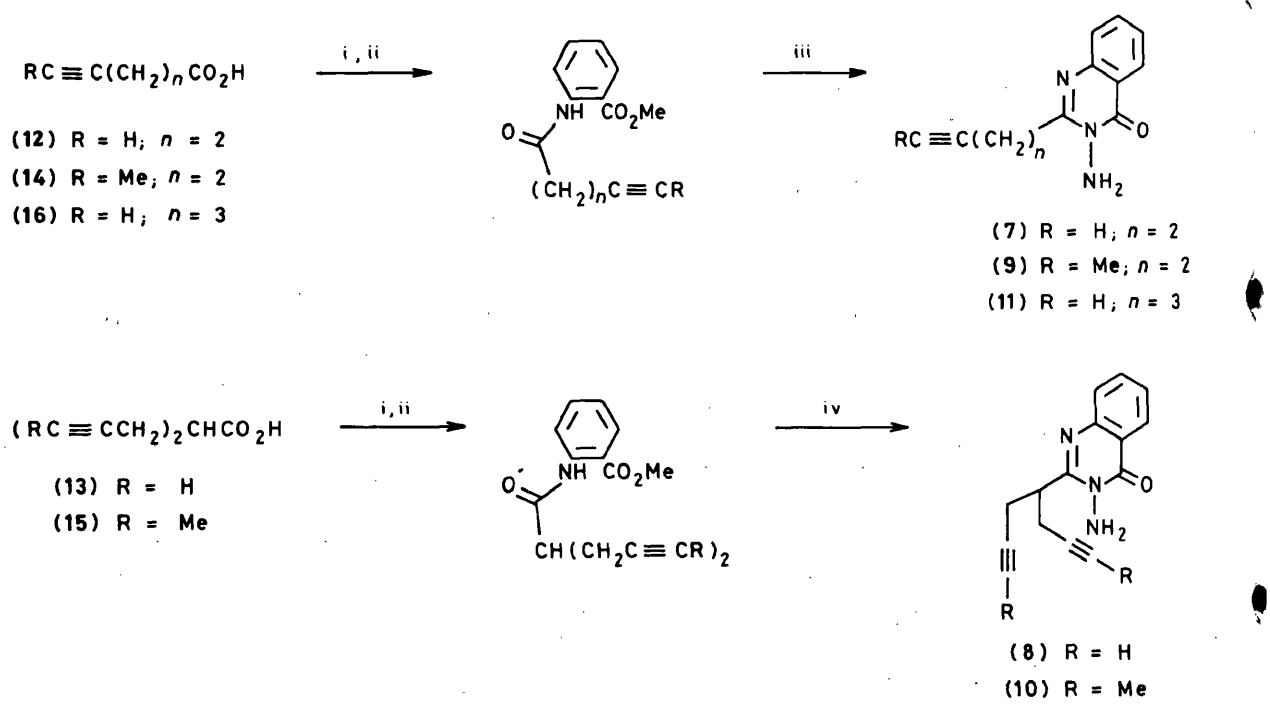
The 2-(alkynylalkyl)-3-aminoquinazolones (**7**)—(**11**) were synthesised from the corresponding acids (**12**)—(**16**) in the usual way (Scheme 2).

The acids (**12**)—(**15**) were obtained by mono- or di-alkylation of malonate esters with the appropriate alkynyl bromide or toluene-*p*-sulphonate followed by hydrolysis and decarboxylation: the acid (**16**) was obtained by chain extension of the acid (**12**) (Scheme 3).

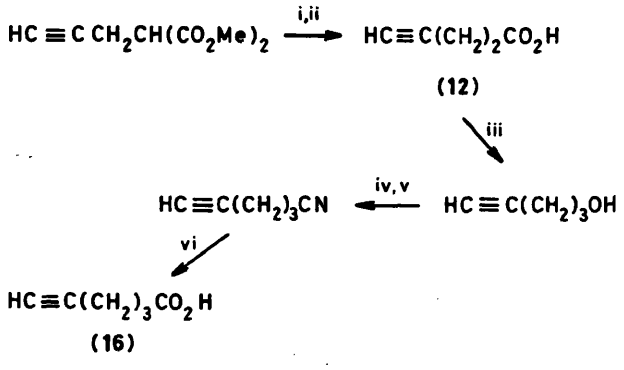
The oxidations of compounds (**7**)—(**11**) were carried out by slow and simultaneous addition of the *N*-aminoquinazolone and lead tetra-acetate (LTA) as solutions in dry dichloro-



Scheme 1.



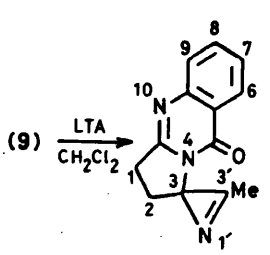
Scheme 2. *Reagents:* i, $SOCl_2$; ii, methyl anthranilate; iii, NH_2NH_2–EtOH; iv, NH_2NH_2–EtOH, 120 °C (sealed tube).



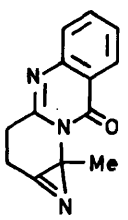
Scheme 3. *Reagents:* i, NaOH–EtOH; ii, 160 °C; iii, $LiAlH_4$; iv, TsCl–pyridine; v, KCN–DMSO; vi, NaOH–water.

methane in different separating funnels to stirred dry dichloromethane. In the oxidation of compound (**9**), a crystalline product was obtained in quantitative yield after separating the lead diacetate, washing the dichloromethane solution with aqueous sodium hydrogen carbonate, and then evaporating this dried solution. The spectroscopic data for this oxidation product were in agreement with its formulation as the spiro-azirine (**17**). Although the alternative isomer (**18**) was compatible with this data, bicyclo[*n*.1.0] ring fused azirines have been previously isolable only $n \geqslant 6$ *e.g.* (**19**).[4]

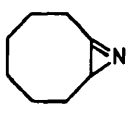
Confirmation of the structure of this oxidation product as (**17**) was eventually obtained by carrying out an *X*-ray crystal structure determination[5] (see below) but meanwhile, a similar oxidation of compound (**7**) gave a product whose spectroscopic data unambiguously supported (**20**) as its structure.



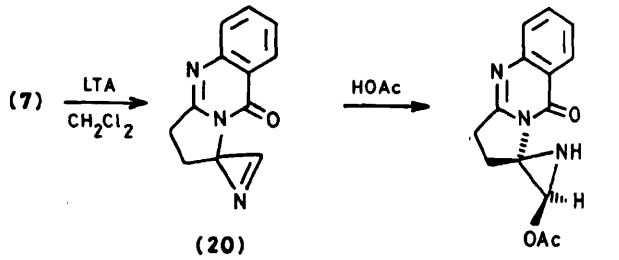
(**17**)



(**18**)



(**19**)



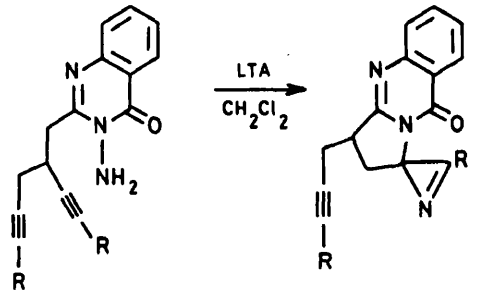
(**20**) (**21**)

Thus compound (**20**) shows a characteristic low-field resonance at δ 10.41 (*J* 2.8 and 0.6 Hz) for the azirine ring proton. Coupling of the azirine ring protons at C-3 over four bonds has been previously reported[6] but it is clear that only one of the methylene protons adjacent to the spiro-centre in (**20**) is significantly coupled in this way, *i.e.* the magnitude of the coupling is dependent on geometrical factors. The C=N azirine stretching frequency in the i.r. spectrum of compound (**17**) was apparent as a weak band at 1 785 cm^{-1}. No band of even weak intensity is observed in this position in the i.r. spectrum of (**20**) [or other azirines bearing hydrogen at C-3 (azirine) reported below] and this has been noted previously for azirines unsubstituted at C-3.[6]

The azirine (**20**) is more reactive than (**17**) and the yield of this product was maximised when contact with acetic acid (a by-product of the oxidation using LTA) in the reaction medium

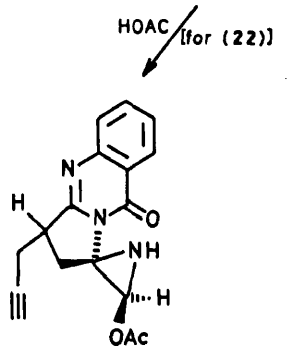
was minimised: if work-up was carried out after setting the reaction mixture aside overnight the only product isolated was the acetic acid addition product (**21**). Addition of acetic acid or formic acid to the azirine (**20**) in more concentrated solution was very rapid and could be readily monitored by n.m.r. spectroscopy by gradual addition of either of these acids in small quantities (as solutions in deuterio-chloroform) to deuteriochloroform solutions of the azirine (**20**). By contrast, the azirine (**17**) was markedly less reactive towards acetic acid and no measurable loss of signals from this azirine in its n.m.r. spectrum was apparent after several hours in contact with two mol equiv. of acetic acid in chloroform solution. This lesser reactivity of (**17**) suggests that addition of acetic acid does not proceed *via* initial protonation of the azirine ring nitrogen with the generation of a carbonium ion as an intermediate.

Oxidation of the *N*-aminoquinazolones (**8**) and (**10**) bearing bifurcated chains also proceeded in excellent yield to give the corresponding azirines (**22**) and (**23**). Like the C-3 unsubstituted azirine (**20**), (**22**) is also very reactive towards the acetic acid generated in its formation. The addition product (**24**) which



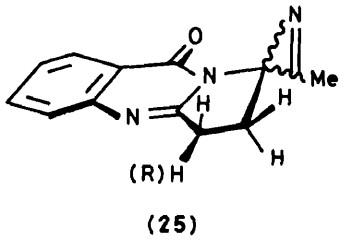
(**8**) R = H
(**10**) R = Me

(**22**) R = H
(**23**) R = Me

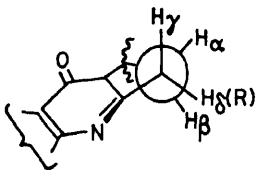


(**24**)

results is assigned the stereochemistry shown at the acetoxy-bearing carbon [as is the case with (**21**)] with the assumption of attack by acetic acid from the side of the azirine ring opposite to the quinazolone.



(**25**)



	$J\alpha\gamma$	$J\alpha\delta$	$J\beta\gamma$	$J\beta\delta$
(**17**)	9.3	1.3	10.9	9.6
(**20**)	8.1	—	10.6	—
(**22**)	9.3	1.5	10.9	9.7
(**23**)	8.3	—	10.5	—

Figure 1. Approximate Newman projection along the CH_2–CH_2-(CHR–CH_2) bond in azirines (**17**), (**20**), (**22**), and (**23**) as deduced from the vicinal coupling constants (in Hz) in their n.m.r. spectra as indicated.

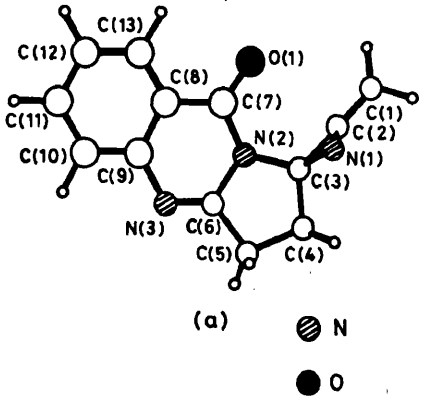


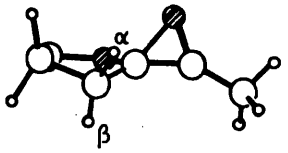
Figure 2. *X*-Ray crystal structure of the azirine (**17**).

Comparison of the n.m.r. spectra of the azirines (**17**), (**20**), (**22**), and (**23**), showed clearly that they all had the same conformation for the five-membered ring whose envelope shape (**25**) accorded with the magnitude of the vicinal coupling constants between the five-membered ring protons as shown in the Newman projection along the CH_2–CH_2 [$CH(R)$–CH_2] bond (Figure 1). The orientation of the azirine ring with respect to the envelope flap was, at this stage, unknown.

Although these assignments were self-consistent, it was not obvious to us why the five-membered ring should apparently have a conformational preference for the envelope flap to be located on one side rather than the other of the plane containing the quinazolone ring. The two sides of the quinazolone ring in compounds (**17**) and (**20**) are defined by the orientation of the azirine ring and it was logical to assume that the origin of the conformational preference of the five-membered ring was to be found in a corresponding preference of the C–N (or C–C) bond of the azirine ring for one of the two differentiated positions on the five-membered ring at the spiro-centre.

An *X*-ray structure determination was carried out on the azirine (**17**) and gave the result shown in Figure 2.* More informative is a view of the spiro ring-fusion from a direction orthogonal to the azirine ring (Figure 3) with the remnant of the quinazolone ring removed for clarity.

* Figure 2 differs from the same Figure in our original communication in that a hydrogen atom in the latter on the carbon atom of the 5-membered ring adjacent to the spiro centre (C-4) was inadvertently drawn in when in fact it is not visible from the perspective drawn.

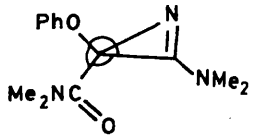


(b)

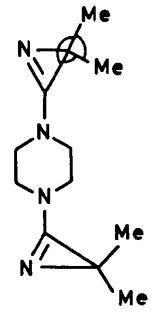
Figure 3. *X*-Ray crystal structure of azirine (**17**) viewed perpendicularly to the azirine ring with the quinazolone ring residue removed for clarity.

long C–N bond in azirines has been ascribed to high p-character in the C-2 derived component of this bond.[10]

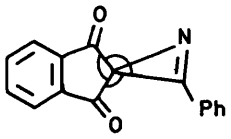
Our analysis of the n.m.r. spectrum of compound (**17**) [together with compounds (**20**), (**22**), and (**23**)] is in agreement with the same geometry at the spiro-centre in solution as in the crystal structure. In particular, the chemical shift upfield of the signal from H_α (Figure 3) by comparison with H_β (δ 1.75 versus 2.65, respectively) can be ascribed to shielding of H_α by the adjacent azirine ring.[12,]† However, there remains the problem of why conformation (**26**) is preferred over (**27**) for these five-membered ring spiro-fused azirines. Both these conformations



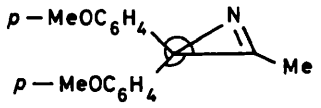
357·2°
Ref. 10



356·7°
Ref. 9



357°
Ref. 8

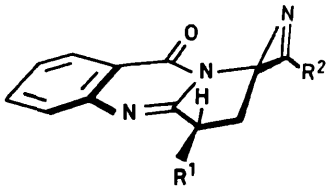


358·1°
Ref. 7

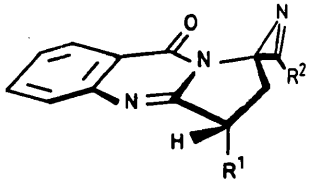
Figure 4. (Metal free) Azirine ring containing crystal structures retrieved from the Cambridge crystallographic data file with the reported angle summations at C-2 indicated.

From this viewpoint it can be seen that the C–C bond of the azirine ring is close to the plane defined by the C–N and C–C bonds of the five-membered ring to the spiro-centre: in fact the C–C and C–N bonds of the azirine ring have angles of 5.9° and 45.9°, respectively, to this plane. Alternatively, the near-coplanarity of C–N and C–C bonds of the five-membered ring and the C–C bond of the azirine ring can be quantified by summation of the angles between them which gives a value of 358 ± 1.2°: a perfect plane would, of course, require a value of 360°.

This unexpected feature of the azirine ring geometry in compound (**17**) was the more surprising when it was found to be also present, but unremarked upon, in the four azirine ring-containing crystal structures[7,8,9,10] available from the Cambridge Data File. The appropriate angle summations in these four structures are shown in Figure 4 and it is clear that the substantial deformation towards coplanarity at C-2 as in (**17**) has taken place in all cases. This deformation at C-2 in (presumably all) azirines can be accommodated by assuming hybridisation for the carbon atom at this position which is close to sp^2 with the C–N bond of the azirine formed by overlap of the p-orbital at C-2 with the nitrogen hybrid orbital. In fact, sp^2-hybridisation for C-2 in azirines has been suggested by Hassner[11] to account for the particular value of the ^{13}C–H coupling constant at this position.* In addition, the abnormally



(**26**)

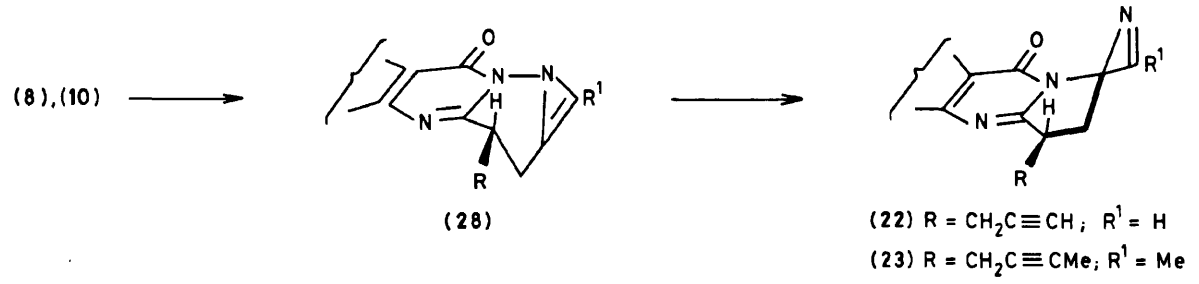


(**27**)

have the azirine C–C bond close to the plane containing the two five-membered ring bonds to the spiro-centre and they are interconverted by movement of the envelope flap from one side to the other. Of course, in the ring-substituted compounds (**22**) and (**23**) there may be a contribution to the stabilisation of (**26**) over (**27**) from the preferred siting of the side-chain R in an 'equatorial' rather than an 'axial' position but (**17**) and (**20**) are free from this complication and yet still have the same preferred conformation for the five-membered ring. An examination of models of (**26**) and (**27**) suggests that the origin of the greater stability of (**26**) may be the result of an alignment of the (bonded) p-orbital at the spiro-centre in the latter with the filled p-orbital of the quinazolone ring nitrogen. The tilting of the p-

* Hassner has also suggested that both C-3 and N or the azirine ring have sp-hybridisation.

† Exactly which part of the azirine ring brings about this shielding is not clear.

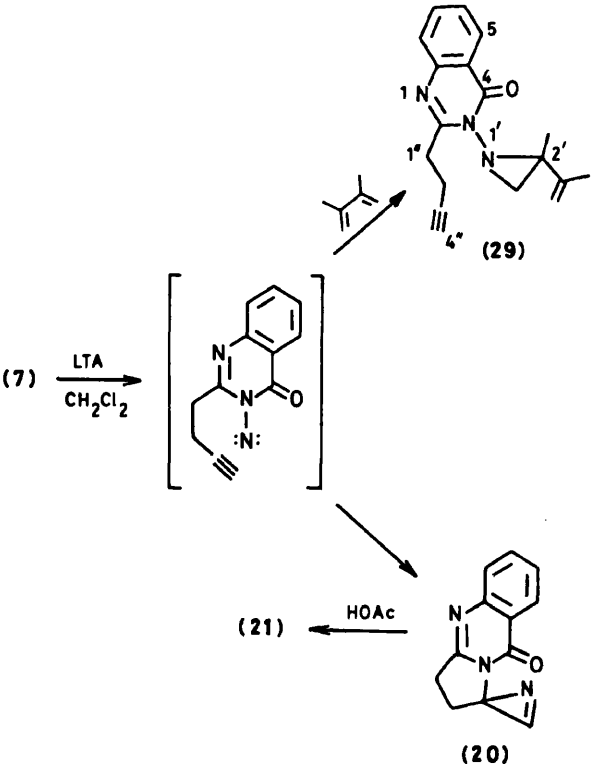


orbital at the spiro-centre which is anticipated (if only because the three bonds to the spiro-centre referred to earlier are not completely coplanar) would serve to improve this alignment in (**26**) but to reduce it in (**27**).

The stereospecific formation of (**22**) and (**23**) with the side-chain and C–N bond of the azirine ring *trans* is of interest. If the addition of the nitrene to the triple bond resembles the corresponding intramolecular addition to a double bond,[1] then the rigid boat-shaped 6-membered ring 1*H*-azirine intermediate (**28**) results.

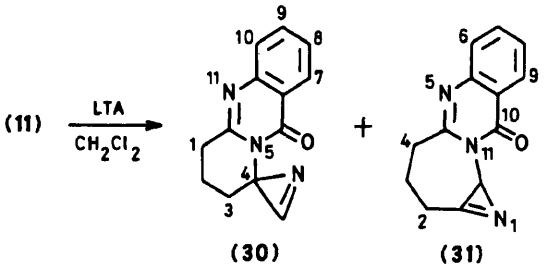
[1,2]-Migration of the N–N bond in this 1*H*-azirine delivers (**22**) and (**23**) *directly* in their stable conformations [*cf.* (**26**)]. Although the envelope conformations (**26**) of azirines (**17**), (**20**), (**22**), and (**23**) would, therefore, be the kinetically favoured products of rearrangement, it is likely that they are also the thermodynamically favoured conformations since the n.m.r. spectrum of compound (**17**) in chlorobenzene was unchanged when recorded at 120 °C.

Our attempts to trap the 1*H*-azirines have not proved successful. Oxidation of 3-aminoquinazolone (**7**) at −78 °C under our conditions proceeds very slowly if at all. Addition of a large excess of 2,3-dimethylbutadiene to the solution at this low temperature and then allowing the temperature to rise slowly to ambient with vigorous stirring gave the aziridine (**29**) and, significantly, some of the azirine (**20**) together with its acetic acid addition product (**21**) (Scheme 4). Clearly the nitrene is intercepted for the most part by the diene but the formation of the azirine (**20**) in the same reaction mixture indicates that either the 1*H*-azirine to 2*H*-azirine rearrangement is very fast or that the 1*H*-azirine is not particularly reactive towards 2,3-dimethylbutadiene.



Scheme 4.

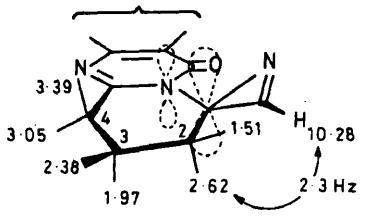
Oxidation of the *N*-aminoquinazolone (**11**) was carried out as described previously for compounds (**7**)—(**10**) and an n.m.r. spectrum of the crude reaction product revealed that a mixture of the azirines (**30**) and (**31**) was present in a 9:4 ratio, respectively. Crystallisation from methanol gave a pure sample of (**30**). Interestingly, the azirine (**30**) was significantly more resistant towards attack by acetic acid than its spiro-fused five-membered ring analogues (**20**) and (**22**) and none of the acetic acid addition product [analogous to (**21**)] was isolated; n.m.r. monitoring of the solution showed that the mixture of (**30**) and (**31**) was stable to two mol equiv. of acetic acid in deuteriochloroform over several hours.



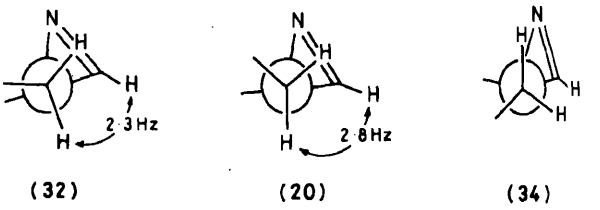
Analysis of the n.m.r. spectrum of (**30**) shows that it is present in solution in the single skew boat conformation (**32**). This conclusion follows from the vicinal coupling constants in the trimethylene unit and assumes the same near coplanarity of the azirine C–C bond and the two six-membered ring bonds at the spiro-centre. The spatial relationship of the protons on the carbon (C-2) adjacent to the spiro-centre *vis-à-vis* the azirine ring is very similar to the situation in (**20**) (*cf.* Figure 3) with a higher field proton (δ 1.51 versus 1.75) and a lower field proton (δ 2.62 versus 2.65), the latter coupled in both cases to the azirine ring proton (*J* 2.3 versus 2.8 Hz, respectively).

Newman projections looking along the C(3)–C(2) and C(3)–C(4) bonds in (**32**) are represented in Figure 5 with the vicinal coupling constants as shown. The magnitude of these vicinal coupling constants for C(2)H–C(3)H excludes half-chair conformations for (**30**) *e.g.* (**33**) since none of them is large enough for an axial-axial coupling (*ca.* 12 Hz). Although the coupling constants in Figure 5 are compatible with the alternative skew-boat (**34**), this conformation has a different Newman projection along the C(2)–C(spiro) bond to those of (**32**) and (**20**) Figure (**6**) and the chemical shift of the methylene proton signals at C-2 and, in particular, the coupling constant of the azirine ring H to the lower field proton would not be expected to be so similar for conformations (**34**) and (**20**).

Why should the skew-boat (**32**) be favoured to the exclusion

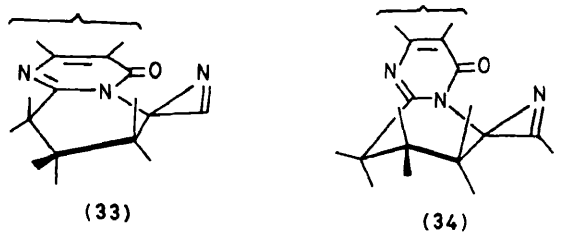


(32)



(32) (20) (34)

Figure 6. Approximate Newman projections along the C(2)–C(spiro) bonds in compounds (**32**), (**20**), and (**34**) [the alternative skew boat conformation of (**32**)] as drawn from models.



(33) (34)

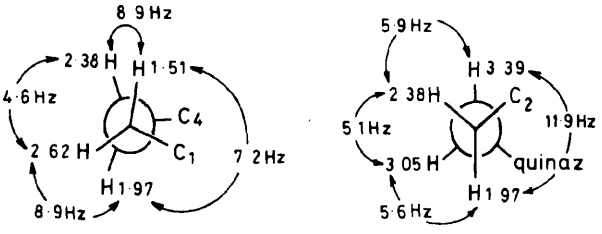
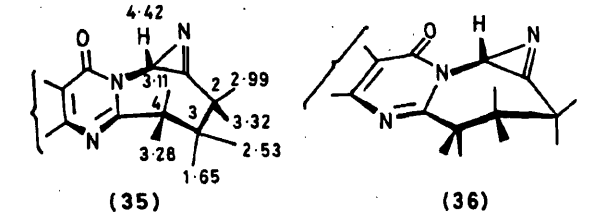


Figure 5. Approximate Newman projections along the C(2)–C(3) and C(3)–C(4) bonds in the azirine (**32**) as deduced from the vicinal coupling constants (in Hz) in its n.m.r. spectrum as indicated.



(35) (36)

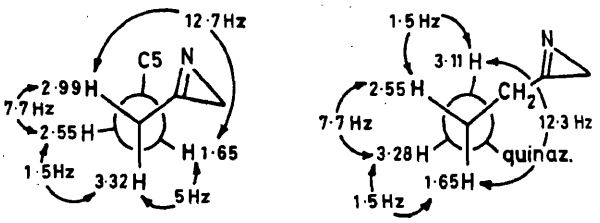
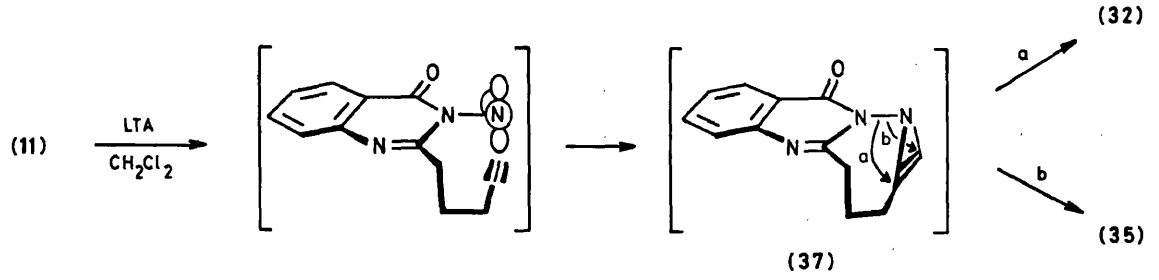
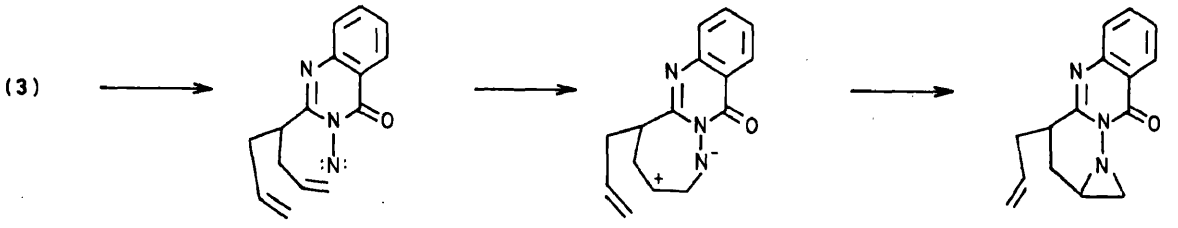


Figure 7. Approximate Newman projections along the C(3)–C(4) and C(4)–C(5) ring bonds of the azirine (**31**) as deduced from the vicinal coupling constants (in Hz) in its n.m.r. spectrum as indicated.



Scheme 5.



Scheme 6.

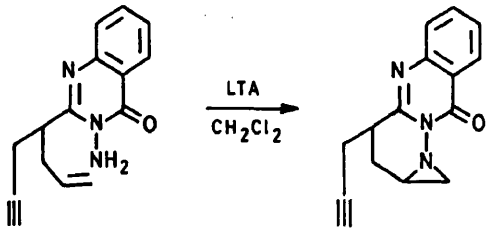
of other conformations? An examination of models suggests that, as in the case of (**26**), it is in conformation (**32**) that the p-orbital at the spiro-centre may have the best alignment with the adjacent p-orbital of the quinazolone nitrogen [see (**32**)].

The ring-fused azirine (**31**) has not been separated from (**30**) but in the 400 MHz spectrum of the mixture, signals from compound (**31**) are sufficiently separated from those of (**30**) for the structure of the former to be assigned. Thus the azirine ring proton signal is a singlet at δ4.42 and the vicinal coupling constants within the trimethylene chain show the ring to have the conformation shown in (**35**). Figure 7 shows Newman projections along the C(2)–C(3) and C(3)–C(4) bonds with the measured vicinal coupling constants. Models of (**31**) suggest that besides (**35**) there is an alternative conformation (**36**) for

this ring-fused azirine in which there is even better staggering of bonds in the trimethylene chain but which, nevertheless, is incompatible with the vicinal coupling constants in Figure 7.*

By analogy with the intramolecular addition of *N*-nitrenes to alkenes,[1] the addition of the nitrene derived by oxidation of (**11**) to the alkyne bond would be expected to lead to the conformation of the 1*H*-azirine indicated in Scheme 5. Migration of the N–N bond in the 1*H*-azirine (**37**) as indicated leads *directly* to compounds (**30**) and (**31**) in the conformations in which they are shown [(**32**) and (**35**), respectively] [*cf.* the rearrangement of (**28**)].

In the oxidation of 2-alkenylethyl-3-aminoquinazolones *e.g.* (**3**), intramolecular addition of the nitrene was believed to take place *via* a transition state having dipolar character (Scheme 6).[1] In the oxidation of compound (**38**), only the aziridine (**39**),



(**38**) (**39**) 84%

from addition of the *N*-nitrene to the alkene was isolated (84%). This preference for attack on the double bond by the nitrene can be rationalised in terms of the lesser stability of the partial vinyl cation which would result from electrophilic attack of the nitrene on the triple bond.

Experimental

N.m.r. spectra refer to those run at 90 MHz unless otherwise indicated. I.r. spectra were run as Nujol mulls on a Perkin-Elmer 298 spectrophotometer. Prop-2-ynyl bromide was purchased as an 80% solution in toluene (Aldrich) and was used as received. But-2-yn-1-yl toluene-*p*-sulphonate was prepared from but-2-yn-1-ol (Aldrich) and toluene-*p*-sulphonyl chloride using the method of Brandsma.[13] But-2-ynyl bromide was obtained by treatment of the corresponding alcohol with phosphorus tribromide.[14] Lead tetra-acetate was freed from acetic acid prior to use by placing in a vacuum desiccator and evacuating using a water-pump for 5 min. Dichloromethane was distilled prior to use by distillation from calcium hydride.

Dimethyl Disubstituted Propanedioates $R_2C(CO_2Me)_2$.—These were prepared by reaction of the sodium salt of dimethyl malonate with prop-2-ynyl bromide or 1-bromobut-2-yne in dry methanol followed by successive addition of a further mol equiv. of sodium methoxide and an additional mol equiv. of an alkylating agent. The following esters were prepared in this way: *Dimethyl 2,2-dibut-2-ynylpropan-1,3-dioate* (using 1-bromobut-2-yne). A colourless solid (81%), m.p. 53—55 °C (from ethyl acetate–light petroleum) (Found: C, 66.0; H, 6.8. $C_{13}H_{16}O_4$ requires C, 66.1; H, 6.8%); δ3.68 (s, CO_2Me), 2.84 (q, *J* 2 Hz, CH_2), and 1.70 (t, *J* 2 Hz, Me); Dimethyl 2,2-diprop-2-ynylpropane-1,3-dioate (using prop-2-ynyl bromide). A colourless solid (81%), m.p. 85—87 °C (from ethyl acetate–light petroleum) (lit.,[15] m.p. 87—88 °C). Dimethyl 2-(prop-2-enyl)-2-(prop-2-ynyl)propane-1,3-dioate was prepared similarly by reaction of dimethyl 2-(prop-2-enyl)propane-1,3-dioate, $H_2C{=}CHCH_2CH(CO_2Me)_2$[16] with prop-2-ynyl bromide and was obtained as a colourless liquid (78%), b.p. (Kugelrohr) 120—123 °C/14 mmHg; δ 5.58 (m, C*H*=CH_2), 5.16 (m, CH=CH_2), 3.78 (s, 2 × CO_2Me), 2.62 (m, 2 × CH_2), and 2.02 (t, *J* 2.5 Hz, C≡C*H*); $\nu_{max.}$ 3 345w, 3 000w, 1 760s, 1 450m, 1 305m, 1 240s, and 940w cm^{-1}.

Dimethyl Monosubstituted Propanedioates $RCH(CO_2Me)_2$.—These were prepared as above by reaction of the sodium salt of dimethyl malonate with prop-2-ynyl bromide or but-2-yn-1-yl toluene-*p*-sulphonate (1 mol equiv.) in dry methanol but in both cases substantial di-substitution occurred. The mixture for the case of R = $CH_2C{\equiv}CH$ (ratio mono:disubstitution 2.3:1) was partially separated in the following way: to its solution in methanol was added sodium methoxide (1 mol equiv. based on quantity of mono- and di-substitution product present) in methanol and, after stirring the reaction briefly, the methanol was removed under reduced pressure. The residue was extracted between ether and water, the aqueous layer re-extracted with ether and the combined ether layers dried and evaporated to yield a mixture of the starting mono- and disubstituted esters (ratio 1:3, respectively). After acidification of the aqueous layer above to pH 1, it was extracted twice with ether and the combined ether layers dried and evaporated to yield a mixture of acids of the starting esters (ratio mono- to di-substitution; 11:1). Approximately equal amounts of material were recovered from the original aqueous and ether layers in extraction of the residue above.

The mixture for the case of R = $MeC{\equiv}CCH_2$ (ratio mono: disubstitution 6:1) was separated as described above to give the dioic acid $MeC{\equiv}CCH_2CH(CO_2H)_2$ (35%) after recovery from the aqueous layer. The combined ether layers on evaporation gave a mixture of mono- and di-substituted esters (ratio 2.8:1). Repetition of this separation procedure using more sodium methoxide (1 mol equiv.) gave a further quantity (16%) of the same dioic acid (total 51%). Both the monosubstituted dioic acids above were used directly as described below.

Hydrolysis and Decarboxylation of Substituted Dimethyl Propanedioates.—Disubstituted propane-1,3-dioic acids were obtained by heating the above substituted propanedioates and sodium hydroxide (2M; 4 mol. equiv.) to boiling, adding sufficient ethanol to ensure a homogeneous solution and then heating under reflux for 4 h. After removal of the ethanol under reduced pressure, the residual solution was extracted with ether (the ether layer was then discarded) and the aqueous layer separated, cooled in ice and acidified to pH 1 by the dropwise addition of conc. hydrochloric acid. The mixture was extracted twice with ether and the ether layers combined, dried and evaporated to give the corresponding 1,3-dioic acids in 80—90% yields. 2,2-Di(prop-2-ynyl)propane-1,3-dioic acid[17] was obtained as colourless crystals, m.p. 125—137 °C (from 5M-hydrochloric acid); δ 8.92 (br s, CO_2H), 2.99 (d, *J* 3 Hz, CH_2), and 2.08 (t, *J* 3 Hz, C≡CH).

Decarboxylation of the crude disubstituted dioic acids, prepared as above, or the corresponding monosubstituted dioic acids, isolated by the separation procedure described earlier, was carried out by heating the acid in an oil-bath at 140—175 °C until gas evolution ceased (*ca.* 1 h). Distillation of the residue (Kugelrohr) gave the following acids in 76—90% yields: pent-4-ynoic acid (**12**), b.p. 90—110 °C/0.1 mmHg, solidified on standing (lit.,[18] m.p. 53—55 °C); δ 10.42 (br s, CO_2H), 2.53 (m, CH_2CH_2), and 1.96 (t, 3 Hz, C≡CH); hex-4-ynoic acid (**14**) b.p. 130—150 °C/0.1 mmHg, solidified with time (lit.,[19] m.p. 100—101 °C); δ 10.42 (br s, CO_2H), 2.47 (m, CH_2CH_2), and 1.72 (t, *J* 2

* It seems likely that, as in the case of (**32**) and (**26**), conformation of (**35**) for this ring fused azirine is preferred for a similar reason although difficulties in constructing a precise model in the case of (**35**) make this conclusion less secure.

Hz, Me); 2-(prop-2-ynyl)pent-4-ynoic acid (**13**) (not distilled); δ 10.91 (br s, CO_2H), 2.69 (m, 2 × CH_2, CH), and 2.02 (t, *J* 3 Hz, 2 × C≡CH); 2-(but-2-ynyl)hex-4-ynoic acid (**15**), b.p. 130—150 °C/1.5 mmHg, solidified on standing; δ 11.44 (br s, CO_2H), 2.53 (m, 2 × CH_2, CH), and 1.71 (t, *J* 2 Hz, 2 × Me); 2-(prop-2-ynyl)pent-4-enoic acid, b.p. 130—132 °C/19 mmHg; δ 11.02 (br s, CO_2H), 5.50 (m, CH=CH_2), 2.40 (m, 2 × CH_2, CH), and 2.02 (t, *J* 2.5 Hz, C≡CH).

Conversion of Pent-4-ynoic Acid (**12**) *to Hex-5-ynoic Acid* (**16**).—Pent-4-ynoic acid (12.8 g) in dry ether (81 ml) was added dropwise with stirring to a rapidly stirred solution of lithium aluminium hydride (10 g) in dry ether (300 ml). After the addition, the solution was heated under reflux for 2 h, cooled, and sufficient acetone was added to destroy excess hydride. Water was then added dropwise with vigorous stirring until the suspension changed from grey to white. The precipitated salts were separated, and the ether solution was dried and evaporated and the residual oil distilled to give pent-5-ynol, b.p. 78—82 °C/29 mmHg (9.3 g, 85%); δ3.67 (t, *J* 7 Hz, CH_2OH), 2.71 (br s, OH), 2.27 (td, *J* 7 and 2 Hz, CH_2C≡CH), 1.95 (t, *J* 2 Hz, C≡CH), and 1.74 (quint., *J* 7 Hz, $CH_2CH_2CH_2$). Pent-5-ynol was converted to its toluene-*p*-sulphonate[13] and the crude sulphonate (17.7 g) together with potassium cyanide (9.9 g) in dimethyl sulphoxide (200 ml) was heated in an oil-bath at 50—60 °C with stirring for 2 h, then for 2 days at room temperature. The mixture was poured into water and extracted three times with ether. The combined ether layers washed twice with water, dried, and the bulk of the ether was removed by distillation at atmospheric pressure keeping the temperature of the oil-bath at 45—50 °C. Hydrolysis of the residual oil, [pent-5-ynyl cyanide, δ 2.48 (t, *J* 7 Hz, CH_2CN), 2.31 (td, *J* 7 and 2 Hz, CH_2C≡CH), 2.01 (t, *J* 2 Hz, C≡CH), and 1.84 (quint., *J* 7 Hz, $CH_2CH_2CH_2$); $\nu_{max.}$ 2 260 and 2 160 cm^{-1}] was carried out using aqueous potassium hydroxide [43 g in water (125 ml)] and methanol (100 ml) by heating under reflux overnight. The solution was worked up as described earlier for disubstituted propane-1,3-dioic acids. Hex-5-ynoic acid (**16**) was obtained as an oil (lit.,[18] m.p. 41—43.5 °C); δ 8.30 (br s, CO_2H), 2.48 (t, *J* 8 Hz, CH_2CO_2H), 2.26 (td, *J* 8 and 3 Hz, CH_2C≡CH), 1.96 (t, *J* 3 Hz, C≡CH), and 1.83 (quint., *J* 8 Hz, $CH_2CH_2CH_2$); $\nu_{max.}$ 2 120 and 1 700 cm^{-1}. This was used directly as described below.

Methyl N-*Substituted Anthranilates*.—These derivatives of the above carboxylic acids were obtained in 77—81% yields by successive treatment with thionyl chloride and methyl anthranilate as described previously.[2] The following compounds were obtained in this way: methyl *N*-(pent-4-ynoyl)anthranilate as colourless crystals, m.p. 48—51 °C (from ethanol); δ 11.04 (br s, NH), 8.65 (dd, *J* 8 and 1 Hz, 3-H), 7.96 (dd, *J* 8 and 2 Hz, 6-H), 7.49 (ddd, *J* 8, 8 and 2 Hz, 4-H), 7.02 (ddd, *J* 8, 8, and 1 Hz, 5-H), 3.86 (s, OMe), 2.62 (m, 2 × CH_2), and 1.95 (t, *J* 2 Hz, C≡CH); methyl *N*-(hex-4-ynoyl)anthranilate as an oil; δ 10.93 (br s, NH), 8.68 (dd, *J* 8 and 1 Hz, 3-H), 7.94 (dd, *J* 8 and 2 Hz, 6-H), 7.48 (ddd, *J* 8, 8, and 2 Hz, 4-H), 7.02 (ddd, *J* 8, 8, and 1 Hz, 5-H), 3.86 (s, OMe), 2.56 (m, 2 × CH_2), and 1.72 (t, *J* 2 Hz, C≡CMe); methyl *N*-(hex-5-ynoyl)anthranilate as an oil; δ 11.3 (br s, NH), 8.9 (dd, *J* 8 and 1 Hz, 3-H), 8.15 (dd, *J* 8 and 2 Hz, 6-H), 7.65 (ddd, *J* 8, 8, and 2 Hz, 4-H), 7.15 (ddd, *J* 8, 8, and 1 Hz, 5-H), 3.96 (s, OMe), and 2.75—1.90 (m, $CH_2CH_2CH_2$, C≡*CH*); *methyl* N-(*hepta*-1,6-*diyn*-4-*oyl*)*anthranilate* as colourless crystals, m.p. 90.5—92 °C (from ethanol) (Found: C, 71.2; H, 5.6. N, 5.2. $C_{16}H_{15}NO_3$ requires C, 71.4; H, 5.6; N, 5.2%); δ 11.18 (br s, NH), 8.66 (dd, *J* 8 and 1 Hz, 3-H), 7.97 (dd, *J* 8 and 2 Hz, 6-H), 7.48 (ddd, *J* 8, 8, and 2 Hz, 4-H), 7.03 (ddd, *J* 8, 8, and 1 Hz, 5-H), 3.88 (s, OMe), 2.64 (m, 2 × CH_2, CH), and 1.99 (t, *J* 2 Hz, 2 × C≡CH); methyl *N*-(nona- 2,7-diyn-5-oyl)anthranilate as colourless crystals, m.p. 65—68 °C (from ethanol), δ 11.11 (br s, NH), 8.70 (dd, *J* 8 and 1 Hz, 3-H), 7.96 (dd, *J* 8 and 2 Hz, 6-H), 7.48 (ddd, *J* 8, 8, and 2 Hz, 4-H), 7.03 (ddd, *J* 8, 8, and 1 Hz, 5-H), 3.88 (s, OMe), 2.64 (m, 2 × CH_2, CH), and 1.7 (m, 2 × C≡CMe); methyl *N*-(hept-6-en-1-yn-4-oyl)anthranilate as an oil; δ (60 MHz) 11.02 (br s, NH), 8.76 (d, *J* 8 Hz, 3-H), 7.96 (d, *J* 8 Hz, 6-H), 7.51 (dd, *J* 8 and 8 Hz, 4-H), 7.01 (dd, *J* 8 and 8 Hz, 5-H), 5.66 (m, C*H*=CH_2), 5.08 (m, CH=CH_2), 3.91 (s, OMe), 2.56 (m, 2 × CH_2), and 2.00 (m, C≡CH).

3-*Amino*-2-*substituted Quinazolones*.—The above amides in which the acid part was unbranched, were heated with hydrazine hydrate (96%) in methanol or ethanol as previously described[2] and the following compounds were obtained as colourless crystals: 3-*amino*-2-(*but*-1-*yn*-4-*yl*)*quinazolin*-4(3H)-*one* (**7**) (46%), m.p. 157—159.5 °C (from methanol) (Found: C, 67.5; H, 5.3; N, 19.7. $C_{12}H_{11}N_3O$ requires C, 67.6; H, 5.2; N, 19.7); δ 8.18 (d, *J* 8 Hz, 5-H), 7.63—7.29 (m, 6-, 7-, and 8-H), 4.88 (br s, NH_2), 3.28 (t, *J* 7 Hz, CH_2CH_2C≡), 2.75 (td, *J* 7 and 2 Hz, CH_2C≡CH), and 1.96 (t, *J* 2 Hz, C≡CH); $\nu_{max.}$ 3 290m, 3 230m, 1 665s, 1 620s, 770s, and 690s cm^{-1}; 3-*amino*-2-(*pent*-3-*yn*-1-*yl*)*quinazolin*-4(3H)-*one* (**9**) (90%), m.p. 147—150 °C (from ethanol) (Found: C, 68.7; H, 5.8; N, 18.5. $C_{13}H_{13}N_3O$ requires C, 68.7; H, 5.8; N, 18.5%); δ 8.15 (d, *J* 8 Hz, 5-H), 7.60—7.26 (m, 6-, 7-, and 8-H), 4.94 (br s, NH_2), 3.20 (t, *J* 7 Hz, CH_2CH_2C≡), 2.70 (m, CH_2C≡CMe), and 1.70 (t, *J* 2 Hz, C≡CMe); $\nu_{max.}$ 3 300m, 3 205w, 1 640s, 1 595s, 760m, and 690s cm^{-1}; 3-*amino*-2-(*pent*-5-*yn*-1-*yl*)*quinazolin*-4(3H)-*one* (**11**) (70%) m.p. 106—107 °C (from ethanol) (Found: C, 68.5; H, 5.9; N, 18.5; $C_{13}H_{13}N_3O$ required C, 68.7; H, 5.8; N, 18.5%); δ 8.15 (d, *J* 8 Hz, 5-H), 7.6—7.1 (m, 6-, 7-, and 8-H), 4.84 (br s, NH_2), 3.10 (t, *J* 7 Hz, $CH_2(CH_2)_2C$≡), 2.35 (td, *J* 7 and 2 Hz, CH_2CH_2C≡), 2.05 (quint. *J* 7 Hz, CH_2C≡), and 1.96 (t, *J* 2 Hz, C≡CH); $\nu_{max.}$ 3 315m, 3 240m, 1 672s, 1 596s, 781m, and 696 cm^{-1}. The methyl *N*-substituted anthranilates above in which the acid part contained a branched chain were heated with hydrazine hydrate (96%) in methanol or ethanol in a sealed tube in the absence of oxygen as described previously[1] and the following compounds were obtained as colourless crystals: 3-*amino*-2-(*hepta*-1,6-*diyn*-4-*yl*)*quinazolin*-4(3H)-*one* (**8**) (63%), m.p. 124—125.5 °C (from ethanol) (Found: C, 71.6; H, 5.3; N, 16.7. $C_{15}H_{13}N_3O$ requires C, 71.7; H, 5.2; N, 16.7%); δ 8.20 (d, *J* 8 Hz, 5-H), 7.64—7.31 (m, 6-, 7-, and 8-H), 4.96 (br s, NH_2), 4.20 (quint., *J* 7 Hz, CH), 2.76 (dd, *J* 7 and 2 Hz, 2 × CH_2), and 1.92 (t, *J* 2 Hz, 2 × C≡CH); 3-*amino*-2-(*nona*-2,7-*diyn*-5-*yl*)*quinazolin*-4(3H)-*one* (**10**) (59%), m.p. 104—105 °C (from ethanol) (Found: C, 72.8; H, 6.2; N, 15.0. $C_{17}H_{17}N_3O$ requires C, 73.1; H, 6.1; N, 15.0%); δ 8.22 (d, *J* 8 Hz, 5-H), 7.72—7.30 (m, 6-, 7-, and 8-H), 5.10 (br s, NH_2), 4.09 (quint., *J* 7 Hz, CH), 2.67 (m, 2 × CH_2), and 1.69 (t, *J* 2 Hz, 2 × C≡CMe); $\nu_{max.}$ 3 310m, 1 680s, 1 600s, 1 583s, 768s, and 691s cm^{-1}; 3-*amino*-2-(*hept*-1-*en*-6-*yn*-4-*yl*)*quinazolin*-4(3H)-*one* (**38**) (53%), m.p. 60—62 °C (from ethanol) (Found: C, 71.1; H, 5.9; N, 16.5. $C_{15}H_{15}N_3O$ requires C, 71.1; H, 6.0; N, 16.6%); δ 8.18 (d, *J* 8 Hz, 5-H), 7.63—7.29 (m, 6-, 7-, and 8-H), 5.73 (m, C*H*=CH_2), 5.07 (m, CH=CH_2), 4.89 (br s, NH_2), 4.06 (quint., *J* 7 Hz, CH), 2.65 (dd, *J* 7 and 2 Hz, CH_2C≡CH), 2.57 (m, CH_2CH=CH_2), and 1.88 (t, *J* 2 Hz, C≡CH); $\nu_{max.}$ 3 320m, 3 260s, 1 660s, 1 590s, 925m, 780s, and 700s cm^{-1}.

Oxidation of 2-*Substituted* 3-*Aminoquinazolin*-(3H)-4-*ones* (**7**)—(**11**) *with Lead Tetra-acetate under Conditions of High Dilution*.—In these experiments all glassware was flame-dried under a current of dry nitrogen immediately prior to use. The foregoing aminoquinazolones (100 mg or 200 mg, 1 mol equiv.) was dissolved in dry dichloromethane (50 ml) and lead tetra-acetate (1.15 mol equiv.) was also dissolved in an equal volume of dry dichloromethane. Both solutions were added simultaneously at the same rate over 20—40 min. to rapidly stirred dry dichloromethane (100 ml) which was cooled in an ice bath.

After the reaction had been stirred for a further 10—30 min the precipitated lead diacetate was separated and the solution washed with aqueous sodium hydrogen carbonate, dried, and evaporated to give the product. Oxidation of compound (**9**) in this way gave a solid product in quantitative yield. Crystallisation from ethyl acetate–light petroleum gave the *azirine* (**17**) as colourless prisms (78%), m.p. 135—136 °C (Found: C, 69.2; H, 5.0; N, 18.6. $C_{13}H_{11}N_3O$ requires C, 69.3; H, 4.9; N, 18.7%) δ_H (400 MHz) 8.05 (ddd, *J* 8, 1.5, and 0.5 Hz, 6-H), 7.64 (ddd, *J* 8, 7, and 1.5 Hz, 8-H), 7.56 (ddd, *J* 8, 1.5, and 0.5 Hz, 9-H), 7.34 (ddd, *J* 8, 7, and 1.5 Hz, 7-H), 3.48 (ddd, *J* 17.5, 10.9, and 9.3 Hz, 1-H), 3.03 (ddd, *J* 17.5, 9.7, and 1.5 Hz, 1-H), 2.71 (s, Me), 2.61 (ddd, *J* 13.9, 10.9, and 9.7 Hz, 2-H), and 1.73 (ddd, *J* 13.9, 9.3, and 1.5 Hz, 2-H); δ_C (100 MHz) 171.50 (s), 160.80 (s), 158.48 (s), 148.70 (s), 134.30 (d), 126.92 (d), 126.34 (d), 126.16 (d), 120.92 (s), 55.91 (s), 29.42 (dd), 28.15 (dd), and 14.96 (q); $\nu_{max.}$ 1 780w, 1 675s, 1 630s, 1 610s, 780s, and 700m cm^{-1}.

The oxidation of compound (**10**) (1 g) as described above gave a solid (950 mg) whose n.m.r. spectrum indicated it was pure. Crystallisation from ethanol gave *azirine* (**23**) as colourless needles, m.p. 140.5—141.5 °C (Found: C, 73.7; H, 5.5; N, 15.2. $C_{17}H_{15}N_3O$ requires C, 73.6; H, 5.5; N, 15.2%); δ (400 MHz) 8.14 (ddd, *J* 8, 1.5, and 0.6 Hz, 6-H), 7.72 (ddd, *J* 8.2, 6.5, and 1.5 Hz, 8-H), 7.68 (ddd, *J* 8.2, 1.7, and 0.6 Hz, 9-H), 7.42 (ddd, *J* 8, 6.5, and 1.7 Hz, 7-H), 3.79 (dddd, *J* 10.5, 8.3, 7.4, and 4.4 Hz, 1-H), 2.94 (ddq, *J* 16.8, 4.4, and 2.5 Hz, C*H*HC≡CMe), 2.79 (s, azirine Me), 2.76 (ddq, *J* 16.8, 7.4, and 2.5 Hz, CH*H*C≡CMe), 2.65 (dd, *J* 13.7 and 10.5 Hz, 2-H), 1.97 (dd, *J* 13.7 and 8.3 Hz, 2-H), and 1.74 (t, *J* 2.5 Hz, MeC≡C); $\nu_{max.}$ 1 760w, 1 690s, 1 628m, 1 610m, 1 330m, and 780s cm^{-1}.

The oxidation of compound (**7**) as described above and examination of the crude product by n.m.r. showed the presence of the azirine (**20**) and the acetic acid addition product (**21**) in the ratio 79:21, respectively. The azirine (**20**) showed δ (400 MHz) 10.41 (dd, *J* 2.8 and 0.6 Hz, azirine CH), 8.02 (dd, *J* 8 and 1.5 Hz, 6-H), 7.63 (ddd, *J* 8.1, 6.9 and 1.5 Hz, 8-H), 7.54 (dd, *J* 8.1 and 1.7 Hz, 9-H), 7.32 (ddd, *J* 8, 6.9, and 1.7 Hz, 7-H), 3.47 (ddd, *J* 17.5, 10.9, and 9.3 Hz, 1-H), 3.03 (ddd, *J* 17.5, 9.6, and 1.3 Hz, 1-H), 2.65 (dddd, *J* 13.9, 10.9, 9.6, and 2.8 Hz, 2-H), and 1.75 (dddd, *J* 13.9, 9.3, 1.3, and 0.6 Hz, 2-H). When the above reaction mixture was set aside overnight before work-up, an n.m.r. spectrum of the crude product showed the presence of the aziridine (**21**) only, which was isolated as an unstable (non-distillable) oil; δ 8.00 (d, *J* 8 Hz, 6-H), 7.68—7.24 (m, 7-, 8-, and 9-H), 6.10 (d, *J* 8 Hz, C*H*OAc), 3.88 [br d, *J* 8 Hz, (exch. D_2O), NH], 3.08 (t, *J* 9 Hz 1-H_2), 2.31 (t, *J* 9 Hz, 2-H_2), and 2.09 (s, OCOMe). On shaking with D_2O, δ 6.10 (d) collapsed to δ 6.10 (s).

The oxidation of compound (**8**) was carried out as described above but the reaction was worked up 10 min after the reagents had been mixed together and this gave only the azirine (**22**), m.p. 163—168 °C as a colourless solid (from ether–dichloromethane). A satisfactory analysis of this material was not obtained; δ (400 MHz) 10.48 (dd, *J* 2.8 and 0.6 Hz, azirine CH), 8.13 (dd, *J* 8 and 1.4 Hz, 6-H), 7.73 (ddd, *J* 8.2, 6.8, and 1.4 Hz, 8-H), 7.69 (dd, *J* 8.2 and 1.3 Hz, 9-H), 7.43 (ddd, *J* 8, 6.8, and 1.3 Hz, 7-H), 3.88 (dddd, *J* 10.6, 8.1, 7.3 and 4.4 Hz, 1-H), 2.99 (ddd, *J* 17, 4.4, and 2.6 Hz, H*H*CC≡CH), 2.86 (ddd, *J* 17, 7.3, and 2.6 Hz, *H*HCC≡CH), 2.75 (ddd, *J* 13.7, 10.6, and 2.8 Hz, 2-H), 2.04 (dd, *J* 13.7 and 8.1 Hz, 2-H), and 1.99 (t, *J* 2.6 Hz, C≡CH). When the above reaction mixture was set aside overnight prior to work-up, an n.m.r. spectrum of the crude product showed the presence of the acetic acid addition product (**24**) only. Crystallisation from ether–dichloromethane gave the *aziridine* (**24**), m.p. 128—131 °C (decomp.) (Found: C, 66.1; H, 5.0; N, 13.6. $C_{17}H_{15}N_3O_3$ requires C, 66.0; H, 4.9; N, 13.6%); δ (400 MHz) 8.18 (ddd, *J* 8, 1.5, and 0.5 Hz, 6-H), 7.75 (ddd, *J* 8.2, 7, and 1.5 Hz, 8-H), 7.66 (ddd, *J* 8.2, 1.1, and 0.5 Hz, 9-H), 7.46 (ddd, *J* 8, 7, and 1.1 Hz, 7-H), 6.35 (d, *J* 8.5 Hz, C*H*OAc), 3.69 (br d, *J* 8.5 Hz, NH), 3.54 (dddd, *J* 9.4, 7.9, 5.5, and 4.4 Hz, 1-H), 2.85 (ddd, *J* 16.9, 4.4, and 2.6 Hz, H*H*CC≡CH), 2.75 (ddd, *J* 16.9, 7.9, and 2.6 Hz, *H*HCC≡CH), 2.57 (dd, *J* 14.3 and 9.4 Hz, 2-H), 2.45 (dd, *J* 14.3 and 5.5 Hz, 2-H), 2.16 (s, OCOMe), and 1.98 (t, *J* 2.6 Hz, C≡CH); $\nu_{max.}$ 3 230br s, 1 745s, 1 670s, 1 615s, 1 225s, 1 140s, 995m, 775s, and 695m cm^{-1}.

The oxidation of compound (**11**) (1 g) as described above and examination of the crude reaction product by n.m.r. showed the presence of the azirines (**30**) and (**31**) in a 9:4 ratio, respectively. Crystallisation from methanol gave a pure sample of the azirine (**30**) (250 mg), m.p. 120—124 °C, but an analytical sample could not be obtained since the (colourless) azirine produced an orange polymeric substance when allowed to stand overnight; δ (400 MHz) 10.28 (d, *J* 2.3 Hz), 8.14 (dd, *J* 7.9 and 1.5 Hz, 7-H), 7.73 (ddd, *J* 8.1, 7.1, and 1.5 Hz, 9-H), 7.62 (dd, *J* 8.1 and 1.3 Hz, 10-H), 7.42 (ddd, *J* 7.9, 7.1, and 1.3 Hz, 8-H), 3.39 (ddd, *J* 15.4, 11.9, and 5.9 Hz, 1-H), 3.05 (ddd, *J* 15.4, 5.6, and 5.1 Hz, 1-H), 2.62 (dddd, *J* 14.9, 8.9, 4.6, and 2.3 Hz, 3-H), 2.38 (ddddd, *J* 13.6, 8.9, 5.9, 5.1, and 4.6 Hz, 2-H), 1.97 (ddddd, *J* 13.6, 11.9, 8.9, 7.2, and 5.6 Hz, 2-H), and 1.51 (ddd, *J* 14.9, 8.9, and 7.2 Hz, 3-H); $\nu_{max.}$ 1 668s, 1 610s, 790m, and 720m cm^{-1}. The n.m.r. spectrum of the azirine (**31**) was obtained from that of the crude reaction product above by subtraction of those signals belonging to azirine (**30**) and showed δ (400 MHz) 8.29 (dd, *J* 7.9 and 1.5 Hz, 9-H), 7.71 (ddd, *J* 8.1, 7.1, and 1.5 Hz, 7-H), 7.56 (dd, *J* 8.1 and 1.3 Hz, 6-H), 7.46 (ddd, *J* 7.9, 7.1, and 1.3 Hz, 10-H), 4.42 (s, 11a-H), 3.32 (ddd, *J* 13, 5, and 1.5 Hz, 2-H), 3.28 (ddd, *J* 15, 7.7, and 1.5 Hz, 4-H), 3.11 (ddd, *J* 15, 12.3, and 1.5 Hz, 4-H), 2.99 (ddd, *J* 13, 12.7, and 7.7 Hz, 2-H), 2.55 (ddddd, *J* 13.5, 7.7, 7.7, 1.5 and 1.5 Hz, 3-H), and 1.65 (ddddd, *J* 13.5, 12.7, 12.3, 5, and 1.5 Hz, 3-H).

Attempted Trapping of a 1H-*Azirine Intermediate.*—The *N*-aminoquinazolin-4(3*H*)-*one* (**7**) (200 mg, 1 mol equiv.) was dissolved in dry dichloromethane (50 ml) and lead tetra-acetate (0.9 mol equiv.) was also dissolved in an equal volume of dry dichloromethane. Both solutions were added simultaneously at the same rate over 20 min to rapidly stirred dry dichloromethane (100 ml) which was cooled in a solid CO_2–acetone bath at −78 °C. After the addition was complete, the solution was stirred for a further 8 h. No precipitated lead diacetate was visible in the solution after this time, however, and testing with starch-iodide paper suggested that unchanged LTA was still present. 2,3-Dimethylbutadiene (1.3 g, 16 mol equiv.) was then added to the reaction mixture and the temperature of the solution allowed to rise slowly to ambient, with stirring throughout. The solution was washed twice with aqueous sodium hydrogen carbonate, dried, and evaporated. An n.m.r. spectrum of the crude reaction mixture showed the presence of the acetoxyaziridine (**21**) and aziridine (**29**) in a ratio of 3:2, respectively. Rapid chromatography on alumina and elution with light petroleum–ethyl acetate (4:1) gave the *aziridine* (**29**) (18 mg) as colourless laths, m.p. 96—97 °C (from ethanol) (Found: C, 73.7; H, 6.5; N, 14.4. $C_{18}H_{19}N_3O$ requires C, 73.7; H, 6.5; N, 14.3%); δ (400 MHz) 8.11 (dd, *J* 8 and 1.5 Hz, 5-H), 7.63 (ddd, *J* 8.2, 6.9, and 1.5 Hz, 7-H), 7.57 (dd, *J* 8.2 and 1.4 Hz, 8-H), 7.36 (ddd, *J* 8, 6.9, and 1.4 Hz, 6-H), 5.16 (br s, =C*H*H), 5.10 (m, =CH*H*), 3.13 (ddd, *J* 16.2, 8.3, and 6.4 Hz, 1″-H), 3.02 (m, 2, 3′-H_2), 2.90 (ddd, *J* 16.2, 7.9, and 7.9 Hz, 1″-H), 2.71 (m, CH_2C≡CH), 1.89 (t, *J* 2.6 Hz, C≡CH), 1.76 (br s, =CMe), and 1.22 (s, aziridine Me). Minor invertomer, 1.59 (s, aziridine Me), and 1.43 (s, =CMe). The ratio of the two invertomers was *ca.* 17:1; $\nu_{max.}$ (Nujol) 3 250m, 1 660s, 1 590s, 1 300w, 1 120w, 900m, and 780m cm^{-1}.

The oxidation of compound (**7**) (0.3 g) with LTA (0.65 g, 1.15 mol equiv.) in dichloromethane (5 ml) and 2,3-dimethylbutadiene (5 ml) at 0 °C in the usual way gave the aziridine (**29**)

only. Rapid chromatography on alumina and elution with light petroleum–ethyl acetate (3:1) gave the pure aziridine (51%).

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