

N-NITRENES AND ELECTROCYCLIC REACTIONS IN NITROGEN

HETEROCYCLES

by

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A thesis submitted for the degree of Doctor of Philosophy at the

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STATEMENT

The work described in this thesis was carried out by the author in the Department of Chemistry of the University of Leicester under the supervision of Professor C.W. Rees. No part of it is concurrently being submitted for any other degree.

October 1967 - September 1970.

(Signed)

David Horwell

DAVID HORWELL

To Gillian

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ABSTRACT

This thesis is divided into 3 parts.

The first describes the preparation of several heterocyclic N-amino compounds and the generation from these of singlet amino-nitrene, by lead tetraacetate oxidation. These nitrenes, which undergo several different electrocyclic reactions, are of two broad types. The first, formed from N-aminoquinazolones, and an N-aminoquinolone, pyrimidone, pyridone and benzimidazole undergo intermolecular reactions, such as tetrazene formation and deamination. With a wide range of electrophilic and nucleophilic olefins they give aziridines stereospecifically, and with dimethyl sulphoxide they give the sulphoximines in high yield. The second type of amino-nitrene, formed from N-aminophthalazones and indazoles, mainly undergo intramolecular reactions involving extrusion of nitrogen. The phthalazones gave highly reactive 1-oxoisindoles or azacyclopentadienones. The indazoles gave a complex pattern of products which could be rationalized by the intermediacy of a new anti-aromatic system, 2,3 benzoazete, or 1-azabenzocyclobutadiene. Differences between the two types of N-amino compounds are explained simply in terms of their structure.

In the second part, the synthesis of indano[1,2-b]aziridine and its N-substituted derivatives is described, and their subsequent ring expansion to isoquinoline, in an aza-analogue of the cyclopropyl to allyl cation rearrangement. This is discussed in terms of orbital symmetry control. Rearrangement occurs in low yield with the N-chloro compound and in high yield by lead tetraacetate oxidation.

In the third part, a PMR investigation of slow nitrogen inversion in aziridines, prepared from five N-amino compounds by their

oxidation in the presence of acrylate and methacrylate esters, revealed an unexpected change in invertomer ratio as the size of the ester alkyl group was increased. This trend is rationalized in terms of an attractive interaction between the ester carbonyl group and the N-heterocyclic substituent. The use of this technique to compare group sizes provides a valuable supplement to cyclohexane conformational analysis.

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INTRODUCTION

Section 1: The Generation and Reactions of N-Nitrenes

Nitrenes are neutral, monovalent, hence electron deficient, highly reactive intermediates, which may exist in a spin paired ("singlet") or a spin parallel ("triplet") state. This follows from the fact that spin multiplicity is given by $2S + 1$, where S = total spin.

Therefore for two spin paired electrons, $S = +\frac{1}{2} + (-\frac{1}{2}) = 0$

therefore $2S + 1 = 1$, hence the term "singlet".

For two parallel spin electrons, $S = +\frac{1}{2} + \frac{1}{2} = 1$

therefore $2S + 1 = 3$, hence the term "triplet".

The possible arrangements of two electrons between two orbitals of different energy are as shown in Fig. 1.

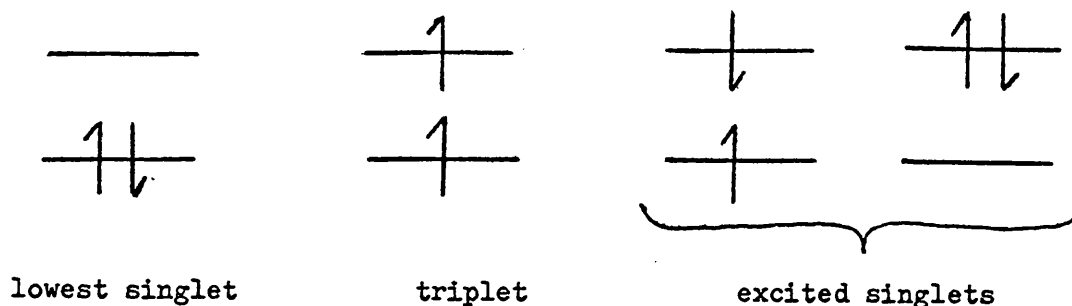


Fig. 1

A reasonable structure for a nitrene is a "bent" sp^2 hybrid, (Fig. 2).

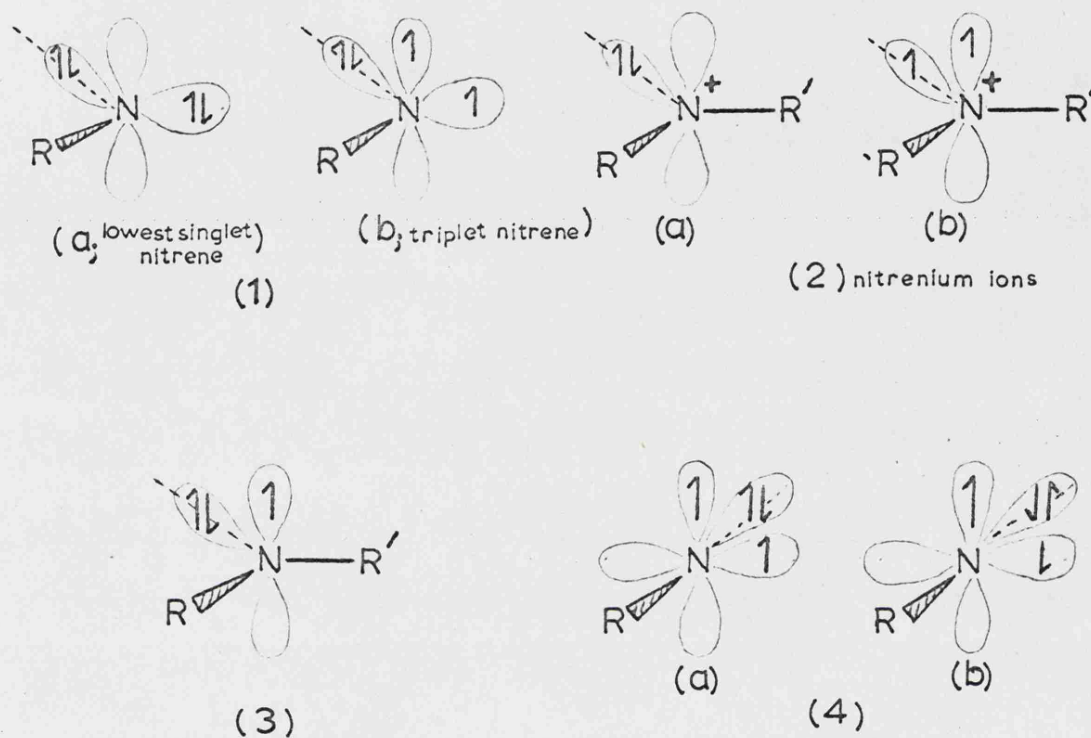
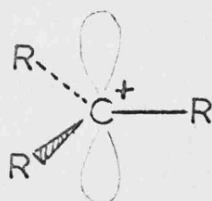


Fig. 2

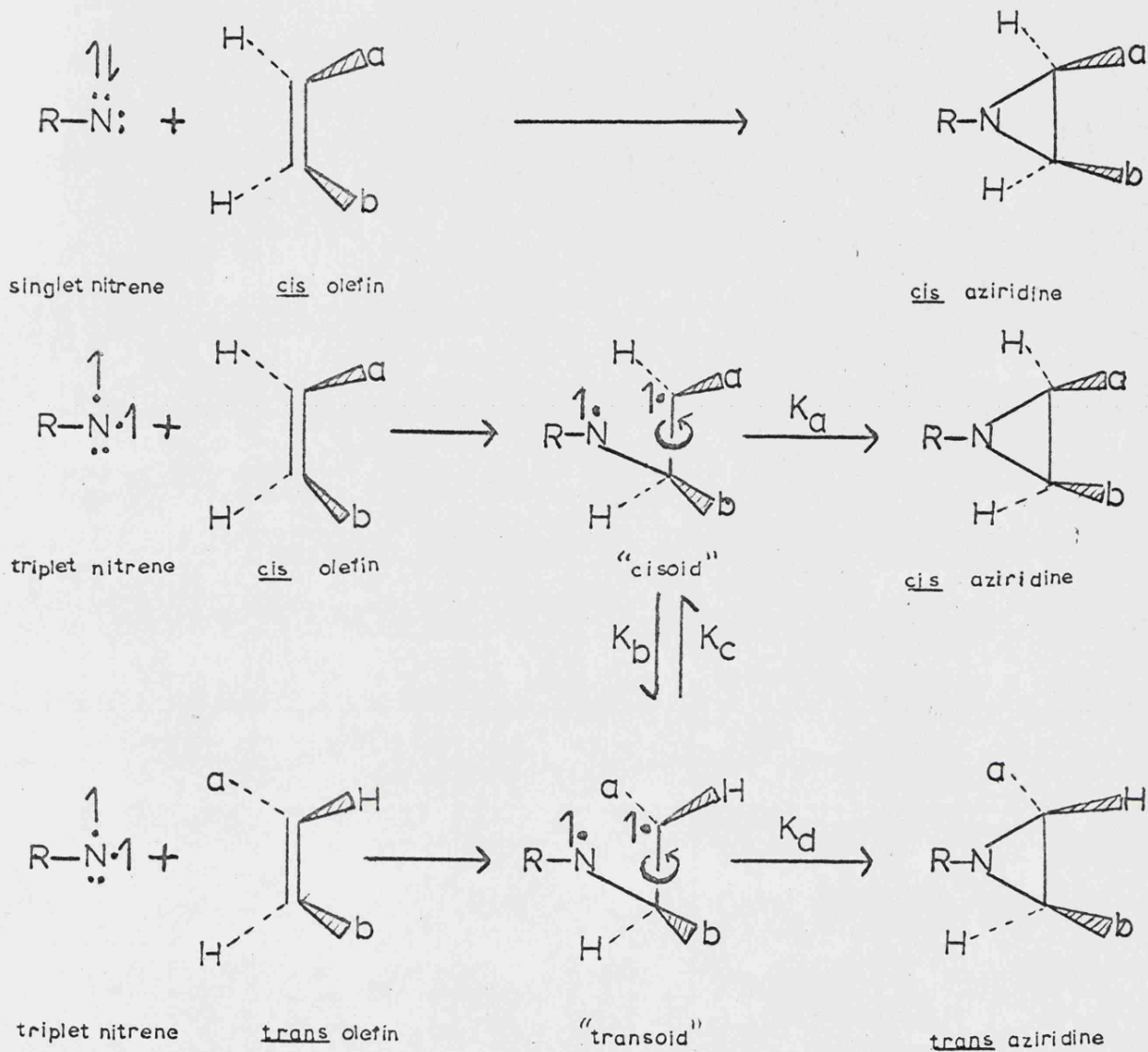
These structures have corresponding analogues with carbenes, where the lone pair of electrons of the nitrene is replaced by a covalent bond. It is interesting to note that a nitrene in the lowest singlet state (1a) resembles a singlet nitrenium ion (2a) which may, in principle, have a triplet counterpart (2b) as suggested by Gassman [1], whereas the analogous carbonium ion can only be:



A nitrene in the triplet state (1b) resembles a nitrogen free radical (3). Alternative structures for the triplet nitrene and for the excited singlet are the linear sp hybrids (4a) and (4b) respectively. Structures intermediate between (1) and (4) are also possible.

Nomenclature for nitrenes parallels that used for carbenes. Thus $\text{:}\ddot{\text{N}}\text{H}$ is nitrene; $\text{:}\ddot{\text{N}}\text{Ph}$ is phenyl nitrene etc.; other names used for these intermediates have been "imidogens", "azenes", "azacarbenes" and "imenes".

By Hund's Rules, the triplet would appear to be the most likely ground state. Acyl and alkoxy nitrenes have a triplet ground state but often appear to be generated in the singlet state. That this is so has been admirably demonstrated by Lwowski. He found that ethoxycarbonyl nitrene, generated either by pyrolysis or photolysis of ethyl azidoformate [2], or by base induced α -elimination of arylsulphonate ion from N- (p-nitrobenzenesulphonyloxy) urethane [3], was trapped by olefins to give aziridines, stereospecifically at high olefin concentration but non-stereospecifically at low olefin concentration. He rationalized these significant observations in terms of Skell's hypothesis (which had already been successfully applied to the corresponding addition of carbenes to olefins to give cyclopropanes [4]) according to the scheme outlined in Fig. 3:

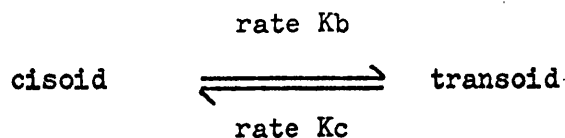


$$K_d \approx K_a < K_b \approx K_c$$

Fig. 3

Thus, in Fig. 3, the singlet nitrene could add to an olefin in a concerted manner, since the two new σ -bonds of the aziridine could be formed without changing the spin of any of the electrons involved. On the other hand, for a triplet nitrene the cycloaddition would involve the triplet diradical; with a cis olefin this would be the "cisoid" diradical, with a trans olefin this would be the "transoid"

diradical. Both could then ring close to give a cis aziridine (rate K_a) and trans aziridine (rate K_d) respectively, after electron pairing. However, C - C bond rotation may be faster than this, causing the interconversion



before ring closure (i.e. $K_d \approx K_a < K_b \approx K_c$) and hence non-stereospecific addition.

Iwowski argued that at high olefin concentration the singlet nitrene is mainly present, (α -elimination and the thermolysis generate pure singlet, but photolysis gives approximately one-third as triplet [3]) therefore stereospecific addition was mainly found, but at low olefin concentration (olefin/^{diluted}with methylene chloride, an inert solvent, as shown [3]) the singlet has time to decay to the triplet state before reacting with the olefin, to give a mixture of cis and trans aziridines.

A more sophisticated treatment of cycloaddition than that of Skell for the analogous case of cycloaddition of methylene (carbene) to ethylene has been given by Hoffmann [5]. Woodward and Hoffmann have successfully applied the principle of conservation of orbital symmetry to cycloaddition reactions [6, 14]. Here, Hoffmann concludes that a bent (i.e. lowest) singlet methylene approaches the ethylene initially through an unsymmetrical transition state (Fig. 4a); the ethylene and methylene can then correlate with the ground state of the product, cyclopropane, hence giving a "symmetry-allowed" process. However, for methylene in the triplet state (or the excited singlet state) a different favourable geometry is predicted for the transition state, the ethylene and methylene now correlate, not with the ground

state cyclopropane, but with a triplet state of excited configuration of the trimethylene diradical (Fig. 4,b). In this, C - C bond rotation is not restricted, hence non-stereospecific addition will occur.

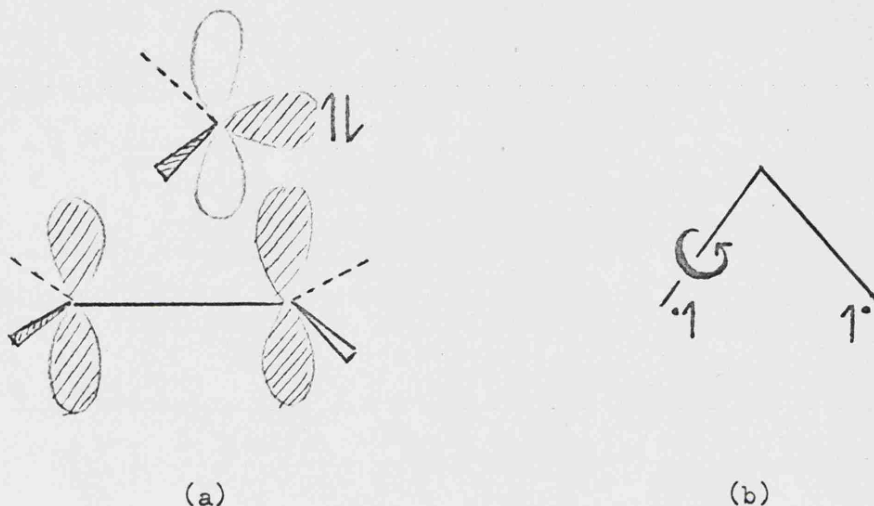


Fig. 4

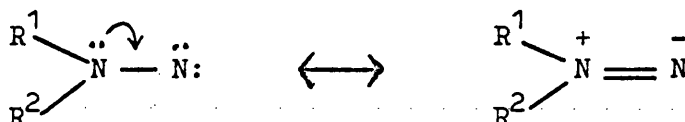
This theory leads to the same result as Skell's hypothesis for the addition of the lowest singlet and triplet states of carbenes, and in an analogous manner for nitrenes. The difference is that it is not primarily the spin state that determines stereospecificity, but the spatial distribution of the wave function (i.e. the orbitals concerned in the reaction).

This "test" that singlet nitrene addition to olefins gives a stereospecific product is valid when dealing with cis olefin \longrightarrow cis aziridine, as the product is the less thermodynamically stable isomer. If a cis olefin \longrightarrow trans aziridine, it can be argued that the cause of this is thermodynamic, rather than kinetic control, as the trans isomer is the more stable. However, in some cases, cis isomers are the more stable, due to special intramolecular attractions. Thus such "tests" can only be rigidly applied by comparing the stereospecificity of both isomers.

It can be concluded from Lwowski's work that product analysis will only indicate the state in which the nitrene is intercepted, which need not necessarily be the ground state.

N-nitrenes may have especially stabilized singlet states,

i.e.



hence reactions of N-nitrenes are more likely to involve the singlet, rather than triplet state.

N-nitrenes have been postulated as the common intermediate in the oxidation of many 1,1-disubstituted hydrazines and other related reactions. Their reactions are numerous and it appears that subtle changes in the nature of the substituents, their mode of generation, solvent effects and temperature can lead to a wide variety of products [7].

Methods of Generation of N-Nitrenes

- (1) By oxidation of 1,1-disubstituted hydrazines by a wide variety of oxidizing agents, of which the most common are yellow mercuric oxide, active manganese dioxide, and lead tetraacetate.
- (2) By α -elimination of N-arylsulphonamides either by treatment with base, pyrolysis, or photolysis of their lithium salts [9v].
- (3) Treatment of secondary amines with Angeli's salt [8j, 9u] (sodium nitrohydroxylamate $Na_2N_2O_3$)
- (4) Treatment of secondary amines with difluoramine [9n]
- (5) By reduction of N-nitroso compounds with sodium hydrosulphite [9e, 9n].

Reactions of N-Nitrenes

It is convenient to classify these reactions as following either an intramolecular or intermolecular pathway. They may be generalised as in Fig. 5:

Fig. 5.

<u>Pathway</u>	<u>Comment</u>	<u>Ref.</u>
<u>INTRAMOLECULAR</u>		
(a) <u>With loss of nitrogen</u>	Common	9
$\begin{array}{l} \text{R}^1 \\ \diagdown \\ \text{N}-\ddot{\text{N}}: \\ \diagup \\ \text{R}^2 \end{array}$	1. $\text{R}^1-\text{R}^2 + \text{N}_2$ May fragment further in concert with loss of nitrogen. 2. $\text{R}^1\cdot + \text{R}^2\cdot + \text{N}_2 \longrightarrow$ products, e.g. dimers.	
(b) <u>Without loss of nitrogen</u>		
1. $\begin{array}{l} \text{R}^1 \\ \diagdown \\ \text{N}-\ddot{\text{N}}: \\ \diagup \\ \text{R}^2 \end{array}$	$\text{R}^1-\text{N}=\text{N}-\text{R}^2$, may tautomerize.	Not common 12
2. $\begin{array}{l} \text{R}^1-\text{CH}_2 \\ \diagdown \\ \text{N}-\ddot{\text{N}}: \\ \diagup \\ \text{R}^2-\text{CH}_2 \end{array}$	$\text{R}^1\text{CH}_2\text{NHN}=\text{CHR}^2$	Not common. 11 Probably not via discrete nitrene.

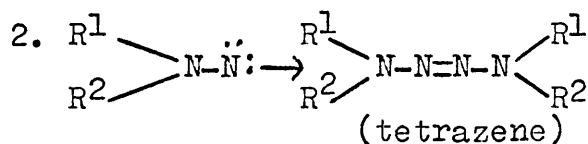
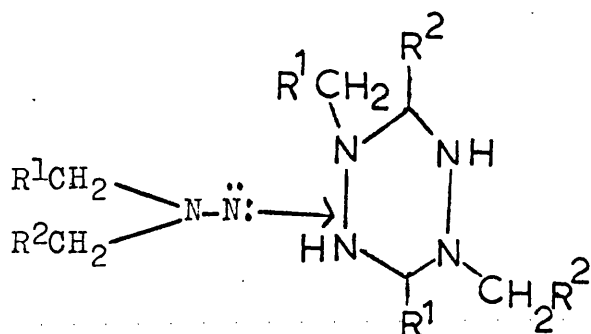
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INTERMOLECULAR(c) "dimerization"

Not common

13

1.



Common

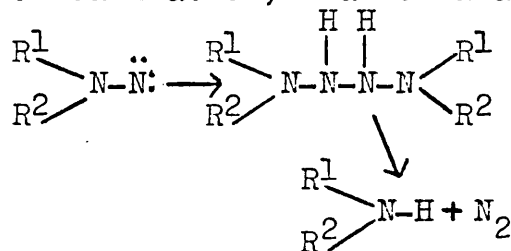
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(d) Reactions with nucleophiles.

1. Deamination, via tetrazane?

Not common until

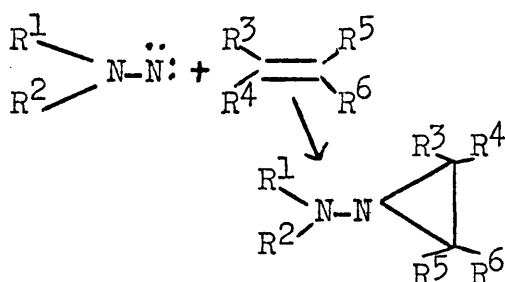
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the present time,
see Discussion,
Section I.

2. Aziridine formation with olefins

Not common (but

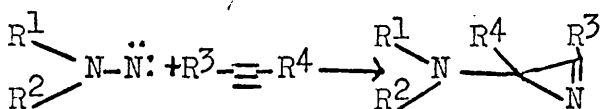
46

see Discussion,
Section I.).

3. Azirine formation with acetylenes

Not common

76



It should be pointed out that the different modes of reactions, outlined in Fig. 5, may occur simultaneously. That the reaction pathway can sometimes be complicated is illustrated below, with reference to reactions particularly relevant to this thesis.

That several reaction products may be obtained depending on the mode of generation of the nitrene has been shown by Lemal *et al.* Decomposition of the arylsulphonamide (1, Fig. 6) in aqueous solution (i.e. a protic solvent) gave tetrahydropyridazine [12a] (56%) (ROUTE A), but in diglyme (i.e. an aprotic solvent) at 175° gave complete fragmentation to ethylene and nitrogen [9n] (ROUTE B). Treatment of pyrrolidine (2) with Angeli's salt also gave the tetrahydropyridazine [12a] (ROUTE C), all three following the intramolecular pathways generalized in Fig. 5. However, oxidation of *N*-amino pyrrolidine (3) with mercuric oxide gave the tetrazene [9m] (ROUTE D) which clearly follows an intermolecular pathway.

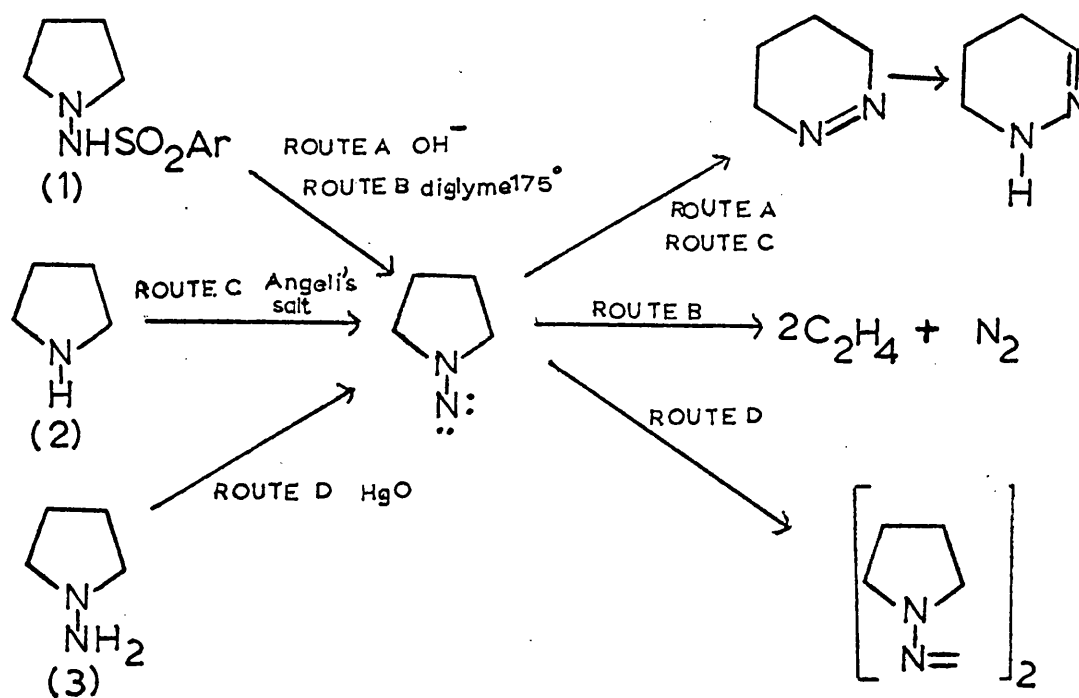


Fig. 6

An excellent example of reaction pathway (a) (Fig. 5) where nitrogen extrusion occurs is given by Carpino [9j]: thus, N-aminodihydroisoindole (1, Fig. 7) was oxidized by mercuric oxide and the arylsulphonate (2) treated with base to give the same dimeric product (4), via (3).

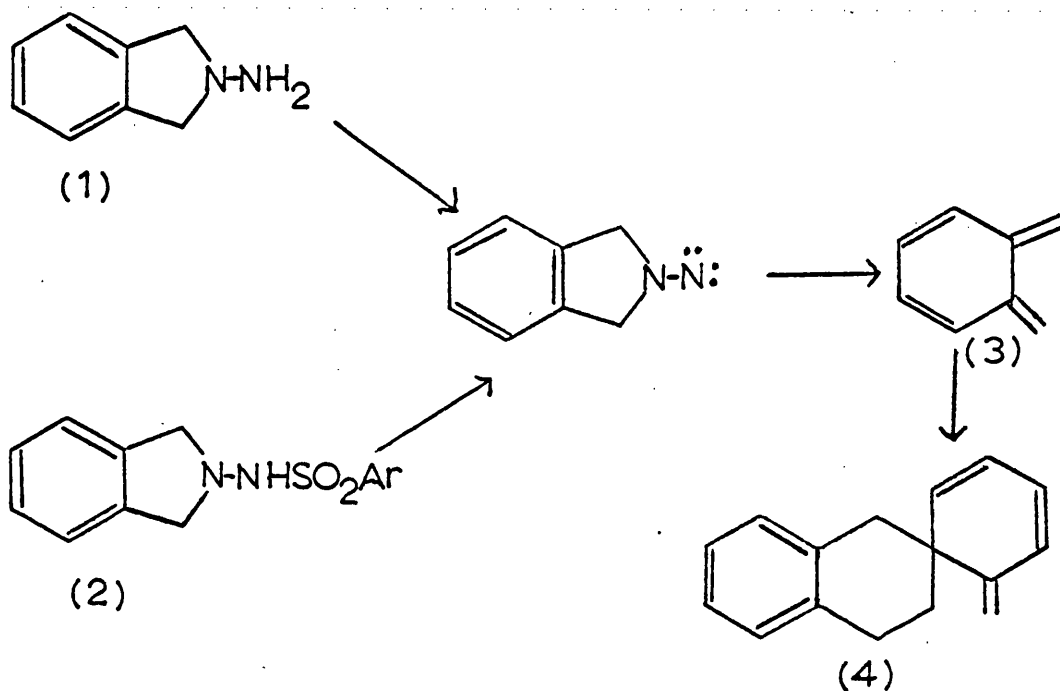


Fig. 7

McOmie et al. [9k], however, obtained different products from the aryl sulphonate. Thus thermal decomposition of the 2-thiaindanedioxid (2, Fig. 8) also gave the same products in the same yields via the postulated intermediate (1), which is more likely to exist as (3, Fig. 7) as postulated by Carpino.

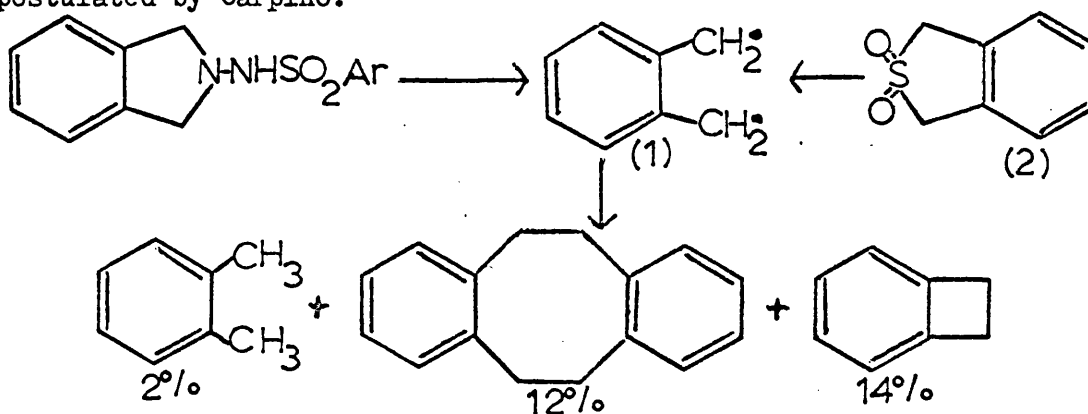


Fig. 8

That the intermediate is most probably (3, Fig. 7) is illustrated by a later stereochemical study by Carpino [91]. Thus cis-2-amino-1,3-dihydro-1,3-diphenylisoindole (1, Fig. 9) on oxidation gave trans-1,2-diphenylbenzocyclobutene (3) via intermediate (2), and trans-2-amino-1,3-dihydro-1,3-diphenylisoindole (4) on oxidation gave cis-1,2-diphenylbenzocyclobutene (6) via intermediate (5). That ring opening of (1) and (4) follows an outward disrotatory mode, followed by collapse of intermediates (2) and (5) by a conrotatory mode of closure to give the observed isomers is in accordance with the principle of conservation of orbital symmetry [14]. The symmetries of the highest filled orbitals at C_1 and C_3 are indicated in intermediates (2) and (5).

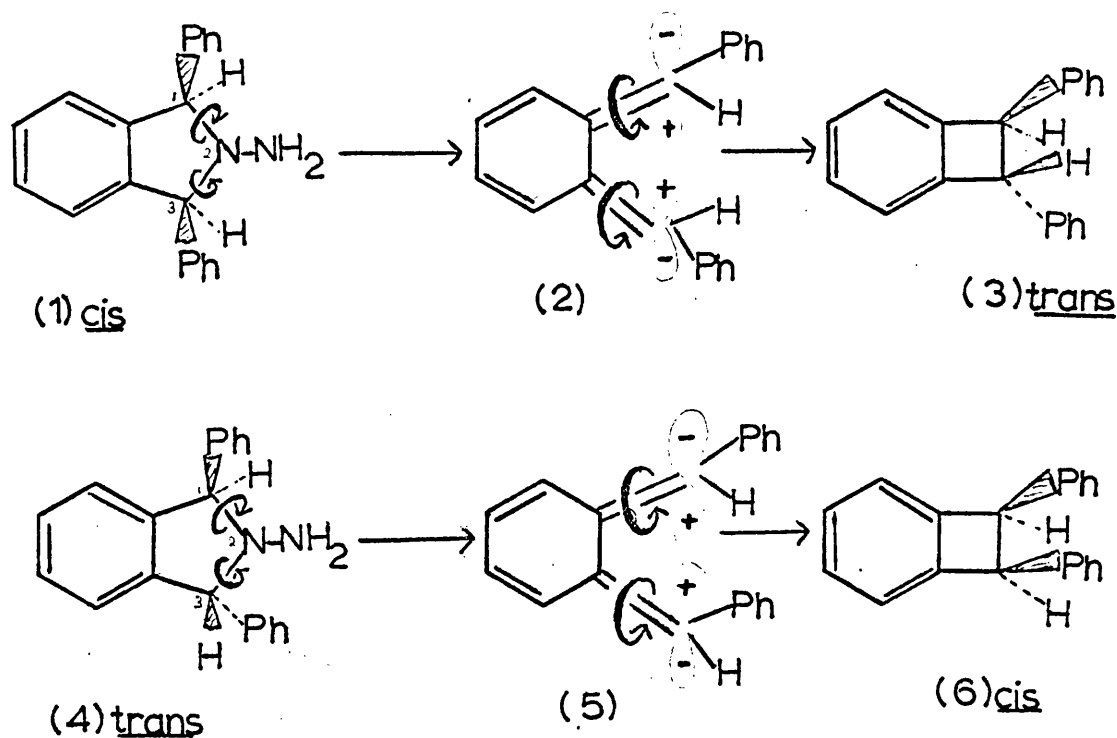


Fig. 9

This mode of reaction is also exemplified by the treatment of 3-pyrrolines with nitrohydroxylamine, generated by treatment of Angeli's salt, $\text{Na}_2\text{N}_2\text{O}_3$, with dil. HCl. Lemal and McGregor [9u] thus converted trans-2,5-dimethyl-3-pyrroline (1, Fig. 10) into cis, trans-2,4-hexadiene (2) and cis-dimethyl-3-pyrroline (3) into trans,trans-2,4-hexadiene (4) which must follow an outward disrotatory mode of ring opening (termed "sigmasymmetric" by Lemal in this case). They constructed the correlation diagram showing that this mode obeys the "non-crossing" rule of orbital symmetry correlation [14].

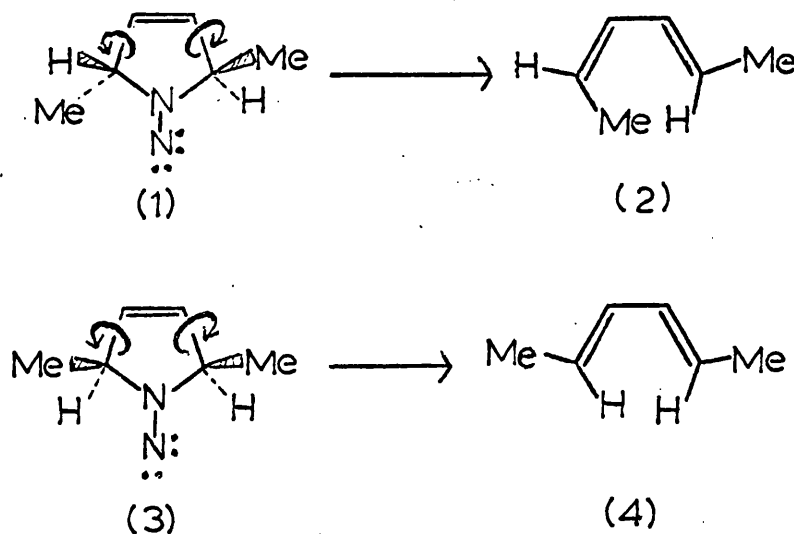
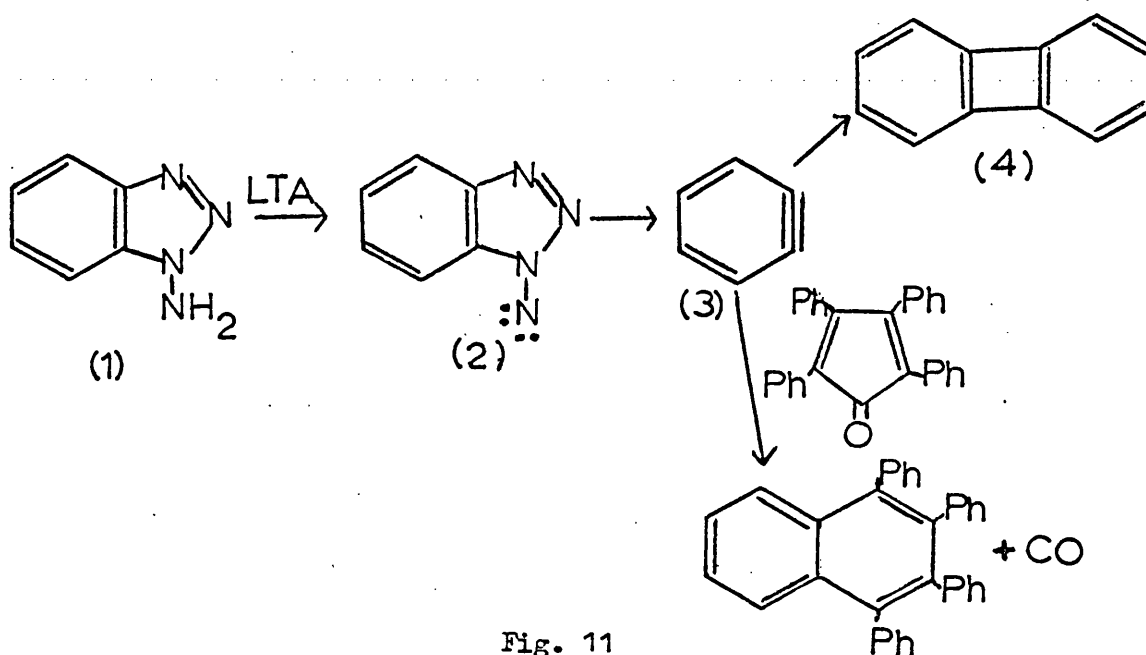


Fig. 10

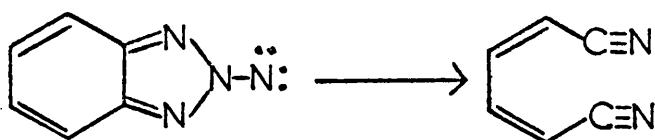
It is interesting that (3, Fig.10) could, in principle give cis,cis-2,4-hexadiene by an inward disrotatory mode of ring opening. However, the observed outward mode is preferred where severe cis,cis methyl-methyl interactions are avoided.

Other examples of the mode (a)(Fig. 5) reaction pathway listed below are due to Rees and his coworkers:

1. Oxidation of 1-aminobenzotriazole (1, Fig. 11) by lead tetraacetate leads to an apparently concerted fragmentation via the nitrene (2) to give benzyne (3) and nitrogen; the benzyne dimerizes in high yield (80%) to biphenylene (4), or can be trapped, e.g. by tetraphenylcyclopentadienone as shown [9q].



2. Oxidation of 2-aminobenzotriazole by lead tetraacetate gave only cis,cis-mucononitrile [9q], via the nitrene fragmentation:



3. Oxidation of 1-amino naphtho[1,8-d,e]triazine (1, Fig. 12) by lead tetraacetate gave 1,8-dehydronaphthalene (3) (a "meta-benzyne") which gave complex tars, but none of the expected dimer, perylene (2).

1,8 dehydronaphthalene was trapped by olefins, acetylenes and aromatic compounds to give the various cycloadducts [9r].

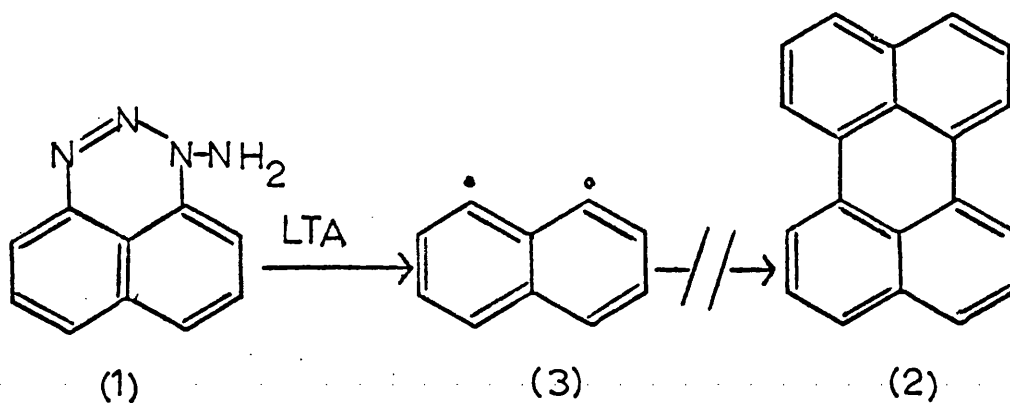


Fig. 12

4. Oxidation of 3-aminobenzotriazinone (1, Fig. 13) by lead tetraacetate gave the indazolone (2) which could be trapped by tetraphenylcyclopentadienone to give the Diels-Alder adduct (3), and also, by further fragmentation, gave benzocyclopropenone (4). This readily reacts with a nucleophile, e.g. methanol, to give, in this case, methyl benzoate [9t]:

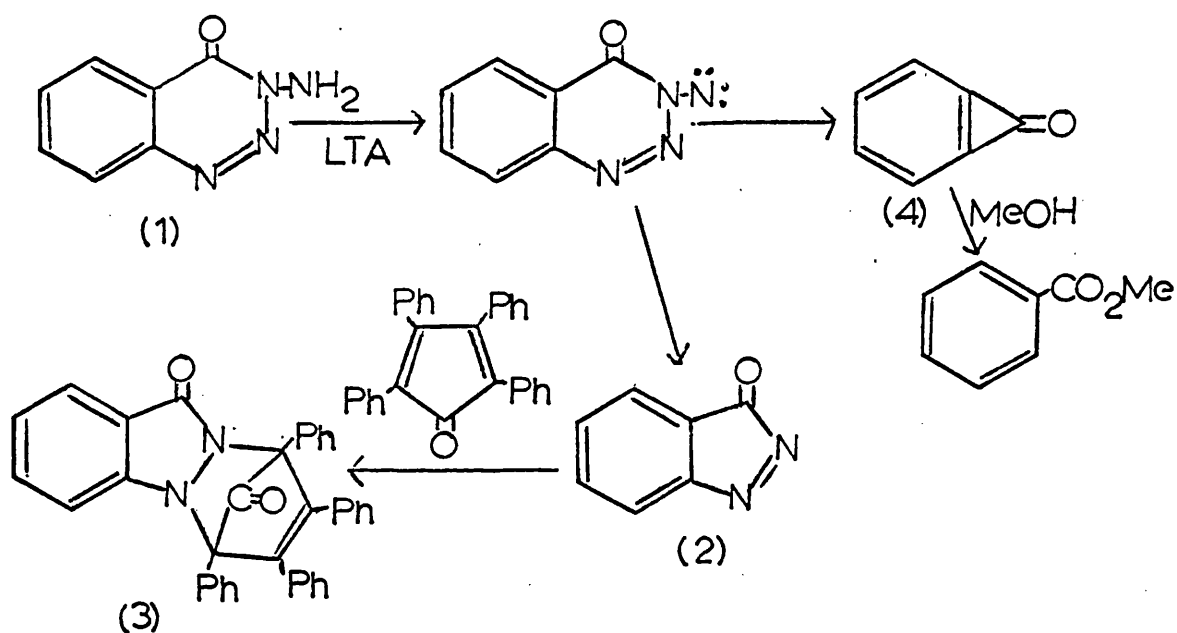


Fig. 13

An additional example of the mode (b) pathway (Fig. 5) is provided by an unusual reaction described by Rees and Yelland [12d]. Oxidation of 1-amino-3,4,5,6-tetraphenylpyrid-2(1H)-one (1, Fig. 14) gave, amongst other products, tetraphenylpyridazine (4) in 60% yield by extrusion of carbon monoxide rather than nitrogen. The authors propose ring expansion by the nitrene to give the 7-membered diazepinone (2), followed by loss of carbon monoxide via the tautomer (3) to give the product (4).

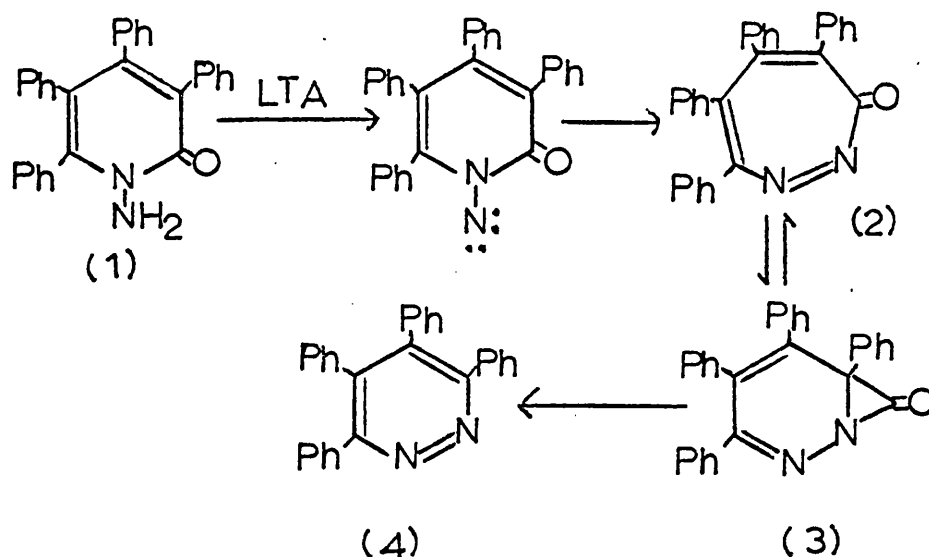
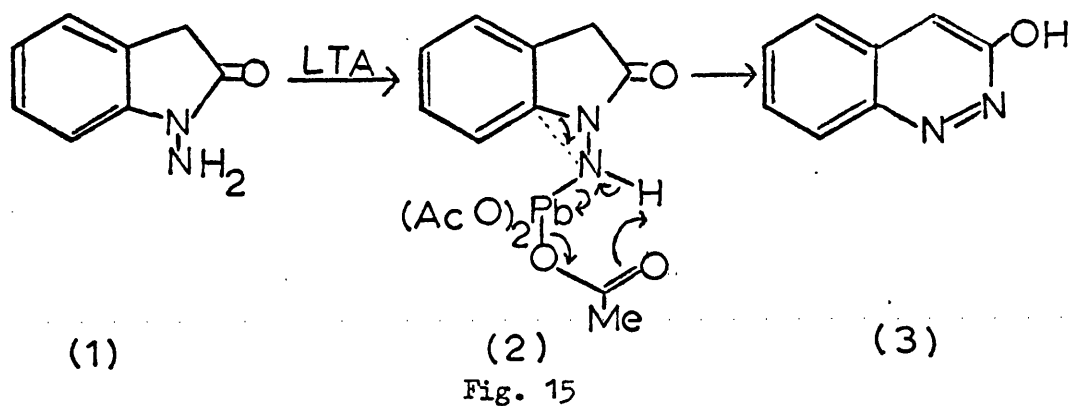


Fig. 14

Another example of this "ring insertion" mode (b) (Fig. 5) has been described by Baumgarten *et al.* [12b]. The oxidation of 1-amino-oxindole (1, Fig. 15) give cinnolin-3-ol (3). He has withdrawn his original mechanism involving a discrete nitrene in favour of the less energetic "nitrenoid" pathway via (2) [12c].



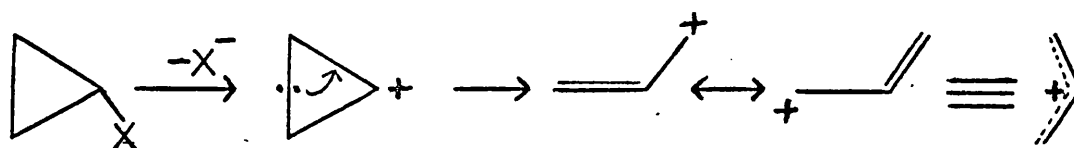
This reaction is considered again later, see Discussion, Section I, page 133

Of the possible intermolecular pathways (Fig. 5) tetrazene formation is the most common. Deamination is considered later in this thesis, see Discussion, Section I. The question of whether tetrazene formation and deamination are formed via the same intermediate, a tetrazane, is considered later, see Discussion, Section I, page 104. The observation that the oxidation of 3-amino benzoxazol -2(3H)-one in the presence of olefins gave aziridines [46] (mode d.2, Fig. 5) prompted investigation into the generality of this reaction, which is a part of the work in this thesis, see Discussion, Section I.

Section II: The Cyclopropyl to Allyl Cation Rearrangement and its
Aza-Analogue

The cyclopropyl to allyl cation rearrangement has been widely studied because of its synthetic potential and theoretical implications. This section will illustrate these factors.

The cyclopropyl cation, formed by heterolytic fission of a substituent on a cyclopropane ring, is transformed into an allyl cation which exists as a delocalized 2π electron system:



An early example of this rearrangement, of particular relevance to this thesis, is that due to Parham *et al.* [16a]. Dichlorocarbene, generated by the action of potassium *t*-butoxide on chloroform, added to indene to give the stable adduct 1,1-dichloro-1a,6a-dihydrocycloprop[*a*]-indene (1, Fig. 16). This adduct rearranged quantitatively on refluxing in aqueous ethanol for 24 hr. via the allyl cation (2), with loss of HCl, to give 2-chloronaphthalene.

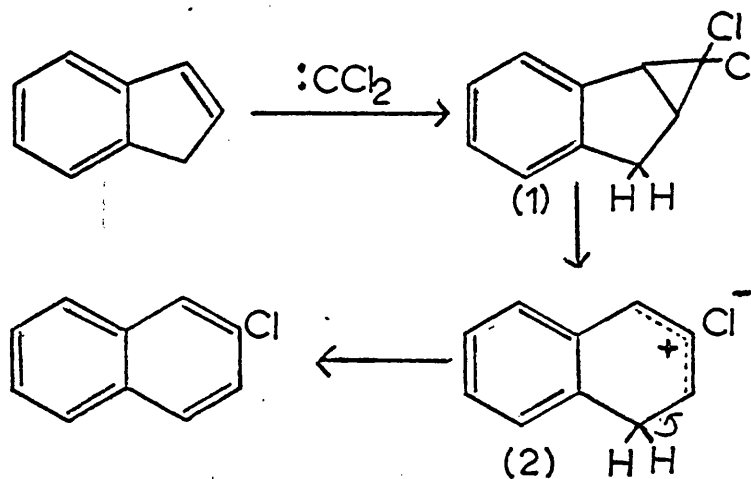


Fig. 16

Certain particularly stable allyl cations have been isolated as their salts. Thus Pettit isolated the reasonably stable crystalline perchlorate salt (2, Fig. 17) on treatment of 3'-chloro-1,2-cyclopropanoacenaphthene (1) with silver perchlorate, through a cyclopropyl to allyl cation rearrangement:

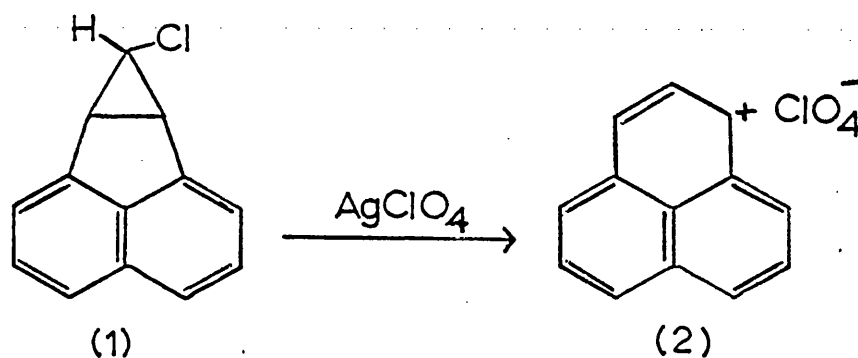
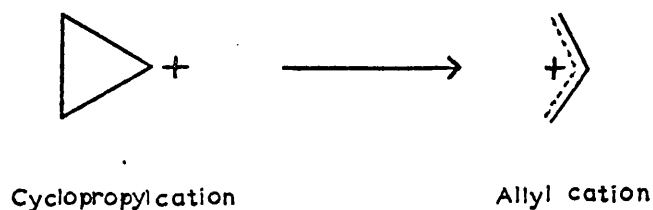
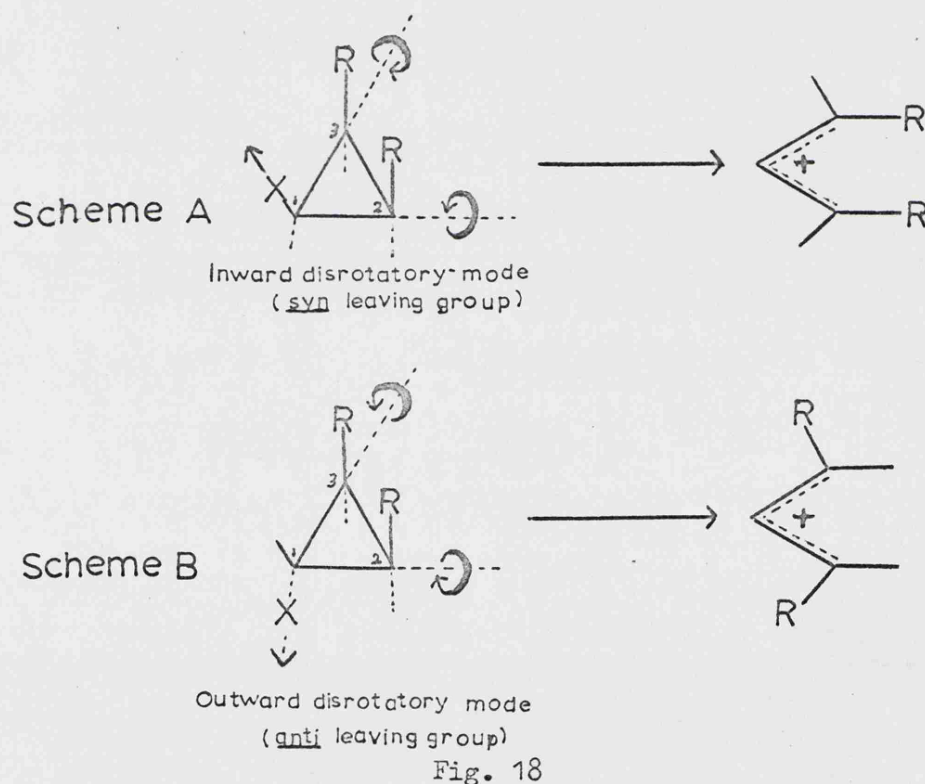


Fig. 17

The stereochemical course of this transformation proceeds in accordance with the principle of conservation of orbital symmetry, as described by Woodward and Hoffmann[14]. This ground state 2π electron electrocyclic reaction follows a disrotatory mode of ring opening as there are $(4n + 2)\pi$ electrons, where $n = 0$, concerned in the transformation:

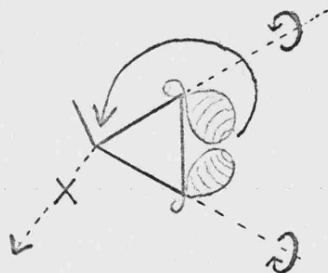


Consider the two possible disrotatory modes with 2,3 disubstituents, R, and leaving group, X. Assume that the leaving of group X is concerted with the 2,3 C - C bond breaking. Extended Hückel calculations show that if the leaving group X is syn to the cis substituents, R, then the groups R rotate towards one another. (designated "inward disrotatory mode", scheme A, Fig. 18). However, if X is anti then the groups R will rotate apart (designated "outward disrotatory mode", scheme B, Fig. 18).



It is important to note that, as shown by De Puy [22], a discrete cyclopropyl cation is not formed in the solvolysis of cyclopropyl tosylates, but that leaving of group X is concerted with the 2,3 C - C bond breaking, as assumed by Woodward and Hoffmann in their calculations. Thus the electron density of the 2,3 bond, which originally was more or less in the plane of the cyclopropane ring,

shifts above the plane of the ring. It is then available for
 rearside displacement of the leaving group X in a normal S_N2 type of
 mechanism:

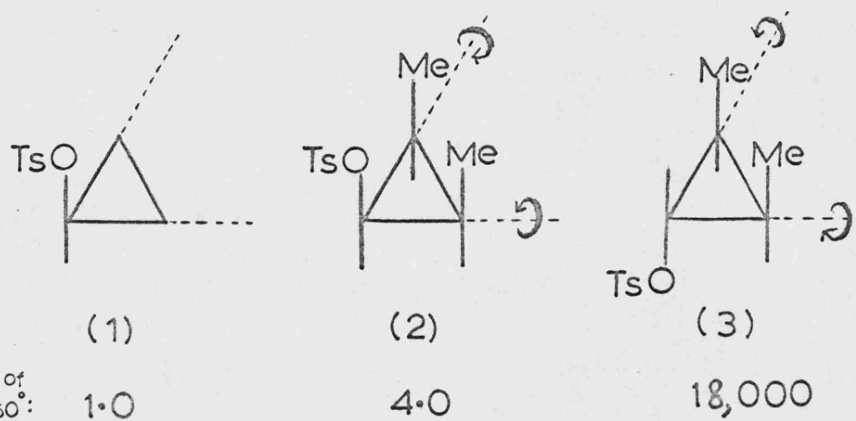


This different rationale leads to the same result as predicted by
 Woodward and Hoffmann.

Now consider the effect of the 2,3 substituent R:

(1) If the groups R are bulky

Here, the inward disrotatory mode (scheme A, Fig. 18) will
 be unfavourable due to increase of steric hindrance, so the outward
 disrotatory mode (scheme B) will be favoured, hence solvolysis of this
 isomer will be faster. This is illustrated by the solvolysis data
 of the cyclopropyl tosylates due to Schleyer *et al.* [23,24]. Thus
 the solvolysis of the syn isomer (2, Fig. 19) is much slower than its
anti isomer (3) as the former will increase the cis Me - Me
 interactions by the necessary inward disrotatory mode; the latter
 can reduce these interactions by the necessary outward disrotatory mode.



(2) If the 2 and 3 substituents are part of a ring

Here, in the bicyclic cyclopropanes, the endo isomer should solvolyse much faster than the exo isomer, because in the latter disrotatory outward rotation would introduce severe strain in the ring system. Schleyer et al. [24] illustrated this by the solvolysis data in Fig. 20:

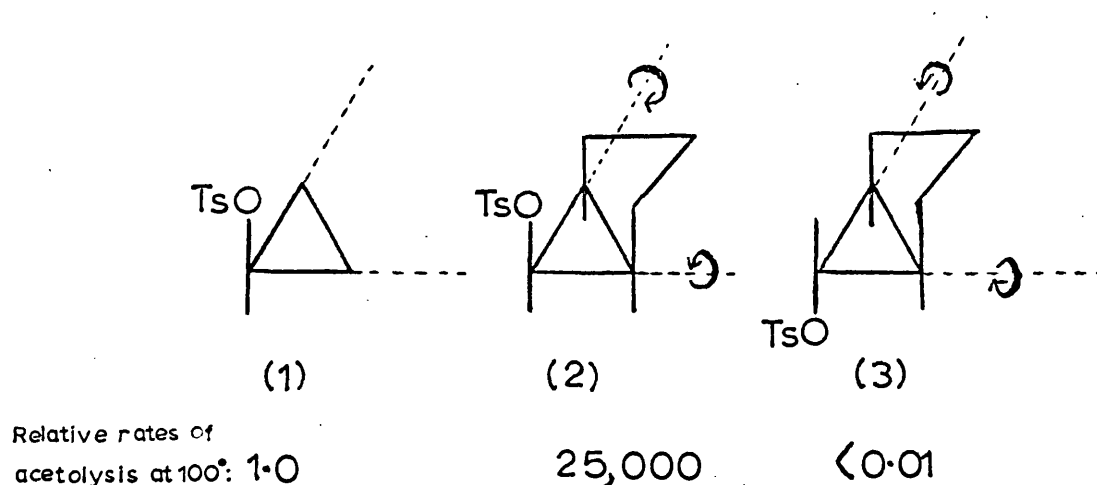


Fig. 20

Thus the endo isomer (2, Fig. 20) solvolyse at least six orders of magnitude faster than the exo isomer (3).

Schleyer et al. [25] have studied the PMR spectra of the allyl cations derived from chlorocyclopropanes similar to the tosylates described above, at -100° . The allyl cations had their stereochemistry assigned by their coupling constants (trans coupling $>$ cis coupling) and this was found to be in accordance with the results of the

solvolysis data, thus providing a direct verification of the stereochemical course of the ring opening.

A further example of such a fused bicyclic cyclopropyl to allyl cation rearrangement is due to Baird and Reese [18].

Thermolysis of the endo and exo 6-chlorobicyclo[3.1.0.]hexanes (1 and 2, Fig. 21) showed that the endo isomer underwent quantitative rearrangement to 3-chlorocyclohexene in 4 hr at 120°, whereas the exo isomer remained unchanged after 4 hr at 250°.

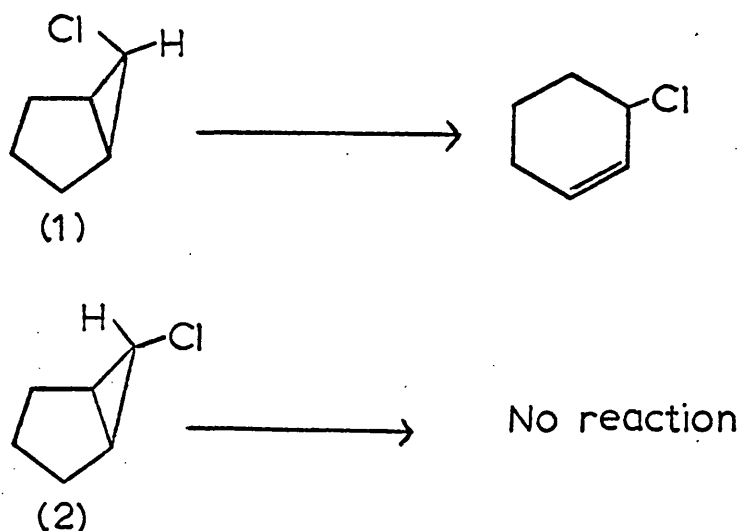


Fig. 21

Ghosez et al. also exemplified this by the scheme outlined in Fig. 22 [19], where (1) is converted into (3) by C - F bond cleavage rather than the normally more favourable C - Cl cleavage, due to fluorine being syn in this case. Conversion of (2) to (4) was spontaneous due to the very favourable syn C - Cl cleavage.

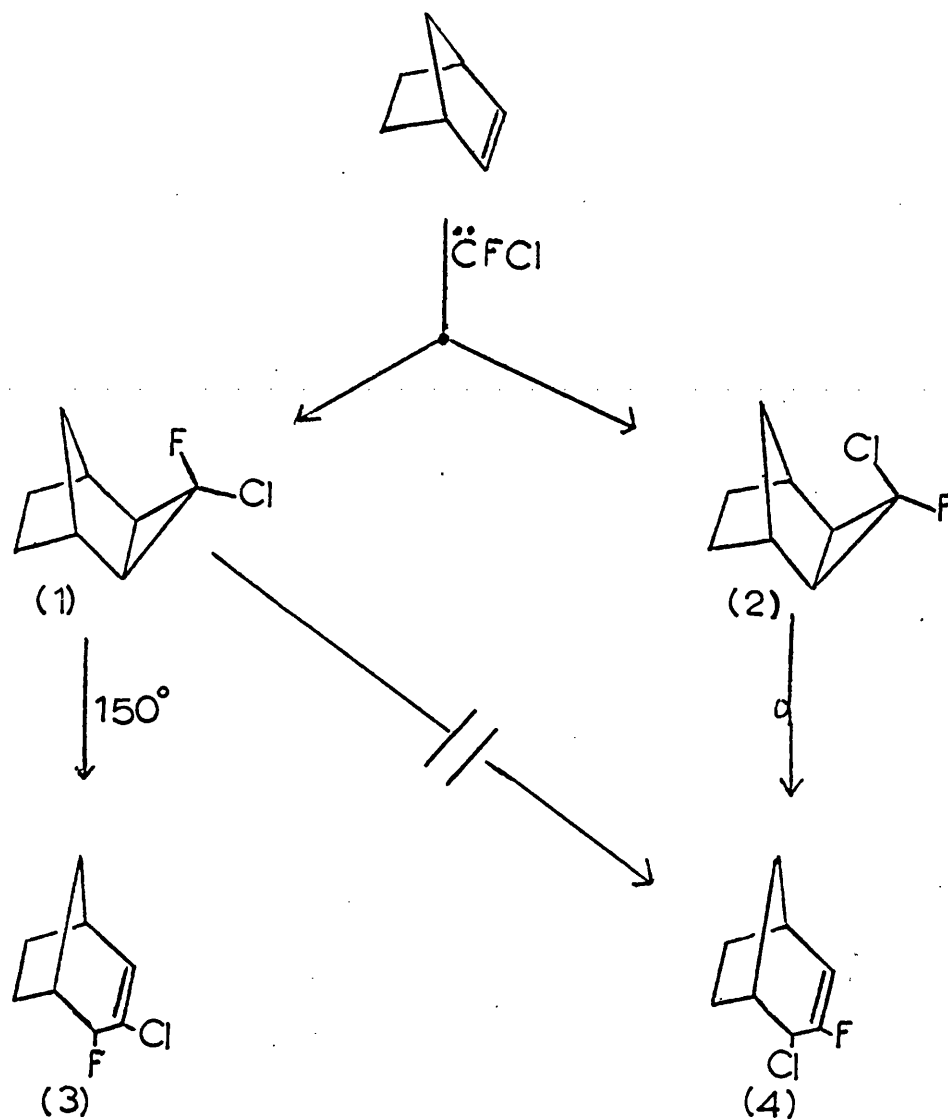


Fig. 22

Other examples of this rearrangement are known [15, 16, 20, 21].

In fact, Parham originally designated the sequence outlined in Fig. 23 [16b], but from the nature of the products, as pointed out by De Puy [22], the structural assignments of the isomers of (1) should be reversed.

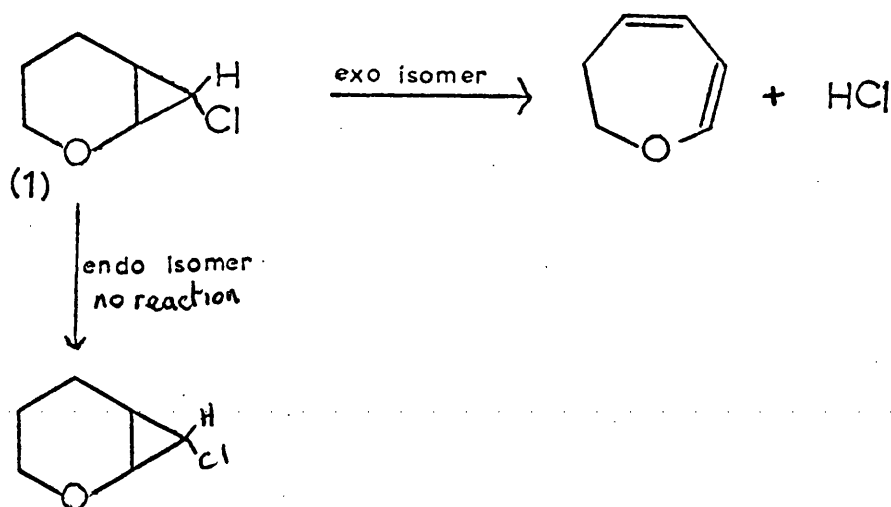


Fig. 23

Gassman has extended these ideas to the analogous rearrangement of aziridines [1]. Utilizing the relative stereochemical stability of *N*-chloroaziridines, as shown by Brois [26], Gassman studied the solvolysis of derivatives of (1, Fig. 24) where R = Me or H. Concerted ionization and ring cleavage of (1) would give, by the necessary disrotatory modes, the allyl cation aza-analogue (2), via a nitrenium ion, which would give (3); this would then hydrolyse, under the reaction conditions to the corresponding carbonyl compounds and ammonium chloride, which were the observed products.

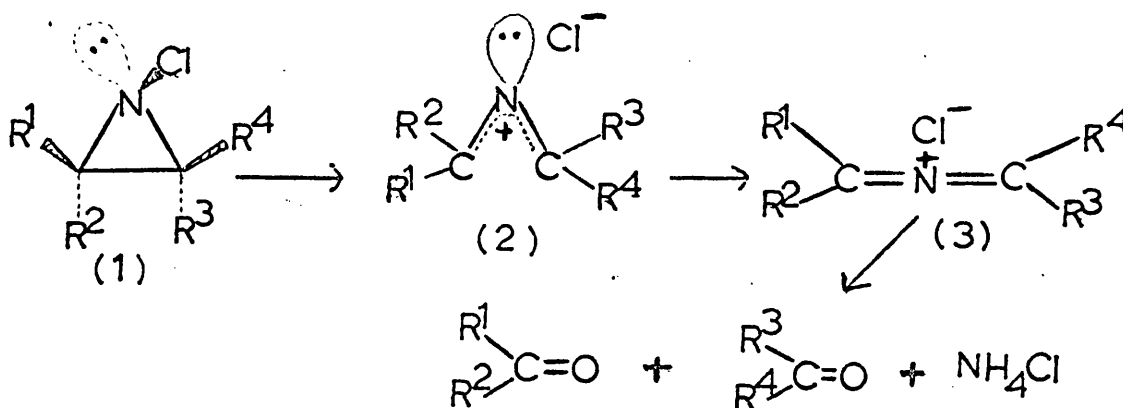
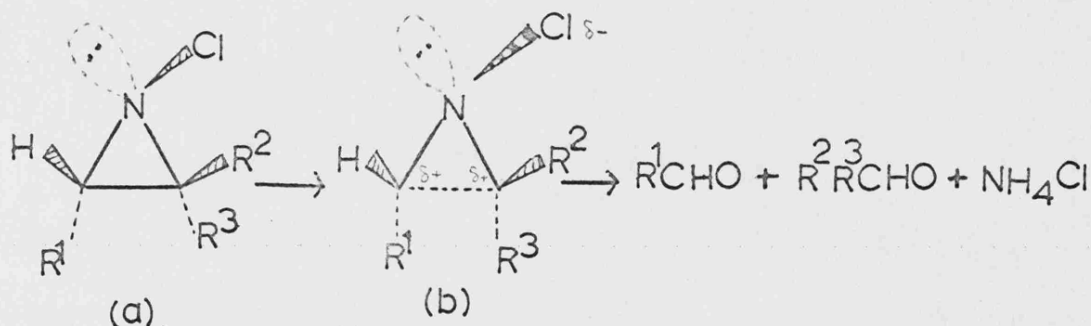


Fig. 24

Of the many N-chloroaziridines studied by Gassman those in Fig. 25 are of special interest:



				Relative rates of solvolysis:
(1)	R ¹ = H,	R ² = H,	R ³ = H;	1.0
(2)	R ¹ = Me,	R ² = Me,	R ³ = H;	1,490
(3)	R ¹ = Me,	R ² = H,	R ³ = Me;	155,000

Fig. 25

Thus the solvolysis of (2) is much faster than (1) in the process of the conversion of a \rightarrow b as the methyl group in (2b) will enhance the stability of both incipient carbonium ion centres. This carbonium ion stabilising effect is the same in (3), but the rate is tremendously greater. This can be clearly rationalized by the fact that, in analogy to the solvolysis of the cyclopropyl tosylates (Fig. 19), the required disrotatory mode will relieve the cis Me,Me interactions in (3), but in (2) these interactions do not effectively alter. That a polar transition state (2, Fig. 24) is involved in this reaction was

demonstrated by the fact that conversion (2) (Fig. 25) occurred 76 times faster in water than in the less polar solvent methanol.

In conclusion, the cyclopropyl to allyl cation rearrangement and its aza-analogue proceed by a concerted leaving group loss and disrotatory C - C bond cleavage.

$$\text{or } \Delta G^\ddagger = 4.57 T (10.32 + \log T/Kr) \dots\dots\dots(1)$$

where Kr = rate constant of inversion process, T = absolute temperature, K_B = Boltzmann's constant, h = Planck's constant, R = Gas constant, the free energy of activation at any temperature may be calculated.

Separation of invertomers is possible only if the mean lifetime is of the order of a few hours. This corresponds to a value for Kr of less than 10^{-4} sec^{-1} , or ΔG^\ddagger values greater than 23 Kcal.mole $^{-1}$ (at 25 $^\circ$).

Now when the substituents a,b,c (Fig. 26) are joined in a ring system, the rigidity of the resulting molecule could "lock" the configuration about the nitrogen atom. Such a system is Tröger's base, which exists as two stable enantiomers (Fig. 27). These were resolved by Prelog and Wieland in 1944 by passage through an activated d-lactose hydrate column. This was the first demonstration of optical activity due to an asymmetric nitrogen atom. The base racemizes in acid solution at 20 $^\circ$ in a short time, probably due to the instability of the -N-CH $_2$ -N-group, but it does not lose optical activity when sublimed in high vacuum [29,39].



Fig. 27

Kincaid and Henriques predicted as long ago as 1940 that N-substituted aziridines would offer a good chance of resolution, they

gave an approximate calculation to give a value of 25 Kcal.mole⁻¹ for ΔG^\ddagger of 1-methylaziridine [27]. This value was too high; in fact it is 19 Kcal.mole⁻¹ [30].

An explanation for this high value is that in the planar transition state (2, Fig. 26) the bond angle tends to 120° during inversion. When the nitrogen is incorporated in an aziridine ring, however, this necessary spreading is hindered and the activation energy is increased. Also, the S-character of the lone pair on nitrogen is much higher in the three membered ring than in acyclic amines. That is, the ground state is stabilized with respect to the inversion transition state. Thus the inversion barrier is much higher in azetidines (3, Fig. 28) and remarkably so in aziridines (4) than in the unstrained pyrrolidines (2) and ammonia (1) [28]. (ΔG^\ddagger values given in Kcal.mole⁻¹ under each formula).

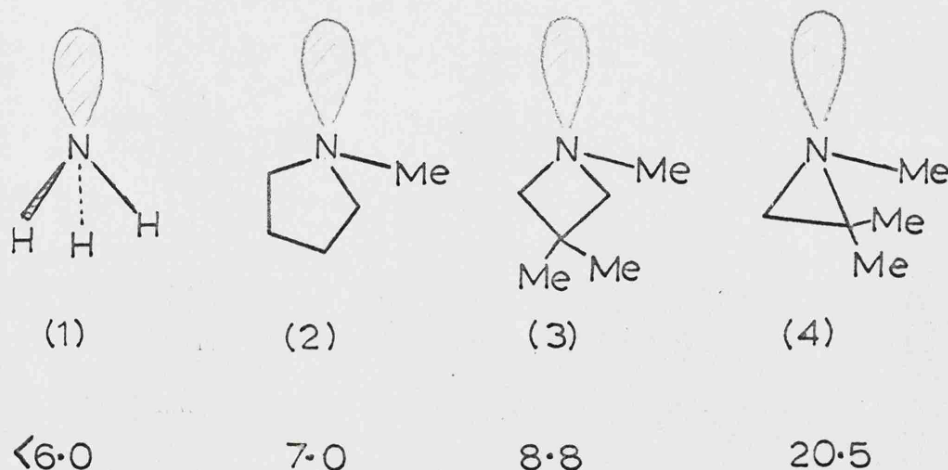


Fig. 28

Due to the high value of ΔG^\ddagger in aziridines, they are inverting only slowly at room temperature. This slow inversion is conveniently studied by using NMR. The most favourable conditions for this being when:

(1) the two invertomers are of approximately equal energy, so that signals due to each invertomer can be seen in the spectrum.

(2) when the inversion is "slow" on the NMR time scale, i.e. when the inversion rate constant $K_r \ll \frac{\pi \Delta\nu}{\sqrt{2}}$ where $\Delta\nu$ = signal splitting, without exchange.

The rate of inversion at coalescence temperature, T_c , is given by

$$K_r = K_c = \frac{\pi \Delta\nu}{\sqrt{2}} \dots\dots\dots(2)$$

where K_c = rate of inversion at T_c , $\Delta\nu$ = maximum signal splitting, without exchange. By combination of equations (1) and (2) the value of ΔG^\ddagger may be calculated.

ΔG^\ddagger values contain the temperature dependent term $T\Delta S^\ddagger$ (where ΔS^\ddagger is the entropy of activation). Therefore, E_a , the Arrhenius activation energy should be used when comparing different compounds. However, due to the inaccuracy of E_a values obtained these comparisons are often of little use [28]. Roberts, in a new approach, has suggested that line shape analysis would give more accurate values of E_a . This, apparently, is also subject to errors [31,32].

The temperature dependence of inversion in N-alkyl and N-aryl aziridines has been extensively studied by the NMR technique. Bottini and Roberts found that in N-ethyl aziridines (Fig. 29) the ring methylene protons appear as two triplets separated by 27 cps at 40 m.c at room temperature. They interpreted the two signals as being due to the protons being trans (designated H_A) and cis (designated H_B) to the N-ethyl group. At $120^\circ - 130^\circ$ the peaks coalesce due to rapid inversion, the protons then becoming magnetically equivalent [33].

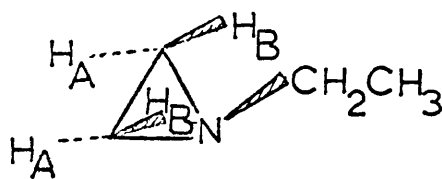


Fig. 29

Later, Bottini and Roberts compared the coalescence temperatures of N-ethyl aziridine (1, Fig. 30), N-ethyl-2-methylene aziridine (2) and N-phenylaziridine (3) [34].

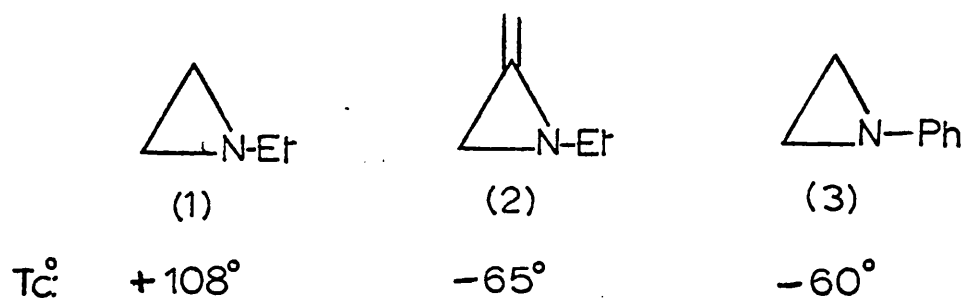
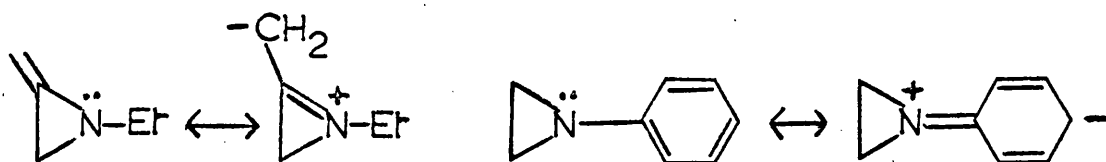
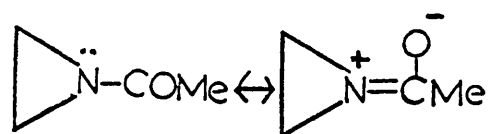


Fig. 30

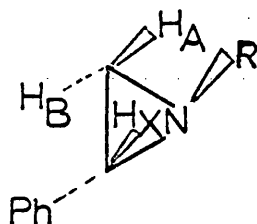
The striking lowering of Tc in (2) and (3) was attributed to resonance stabilization as shown below, which delocalizes the nitrogen lone pair, hence dramatically lowering the energy of the transition state.



Another example of this delocalization is found in N-acetylaziridine, where ΔG^\ddagger is less than 6 Kcal.mole⁻¹ [35].



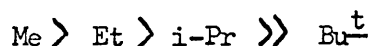
A detailed room temperature PMR study by Brois of the N-alkyl aziridine series:



where $R = \text{Me, Et, } i\text{-Pr}$ and Bu^t led him to the following conclusions [37, 38]:

(1) ring protons cis to the alkyl group R are shielded (i.e. occur at higher field). Thus H_A is at higher field than H_B , except when $R = \text{Bu}^t$ where H_B is at higher field than H_A .

(2) This shielding effect is in the order



contrary to what might be expected from the anisotropic shielding of N-alkyl C - C bonds. The deshielding trend in the series may be explained by the fact that the van der Waals forces (dispersive forces) between ring and N-alkyl hydrogen atoms cause a distortion of the electron clouds about the ring protons, hence causing deshielding of the latter. This is especially striking where $R = \text{Bu}^t$.

(3) The rate of inversion where $R = \text{Bu}^t$ is greatly accelerated as the severe steric interactions stabilize the transition state with respect to the more crowded ground state.

The observation that ΔG^\ddagger values in N-alkylaziridines are well below $23 \text{ Kcal.mole}^{-1}$ led Bottini and Roberts to conclude that "substituted aziridines with molecular asymmetry due to trivalent

nitrogen are likely only to be resolvable into reasonably stable optical antipodes at temperatures below -50° [34].

However, in 1968 Brois isolated a stable nitrogen pyramid from N-halogenated aziridines [26]. Here, 2-methyl aziridine was N-chlorinated by N-chlorosuccinimide in refluxing ether; two components were isolated by g.l.c. in the ratio 2 : 1, being the trans and cis isomers respectively of N-chloro-2-methylaziridine (Fig. 31).

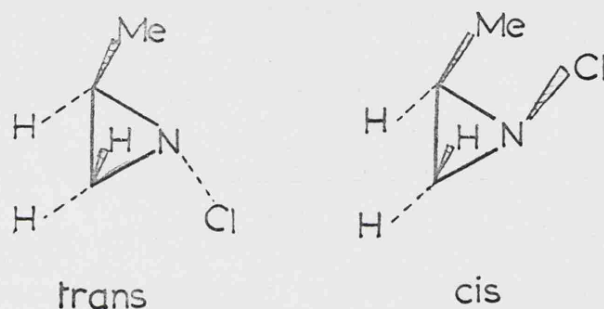


Fig. 31

These two particular compounds were thermally labile, but what is really significant is that the spectra of similar N-chloroaziridines did not show coalescence even at 120° . Other workers, in a study of the rates of epimerization of the cis to trans N-chloro-2-methylaziridines, give an estimated value of ΔG^{\ddagger} as $20 \text{ Kcal.mole}^{-1}$ for the inversion process [40].

Felix and Eschenmoser, at the same time, prepared the stable invertomers, cis and trans N-chloro-7-azabicyclo[4,1,0]heptane (Fig. 32)[41]

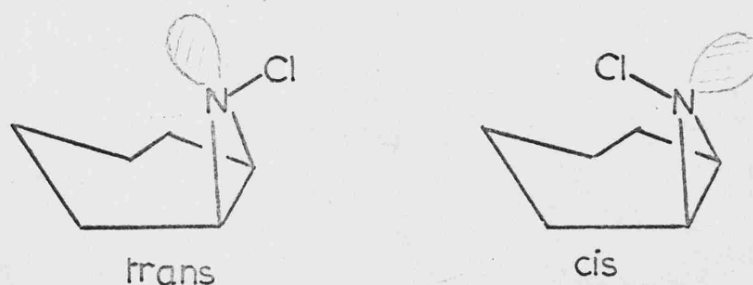


Fig. 32

Here, the cis isomer isomerizes to the trans completely in one day; this corresponds to the rate of inversion of approximately $4.3 \times 10^{-5} \text{ sec.}^{-1}$

Lehn and Wagner have calculated ΔG^\ddagger values from Tc values for various N-halogenated aziridines by the NMR technique, finding that for 2,2-dimethyl-N-chloroaziridine, Tc $> 180^\circ$ ($\Delta G^\ddagger > 23.5 \text{ Kcal.mole}^{-1}$) and 2,2-dimethyl-N-bromoaziridine, Tc $> 140^\circ$ ($\Delta G^\ddagger > 21.3 \text{ Kcal.mole}^{-1}$) [42].

Hence it must be concluded that in N-halogenated aziridines the barrier to inversion is considerably higher than N-alkylaziridines. This is probably due to two factors:

(1) as the electronegativity of the N-substituent increases so also does the S-character of the lone pair on the nitrogen [43], the effect being that the ground state-transition state energy gap is widened (since in the planar transition state the lone pair must have predominantly p-character).

(2) the transition state is destabilized with respect to the ground state by the increase of repulsion of the nitrogen lone pair and the halogen lone pairs.

It is not yet possible to say which effect predominates.

Thus any highly electronegative N-substituent in aziridines should retard the inversion rate. That this is so was shown by Brois where the N-substituent is oxygen [44]. The PMR of 1-methoxy-2,2,3,3-tetramethylaziridine (Fig. 33) at room temperature showed non-equivalence of the cis and trans geminal methyl groups. The methoxy group appeared as a singlet as the O - Me protons are magnetically equivalent in both invertomers. The peaks did not coalesce in xylene even at 130° , corresponding to $\Delta G^\ddagger > 22 \text{ Kcal.mole}^{-1}$.

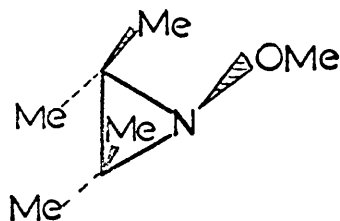


Fig. 33

When the N-substituent is nitrogen, Brois studied the PMR of N-aminoaziridine [45], showing the non-equivalence of ring protons at room temperature; coalescence did not occur even at approximately 150° (ΔG^\ddagger) 22 Kcal.mole⁻¹). Atkinson studied the temperature dependence of nitrogen inversion in the aziridines (1 and 2, Fig. 34) [46]:

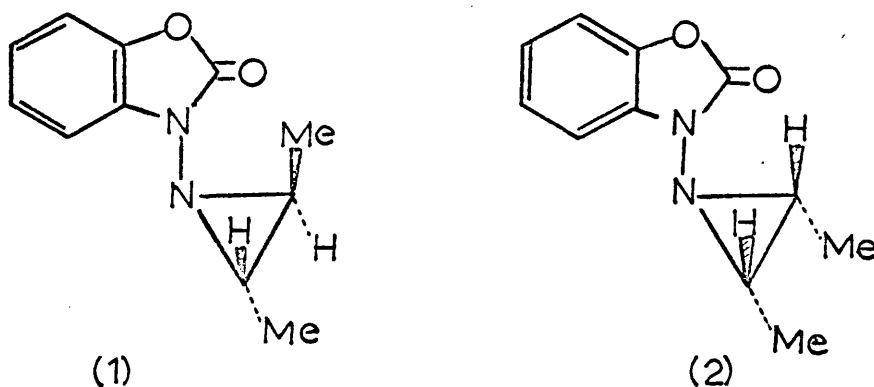


Fig. 34

He found that T_c for (1) was $\approx 160^\circ$, but the ring methyl signals in (2) did not coalesce even at 180° , due to a larger free energy difference between the two invertomers of (2) compared to that of (1).

Low electronegativity second row N-heterosubstituents, however, show a more rapid rate of inversion, in many cases T_c being well below room temperature. This has been shown by Anet and Cram in the case of aziridine N-sulphur substituents [36], and by others for aziridine N-silicon and N-phosphorus substituents [47]. This is considered to

be mainly due to stabilization of the transition state by delocalization of the nitrogen lone pair in $d\pi - p\pi$ overlap with the second row element [36, 48]. Although another contribution, in a special case, includes the $p\pi - p\pi$ resonance stabilization, e.g. (Fig. 35):

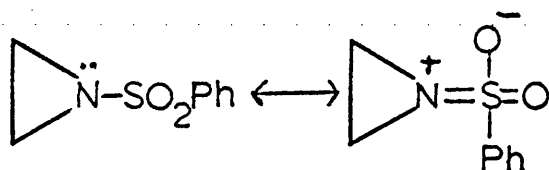


Fig. 35

Also steric stabilization of the transition state with respect to the ground state will increase the inversion rate, although this contribution is probably small [28, 36].

When the highly electronegative first row hetero-substituent is incorporated into the three membered ring itself, in oxaziridines [49, 50] and diaziridines [51, 52, 53] the invertomers are stable compounds at room temperature.

Thus Montanari et al. [50] prepared the optically active oxaziridine (Fig. 36) by treatment of the benzophenone-N-methylimine with a series of optically active peroxy-acids. In each case, the oxaziridine was optically active and its chirality was related to the chirality of the peroxy-acid used. No detectable optical activity was lost on vacuum distillation. The optical activity of the molecule can only be due to the asymmetry about the stable nitrogen pyramid.

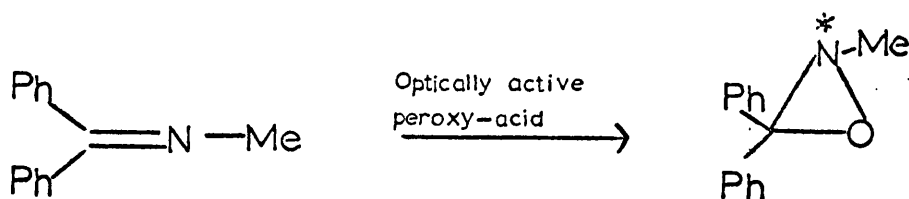


Fig. 36

Having the first row highly electronegative N-hetero substituent in the ring will substantially retard inversion even in five and six membered rings [54 - 58]. A good example of this is the case reported by Eschenmoser and Müller [58], where the two crystalline diastereoisomeric N-methoxyl-3,3-dimethoxycarbonyl-5-cyano-1,2-oxazolidines (1 and 2, Fig. 37) have been isolated; here, the nitrogen is bonded to two oxygen atoms. The Arrhenius activation energy, E_a , for the epimerization was found to be $29.2 \text{ Kcals.mole}^{-1}$, which is extremely high.

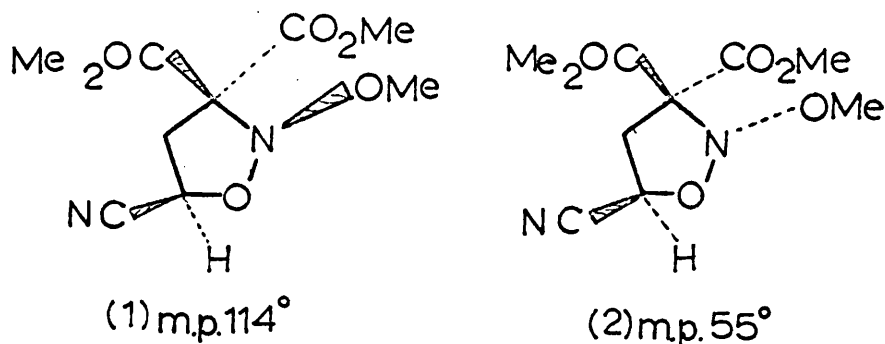


Fig. 37

An example of hindered nitrogen inversion due purely to steric hindrance has been observed with the dihydroquinoline (Fig. 38) [59].

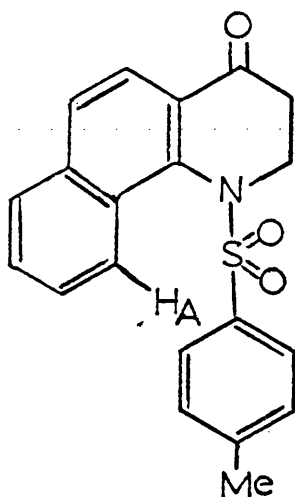


Fig. 38

Here, steric hindrance between aromatic hydrogen H_A and the large tosyl group is maximum in the planar transition state for the inversion process.

In conclusion, it is clear that appreciable stability of the nitrogen pyramid is achieved by combination of ring strain, particularly in three membered rings, and by the presence of a N-hetero-substituent, when the hetero atom is either N, O or Cl.

INSTRUMENTATION AND EXPERIMENTAL TECHNIQUES

1. Infrared (i.r.) spectra were recorded in the range $4000-625\text{ cm}^{-1}$ on a Perkin-Elmer 237 grating spectrophotometer. Solid samples were run as nujol mulls; liquid samples were run as thin films, using polystyrene as reference.
2. Proton magnetic resonance (p.m.r.) spectra were recorded on a Varian A60 or a Varian T60 instrument. Carbon tetrachloride, deuteriochloroform, hexadeuteroacetone and hexadeuterodimethylsulfoxide were used as solvents with tetramethylsilane as internal reference.
3. Ultraviolet (u.v.) spectra were recorded in the range 200-450 nm on a Unicam SP800 spectrophotometer. Absolute ethanol was used as solvent in 1 cm cells.
4. Mass spectra were recorded on an Associated Electrical Industries M.S.9 spectrometer.
5. Melting point (m.p.) determinations were carried out on a Kofler Micro Heating Stage using corrected thermometers.
6. Thin layer chromatography (t.l.c.) was used extensively as a qualitative guide to the composition of reaction mixtures and as a means of assessing the purity of compounds. Samples were run in suitable solvent mixtures on glass plates coated with a 250μ layer of Kieselgel G (E. Merck), or aluminium oxide G (Type E, pH 7.5) (E. Merck). The plates were observed under ultraviolet light or developed by spraying with iodine.
7. Preparative thin layer chromatography (Preparative t.l.c.) was used to separate small amounts of reaction mixtures by a similar technique to that of t.l.c.; 20 x 20 and 100 x 20 cm glass plates coated with a 1 mm layer of Kieselgel PF 254 with a fluorescent indicator were used.

8. Column chromatography was carried out using silica gel MFC (B.D.H.) basic alumina (Spence type H), and deactivated alumina (prepared by deactivation of basic alumina with 6% by weight of water in a ball-mill for 12 hr). The mixture to be chromatographed was dissolved in the minimum volume of a suitable solvent and dropped carefully onto the top of the column. Alumina columns were packed under petrol and silica gel columns were either packed by this method or packed dry, and then eluted with solvent mixtures of gradually increasing polarity.
9. Solvents were purified as follows:

Benzene and other aromatic solvents, methylene chloride, methanol, ethanol, acetonitrile, and ether were purified by refluxing over and distilling from calcium hydride. Aromatic solvents, methylene chloride, methanol, ethanol and acetonitrile were stored over molecular sieves (type 4A) and ether over sodium wire.

Dimethyl sulfoxide (DMSO) and dimethyl formamide (DMF) were dried by storage over molecular sieves (type 4A).
10. Petrol used for chromatography and for recrystallisations with ether was light petroleum, b.p. 40-60°. Petrol used for recrystallisations with benzene, chloroform or ethyl acetate was petroleum b.p. 60-80°, unless stated otherwise.
11. Lead tetraacetate (LTA) (B.D.H. or Hopkin and Williams) was freed from acetic acid by filtration and stored over concentrated sulfuric acid.
12. Hydroxylamine-O-sulfonic acid (HOS) was prepared by the method of Goesl and Meuwsen [60] and stored over concentrated sulfuric acid.
13. Chloroamine was prepared in ether solution by a modification [61] of the method of Theilacker and Wegner [62] and gave a chloramine concentration of about 0.17 M.
14. Where possible, compounds were characterised by comparison of their melting points (m.p.) and mixed melting points (m.m.p.) and i.r. spectra

with those of authentic specimens. Literature m.p. and b.p. values are given with references, except from well authenticated compounds for which the values quoted are those given in the Heilbron Dictionary of Organic Compounds (4th Edition)[107].

15. Organic solvents, used to extract aqueous solutions, were dried over sodium sulphate and evaporated to dryness in a rotary evaporator under reduced pressure.

EXPERIMENTAL1. Preparation of N-Amino Compounds(a) 3-Amino-2-methyl-4-quinazolane

This was prepared by a modification of the method of Klossa [65]:

Methylantranilate (18.7g) and acetic anhydride (15.0g) were heated together for 15 min at 60°. The solution was cooled, poured onto ice-water mixture, stirred, and the precipitate was filtered off, washed with cold water and dried. The N-acetyl ester (22.5g), m.p. 98-99°, thus obtained, was heated under reflux for 35 hr with hydrazine hydrate (10.0 ml) in ethanol (100 ml). The solution was evaporated to dryness and the residue recrystallized from benzene-petroleum to give needles of 3-amino-2-methyl-4-quinazolone (16.7g 76% overall), m.p. 148-149° (lit., [65], 152°).

(b) 3-Amino-4-quinazolone

Anthranilic acid (5.0g) was mixed with formamide (1.9 ml) and heated at 175° for 2.5 hr. The solution, on cooling, was mixed with cold water, the resulting solid was broken up in a mortar, filtered off, allowed to dry and recrystallized from boiling ethanol to yield 3H-4-quinazolone (2.85g), m.p. 214-215° (lit. [64], 215°). This product was mixed with hydrazine hydrate (1.4g) and refluxed for 2 hr. Boiling ethanol (25 ml) was added. On cooling, crystals were obtained which were filtered and dried to yield 3-amino-4-quinazolone (26%) (1.55g), m.p. 210-211° (lit., [66], 209-210°).

(c) 3-Amino-2-phenyl-4-quinazolone

cf. Method of Johsi and Gambir [67].

Anthranilic acid (5.0g) was mixed with benzoyl chloride (40 ml) and a few drops of pyridine were added. The solution was heated at 130° for 3 hr. On cooling, the mixture was diluted with ether to give yellow crystals which were filtered off, dried and recrystallized from boiling acetic acid to yield 2-phenyl-3,1,4-benzoxazone (5.0g), m.p. 109-110°.

The benzoxazone (0.35g) was dissolved in hot glacial acetic acid (5.0 ml) and hydrazine hydrate (0.1g) was added. The solution was refluxed for 1 hr, cooled, made alkaline with 2N sodium hydroxide solution, and extracted with ethyl acetate (3 x 50 ml). The combined extracts were washed with water (2 x 10 ml), dried, and evaporated to dryness. The product was recrystallized from ethanol to yield 3-amino-2-phenyl-4-quinazolone (0.2g), m.p. 179-180° (lit., [106] 178-179°).

(d) 1-Amino-2-quinolone (N-aminocarbostyryl)

2-Hydroxyquinoline (10.0g, 0.069 mole) was dissolved in aqueous 2N potassium hydroxide (250 ml) at 60°. HOS (23.4g, 0.21 mole) was added to the rapidly stirred solution at a rate such as to maintain the temperature between 50-70°. After a further 20 min, the solution was cooled and extracted with ether (2 x 50 ml). The combined extracts were dried, filtered and evaporated to dryness. The residue was recrystallized from ethylacetate-petrol to give 1-amino-2-quinolone (9.9g, 90%), m.p. 126-127° (lit. [68], 130°).

(e) 1-Amino-2-pyridone

cf. Method of Hoergerle and Erlenmeyer [70].

(i) Aqueous chloramine

"12% Available chlorine" sodium hypochlorite solution (76 ml) was added, very slowly at first, to a stirred solution of 34% w/w aqueous ammonia solution (37.5 ml) in water (200 ml) at -10° . The solution was allowed to stand at -5° for 1 hr.

(ii) A concentrated aqueous solution of 2-hydroxy pyridine (24.0g) was mixed with 50% aqueous sodium hydroxide solution (200 ml). The precipitate was filtered off and dried and used without further purification. This sodium salt was added to the chloramine solution at -5° . The solution was stirred overnight and then continuously extracted with ether for 48 hr. The extracts were dried, filtered, and evaporated to dryness. The residue was recrystallized from ethyl acetate-petrol with rapid cooling in an ice-bath to yield 1-amino-2-pyridone (2.1g), ^{7.5%} m.p. $63-64^{\circ}$, as grey crystals (lit. [70], $64-66^{\circ}$).

(f) 3-Amino-2-methyl-4-pyrimidone

(i) 2-Methyl-4-pyrimidone was prepared by the method of Gabriel [71], and purified by vacuum sublimation.

(ii) Amination of 2-methyl-4-pyrimidone

2-Methyl-4-pyrimidone (0.6g) was dissolved in dry chloroform (20 ml) (dried over sodium hydride). The solution was cooled to 0° and magnetically stirred. Sodium hydride (0.3 g of a 50% dispersion in oil) was added to give an evolution of hydrogen gas. The solution was stirred for 40 min at 0° , then anhydrous ethereal chloramine solution [61] (50 ml) was added. The solution was stirred at 0° overnight, filtered and evaporated to dryness. The product was column chromatographed on basic alumina to yield two products:

(a) elution with 5 : 1 ether-ethylacetate gave needles (0.004g) m.p. 97-99°, possibly 1-amino-2-methyl-4-pyrimidone ν_{\max} ; 3300, 3200 (NH₂), 1670 (C = O), 1630, 1280, 1185, 1075, 965, 850, 830, 765⁻¹cm.

(b) elution with 5 : 1 ethylacetate-ether yielded 3-amino-2-methyl-4-pyrimidone (0.076g, 11%) which was recrystallized from benzene-petrol as needles, m.p. 113-114.5° (Found : C, 47.8; H, 5.2; N, 33.9; C₅H₇N₃O requires C, 48.0; H, 5.6; N, 33.6%), ν_{\max} ; 3300, 3200 (NH₂), 1665 (C = O), 1630, 1425, 1260, 1200, 1095, 1000, 960, 830, 760⁻¹cm. λ_{\max} ; 214, 280 (ϵ ; 6,250); δ (CDCl₃); 2.63 (s, 3H), 5.22 (broad singlet, disappears on adding D₂O, 2H), 7.82 (d J13 c.p.s., ortho coupling, 1H), 6.39 (d, J 13 c.p.s., ortho coupling, 1H), m/e 125, 110, 96, 84.

p-Methoxybenzylidene derivative

3-Amino-2-methyl-4-pyrimidone (0.02g) was dissolved in glacial acetic acid (2 ml) and freshly distilled p-methoxybenzaldehyde (2 drops) was added. The solution was heated on a steam bath under nitrogen for 0.5 hr, cooled, and poured into cold water (30 ml). The solution was extracted with chloroform (3 x 5 ml). The combined extracts were washed with water (5 ml), dried, filtered, and evaporated to dryness. The residue was recrystallized twice from benzene-petrol to yield the p-methoxybenzylidene derivative (0.015g) as needles, m.p. 136-136.5° (Found: C, 64.1; H, 5.6; N, 17.1; C₁₃H₁₃N₃O₂ requires; C, 64.2; H, 5.4; N, 17.3%), ν_{\max} ; 1680, 1612, 1575, 1265, 1030, 835, 820, cm⁻¹; δ (CDCl₃); 2.45 (s, 3H), 3.80 (s, 3H), 6.2-8.0 (M, 6H), 8.5 (s, 1H).

Verification of the 3-amino rather than the 1-amino structure, as a bidentate ligand to copper^{II}, is described under Miscellaneous Experiments, (p. 97).

(g) 1-Aminobenzimidazole

This compound was prepared by two methods.

(i) The method of Sheng and Day [75] from o-nitrophenylhydrazine which is an improved modification of the method of Abramovitch and Schofield [78].

(ii) By direct HOS Amination

Benzimidazole (20.0g) was suspended in water at 60° (250 ml) and solid potassium hydroxide (60.6g) was added portionwise. HOS (50.0g) was added to the stirred yellow brown solution at such a rate as to maintain the temperature between 50-70°. The solution was stirred for a further 20 min, cooled, extracted with ethyl acetate (4 x 50 ml) and the combined extracts washed with water (25 ml), dried, filtered and evaporated to dryness. The residue was recrystallized twice from ethylacetate-petrol to yield 1-aminobenzimidazole (16.5g, 72%) as off-white plates, m.p. 146-152°. i.r. and t.l.c. showed this to be identical with the sample prepared by the longer route described above, but with a small impurity which was not removed on successive recrystallizations.

(h) 3-Amino-4-phthalazone

(i) Phthalaldehydic acid (2.0g) was dissolved in hot 50% aqueous ethanol (25 ml) and hydrazine hydrate (1.0g) was added. The solution was refluxed for 1 hr. Excess of ethanol was distilled off, the solution on cooling yielded 4-phthalazone (2.0g), m.p. 183-184°, as needles. (lit. [107], 183-184°). This was essentially the general synthetic method of 4-phthalazones as described by Vaughan [88].

(ii) 4-Phthalazone (2.0g) was dissolved in an aqueous solution of sodium hydroxide (4.0g in 25 ml) at 60°. HOS (3.0g) was added to the stirred solution at such a rate as to maintain the temperature between 50-70°. The crystals which separated on cooling to 0° were filtered

and recrystallized from hot chloroform-petrol to yield 3-amino-4-phthalazone as needles (1.7g, 90%), m.p. 133-134° (Found: C, 59.2; H, 4.3; N, 25.9; $C_8H_7N_3O$ requires C, 59.6; H, 4.4; N, 26.1%)
 ν_{\max} ; 3300, 3200 (NH_2), 1660 (C = O), 1110, 1050, 945, 755, 680, cm^{-1} ; m/e , 161, 146, 132, 104.

(i) 3-Amino-1-methyl-4-phthalazone

(i) o-Acetylbenzoic acid was prepared by the method of Yale from phthalic anhydride and malonic acid [108].

(ii) o-Acetylbenzoic acid (1.0g) was dissolved in 50% aqueous ethanol (25 ml) and hydrazine hydrate (0.48g) was added. The solution was refluxed for 3 hr, excess of ethanol was distilled off, the solution was cooled and filtered to yield 1-methyl-4-phthalazone (0.85g) as needles, m.p. 226-227° (lit. [109], 222-224°). This was essentially the general synthetic method of 4-phthalazones as described by Vaughan [88].

(iii) 1-Methyl-4-phthalazone (1.0g) was aminated with HOS exactly as described for the amination of 4-phthalazone (see h) to yield 3-amino-1-methyl-4-phthalazone as needles (0.9g, 81%), m.p. 180-181° (Found: C, 61.5; H, 5.2; N, 24.25; $C_9H_9N_3O$ requires C, 61.7; H, 5.2; N, 24.0%), ν_{\max} ; 3300, 3250 (NH_2), 1640 (C = O), 1050, 950, 750, 680, cm^{-1} ; λ_{\max} ; 223, 256 (ϵ ; 5,650), 265 (shoulder), 305 (ϵ ; 7,150); δ ($CDCl_3$); 2.6 (s, 3H), 5.65 (broad singlet, disappears on adding D_2O , 2H), 7.8 (m, 3H) 8.5 (doublet, split further, 1H).

(j) 3-Amino-1-phenyl-6,7-benzophthalaz-4-one

(i) 2-Benzoyl-3-naphthoic acid

This compound was prepared by the "inverse" Grignard reaction

from 2,3-naphthoic anhydride and phenyl magnesium bromide according to the method of Weizmann *et al.* [89].

(ii) 1-Phenyl-6,7-benzophthalaz-4-one

2-Benzoyl-3-naphthoic acid (0.5g) was dissolved in hot ethanol (8 ml) and hydrazine hydrate (0.12g) was added. The solution was refluxed for 10 min. to yield a flocculent white precipitate. The solution was cooled and filtered and the crystals recrystallized from hot chloroform-petrol to yield 1-phenyl-6,7-benzophthalaz-4-one (0.46g, 93%) as needles, m.p. 320-322° (Found: C, 79.2; H, 4.5; N, 10.4; $C_{18}H_{12}N_2O$ requires C, 79.4; H, 4.4; N, 10.3%) ν_{max} ; 3170 (NH), 1680 (C = O), 1630, 750, cm^{-1} ; λ_{max} ; 210, 253 (ϵ ; 62,000), 322 (shoulder), 335 (ϵ ; 13,600), 368 (shoulder).

(iii) 3-Amino-1-phenyl-6,7-benzophthalaz-4-one

1-Phenyl-6,7-benzophthalaz-4-one (1.4g) was dissolved in hot ethanol (200 ml) and 2N sodium hydroxide solution (50 ml) was added to give a yellow-green solution. This was warmed to 60° and HOS (6.0g) was added at such a rate as to maintain the temperature of the stirred solution between 50-70°. After a further 10 min. a solid separated; on addition of water (100 ml) this dissolved. Excess of the ethanol was distilled off to give a flocculent precipitate on cooling. This was filtered off, dried, and recrystallized from hot ethanol to yield 3-amino-1-phenyl-6,7-benzophthalaz-4-one (1.1g, 75%) as green-yellow flakes, m.p. 179-180° (Found: C, 74.9; H, 4.8; N, 14.8; $C_{18}H_{13}N_3O$ requires C, 75.2; H, 4.6; N, 14.6%), ν_{max} ; 3360, 3190 (NH₂), 1685 (C = O), 1665, 895, 695, cm^{-1} ; λ_{max} ; 213, 253 (ϵ ; 62,000), 348 (shoulder), 357 (ϵ ; 15,800); δ (CDCl₃); 5.65 (broad singlet, disappears on adding D₂O, 2H), 7.33-8.15 (m, 9H), 8.18 (s, 1H), 8.68 (s, 1H); m/e ; 287, 272, 202, 180.

(k) 1- and 2-Aminoindazole

Indazole (1.0g) was suspended in water (5 ml) and warmed to 60°C; ethanol was added to the stirred suspension until all the crystals dissolved. Solid potassium hydroxide (4.0g) was added to give a yellow solution. HOS (4.0g) was added to the stirred solution at such a rate as to maintain the temperature between 50-70°. After a further 20 min excess of ethanol was removed under reduced pressure. Water was added to just dissolve the precipitate of potassium sulphate, and the solution was then extracted with chloroform (3 x 20 ml). The combined extracts were washed with water (5 ml), dried, filtered and evaporated to dryness to yield a mixture of 1- and 2-aminoindazole (1.03g, 90%). The mixture was carefully chromatographed on a silica column; elution with 10 : 1 methylene chloride-ethyl acetate gave 1-aminoindazole which was recrystallized from benzene-petrol as off-white granules (0.55g, 49%), m.p. 104-108°, which contained a minor impurity which could not be removed on successive recrystallizations. (Found: C, 65.3; H, 5.2; N, 29.7; $C_7H_7N_3$ requires C, 63.1; H, 5.3; N, 31.6%), ν_{\max} ; 3330, 3200 (NH₂), 1650, 1620, 1075, 735, cm⁻¹; λ_{\max} ; 217, 253 (ϵ ; 5,200), 280 (shoulder), 290 (ϵ , 5,200), 292 (ϵ , 5,100); δ (CDCl₃); 5.41 (broad singlet, disappears on adding D₂O, 2H), 6.85-7.95 (m, 4H), 8.05 (s, 1H), ^m/e; 133, 118, 104, 58, 43.

Further elution with 1 : 5 methylene chloride-ethyl acetate gave 2-aminoindazole as large pink plates (0.27g, 24%) after recrystallization from benzene-petrol, m.p. 97-99° (Found: C, 62.8; H, 5.3; N, 31.7; $C_7H_7N_3$ requires C, 63.1; H, 5.3; N, 31.6%) ν_{\max} ; 3240, 3160 (NH₂), 1665, 1625, 1220, 795, 755, 740, cm⁻¹; λ_{\max} ; 217, 276 (ϵ ; 8,000) (broad peak); δ (CDCl₃); 6.0 (broad singlet, disappears on adding D₂O, 2H), 6.75-7.75 (m, 4H), 7.75 (s, 1H);

m/e 133, 118, 104, 58, 43.

p-Methoxybenzaldehyde derivatives

(i) 1-Aminoindazole (0.2g) was dissolved in glacial acetic acid (2 ml) and freshly distilled p-methoxybenzaldehyde (0.25g) was added. The solution was warmed to 80° under nitrogen for 1 hr and evaporated to dryness under reduced pressure. The residue was recrystallized from hot ethanol to yield the p-methoxybenzylidene derivative (0.21g) as long fine needles, m.p. 80-81° (Found: C, 71.2; H, 5.2; $C_{15}H_{13}N_3O$ requires C, 71.7; H, 5.2; N, 16.7; %); ν_{max} ; 1610, 1600, 1255, 825, 740, cm^{-1} .

(ii) 2-Amino indazole was treated with p-methoxybenzaldehyde in the same manner as described for 1-aminoindazole to yield the p-methoxybenzaldehyde derivative as long fine needles, m.p. 120-121° (Found: C, 71.3; H, 5.3; N, 16.3; $C_{15}H_{13}N_3O$ requires, C, 71.7; H, 5.2; N, 16.7; %), ν_{max} ; 1625, 1610, 1595, 1255, 830, 760, cm^{-1} .

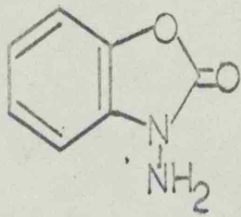
(1) Attempted preparation of 2-amino-3-methyl-1,2,4-benzothiadiazine-1,1-dioxide

(i) 3-Methyl-2H,1,2,4-benzothiadiazine-1,1-dioxide was prepared from othanilamide according to the method of Parke and Williams [110].

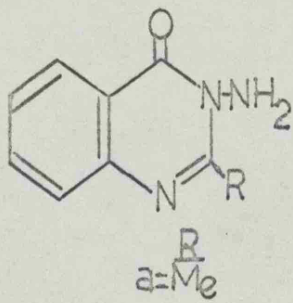
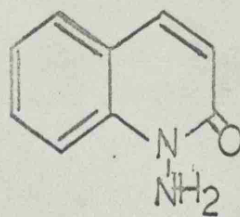
(ii) Attempted aminations

With HOS

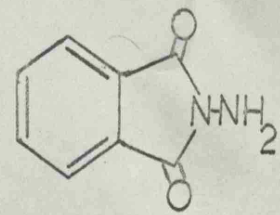
3-Methyl-2H,1,2,4-benzothiadiazine-1,1-dioxide (0.25g) was dissolved in 2N sodium hydroxide and the solution was warmed to 60°. HOS (0.4g) was added portionwise at such a rate as to maintain the temperature of the stirred solution between 50-70°. After a further 20 min the solution was cooled, extracted with ethyl acetate (3 x 20 ml),

LOOSE COPY OF N -AMINO COMPOUNDS.

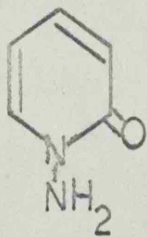
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(2) $a=Me$
 $b=H$
 $c=Ph$ 

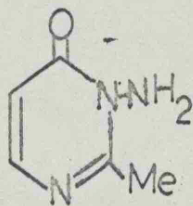
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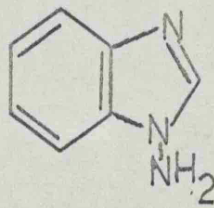
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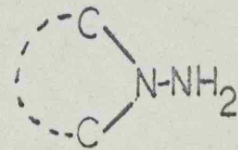
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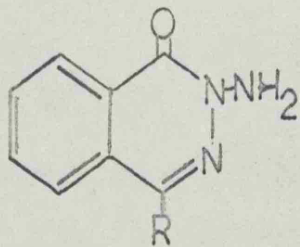
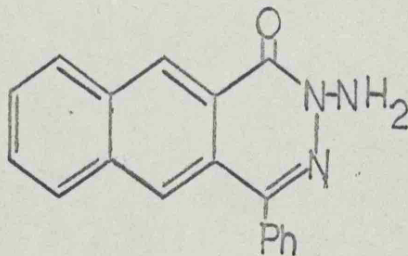
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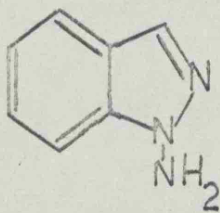
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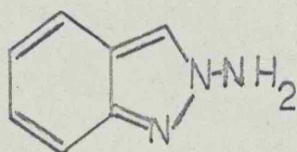
(8) TYPE "A"

(33) $a=H$
 $b=Me$ 

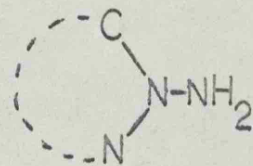
(34)



(35)



(36)



(37) TYPE "B"

in thionyl chloride (20 ml) and DMF (12 drops) added. The mixture was refluxed for 1 hr then evaporated to dryness. The residue was extracted with methylene chloride (100 ml) and filtered. The filtrate was concentrated to approximately 25 ml and hydrazine hydrate (3 ml) slowly added, with vigorous stirring. The mixture was stirred for 10 min, diluted with water (50 ml), cooled to 0° and acidified with concentrated hydrochloric acid. This was extracted with chloroform (3 x 100 ml). The combined chloroform extracts were extracted with 5% sodium hydroxide (3 x 50 ml), and the combined alkaline extracts were cooled and acidified with concentrated hydrochloric acid. The acidified mixture was extracted with chloroform (3 x 100 ml), the combined extracts were dried, filtered and evaporated to dryness to yield 2H-1,2,3-benzothiadiazine-1,1-dioxide (2.08g, 62%) which was recrystallized from chloroform to yield needles, m.p. 141-142° (lit. [111], 141-142°).

* I thank Professor J.F. King, University of Western Ontario, London, Canada, for these experimental details.

(ii) Attempted aminations

Amination with HOS and with ethereal chloramine were performed exactly as described with 3-methyl-2H-1,2,4-benzothiadiazine-1,1-dioxide above; the only product was the sodium salt of 2H-1,2,3-benzothiadiazine-1,1-dioxide.

2. Oxidation of N-Amino Compounds

General Procedure

The N-amino compound (1 mole) was dissolved in dry methylene chloride (15 ml per gram) and the "trap", e.g. olefin or sulphoxide (5 mole) was added.*

Solid powdered lead tetraacetate (1.2 mole) was then added to the vigorously stirred solution at room temperature over 10 min. After a further 15 min the mixture was filtered, the residue washed several times with methylene chloride, and the combined filtrate and washings evaporated to dryness under reduced pressure. The residue was examined by t.l.c. (alumina plates, ethyl acetate solvent) to determine the subsequent purification procedure, which was either:

(i) column chromatography on deactivated basic alumina, this being the preferred method, giving pure products directly.

(ii) In the case of the DMSO adducts from 3-amino-2-methyl-4-quinazolone, 1-amino-2-quinolone, 1-amino-2-pyridone, 3-amino-3-methyl-4-pyrimidone and 1-aminobenzimidazole, excess of DMSO was removed from the residue by distillation under high vacuum at 90°. The residue was then digested with hot "Analar" acetone and filtered to remove the precipitate of lead diacetate. The residue was washed several times with hot acetone. The combined filtrate and washings were evaporated to dryness, the sulphoximines being recrystallized from the solvents indicated.

(iii) In the case of the adduct from 3-amino-2-methyl-4-quinazolone and trans-dichloroethylene, the crude reaction mixture was poured into a large volume of ether to precipitate the lead diacetate, which was filtered off; the filtrate was evaporated to dryness and the adduct recrystallized from the solvent indicated.

* (a) Oxidations without any external trap were performed in neat methylene chloride.

(b) With polar traps; i.e. the acrylate, methacrylate and crotonate esters and DMSO, the neat liquid itself was used as the solvent.

(c) With non-polar traps, i.e. cyclohexene, cyclooctene, styrene, trans dichloroethylene and indene, or gaseous traps, i.e. butadiene, and cis and trans butene, or solid traps, i.e. tetraphenylcyclopentadienone, methyl phenyl sulphoxide, diphenyl sulphoxide and dibenzothiophene sulphoxide, optimum yields of adducts were obtained using the trap: methylene chloride ratio as stated above, unless indicated as otherwise.

The oxidation reactions of the N-amino compounds are described in the same order as their preparation.

(a) Oxidation of 3-amino-2-methyl-4-quinazolone:

(i) alone

3-Amino-2-methyl-4-quinazolone (1.0g) was dissolved in dry methylene chloride (50 ml). Lead tetraacetate (2.8g) was added portionwise over 10 min. The solution became warm during this time; nitrogen was evolved and the solution became yellow. The solution was evaporated to dryness; column chromatography on basic alumina gave two fractions:

1. elution with ether gave a negligible amount of a brown oil with a characterless i.r. spectrum.

2. further elution with ethylacetate gave 2-methyl-3H,4-quinazolone (0.64g, 70%) as needles, m.p. 239-240° (lit. [106], 240-241°, 234-236°).

Synthesis of 2-methyl-3H-4-quinazolone

Anthranilic acid (1.0g) was mixed with acetamide (0.6g) and heated at 180° for 6 hr in an open vessel, then left overnight at 140°.

The product was shaken with water, extracted with ethylacetate (3 x 20 ml), the combined extracts were then evaporated to dryness and the residue recrystallized from ethyl acetate-petrol to yield 2-methyl-3H,4-quinazolone, m.p. and mixed m.p., 239-240°, having an identical i.r. spectrum to the product obtained above.

(i) in the presence of an olefin

The following aziridines were obtained by chromatography on a short column of deactivated basic alumina with 9 : 1 petroleum-methylene chloride as eluent,* followed by crystallization from ethyl acetate-petrol. In all cases, further elution with 1 : 10 methanol-ethylacetate gave 2-methyl-3H,4-quinazolone in 10-50% yields.

*In case (h), 2 molar equivalents of tetraphenylcyclopentadienone were used, excess of unreacted tetraphenylcyclopentadienone (1.5 molar equivalents) being carefully eluted before the aziridine, using 20 : 1 petroleum-methylene chloride.

(a) 1-(3,4-dihydro-2-methyl-4-oxoquinazolin-3-yl)-2-vinylaziridine from 3-amino-2-methyl-4-quinazolone and butadiene, flakes (81%), m.p. 93-95° (Found: C, 69.0; H, 5.7; N, 18.6; $C_{13}H_{13}N_3O$ requires C, 68.7; H, 5.8; N, 18.5%), ν_{max} ; 1665, 1595, 770 cm^{-1} ; δ ($CDCl_3$) 2.60 (m, 1H); 2.63 (s, 3H), 3.10 (m, 2H), 5.50 (m, 3H), 7.50 (m, 3H) and 8.10 (m, 1H); m/e , 227, 186, 160.

(b) 1-(3,4-dihydro-4-oxoquinazolin-3-yl)-cis-2,3-dimethylaziridine from 3-amino-2-methyl-4-quinazolone and cis but-2-ene, plates (48%), m.p. 153-154° (Found: C, 67.4; H, 6.6; N, 18.6, $C_{13}H_{15}N_3O$ requires C, 68.1; H, 6.6; N, 18.3%) ν_{max} ; 1665, 1600, 780, cm^{-1} ;

δ ($CDCl_3$) 1.40 and 1.49 (d, 5.5 c.p.s., 6H, aziridine C-Me groups trans to quinazolone), 2.55 (m, 2H), 2.70 (s, 3H), 7.60 (m, 3H), 8.25 (m, 1H). The p.m.r. spectrum of the mother liquors left after crystallization of the cis-aziridine showed none of the signals of

the trans-isomer (see below); m/e ; 229, 214, 200, 160.

(c) 1-(3,4-dihydro-2-methyl-4-oxoquinazolin-3-yl)-trans-2,3-dimethyl-aziridine from 3-amino-2-methyl-4-quinazolone and trans but-2-ene, granules (46%), m.p. 105-108° (Found: C, 68.6; H, 6.8; N, 18.3; $C_{13}H_{15}N_3O$ requires C, 68.1; H, 6.6; N, 18.3%); ν_{max} ; 1665, 1600, 780 cm^{-1} ; $\delta(CDCl_3)$ 1.09 and 1.19 (total 3H, aziridine C-Me cis quinazolone), 1.49 and 1.59 (total 3H, aziridine C-Me trans to quinazolone), 2.50 (m, 1H), 2.71 (s, 3H), 2.97 (m, 1H), 7.50 (m, 3H), 8.20 (m, 1H); m/e ; 229, 214, 200, 160.

(d) 9-(3,4-dihydro-2-methyl-4-oxoquinazolin-3-yl)-9-aza-bicyclo[6,1,0]nonane from 3-amino-2-methyl-4-quinazolone and cyclooctene, needles (43%), m.p. 168-170° (Found: C, 71.6; H, 7.7; N, 14.8; $C_{17}H_{21}N_3O$ requires C, 72.0; H, 7.5; N, 14.8%); ν_{max} ; 1665, 1600, 780 cm^{-1} ; $\delta(CDCl_3)$; 1.53 (m, 10H), 2.59 (m, 4H), 2.70 (s, 3H), 7.50 (m, 3H), 8.10 (m, 1H); m/e 283, 212, 160.

(e) 7-(3,4-dihydro-2-methyl-4-oxoquinazolin-3-yl)-7-azabicyclo[4,1,0]heptane from 3-amino-2-methyl-4-quinazolone and cyclohexene, needles (53%), m.p. 129-130° (Found: C, 70.4; H, 6.5; N, 16.2; $C_{15}H_{17}N_3O$ requires C, 70.6; H, 6.7; N, 16.5%); ν_{max} ; 1665, 1595, 780, cm^{-1} ; $\delta(CDCl_3)$; 1.42 (m, 4H), 2.20 (m, 4H), 2.60 (m, 5H), 7.50 (m, 3H), 8.10 (m, 1H); m/e ; 255, 212, 186, 160.

(f) 2,3-benzo-6-(3,4-dihydro-2-methyl-4-oxoquinazolin-3-yl)-6-azabicyclo[3,1,0]hexane from 3-amino-2-methyl-4-quinazolone and indene, needles (41%), m.p. 183-184° (Found: C, 75.2; H, 5.1; N, 14.5; $C_{18}H_{15}N_3O$ requires C, 74.7; H, 5.2; N, 14.5%); ν_{max} ; 1665, 1600, 780 cm^{-1} ; $\delta(CDCl_3)$; 2.75 (s, 3H), 3.45 (d, 5 c.p.s.; 2H), 3.70 (m, 1H), 4.25 (d, 5 c.p.s., 1H), 7.40 (m, 4H), 7.65 (m, 3H), 8.15 (m, 1H),

- (g) 1-(3,4-dihydro-2-methyl-4-oxoquinazolin-3-yl)-2-phenyl-aziridine from 3-amino-2-methyl-4-quinazolone and styrene, plates, (64%), m.p. 123-124° (Found: C, 73.4; H, 5.5; N, 15.5; $C_{17}H_{15}N_3O$ requires C, 73.6; H, 5.45; N, 15.15%); ν_{\max} ; 1665, 1590, 780 cm^{-1} ; δ ($CDCl_3$), 2.65 (s, 3H), 2.87 (d, d J 5.5 and 2 c.p.s., 1H), 3.10 (d, d J 8 and 2 c.p.s., 1H), 3.69 (d, d J 8 and 5.5 c.p.s., 1H), 7.45 (m, 5H), 7.6 (m, 3H), 8.1 (m, 1H); m/e 277, 262, 260, 248, 186, 160.
- (h) 1,2,3,5-tetraphenyl-6-(3,4-dihydro-2-methyl-4-oxoquinazolin-3-yl)-6-azabicyclo[3,1,0]hex-2-ene-4-one from 3-amino-2-methyl-4-quinazolone and tetraphenylcyclopentadienone, yellow crystals (47%), m.p. 186-188° (Found: C, 81.5; H, 4.7; N, 7.5; $C_{38}H_{27}N_3O$ requires C, 81.8; H, 4.9; N, 7.5%); ν_{\max} : 1700 (C = O) 1680 (C = O), 770, 690, cm^{-1} ; m/e 557, 397, 371, 320, 160.
- (i) trans-2,3-dichloro-1-(3,4-dihydro-2-methyl-4-oxoquinazolin-3-yl)-aziridine from 3-amino-2-methyl-4-quinazolone and trans-dichloroethylene, needles (60%), m.p. 138° (Found: C, 49.5; H, 3.5; Cl, 26.1; N, 15.5; $C_{11}H_9Cl_2N_3O$ requires C, 48.9; H, 3.3; Cl, 26.3; N, 15.55%); ν_{\max} ; 1680, 1600, 1330, 800, 770 cm^{-1} ; δ ($CDCl_3$) 2.75 (s, 3H), 5.29 (2H), 6.60 (d, J 10 c.p.s., 1H) 7.65 (m, 3H), 8.15 (m, 1H).
- (j) methyl-(3,4-dihydro-2-methyl-4-oxoquinazolin-3-yl)aziridine-2-carboxylate from 3-amino-2-methyl-4-quinazolone and methyl acrylate, needles (30%), m.p. 114-116° (Found: C, 59.9; H, 4.9; N, 16.4; $C_{13}H_{13}N_3O_3$ requires C, 60.2; H, 5.05; N, 16.2%); ν_{\max} ; 1730 (C = O), 1675, 1600, 1330, 780 cm^{-1} ; δ ($CDCl_3$) 2.75 and 2.72 (quinazolone ring C-Me, two invertomers, 3H) 3.00 (2 overlapping d) J 5.5 c.p.s., showing further splitting, 2H), 3.55 (2 overlapping d, J 8.5 c.p.s., 1H), 3.55 (?) and 3.85 (invertomers CO_2 me, 3H), 7.50 (m, 3H), 8.10 (c, 1H).

- (k) methyl-1-(3,4-dihydro-2-methyl-4-oxoquinazolin-3-yl)-2-methylaziridine-2-carboxylate from 3-amino-2-methyl-4-quinazolone and methyl methacrylate, granules (36%), m.p. 77-79° (Found: C, 61.6, H, 5.6; N, 15.5; $C_{14}H_{15}N_3O_3$ requires C, 61.5; H, 5.5; N, 15.4%); ν_{\max} ; 1730 (C = O), 1675, 1600, 1310, 1170, 780 cm^{-1} . For PMR spectrum details, see Table 11 in Discussion, p. 152
- (l) ethyl-1-(3,4-dihydro-2-methyl-4-oxoquinazolin-3-yl)-2-methylaziridine-2-carboxylate from 3-amino-2-methyl-4-quinazolone and ethyl methacrylate, granules (62%), m.p. 107-109° (Found: C, 62.6; H, 6.4; N, 14.4; $C_{15}H_{17}N_3O_3$ requires C, 62.7; H, 6.0; N, 14.6%); ν_{\max} ; 1740 (C = O), 1665, 1600, 1180, 795, cm^{-1} . For PMR spectrum details see Table 11, Discussion, p. 152
- (m) isopropyl 1-(3,4-dihydro-2-methyl-4-oxoquinazolin-3-yl)-2-methylaziridine-2-carboxylate from 3-amino-2-methyl-4-quinazolone and isopropyl methacrylate,* granules (49%), m.p. 75-76° (Found: C, 63.95; H, 6.5; N, 14.2; $C_{16}H_{19}N_3O_3$ requires C, 63.8; H, 6.4; N, 13.95%); ν_{\max} ; 1730 (C = O), 1680, 1330, 1180, 780 cm^{-1} . For PMR spectrum details see Table 11, Discussion, p. 152
- (n) tertiarybutyl 1-(3,4-dihydro-2-methyl-4-oxoquinazolin-3-yl)-2-carboxylate from 3-amino-2-methyl-4-quinazolone and t-butylmethacrylate*, granules (48%), m.p. 101-102° (Found: C, 64.5; H, 6.7; N, 13.2; $C_{17}H_{21}N_3O_3$ requires C, 64.7; H, 6.7; N, 13.3%); ν_{\max} ; 1730 (C = O), 1680, 1340, 780 cm^{-1} . For PMR spectrum details see Table 11, Discussion, p. 152
- * Isopropyl ester prepared by the same method as described for preparation of the t-butyl ester [112], using isopropyl alcohol instead of t-butyl alcohol.

(o) methyl trans-1-(3,4-dihydro-2-methyl-4-oxoquinazolin-3-yl)-2-methylaziridine-3-carboxylate, from 3-amino-2-methyl-4-quinazolone and methyl crotonate, granules (32%), m.p. 108-109° (Found: C, 61.2; H, 5.5; N, 15.4; $C_{14}H_{15}N_3O_3$ requires C, 61.5; H, 5.5; N, 15.4%); ν_{\max} : 1340 (C = O), 1670, 1605, 1200, 770, cm^{-1} ; δ ($CDCl_3$), 1.27 and 1.55 (each d, two invertomers CMe total 3H), 3.18 (d, 1H), 3.51 (q, 1H), 3.63 and 3.89 (two invertomers CO_2Me , total 3H), 7.50 (m, 3H), 8.25 (m, 1H).

(iii) in the presence of a sulphoxide

To yield the following sulphoximines:

In the case of (a) work up was performed as described on page 53 footnote (ii). In the case of (b) and (c) 3 molar equivalents of sulphoxide were used in the reaction and the product was chromatographed on a column of deactivated alumina to yield three fractions:

case (b): elution with 3: 1 petroleum-methylene chloride gave diphenylsulphoxide (2.5 molar equivalents); elution with 2: 3 petroleum-methylene chloride gave the sulphoximine; elution with 1: 10 methanol-ethyl acetate gave 2-methyl-3H-4-quinazolone (0.3 molar equivalents).

case (c): elution with 1: 5 petroleum-methylene chloride gave dibenzothiophenesulphoxide (2.6 molar equivalent); elution with 5: 1 methylene chloride-petroleum gave the sulphoximine; elution with 1: 10 methanol-ethylacetate gave 2-methyl-3H-4-quinazolone (0.5 molar quantity).

(a) N-(3,4-dihydro-2-methyl-4-oxoquinazolin-3-yl)-S,S dimethyl sulphoximine

from 3-amino-2-methyl-4-quinazolone and dimethylsulphoxide, golden yellow granules from ethanol (100%), m.p. 176-178° (Found: C, 52.4; H, 5.15; N, 16.8; S, 12.7; $C_{10}H_{13}N_3O_2S$ requires C, 52.6; H, 5.2; N, 16.7; S, 12.8%); ν_{\max} ; 1670, 1595, 1210, 1050 (S = O), cm^{-1} ; δ ($CDCl_3$); 2.75 (s, 3H), 3.3 (s, 6H) 7.65 (m, 3H), 8.15 (m, 1H); m/e 251, 160, 147, 145.

(b) N-(3,4-dihydro-2-methyl-4-oxoquinazolin-3-yl)-S,S-diphenylsulphoximine from 3-amino-2-methyl-4-quinazolone and diphenylsulphoxide, shining granules from ethanol (64%), m.p. 137-138° (Found: C, 66.9; H, 4.5; N, 11.3; $C_{21}H_{17}N_3O_2S$ requires C, 67.2; H, 4.6; N, 11.2%); ν_{\max} ; 1670, 1600, 1230, 1090, 770 cm^{-1} ; m/e 375, 250, 202, 160.

(c) N-(3,4-dihydro-2-methyl-4-oxoquinazolin-3-yl)-S,S-dibenzothio-phenesulphoximine from 3-amino-2-methyl-4-quinazolone and dibenzothiophenesulphoxide [113], crystals from ethanol (13%), m.p. 238-240°; (Found: C, 67.5; H, 4.0; N, 11.5; S, 8.4; $C_{21}H_{15}N_3O_2S$ requires C, 67.55; H, 4.05; N, 11.3; S, 8.6%); ν_{\max} ; 1670, 1600, 1210, 980, 760 cm^{-1} ; m/e 373, 160.

(b) Oxidation of 3-amino-4-quinazolone

This was performed exactly as described for 3-amino-2-methyl-4-quinazolone (see page 54). Elution of the column with ethylacetate gave only 3H 4-quinazolone (70%) as needles, m.p. 217-218°. This sample had on identical R_f value on t.l.c. and identical i.r. spectrum as the sample prepared as described as the intermediate in the synthesis of 3-amino-4-quinazolone (see p.42)

(c) Oxidation of 3-amino-2-phenyl-4-quinazolone

(i) alone

This was performed exactly as described for 3-amino-2-methyl-4-quinazolone (see page 54). Elution of the column with ethylacetate gave 3H, 2-phenyl-4-quinazolone (70%) as needles, m.p. 240-242° (lit. [106], 235-238°); ν_{\max} ; 3150 (N - H), 1665, (C = O), 1600, 770, 695, cm^{-1} (consistent with this structure).

(ii) in the presence of an olefin

To yield the aziridine: methyl 1-(3,4-dihydro-2-phenyl-4-oxoquinazolin-3-yl)-2-methylaziridine-2-carboxylate, after column chromatography with 1 : 10 methylene chloride-petroleum; elution with ethylacetate gave 3H-2-phenyl-4-quinazolone (25%).

from 3-amino-2-phenyl-4-quinazolone and methyl methacrylate, granules (30%), m.p. 104-106° (Found: C, 67.7; H, 6.0; N, 12.45; $\text{C}_{19}\text{H}_{17}\text{N}_3\text{O}_3$ requires C, 68.05; H, 5.1; N, 12.5%) ν_{\max} ; 1730 (C = O), 1680 (C = O), 1610, 1590, 1570, 780, 700, cm^{-1} ;

δ (CDCl_3), 1.09 and 1.42 (two C-Me ring invertomers, total 3H), 2.26 (d, 51.5 c.p.s., 1H), 2.65 (d, J 1.5 c.p.s., 1H) 3.42 and 3.52 (two CO_2Me invertomers, total 3H), 7.4 (m, 5H), 7.7 (m, 3H), 8.2 (m, 1H).

(d) Oxidation of 1-amino-2-quinolone (N-aminocarbostyryl)(i) alone

1-Amino-2-quinolone (1.0g) was dissolved in methylene chloride (15 ml) and rapidly stirred magnetically. Solid, powdered, lead tetraacetate (3.8g) was added over 10 min. An evolution of nitrogen gas was observed and the mixture turned a deep red colour. The mixture was stirred for a further 10 min, filtered, and the residue washed with methylene chloride. The combined filtrate and washings

were evaporated to dryness and chromatographed on basic alumina to give two fractions:

1. elution with 9 : 1 methylene chloride ethyl acetate gave red oily crystals (0.002g, m.p. 250-270°) which were assumed to be the tetrazene 1,1'-azobis (2-quinolone) as previously described [114].

2. further elution with 1 : 1 ethanol-ethylacetate gave 2-hydroxyquinoline (0.5g, 55%) which was recrystallized from hot ethanol (charcoal) as crystals, m.p. 196-199° (lit. [107], 199-200°). This sample had identical R_f value on t.l.c. and identical i.r. spectrum to an authentic sample; mixed m.p. 197-199°.

(ii) in the presence of an olefin

To yield the following aziridines on chromatography on a short column of deactivated basic alumina with 9 : 1 petroleum-methylene chloride, followed by recrystallization from ethyl acetate-petroleum. In all cases, further elution with 9 : 1 methylene chloride-ethyl acetate gave red oily crystals of the tetrazene (~1%) and further elution with 1 : 1 ethyl acetate-ethanol yielded 2-hydroxy quinoline (10-40%).

(a) 7-(1,2-dihydro-2-oxoquinolin-1-yl)-7-azabicyclo[4,1,0]heptane from 1-amino-2-quinolone and cyclohexene off white plates (20%), m.p. 160-162° (Found: C, 74.8; H, 6.8; N, 12.0; $C_{15}H_{16}N_2O$ requires C, 75.0; H, 6.7; N, 11.7%); ν_{max} ; 1650, 1590, 830, 770 cm^{-1} ; δ ($CDCl_3$) 1.50 (m, 4H), 2.25 (m, 4H), 2.65 (m, 2H), 6.60 (d, J 10 c.p.s., 1H), 7.60 (m, 5H).

(b) methyl 1-(1,2-dihydro-2-oxoquinolin-1-yl)aziridine-2-carboxylate

from 1-amino-2-quinolone and methyl acrylate; needles (29%), m.p.

130-131° (Found: C, 64.2; H, 5.1; N, 11.5; $C_{13}H_{12}N_2O_3$ requires C, 63.9; H, 4.95; N, 11.5%); ν_{\max} ; 1760, 1650, 1600, 755 cm^{-1} ; δ ($CDCl_3$), 3.15 (m, 3H), 3.42 (?) and 3.88 (two invertomers CO_2Me , total 3H), 6.60 (d, J 10 c.p.s., 1H), 7.60 (m, 5H).

(c) methyl 1-(1,2-dihydro-2-oxoquinolin-1-yl)-2-methylaziridine-2-carboxylate

from 1-amino-2-quinolone and methyl methacrylate, granules (40%), m.p. 94-97° (Found: C, 65.3; H, 5.6; N, 11.0; $C_{14}H_{14}N_2O_3$ requires C, 65.1; H, 5.5; N, 10.85%); ν_{\max} ; 1730 (C = O), 1650, 1600, 750 cm^{-1} . For PMR spectrum details see Table 11, Discussion, p. 152

(d) ethyl 1-(1,2-dihydro-2-oxoquinolin-1-yl)-2-methylaziridine-2-carboxylate

from 1-amino-2-quinolone and ethyl methacrylate, granules (39%), m.p. 64-65° (Found: C, 65.9; H, 5.9; N, 10.4; $C_{15}H_{16}N_2O_3$ requires C, 66.2; H, 5.9; N, 10.3%); ν_{\max} ; 1725, 1655, 1590, 1180, 825, 745. For PMR spectrum details see Table 11, Discussion, p. 152 ; m/e 272, 244, 198, 171, 145.

(e) isopropyl 1-(1,2-dihydro-2-oxoquinolin-1-yl)-2-methylaziridine-2-carboxylate

from 1-amino-2-quinolone and isopropyl methacrylate [cf. ref. 112,], crystals (44%), m.p. 63-65° (Found: C, 67.5; H, 6.4; N, 9.6; $C_{16}H_{18}N_2O_3$ requires C, 67.1; H, 6.3; N, 9.8%); ν_{\max} ; 3100, 1723 (C = O), 1650, 1585, 1185, 1100, 760, cm^{-1} ; For PMR spectrum details see Table 11, Discussion, p. 152 ; m/e 286, 276, 264, 243, 227, 198, 146, 145.

(f) tertiary butyl 1-(1,2-dihydro-2-oxoquinolin-1-yl)-2-methylaziridine-2-carboxylate

from 1-amino-2-quinolone and *t*-butyl methacrylate [112], crystals

(42%), m.p. 117-118° (Found: C, 68.0; H, 6.8; N, 9.3; $C_{17}H_{20}N_2O_3$ requires C, 68.0; H, 6.7; N, 9.3%); ν_{\max} ; 1710, 1650, 1150, 750 cm^{-1} . For PMR details see Table 11, Discussion p. 152 ;
 m/e 300, 244, 227, 171, 145.

(g) methyl-trans 1-(1,2-dihydro-2-oxoquinolin-1-yl)-2-methylaziridine-2-carboxylate

from 1-amino-2-quinolone and methyl crotonate, granules (33%), m.p. 101-103° (Found: C, 65.4; H, 5.5; N, 10.6; $C_{14}H_{14}N_2O_3$ requires C, 65.1; H, 5.5; N, 10.85%); ν_{\max} ; 1730 (C = O), 1655, 1595, 1450, 1340, 1200, 1185, 840, 755, 700; δ ($CDCl_3$) 1.14 and 1.72 (two d's, J 6 c.p.s., invertomers of aziridine ring CMe, total 3H), 3.38 (m, 1H), 3.40 and 3.95 (invertomers of CO_2Me , total 3H), 3.65 (m, 1H), 6.65 (d, J 10 c.p.s., 1H), 7.5 (m, 5H).

(iii) in the presence of a sulphoxide

To yield the following sulphoximines:

In case (a) work up was as described on page 53, footnote (ii); in cases (b) and (c) 3 molar equivalents of sulphoxide were used. The product was chromatographed on a column of deactivated basic alumina to give three products:

in case (b) elution with 2 : 3 methylene chloride-petroleum gave methylphenyl sulphoxide (2.4 molar equivalents). Further elution with 2 : 3 ethylacetate-methylene chloride gave the sulphoximine. Further elution with 1 : 9 methanol-ethylacetate gave 2-hydroxyquinoline (0.2 molar equivalents).

in case (c) elution with 9 : 1 methylene chloride-petroleum gave diphenyl sulphoxide (2.5 molar equivalents). Further elution with 1 : 9 ethyl acetate-methylene chloride gave the sulphoximine. Further elution with 1 : 9 methanol-ethylacetate

gave 2-hydroxyquinoline (0.2 molar equivalents).

(a) N-(1,2-dihydro-2-oxoquinolin-1-yl)-S,S-dimethylsulphoximine
 from 1-amino-2-quinolone and dimethyl sulphoxide, crystals (52%)
 from ethanol, m.p. 200-201° (Found: C, 56.0; H, 5.3; N, 11.7;
 S, 14.9; $C_{11}H_{12}N_2O_2S$ requires C, 55.9; H, 5.1; N, 11.7; S, 13.6%);
 ν_{\max} ; 1650, 1590, 1210, 1030 (S = O), 750, cm^{-1} ; δ ($CDCl_3$),
 3.35 (s, 6H), 6.6 (d, J 10 c.p.s., 1H), 7.5 (m, 5H); m/e 236, 219,
 160.

(b) N-(1,2-dihydro-2-oxoquinolin-1-yl)-S,S-methylphenylsulphoximine
 from 1-amino-2-quinolone and methyl phenyl sulphoxide [115], crystals
 (32%) from ethanol, m.p. 158-159° (Found: C, 64.5; H, 4.7;
 N, 9.4; S, 10.5; $C_{16}H_{14}N_2O_2S$ requires C, 64.4; H, 4.7; N, 9.4;
 S, 10.85%); ν_{\max} ; 1660, 1230, 1180, 750, 680, cm^{-1} ; δ ($CDCl_3$);
 3.30 (s, 3H), 6.6 (d, J 10 c.p.s., 1H), 7.5 (m, 10H); m/e 298, 283,
 219, 160.

(c) N-(1,2-dihydro-2-oxoquinolin-1-yl)-S,S-diphenylsulphoximine
 from 1-amino-2-quinolone and diphenyl sulphoxide, crystals (45%)
 from ethanol, m.p. 162-163° (Found: C, 70.3; H, 4.5; N, 8.05;
 S, 9.0; $C_{21}H_{16}N_2O_2S$ requires C, 70.0; H, 4.5; N, 7.8; S, 8.9%);
 ν_{\max} ; 1660, 1610, 1330, 1250, 1230, 1170, 1100, 745, 680 cm^{-1} ;
 δ ($CDCl_3$) 6.6 (d, J 10 c.p.s., 1H), 7.5 (m, 15H); m/e 360, 219,
 202, 186, 160.

(e) Oxidation of 1-amino-2-pyridone(i) alone

1-Amino-2-pyridone (0.25g) was dissolved in methylene chloride (20 ml). Solid powdered lead tetraacetate (1.2g) was added portionwise over 10 min. to the rapidly stirred solution. Nitrogen gas was evolved and the solution became black. After a further 10 min the solution was filtered, and the residue washed well with methylene chloride. The combined washings and filtrate were evaporated to dryness. Column chromatography on deactivated basic alumina gave only one identifiable product, on elution with 1 : 5 methanol-ethylacetate, as being 2-hydroxypyridine (0.134g) (61%) as brown crystals, m.p. 103-106°. (lit. [107], 106-107°). The R_f value on t.l.c. and i.r. spectrum were identical to an authentic sample; mixed m.p. 101-105°.

(ii) in the presence of tetraphenylcyclopentadienone

To yield the aziridine after column chromatography on deactivated basic alumina on elution with 3 : 2 methylene chloride-petroleum. Further elution with 1 : 9 methanol-ethyl acetate gave 2-hydroxypyridine (ca. 5%), m.p. 97-102°.

1,2,3,5-tetraphenyl-6-(1,2-dihydro-2-oxopyridin-1-yl)-6-azabicyclo[3,1,0]hex-2-ene-4-one, yellow crystals (18%) from ethylacetate-petrol, m.p. 169-172° (Found; C, 82.5; H, 5.0; N, 5.5; $C_{34}H_{24}N_2O_2$ requires C, 82.9; H, 4.9; N, 5.7%); ν_{max} ; 1700 (C = O), 1660 (C = O), 1585, 740, 685, cm^{-1} ; m/e ; 492, 398, 370, 267.

(iii) in the presence of dimethyl sulphoxide

To yield the sulphoximine after work up as described on p. 53 footnote (ii):

N-(1,2-dihydro-2-oxopyridin-1-yl)-S,S-dimethylsulphoximine from
1-amino-2-pyridone and dimethyl sulphoxide, needles (36%) from
ethanol (charcoal), m.p. 122-123° (Found: C, 82.3; H, 5.0;
N, 5.5; $C_7H_{10}N_2O_2S$ requires C, 82.5; H, 5.0; N, 5.8%); ν_{\max} ;
1650, 1580, 1210, 1040 (S = O), 760 cm^{-1} ; δ ($CDCl_3$) 3.28 (s, 6H),
6.15 (m, 1H) 6.6 (m, 1H), 7.4 (m, 2H).

(f) Oxidation of 3-amino-2-methyl-4-pyrimidone(i) alone

3-Amino-2-methyl-4-pyrimidone (0.1g) was dissolved in methylene chloride (15 ml) and the solution vigorously stirred. Solid, powdered lead tetraacetate (0.5 g) was added portionwise over 10 min. Nitrogen gas was evolved. After a further 10 min. the product was filtered and the residue washed with methylene chloride. The combined filtrate and washings were evaporated to dryness. Column chromatography on deactivated basic alumina yielded 2-methyl-3H, 4-pyrimidone on elution with 1 : 1 ethanol-ethylacetate as crystals, m.p. 210-212° (lit. [71], 212°). This sample had same R_f value on t.l.c. and i.r. spectrum as an authentic sample, prepared as the intermediate in the synthesis of 3-amino-2-methyl-4-pyrimidone, see page 44 ; mixed m.p. 210-212°. No other product was detected.

(ii) in the presence of dimethylsulphoxide

To yield the sulphoximine on work up as described on p. 53 footnote (ii).

N-(3,4-dihydro-2-methyl-4-oxopyrimidin-3-yl)-S,S-dimethylsulphoximine, yellow needles (100%) from ethanol, m.p. 152-153° (Found: C, 41.8; H, 5.6; N, 20.9; S, 16.4; $C_7H_{11}N_3O_2S$ requires C, 41.8; H, 5.5; N, 20.9; S, 15.9%); ν_{max} : 3040, 1680 (C = O), 1585, 1535, 1260, 1205, 1160, 1060, 1035, 830, 805, 755 cm^{-1} ; δ (CDCl₃), 2.58 (s, 3H), 3.28 (s, 6H), 6.3 and 7.69 (two d's, ortho-coupling, J 6.5 c.p.s., 2H).

(g) Oxidation of 1-aminobenzimidazole (1-aminobenzimidazole)(i) alone

1-Aminobenzimidazole (0.5g) was dissolved in methylene chloride (20 ml) and the solution was rapidly stirred. Solid, powdered lead tetraacetate (1.17g) was added portionwise over 10 min. Nitrogen gas was evolved and the solution turned a deep brown colour. After a further 15 min, the solution was filtered, the residue being washed well with methylene chloride. The combined filtrate and washings were evaporated to dryness. The product was chromatographed on a column of deactivated basic alumina to give four fractions:

(i) elution with 1 : 3 ethyl acetate-methylene chloride gave benzimidazole (0.035g, 0.7%), m.p. 168-170° (lit, [107], 170°). This sample had identical R_f on t.l.c. and i.r. spectrum to an authentic sample.

(ii) further elution with 3 : 2 ethylacetate-methylene chloride gave 1-acetylbenzimidazole (0.105g, 24%) as brown crystals which were sublimed in vacuum to give needles, m.p. 112-114° (lit. [107], 113-114°, [116] 113°); ν_{\max} ; 3090, 1730, 1608, 1310, 1290, 1230, 1210, 955, 750, cm^{-1} ; δ (CDCl_3) 2.63 (s, 3H), 7.15-8.2 (m, 4H), 8.28 (s, 1H), m/e 160, 119, 118, 91, 90. This had an identical R_f value on t.l.c. and i.r. spectrum to an authentic sample (see below).

(iii) further elution with more 3 : 2 ethylacetate-methylene chloride gave the tetrazene, 1,1'-azobis(benzimidazole) as needles from (0.02g, 2%) ethylacetate-chloroform, m.p. 273-275° (decomp. with gas evolution); ν_{\max} ; 1600, 1270, 1225, 780, 740 cm^{-1} ; λ_{\max} ; 211, 262 (ϵ ; 19,000) 343 (ϵ , 18,000; m/e 262, 234, 233, 160.

(iv) further elution with 1 : 9 methanol-ethylacetate gave an intractable brown tar (0.02g).

Alternative synthesis of 1-acetylbenzimidazole

Benzimidazole (0.3g) was suspended in methylene chloride (20 ml), and acetic anhydride (2 ml) was added. The solution was left overnight at room temperature and evaporated to dryness. The residue was recrystallized from benzene-petroleum to give 1-acetylbenzimidazole (0.35 g) as needles, m.p. 109-111°.

Control experiments

(1) Benzimidazole (0.5g) was suspended in methylene chloride (20 ml) and anhydrous glacial acetic acid (2 ml) was added. This was stirred for 1 hr at room temperature and evaporated to dryness. Benzimidazole (0.5g) was recovered.

(2) Benzimidazole (0.5g) was suspended in methylene chloride (20 ml), glacial acetic acid (2 ml) followed by lead tetraacetate (1.88g) were added. After 1.5 hr t.l.c. showed no reaction had occurred.

(ii) in the presence of an olefin

To yield the following aziridines on careful chromatography on a column of deactivated alumina with 5 : 1 petroleum-methylene chloride, followed by recrystallization from ethylacetate-petroleum. Further elution with 1 : 9 methanol-ethylacetate gave very crude benzimidazole (5-20%)

(a) methyl 1-(benzimidazol-1-yl)-aziridine-2-carboxylate

from 1-aminobenzimidazole and methylacrylate, needles (43%), m.p. 96-97° (Found: C, 61.0; H, 5.0; N, 19.45; $C_{11}H_{11}N_3O_2$ requires C, 60.8; H, 5.1; N, 19.35%); ν_{max} ; 3120, 3040, 1735 (C=O),

1610, 1225, 740; δ (CDCl₃) 2.8-3.4 (m, 3H), 3.20 (?) and 3.78 (CO₂Me invertomers, total 3H) 7.2-7.9 (m, 4H) 7.9 (s, 1H).

(b) methyl 1-(benzimidazol-1-yl)-2-methylaziridine-2-carboxylate from 1-aminobenzimidazole and methyl methacrylate, needles (45%), m.p. 87-88° (Found: C, 62.3; H, 5.3; N, 18.6; C₁₂H₁₃N₃O₂ requires C, 62.3; H, 5.7; N, 18.2%); ν_{\max} ; 3120, 3045, 1740 (C = O), 1320, 1225, 745 cm⁻¹; δ (CDCl₃) 1.12 (major peak) and 1.70 (two invertomers of aziridine ring CMe, total 3H), 2.70 and 3.80 (two M's, 2H), 3.20 and 3.82 (major peak) (two invertomers of CO₂Me, total 3H), 7.0-7.8 (m, 4H), 7.9 (s, 1H); ^m/e 231, 203, 199, 172, 118.

(c) ethyl 1-(benzimidazole-1-yl)-2-methylaziridine-2-carboxylate from 1-aminobenzimidazole and ethylmethacrylate, colourless oil (50%).

(CDCl₃) 0.6 and 1.3 (major peak) (two t's, J 7 c.p.s., two invertomers of ethyl CH₃ group, 3H), 1.25 (major peak) and 1.70 (two invertomers of aziridine ring CMe, total 3H), 2.95 (m, 2H), 3.6 and 4.3 (major peak) (two q, J 7 c.p.s., two invertomers of ethyl CH₂ group, total 2H), 7.1-7.9 (m, 4H), 8.0 (s, 1H).

(iii) in the presence of dimethylsulphoxide

To yield the sulphoximine after work up as described on page 53 footnote (ii).

N-(benzimidazol-1-yl)-S,S-dimethylsulphoximine needles (100%), m.p. 156-157° (Found: C, 52.0; H, 5.65; N, 20.5, S, 15.05; C₉H₁₁N₃O₂S requires C, 51.7; H, 5.3; N, 20.1; S, 15.3%); ν_{\max} ; 3110, 3010, 1615, 1215, 1035 (S = O), 780, 770, 760 cm⁻¹; δ (CDCl₃) 3.05 (s, 6H), 7.1-7.85 (m, 4H), 7.90 (s, 1H).

(h) Oxidation of 3-amino-4-phthalazone in the presence of ethanol

3-Amino-4-phthalazone (0.5g) was dissolved in a mixture of absolute ethanol (5 ml) and methylene chloride (5 ml). Solid, powdered lead tetraacetate (2.0g) was added to the rapidly stirred solution over 10 min. After a further 10 min, the solution was filtered and the residue washed with methylene chloride. The combined filtrate and washings were evaporated to dryness and the residue chromatographed on deactivated basic alumina. Elution with 4 : 1 methylene chloride-petroleum gave a solid which was recrystallized from ethylacetate-petroleum to give 3-ethoxyphthalimidine (0.33g, 65%) as needles, m.p. 106-108° (lit. [92], 108°), ν_{\max} ; 3200, 3100, 1705, 1620, 1095, 1080, 750, cm^{-1} ; $\delta(\text{CDCl}_3)$; 1.20 (t, J 5 c.p.s., 3H), 3.55 (m, due to optical isomers, 2H), 5.95 (s, 1H), 7.3-8.0 (m, 4H), 8.60 (broad singlet, 1H). This sample had an identical R_f value on t.l.c. and i.r. spectrum to an authentic sample*, mixed m.p. 106-108°.

*Prepared by the method of Dunet and Willemart [92]. I thank Dr. E. Anderson for donation of this sample.

(i) Oxidation of 3-amino-1-methyl-4-phthalazone(i) alone

3-Amino-1-methyl-4-phthalazone (1.0g) was dissolved in methylene chloride (15 ml) and solid, powdered lead tetraacetate (3.0g) was added to the rapidly stirred solution over 10 min. Nitrogen gas was evolved and the solution became yellow in colour. After a further 1 hr, the solution was filtered, the residue being washed with methylene chloride. The combined filtrate and washings were evaporated to dryness. Column chromatography of the residue

on deactivated basic alumina gave a series of yellow oils as the polarity of the solvent was increased. The main fraction, on elution with 1 : 3 methylene chloride-petroleum gave a yellow viscous oil (0.35g) which polymerized to a glass on standing for one day, but immediately on heating to 60°.

(ii) in the presence of an olefin

Oxidation was performed as described above in the presence of styrene, butadiene and tetraphenylcyclopentadienone. No isolable adduct was obtained after chromatography, the only product being the oil which polymerized as described above.

(iii) in the presence of dimethyl sulphoxide

Oxidation was performed as described above in the presence of dimethyl sulphoxide. Chromatography yielded only the same oil which polymerized as described. No adduct with DMSO was isolated.

(iv) in the presence of ethanol

3-Amino-1-methyl-4-phthalazone (1.0g) was dissolved in 3 : 2 absolute ethanol-methylene chloride and oxidized exactly as described above in the oxidation alone. Elution of the column with methylene chloride gave 1,1-ethoxy methyl phthalimidine (0.7g, 64%) which was recrystallized from ethylacetate-petroleum as needles, m.p. 149-151° (Found: c, 69.1; H, 6.8; N, 7.55; $C_{11}H_{13}NO_2$ requires C, 69.1; H, 6.85; N, 7.3%); ν_{max} ; 3210, 1705, 1670, 1610, 1130, 1100, 780, 740, cm^{-1} ; $\delta(CDCl_3)$, 1.08 (T, J 7 c.p.s., 3H), 2.5 - 3.6 (m, due to optical isomers, 2H), 7.13 (broad singlet, 1H), 7.25-8.0 (m, 4H); λ_{max} 213 (shoulder), 222 (ϵ , 8,750), 229 (ϵ ; 8,300), 273 (ϵ ; 660), 281 (ϵ , 460); m/e 191, 174, 145 (base peak, P^+ - EtOH), 130, 118.

(j) Oxidation of 3-amino-1-phenyl-6,7-benzphthalaz-4-one(i) alone

3-amino-1-phenyl-6,7-benzphthalaz-4-one (0.25g) was dissolved in methylene chloride (10 ml) and solid, powdered lead tetraacetate was added over 10 min. to the rapidly stirred solution. Nitrogen gas was evolved and the solution became a yellow colour. After a further 10 min, the product was filtered and the residue washed with methylene chloride. The combined filtrate and washings were evaporated to dryness. The residue was chromatographed on a column of deactivated basic alumina to give two fractions:

(i) elution with 4 : 1 methylene chloride-petroleum gave a meringue and white solid (0.03g).

(ii) further elution with 2 : 3 ethanol-ethylacetate gave crystals (0.108g) which were recrystallized twice from ethylacetate-petroleum to give 1,1-hydroxy phenyl-5,6-benzphthalimidine, m.p. 198-200°.

T.l.c. showed fraction (i) to be mainly this compound. ν_{\max} ; 3300 (broad), 1705 (C = O), 1640, 1050, 885, 790, 770, 745, 710, 695 cm^{-1} ; λ_{\max} (CCl_3 solution); 3420 (broad N - H), 3400-3120 (very broad, OH), 1705 (C = O), 1640. cm^{-1} ; δ (D_6DMSO); 6.90 (1H, disappears on adding D_2O), 7.15-8.1 (m, 9H), 8.2 (s, 1H) 8.65 (m, 1H) (OH not seen); $\lambda_{\max}^{\text{m/e}}$; 239 (ϵ ; 45,800), 284 (ϵ ; 825), 295 (ϵ ; 595); 275 (small parent peak), 257 (base peak, $\text{P}^+ - \text{H}_2\text{O}$), 180, 126.

(ii) in the presence of ethanol

Oxidation in ethanol was performed exactly as described above. Column chromatography gave only a yellow meringue; t.l.c. showed this to be complex. No adduct with ethanol was isolated on further chromatography.

(k) Oxidation of 1-aminoindazole(i) alone

1-Aminoindazole (2.0g) was dissolved in methylene chloride (30 ml) and solid, powdered lead tetraacetate (9.41g) was added over 10 min to the rapidly stirred solution. Nitrogen gas was evolved and the solution became a deep green, turning to a purple colour. After a further 10 min, the solution was filtered, the residue being washed with methylene chloride. The combined filtrate and washings were evaporated to dryness. The product was chromatographed on a column of deactivated basic alumina to give four fractions:

(i) elution with 4 : 1 methylene chloride-petroleum gave yellow oily crystals (0.054g) which was sublimed under high vacuum to give the "straight dimer", dibenzo[b,f][1,5]diazocine (0.005g, 1.6%) as yellow needles, m.p. 163-165°; ν_{\max} ; 1620 (very weak C = N), 1510, 1145, 817, 750, 705 cm^{-1} ; λ_{\max} ; 208, 248 (ϵ ; 122,000), 349 (shoulder), 363 (ϵ ; 20,800); m/e 206, 181, 180 (base peak, P^+ - CN) 179 (P^+ - HCN), 154, 153, 153, 152 (P^+ - 2.HCN), 103, 90, 76.;

(ii) further elution with 4 : 1 methylene chloride-petroleum gave a colourless oil (0.225g) which was sublimed under high vacuum to give N-acetyl-o-aminobenzaldehyde (0.17g, 7%), which was recrystallized from petroleum as needles, m.p. 66-68° (lit. [107], 70-71°); ν_{\max} ; 3250, 1700, 1665, 1610, 1595, 1300, 1200, 1165, 785 cm^{-1} ; δ (CDCl_3) 2.2 (s, 3H), 6.95-7.65 (m, 4H), 8.65 (m, 2H), 9.80 (s, 1H), 11.0 (broad s, disappears on adding D_2O , 1H). This sample had an identical R_f on t.l.c., p.m.r. and i.r. spectra, to an authentic sample (see below); mixed m.p. 66-69°.

(iii) further elution with 1 : 1 ethylacetate-methylene chloride gave

a brown oil and solid (0.81g) which was sublimed under high vacuum to give indazole (0.34g, 19%) as crystals, m.p. 142-145° (lit. [107], 146.5°). This sample had an identical R_f value on t.l.c. and i.r. spectrum to an authentic sample; mixed m.p. 143-144°.

(iv) further elution with ethylacetate gave a brown tar (0.5g).

Synthesis of N-acetyl-o-aminobenzaldehyde

o-Aminobenzaldehyde* (0.2g), prepared by reduction of o-nitrobenzaldehyde [117], was warmed with acetic anhydride (5 drops) for 0.5 hr at 60°. On evaporation to dryness and cooling a solid was produced which was recrystallized from petroleum to give N-acetyl-o-aminobenzaldehyde (0.30g) as needles, m.p. 68-70°.

* I thank Mr, D.L. Forster, University of Leicester, for donation of the sample.

(ii) in the presence of dimethyl sulphoxide

1-Aminoindazole (0.64g) was dissolved in dimethylsulphoxide (6 ml) and solid powdered lead tetraacetate (3.0g) was added over 10 min to the rapidly stirred solution. Nitrogen gas was evolved and the solution became a deep red colour. After a further 10 min, the solution was warmed to 80°, cooled, and poured into water (50 ml). The solution was extracted with ethylacetate (3 x 20 ml). The combined extracts were washed with water (2 x 5 ml), dried, filtered and evaporated to dryness to give a brown oil (0.58g). Chromatography on a column of silica gel M.F.C. gave two fractions:

(i) elution with 2 : 3 petroleum-methylene chloride gave crystals of N-acetyl-o-aminobenzaldehyde (0.14g, 18%) on recrystallization from petroleum, m.p. 66-67° (Characterized as described above).

(ii) further elution with 2 : 3 petroleum-methylene chloride gave indazole (0.086g, 15%), recrystallized from benzene-petrol as crystals,

m.p. 143-145° (Characterised as described above).

This experiment was repeated and no DMSO adduct was isolated.

(iii) in the presence of ethanol

(a) 1: 1 ethanol-methylene chloride at 0°

1-Aminoindazole (0.5g) was oxidized by lead tetraacetate in 1 : 1 ethanol-methylene chloride at 0° as described above for the oxidation alone. The product was chromatographed on a deactivated basic alumina column to give three products:

(i) elution with 1 : 3 methylene chloride-petroleum gave the

"angular dimer" 4,12-diazax11,12-dihydro-1,2-benzobiphenylene (0.035g, 5%), as crystals which were recrystallized from petrol as plates,

m.p. 98-100° (Found: C, 80.3; H, 4.7; N, 13.2; $C_{14}H_{10}N_2$

requires C, 81.5; H, 4.9; N, 13.6%); ν_{max} ; 1615 (strong C = N),

1585, 1565, 1500, 775, 705, 685 cm^{-1} ; δ ($CDCl_3$) 1.22 (s, 1H?),

7.3-8.2 (m, 6H), 8.6 (m, 2H), 9.2 (s, 1H); λ_{max} ; 209, 263 (ϵ ; 13,000),

288 (shoulder) (ϵ , 4,540), 300 (shoulder), 324 (shoulder) (ϵ , 1950),

336 (shoulder) (1,800); m/e 206 (P^+ and base peak), 180, 179 (second

largest peak, P^+ - HCN), 154, 153, 152 (P^+ - 2.HCN), 151, 118, 103,

81.

(ii) further elution with 2 : 3 methylene chloride-petroleum gave

yellow crystals (0.005g) m.p. 318-320°, λ_{max} ; 208, 238 (shoulder),

286 (ϵ ; 11,460), 295 (ϵ , 13,000), 309 (ϵ , 11,400), 360 (shoulder),

376 (ϵ ; 8,000), 398 (ϵ ; 7,050), 424 (shoulder); m/e 382, 326, 320,

311, 310, 232, 206, 118, 103.

(iii) further elution with methylene chloride gave indazole (0.2g, 40%),

m.p. 140-145°, characterized as described above.

(b) in ethanol at -70°

1-Aminoindazole (1.0g) was dissolved in ethanol (30 ml) and

cooled to -70° in an acetone-dry ice bath. Oxidation was performed as described for the oxidation alone, the solution being allowed to warm to room temperature overnight. Column chromatography on deactivated basic alumina gave two products:

(i) elution with 2 : 3 petroleum-methylene chloride gave

2-aminobenzylidene-N-(indazol-1-yl)imine (10%) as light yellow crystals, m.p. $141-142^{\circ}$ (Found: C, 70.8; H, 5.0; N, 23.1; $C_{14}H_{12}N_4$ requires C, 71.2; H, 5.1; N, 23.7%); ν_{\max} ; 3455, 3340 (NH_2), 1615, 1595, 1160, 1140, 1050, 915, 905, 840, 750 cm^{-1} ; λ_{\max} ; 212, 237 (ϵ , 26,000), 262 (shoulder) 274 (shoulder), 315 (ϵ , 12,000), 329 (ϵ ; 15,800), 374 (ϵ , 18,020); δ ($CDCl_3$) 5.9 (broad singlet, 2H, disappears on adding D_2O), 6.6-7.8 (m, 8H) 8.0 (s, 1H), 9.2 (s, 1H); m/e 236, 220, 207, 180, 118, 104, 91, 58. This sample had identical R_f value on t.l.c., i.r., n.m.r. and u.v. spectra to the product synthesized alternatively as described below; m.p. $141-143^{\circ}$.

(ii) further elution with more 2 : 3 petroleum-methylene chloride gave indazole (6%), m.p. $140-144^{\circ}$, characterized as described above.

Alternative synthesis of 2-aminobenzylidene-N-(indazol-1-yl)imine

o-Aminobenzaldehyde [117] (0.022g) was dissolved in warm ethanol (2 ml) and acetic acid (1 drop) was added. 1-Aminoindazole (0.025g) was added and the resulting yellow solution heated at 60° for 1 hr. The solution was evaporated to dryness and the residue recrystallized from ether-petrol to give 2-aminobenzylidene-N-(indazole-1-yl)imine as cream needles, m.p. $141-147^{\circ}$.

(1) Oxidation of 2-aminoindazole

(i) alone

2-Aminoindazole (1.0g) was oxidized by lead tetraacetate

in methylene chloride exactly as described for 1-amino indazole, p. 75

Column chromatography on deactivated basic alumina gave two fractions:

(i) elution with 7 : 3 methylene chloride-petroleum gave a yellow oil (0.21g). Preparative t.l.c. of this oil on silica plates gave two compounds:

(a) N-acetyl-o-aminobenzaldehyde (0.16g, 14%) as needles, m.p. 67-70°, characterized as described above.

(b) the "angular dimer", recrystallized from petrol as plates (0.03g, 2.2%), m.p. 95-97°. This sample had identical R_f values, i.r. spectrum and mass spectrum as the sample prepared from oxidation of 1-aminoindazole, see p. 77 mixed m.p. 95-98°.

(ii) further elution with methylene chloride gave a brown tar (0.21g) which was discarded.

(ii) in the presence of dimethyl sulphoxide

2-Aminoindazole (0.5g) was dissolved in dimethyl sulphoxide (20 ml) and oxidized with lead tetraacetate exactly as described for 1-aminoindazole in dimethyl sulphoxide, p. 76. Column chromatography on deactivated basic alumina gave two fractions:

(i) elution with 2 : 3 methylene chloride-petroleum gave N-acetyl-o-aminobenzaldehyde (0.113g, 18%), m.p. 64-68°, characterized as described above.

(ii) further elution with 1 : 1 methylene chloride-petroleum gave N-(indazole-2-yl)-S,S-dimethylsulphoximine recrystallized from benzene-petrol as light yellow plates (0.07g, 8.3%), m.p. 138-140° (Found: C, 51.5; H, 5.2; N, 19.7; S, 12.2; $C_9H_{11}N_3OS$ requires C, 51.7; H, 5.3; N, 20.1; S, 11.5%); ν_{max} ; 3120, 3020, 1625,

1195, 1035 ($S = O$) 1010, 745 cm^{-1} ; δ (CDCl_3) 3.30 (s, 6H), 6.9-7.8 (m, 4H) 7.8 (s, 1H); m/e 209, 118, 103, 76.

(iii) in the presence of cyclopentadiene

2-Aminoindazole (1.0g) was oxidized by lead tetraacetate in 2 : 3 methylene chloride-cyclopentadiene (freshly distilled) exactly as described for the oxidation of 1-aminoindazole alone, page 75.

Column chromatography on deactivated basic alumina gave two fractions:

(i) elution with 3 : 2 methylene chloride-petroleum gave a solid which was sublimed under high vacuum to give two products:

(a) the "angular dimer" (3 crystals), m.p. 98-100°, characterized by its R_f value on t.l.c. and m.m.p. 97-99° with the sample obtained on oxidations above.

(b) 2-aminobenzylidene-N-(indazol-2-yl)imine (0.3g) 34% bright yellow needles, m.p. 166-167° (Found: C, 70.9; H, 5.0; N, 23.8; $\text{C}_{14}\text{H}_{12}\text{N}_4$ requires C, 71.2; H, 5.1; N, 23.7%); ν_{max} ; 3460, 3330 (NH_2) 1615, 1595, 1210, 970, 790, 750 cm^{-1} ; λ_{max} ; 208, 245 (ϵ ; 24,200), 265 (shoulder), 305 (ϵ , 21,000), 316 (ϵ , 22,900), 390 (μ , 15,500); δ (CDCl_3) 6.0 (broad singlet, disappears on adding D_2O , 2H); 6.5-7.9 (m, 8H), 8.05 (s, 1H), 9.6 (s, 1H); m/e 236, 209, 180, 169, 135, 118. This sample had identical R_f value on t.l.c., i.r., n.m.r. and u.v. spectra to a sample prepared by an alternative synthesis (see below).

(ii) further elution with methylene chloride gave a brown tar (0.3g) which was discarded.

No cyclopentadiene adduct was observed in the crude product.

Alternative synthesis of 2-aminobenzylidene-N-(indazol-2-yl)imine

o-Aminobenzaldehyde (0.26g) was dissolved in ethanol (50ml) and acetic acid (1 drop) was added. The solution was warmed to 60° and 2-aminoindazole (0.3g) was added. The resulting yellow solution was

heated at 40° for 1 hr. On cooling, bright yellow needles of
2-aminobenzylidene-N-(indazol-2-yl)^{imine} (0.4g) m.p. 163-165° crystallized.

3. Reactions of 2,3-Benzo-6-(3,4-dihydro-2-methyl-4-oxoquinazolin-3-yl)-6-azabicyclo[3,1,0]hexane (the indene adduct from 3-amino-2-methyl-4-quinazolone).

(i) Thermolysis

The indene adduct (0.1g) was sealed under high vacuum in a glass tube and heated overnight at 180°. The solid had then become black and white crystals had appeared as the sublimate. On cooling, the tube was opened and t.l.c. showed the product to be complex. No isoquinoline was present (t.l.c.). Attempted sublimation of the solid gave only 2-methyl-3H,4-quinazolone, identified by its t.l.c. and i.r. spectrum.

(ii) Photolysis

The indene adduct (0.005g) was dissolved in dry, oxygen-free benzene (10 ml) and photolysed for 2 days in quartz in the Rayonet apparatus at 2,537 cm⁻¹. T.l.c. showed the product to be complex; no isoquinoline was observed (t.l.c.).

(iii) Acid hydrolysis

The indene adduct (0.15g) was added to 2N-hydrochloric acid (10 ml), in which it quickly dissolved. The solution was refluxed for 1 hr to give 2-indanone (0.06g), m.p. 56° (lit. [107] 58°) as a sublimate in the condenser. This sample had identical R_f on t.l.c. and i.r. spectrum (C = O at 1740 cm⁻¹) as an authentic sample. It formed a 2,4-dinitrophenylhydrazone as orange crystals, m.p. 196-197° (lit. [107] 196-197°dec;).

The aqueous part was made basic with 2N sodium hydroxide solution, extracted with ethyl acetate (3 x 10 ml), and the combined

extracts then washed with water (5 ml). The solution was dried, filtered and evaporated to dryness to give 3-amino-2-methyl-4-quinazolone (0.09g, 100%) as needles, m.p. 147-149°, characterized by t.l.c. and its i.r. spectrum.

4. Syntheses of Fused Aziridines by Reduction of β -Iodo Azides

These were performed essentially by the method of Hassner [119].

(1) Iodineazide adducts of cyclic olefins

(a) preparation of iodineazide

To a stirred slurry of sodium azide (15.0g, 0.25 mole) in dry acetonitrile (100 ml) at -5° was added an iodine monochloride (18.3g, 0.113 mole) solution in acetonitrile (10 ml) over 20 mins. The yellow solution was stirred for a further 10 min at -5° . The resulting solution of iodine azide was used as described below:

(b) addition of iodine azide to olefins

(1) trans-1-azido-2-iodoindane from indene and iodine azide

To the solution of iodine azide prepared as described above, indene (11.69g, 0.1 mole) was added; the solution was allowed to warm to room temperature and was stirred overnight. The yellow solution was poured into water (300 ml) to give a deep red solution. This was extracted with ether (3 x 100 ml), the combined extracts washed with 10% aqueous sodium thiosulphate solution (150 ml), then with water (2 x 50 ml), dried, filtered and evaporated to dryness. trans-1-azido-2-iodoindane (25.0g, 88% based on indene) was crystallized from petrol-ether as yellow prisms, m.p. $55-56^{\circ}$ (Found: C, 38.1; H, 2.8; N, 14.6; $C_9H_8N_3I$ requires C, 37.9; H, 2.8; N, 14.7%); ν_{max} ; 2105 (N_3), 1600 cm^{-1} ; δ ($CDCl_3$) 3.0-3.90 (m, 2H), 4.32 (q, J 5.5 c.p.s. split further, 1H), 5.10 (d, J 5.5 c.p.s., 1H), 7.25 (m, 4H)

The following iodine azide adducts were prepared in the same way:

(2) trans-1-azido-2-iodocyclopentane

From iodine azide and cyclopentene (89%), yellow liquid

turning red on standing. ν_{\max} ; 2100 (N_3), 1250 cm^{-1} ; δ ($CDCl_3$); 1.40-2.80 (m, 6H) 4.0-4.4 (m, 2H). Satisfactory analysis was not obtained due to the instability of this compound.

(3) trans-4-azido-5-iodocyclohex-1-ene

From iodine azide and 1,4 cyclohexadiene (40%), yellow liquid, rapidly turning red on standing. ν_{\max} ; 2100 (N_3), 1600, 1435, 1250 cm^{-1} ; δ (CCl_4) 2.2-2.7 (m, 2H), 2.7-3.1 (m, 2H), 3.6-4.5 (very complex m, 2H), 5.3-6.0 (m, 2H). Satisfactory analysis was not obtained due to the instability of this compound.

(4) trans-1-azido-2-iodo-1,2,3,4-tetrahydronaphthalene

from iodine azide and 1,2 dihydronaphthalene (91%), yellow prisms from petroleum, m.p. 46-47° (Found: C, 40.0; H, 3.3; N, 13.55; $C_{10}H_{10}N_3I$ requires C, 40.0; H, 3.35; N, 14.05%); ν_{\max} ; 2110 (N_3), 1605, 1200, 1095, 750 cm^{-1} ; δ (CCl_4), 1.5-2.10 (m, 2H), 2.6 (m, 2H), 4.35 (q, J 4 c.p.s., 1H), 2.65 (d, J 4 c.p.s., 1H), 7.0 (m, 4H).

(5) Attempted: trans-3-azido-4 iodocyclopent-1-ene

From iodine azide and cyclopentadiene to give a red oil (20%) and brown "polymer" (~40%).

Data on red oil: ν_{\max} ; 2100 (N_3), 1610, 1360, 1250, 1000, 760 cm^{-1} ; δ (neat) 2.2-3.1 (m, 2H or 3H?), 4.5 (m, 2H), 6.1 (m, 2H)

(ii) Reduction of iodine azide adducts by $LiAlH_4$

(1) Indano[1,2,-b]aziridine

trans-1-Azido-2-iodoindane (12.0g) was dissolved in dry ether (50 ml) and the solution was added dropwise over 30 min to a stirred slurry of $LiAlH_4$ [footnote a] (3.2g, 2 molar equivalents) in dry ether at 0°. The solution frothed during the addition; it was allowed to

warm to room temperature overnight. The solution was cooled to -5° and 2N sodium hydroxide solutions (9.0 ml) was added very slowly over 20 min [footnote b], the temperature at no time being allowed to rise above $+5^{\circ}$. The solution was stirred for a further 10 min and filtered. The residue was powdered in a mortar under ethyl acetate and filtered; this procedure being repeated several times [footnote c]. The combined ether-ethyl acetate liquors were dried, filtered and evaporated to dryness [footnote d], to give indano[1,2,-b]aziridine as a colourless oil (5.0g, 90%) which rapidly became brown, becoming a black tar in 24 hr [footnote e].

ν_{max} ; (smear) 3290, 3220, 3090, 3060, 2920, 2850, 1600, 1460, 1430, 1130, 960, 760, 730 cm^{-1} ; δ (CDCl_3) 1.20 (broad singlet, disappears on adding D_2O), variable δ value, depending on concentration, 1H), 2.95 (m, 3H), 3.1 (d, 53.5 c.p.s., further split, 1H), 7.2 (m, 4H) Properties are consistent with those reported by Hassner [119d].

Footnotes on General Procedure

- a] The solution of iodine azide must be added very slowly to prevent excessive frothing.
- b] The first 2.0 ml of sodium hydroxide solution must be added extremely slowly, with vigorous stirring. If the temperature is allowed to rise above $+5^{\circ}$ excessive hydrolysis of the aziridine occurs.
- c] The aluminium salts precipitated adsorb much of the aziridine. This technique greatly improves the yields.
- d] The solution is dried over sodium sulphate for at least 1.5 hr. Traces of water cause excessive decomposition. Evaporation to dryness is performed under reduced pressure at room temperature.
- e] The aziridine can be stored in dry benzene at -40° , under nitrogen for up to 5 days, but reactions performed immediately on isolation gave the best yields of products.

The indano[1,2-b]aziridine on immediate isolation formed a picrate in alcohol as yellow prisms, m.p. 240-245° dec; ν_{\max} ; 3220, 1630, 1570, 1540, 1510, 1270, 1165, 1080, 910, 790, 760, 740, 710 cm^{-1} ; m/e 229 (picric acid), 132 (protonated aziridine).

The following fused aziridines were prepared in the same manner:

(2) 6-Azabicyclo[3,1,0]hexane

From the iodine azide adduct of cyclopentene; (30%) colourless oil, rapidly turning black, becoming a tar in 1 hr. Treatment with phenylisothiocyanate in warm petrol gave the N-phenyl carbamoyl derivative as yellow crystals, m.p. 164-167° (lit. [129], 167-168°).

(3) Attempted: 7-azabicyclo[4,1,0]hept-3-ene

From the iodine azide adduct of cyclohexa-1,4-diene. Only a yellow gum was isolated (~10%) which rapidly resinified.

(4) 2,3-benzo-7-azabicyclo[4,1,0]heptane

From 1,2-dihydronaphthalene, (91%) colourless oil, rapidly becoming black in 1 hr. ν_{\max} ; 3280, 3220, 3010, 2920, 2845, 1600, 1560, 1490, 1280, 850, 790, 740 cm^{-1} ; δ (CDCl_3); 1.60 (broad singlet, disappears on adding D_2O , variable value of δ , depending on concentration). 1.5-3.0 (m, 6H), 7.05 (m, 4H). These properties are consistent with those found by Hassner [119d].

(5) Attempted: 6-azabicyclo[3,1,0]hex-2-ene

From the red oil obtained from the addition of iodine azide to cyclopentadiene to give a brown oil (~40%) which rapidly resinified. ν_{\max} ; 3280, 3050, 1660, 1600, 1375, 1245, 1050, 755 cm^{-1} .

5. Oxidations of Fused Aziridines

(1) Indano[1,2-b]aziridine to isoquinoline

Indano[1,2-b]aziridine (0.5g), obtained by reduction of the iodine azide adduct of indene, was taken immediately on isolation and dissolved in dry methylene chloride (25 ml). The solution was cooled to -70° in an acetone-dry ice bath. Solid powdered lead tetraacetate (1.69g) was added portion-wise to the rapidly stirred solution over 2 min. to give a pale yellow solution. After being allowed to warm to room temperature the solution was evaporated to dryness. The residue was digested with hot "Analar" acetone (30 ml) and the precipitate of lead diacetate (m.p. $202-205^{\circ}$) filtered off. The precipitate was washed well with hot acetone. The combined washings and filtrate were evaporated to dryness. The residue was now digested with ether as described with acetone above. Finally, the residue was treated in the same way with boiling petroleum ($60-80^{\circ}$). Evaporation to dryness of this solution gave pure isoquinoline (0.30g, 16%), m.p. $20-24^{\circ}$ (lit. [107], 24.6°) brown crystals, having an identical i.r. spectrum and Rf value on t.l.c. to an authentic sample. It was further characterized as its picrate, m.p. $224-227^{\circ}$ (lit. [107], 226°), methiodide, m.p. 161° (lit. [107], 159°), and acid sulphate, m.p. $207-208^{\circ}$ (lit. [107], 207.5°). All derivatives had identical i.r. spectra to authentic samples. Four repetitions of this reaction gave yields ranging from 50-60% of isoquinoline.

The following (fused) aziridines were oxidized in the same manner:

(2) Oxidation of 6-azabicyclo[3,1,0]hexane(a) with 1 molar equivalent of lead tetraacetate

T.l.c. showed no reaction had occurred at -70° . On refluxing the solution overnight a very complex product (t.l.c.) was obtained.

(b) with 2 molar equivalents of lead tetraacetate

On refluxing the solution overnight a complex product (t.l.c.) containing no pyridine was obtained.

(3) Oxidation of 2,3-benzo-7-azabicyclo[4,1,0]heptane

T.l.c. showed no reaction with lead tetraacetate (1 molar equivalent) at -70° . The solution was refluxed overnight. After work up with hot acetone as described above, preparative t.l.c. (silica plates, 20% methanol-ethyl acetate solvent) gave a deep brown oil (30%), ν_{\max} ; 3300, 1730 (C=O, acetate), 1370, 1230, 1020, 750 cm^{-1} ; δ (CDCl₃) 2.0 (two singlets (?) COCH₃) 2.5-3.4 (A₂B₂m, 4H), 7.2 (m, 4H).

(4) Oxidation of the brown oil obtained on LiAlH₄ reduction of the iodine azide-cyclopentadiene reaction product

By lead tetraacetate at -70° . Preparative t.l.c. (silica plate, ethyl acetate solvent) gave pyridine (~1%), identified as its picrate, yellow crystals m.p. $151-154^{\circ}$ which had an identical i.r. spectrum to an authentic sample; m.m.p. $152-155^{\circ}$ (lit. [107], $165-166^{\circ}$).
^m/_e 229 (picric acid), 79 (pyridine).

6. Preparation and Solvolysis of N-Chloroindano[1,2-b]aziridine(1) Preparation(a) using t-butyl hypochlorite

Indano[1,2,-b]aziridine (1.0g) was taken immediately on isolation and dissolved in dry methylene chloride and cooled to -70° in an acetone-dry ice bath. Nitrogen was bubbled through the stirred solution for 10 min and t-butyl hypochlorite (0.85g) in methylene chloride (5 ml) was added slowly over 5 min. The solution was stirred for a further 10 min. then allowed to warm to room temperature (see footnotes below). The solution was evaporated to a low bulk (~ 1 ml) under reduced pressure (temperature 20°). On preparative t.l.c. (silica plate, ether solvent) two fractions were obtained:

(1) $R_f \sim 0.9$, consisting of two very close spots, which were inseparable on further t.l.c. due to thermal lability (see footnotes below). The ratio of the higher R_f to lower R_f spot was ca. 4 : 1. These were probably the exo- and endo-N-chloroindano[1,2-b]aziridines (0.72g) isolated as a yellow oil which decomposed to a black tar in 1 hr. Data on the mixture: ν_{\max}^{max} ; (thin film), 3100, 2920, 1620, 1590, 1158, 825, 760, 725, 695 cm^{-1} ; δ (CDCl_3) 3.0-4.0 (m, 4H), 7.0-7.6 (m, 4H). It was not possible to assign peaks for the endo- and exo-isomers due to rapid decomposition in solution; m/e , 167, 165, 130 (P^+-Cl) (base peak), 129 ($\text{P}^+-\text{Cl}-\text{H}$).

(2) R_f 0.6 (0.032g) isoquinoline, characterized as its picrate (m.p. $223-225^{\circ}$) and i.r. spectrum.

(b) using sodium hypochlorite

Indano[1,2-b]aziridine (3.0g) was taken immediately on isolation

and water was added (50 ml). To the rapidly stirred emulsion at 0°, an ice cold solution of sodium hypochlorite (13.65 ml, 1 molar equivalent of a 1.68N solution; diluted with an equal volume of water) was added dropwise over 5 min. After a further 10 min, the solution was diluted with an equal volume of water and extracted with ethyl acetate (3 x 25 ml). The combined extracts were washed with water, dried, filtered and evaporated to dryness to give a brown oil (2.8g) which rapidly turned black. T.l.c. showed it to contain the same mixture of the N-chloro compounds and isoquinoline (together with many other products) as obtained in the t-butyl hypochlorite reaction. The product was not purified.

(c) using N-chlorobenzotriazole [61]

Indano[1,2-b]aziridine was taken immediately on isolation and treated with N-chlorobenzotriazole (1 molar equivalent) in methylene chloride at -70° exactly as described for t-butyl hypochlorite above. Preparative t.l.c. (silica, ether solvent) gave three fractions: the same mixture of N-chloroaziridines and isoquinoline, as described above, and benzotriazole. The latter two products were difficult to separate.

General Notes on Preparations

(1) Heating the solutions above room temperature led to excessive decomposition. Evaporation of the t-butyl hypochlorite crude reaction mixture to complete dryness, before preparative t.l.c., led to an explosion.

(2) t-Butyl hypochlorite gave the cleanest reaction.

(ii) Solvolysis of N-chloro[1,2,-b]aziridine

The mixture of endo- and exo-N-chloro[1,2,-b]aziridines from

the t-butyl hypochlorite chlorination (0.72g) was dissolved in aqueous methanol (50 ml, 4 : 1 methanol-water) and left a room temperature for 40 hr (see footnote). Preparative t.l.c. (silica, ether solvent) of the product gave two fractions:

(1) $R_f \sim 0.4$; isoquinoline (0.1g), identified as its picrate, m.p. 225-227°.

(2) $R_f = 0.0$; colourless oil (0.56g) ν_{\max} ; 3450 (broad), 1650, 1620, 1400, 740, 660 cm^{-1} ; δ (CDCl_3) - very complex.

Similar solvolyses on crude N-chloro compounds from sodium hypochlorite and N-chlorobenzotriazole chlorinations gave 10-15% yields of isoquinoline, overall, based on crude indano[1,2,-b]aziridine.

Footnote The reaction was followed by t.l.c. (silica, ether solvent). The minor spot of lower R_f (designated the endo-isomer) disappeared quicker than the major spot of higher R_f value.

7. Alternative Syntheses and Oxidation of Indano[1,2-b]aziridine(1) (a) From ethyl azidoformate and indene(i) N-ethoxycarbonylindano[1,2-b]aziridine

A mixture of redistilled indene (16g) and freshly prepared ethyl azidoformate [130] (15g) was added dropwise over 0.5 hr to indene (10 ml) which was stirred under nitrogen at 155°. Rapid evolution of gas occurred and the solution became red-brown in colour. After gas evolution had ceased, the solution was heated for a further 2 min, when i.r. spectrum showed no azide (2100 cm^{-1}) in the mixture. The product was cooled and chromatographed on a column of basic alumina to give three fractions:

1. elution with petroleum gave indene (11.4g) identified by its i.r. spectrum.
2. further elution with petroleum gave N-ethoxycarbonylindano[1,2-b]-aziridine (6.7g, 24% based on the azidoformate) recrystallized from petrol as prisms, m.p. 35-38° (Found: C, 71.4; H, 6.4; N, 6.6; $\text{C}_{12}\text{H}_{13}\text{NO}_2$ requires C, 70.9; H, 6.45; N, 6.9%); ν_{max} ; 3030, 1725, 1303, 1215, 1175, 1010, 795, 760, 720 cm^{-1} ; $\delta(\text{CCl}_4)$ 0.81 (t, J 8 c.p.s. 3H) 3.05 (t, J 18 c.p.s., split further into doublets, J 5 c.p.s., 1H), 3.45 (d, J 1 c.p.s., split further, 2H), 3.58 (q, J 8 c.p.s., split further, 2H), 3.65 (m, 1H), 7.0-7.5 (m, 4H) m/e 203, 174, 158, 130.
3. further elution with methylene chloride gave a red-brown tar (10.3g) which was discarded.

(ii) hydrolysis of N-ethoxycarbonylindano[1,2-b]aziridine

The aziridine (0.5g) was dissolved in ethanol (10 ml) and an ethanolic solution of potassium hydroxide was added. [potassium hydroxide

(0.6g, 4.35 molar equivalents) dissolved in water (1 ml) and ethanol (50 ml) added].

The solution was warmed to 60°, then left a room temperature overnight. The precipitate of potassium carbonate (0.2g, 100%) was filtered off and the clear orange solution was evaporated to dryness under reduced pressure at a temperature not exceeding 30°. The dark brown residue was extracted with warm methylene chloride (4 x 20 ml), the extracts dried, filtered and evaporated to dryness under reduced pressure to give indano[1,2-b]aziridine (0.3g, crude) as a brown oil which had an identical i.r. spectrum and Rf value on t.l.c. to the sample prepared as described on p. 85

(iii) Oxidation

This crude indano[1,2-b]aziridine (0.3g) was oxidized with lead tetraacetate as described in p. 88, to give isoquinoline (0.09g, 28% based on the N-carbethoxyaziridine) identified as its picrate and i.r. spectrum.

(b) From t-butylazidoformate and indene

(i) N-t-butoxycarbonylindano[1,2-b]aziridine

Pyrolysis of t-butylazidoformate (15g) in indene (16g) exactly as described above for ethyl azidoformate gave N-t-butoxycarbonyl indano[1,2-b]aziridine (9.0g), recrystallized from petrol as prisms, m.p. 73-75°. (Found: C, 73.7; H, 7.6; N, 6.0; C₁₄H₁₇NO₂ requires C, 72.7; H, 5.4; N, 6.1%); ν_{\max} ; 3060, 3030, 1705, 1365, 1330, 1150, 965, 875, 800, 760, 720 cm⁻¹; δ (CCl₄) 1.0 (s, 9H), 3.05 (t, J 18 c.p.s., split further into doublets, J 5 c.p.s., 1H), 3.35 (2H), 3.65 (1H) 7.05-7.5 (m, 4H) ^m/e 231, 175 (base peak, McLafferty rearrangement), 130.

(ii) Hydrolysis of t-butoxycarbonylindano[1,2-b]aziridine

This was performed exactly as above with the N-ethoxycarbonyl aziridine.

(iii) Oxidation

The crude aziridine was oxidized with lead tetraacetate exactly as described above to give isoquinoline (24%), based on the aziridine ester.

(ii) Addition of chloramine to indene

Indene (undistilled, 10.2g) was dissolved in an ethereal solution of chloramine (500 ml, 0.18m) at -5° , and stirred at room temperature for 7 days. The solution was evaporated nearly to dryness and preparative t.l.c. (silica plates, ether solvent) was performed. The tar remaining at the origin was removed and the remaining silica was shaken with ether. Evaporation of the filtered solution to near dryness, followed by addition of ethanolic picric acid gave isoquinoline picrate (0.32g, 1.3%) characterized by its m.p. and i.r. spectrum.

8. Attempted decomposition of 3-azidoindene to isoquinoline

(i) preparation of 3-azidoindene

1-Azido-2-iodoindane (4.0g) was dissolved in methylene chloride (10 ml) and triethylamine (3.0g, 2 molar equivalents) was added. The solution was left under nitrogen for 2 weeks at room temperature and then diluted with water (50 ml). The aqueous part was extracted with methylene chloride (3 x 10 ml), the combined methylene chloride fractions being washed with water (2 x 5 ml), dried, filtered and evaporated to dryness to give 3-azidoindene (2.07g, 94%) as a

brown oil, purified in a molecular still to give a colourless oil,
m.p. -18° to -15° . ν_{\max} ; 2110 (N_3), 1600, 1570, 1370, 1270, 1223,
975, 755, 715 cm^{-1} ; δ (neat) 3.0 (d, J 2.5 c.p.s., 2H) 5.62 (t,
J 2.5 c.p.s.) 7.0-7.4 (m, 4H).

(ii) Attempted pyrolysis on sand at 180° and in refluxing
xylene, and photolysis in petrol at $2,537\ cm^{-1}$ in quartz at room
temperature led to polymeric products only; no isoquinoline was
detected by t.l.c.

9. Copper^{II} Chloride Complexes(i) Formation of copper^{II} chloride complexes(a) from 3-amino-2-methyl-4-pyrimidone

3-Amino-2-methyl-4-pyrimidone (0.05g) was dissolved in warm methanol (5 ml) and a solution of cupric chloride dihydrate (0.068g, 1 molar equivalent) in methanol (2 ml) was added. The deep green solution was warmed for 10 min. On cooling a precipitate of the copper^{II} chloride complex (0.09g, 90%) was filtered as a light green solid, m.p. 169-170dec. (Found: C, 23.6; H, 2.9; N, 15.85; Cl, 27.1; $C_5H_7N_3OCuCl_2$ requires C, 23.5, H, 2.7; N, 16.2; Cl, 26.8%). For i.r. data see table below:

the following N-amino compounds formed copper^{II} chloride complexes in the same manner:

<u>CuCl₂ complexes from:</u>	<u>Yield %</u>	<u>Colour</u>	<u>m.p.o.</u>	<u>ν_{max} (cm⁻¹)</u>
3-Amino-2-methyl-4-quinazolone	100	light green	174-176 dec;	3500, 3200, 3160, 1630, 1610
3-Amino-4-quinazolone	100	light green	220-223 dec	-
3-Amino-2-phenyl-4-quinazolone	70	turquoise plates	213-216 dec.	-
1-Amino-2-quinolone	100	bright green	217-219 dec.	3390, 3150, 1610
3-Amino-1-methyl-4-phthalazone	60	bright green	210-212 dec.	3220, 3100, 3060, 1610
3-Amino-4-phthalazone	60	light green	216-218 dec.	-
3-Amino-1-phenyl-6,7-benzphthalaz-4-one	60	shiny green	172 dec.	-
1-Amino pyridine	60	green	229-231 dec.	-
3-Amino-2-methyl-4-pyrimidone	90	light green	169-170 dec.	3200, 3190, 3070, 1650, 1625

(ii) Hydrolysis of the copper^{II} chloride of 3-amino-2-methyl-4-quinazolone

(a) with cold water

The copper^{II} complex (0.1g) was dissolved in cold water (20°, 20ml). The deep blue solution deposited crystals of 3-amino-2-methyl-4-quinazolone, m.p. 150-152°, characterized by its i.r. spectrum.

(b) with hot water

The copper^{II} complex (2.5g) was dissolved in water at 80°. The deep blue-green solution, on cooling, deposited long needles, m.p. 204-207° dec; tentatively designated as o-acetylamino-benzhydrazide (0.8g). The crystals were filtered, the solution being extracted with ethyl acetate to give 3-amino-2-methyl-4-quinazolone (0.5g).

ν_{\max} ; 3270, 3205, 3155, 1690, 1605, 1580, 1560, 1260, 1190, 1000, 920, 765, 690 cm^{-1} .

(c) with 2N hydrochloric acid

Treatment with warm 2N hydrochloric acid, on basifying, gave copper hydroxide and 3-amino-2-methyl-4-quinazolone.

Other control experiments

The 3-amino-4-quinazolone and 3-amino-2-phenyl-4-quinazolone complexes hydrolyzed only to give the N-amino compounds under the same conditions. The 3-amino-1-methyl-4-phthalazone and 1-amino-2-quinolone complexes were stable to boiling water.

DISCUSSION OF RESULTS

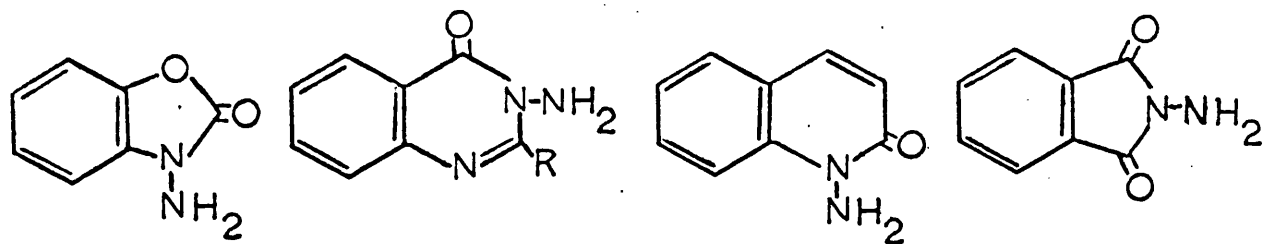
Section I: Preparation and Oxidation of N-Amino Compounds

The cycloaddition of carbenes to olefins has provided a versatile synthetic route to cyclopropanes [63], but the corresponding cycloaddition of nitrenes, to form aziridines is much less common. There are very few useful syntheses of aziridines which involve nitrenes as intermediates, apart from those involving ethoxycarbonyl nitrenes [3].

The oxidation of 1,1-disubstituted hydrazines gives a wide variety of products. Basically, however, the hydrazines can be divided into two broad categories: those which, on oxidation, undergo primarily intermolecular reactions (Type A), such as tetrazene formation and deamination, and those which undergo primarily intramolecular reactions (Type B), such as nitrogen extrusion and rearrangement (see examples in Section I in the Introduction).

Compounds of Type A

The observation that oxidation by lead tetraacetate of the 1,1-disubstituted hydrazine 1-aminobenzoxazolinone (1) in the presence of olefins gave aziridines [46] led to the choice of compounds (2-7) for further study. These compounds are structurally similar to (1) in that the 1,1-disubstituents are carbon atoms which are a part of an heteroaromatic ring system, in general written as (8), which represents the Type A compound. The oxidative reactions of these compounds will be contrasted later with those where $N_{(1)}$ is bonded to nitrogen (Type B) instead of carbon.

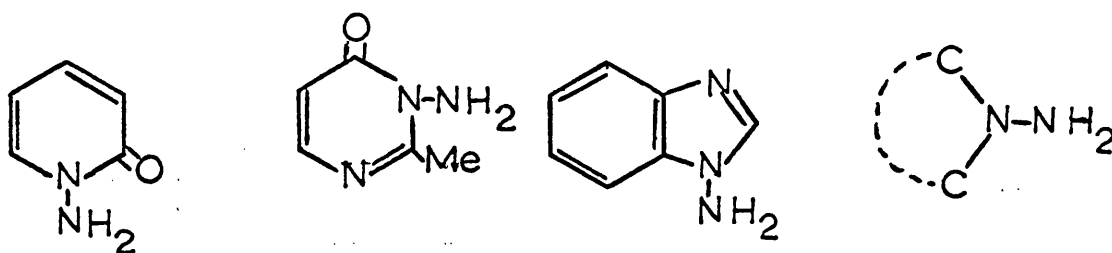


(1)

(2) a; R=Me
b; R=H
c; R=Ph

(3)

(4)



(5)

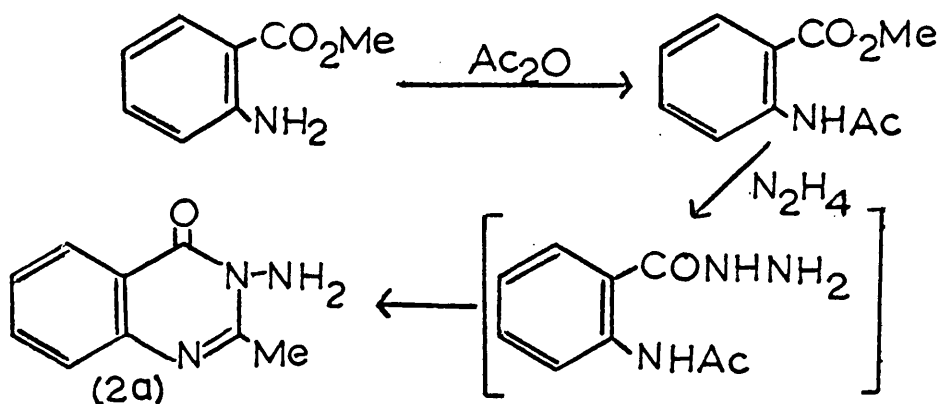
(6)

(7)

(8) TYPE "A"

Preparation of these N-amino compounds

3-Amino-2-methyl-4-quinazolinone (2a) was made (76%) from methyl anthranilate, acetic anhydride and hydrazine hydrate by a Niementowski synthesis [64], using a modification of the method of Klosa [65], as outlined in Scheme 1.

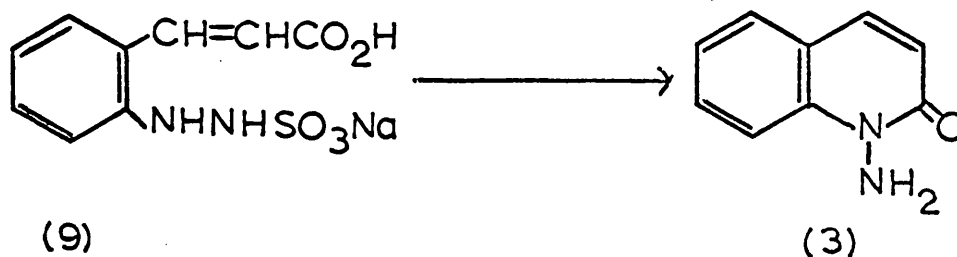


Scheme 1.

The Quinazolones (2b) [66] and (2c) [65] were synthesized by literature methods. (2a) was found to be the most convenient quinazolone to

prepare and was the most extensively studied.

1-Amino-2-quinolone (3) has previously been prepared, in low yield (15%) by Ainsworth, on treatment of (9) with 1N hydrochloric acid [68]:

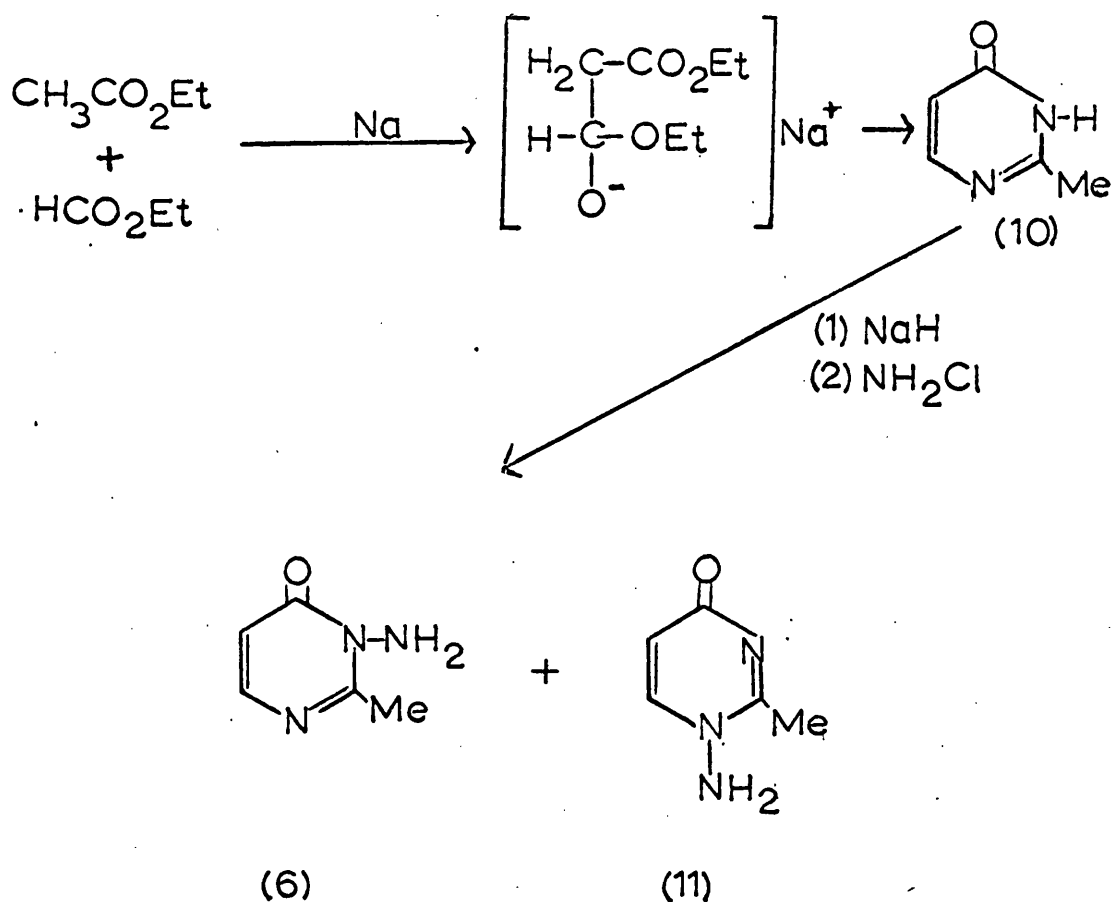


Wittman has also prepared (3) by amination with hydroxylamine-O-sulphonic acid of the sodium salt of 2-hydroxyquinoline [69]; however, the yields were low and variable (0 - 20%), probably due to the insolubility of the sodium salt. In the present study the potassium salt was aminated with ease to give (3) in 90% yield.

N-aminophthalimide (4) was synthesized and studied by D. J. Anderson [76].

1-Amino-2-pyridone (5) was synthesized (30%) by aqueous chloramine amination of the sodium salt of 2-hydroxypyridine, by the method of Erlenmeyer and Hoergerle [70].

3-Amino-2-methyl-4-pyrimidone (6) was synthesized as outlined in Scheme 2, where 2-methyl-4-pyrimidone (10) was prepared by the method of Gabriel, by a Claisen condensation of ethyl acetate with ethyl formate to give the sodium salt, which was condensed with acetamide hydrochloride to give (10) [71]. The sodium salt of (10) was aminated with ethereal chloramine and after chromatography the reaction mixture gave a 30% yield of (6) and a very minor product, tentatively assigned the structure 1-amino-2-methyl-4-pyrimidone (11).

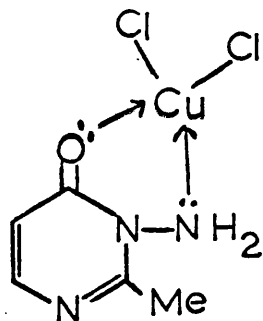


Scheme 2

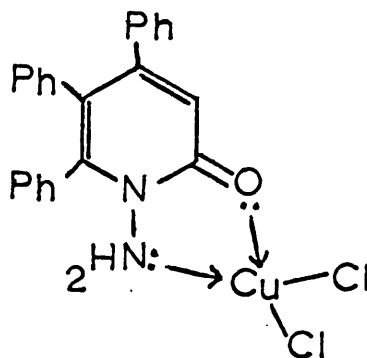
The major isomer was assigned structure (6) rather than (11) for the following reasons:

- (i) Methylation of (10) with methyl iodide [72], or diazomethane [73], gave solely 2,3-dimethyl-3H-4-pyrimidone.
- (ii) The corresponding 2-methyl-3H-4-quinazolone gave only the 3-amino isomer (2a) on amination of its sodium salt with HOS (not given in Experimental)
- (iii) More significantly, (6) formed a highly crystalline green coloured 1 : 1 chelate complex with copper^{II} chloride of structure (12), proposed in analogy to the complex (13) described in the literature [74]. The isomer (11) could not form such a complex. All N-aminoamides studied in this thesis formed such complexes (see Experimental, page 97).

The hydrolysis of one complex is discussed later (see page 177).

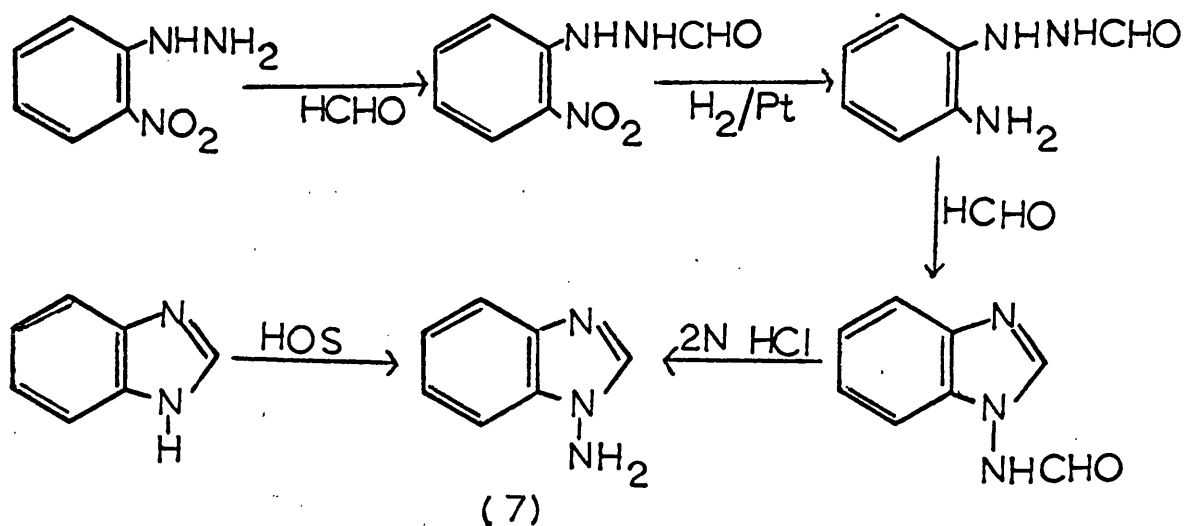


(12)



(13)

1-Aminobenzimidazole (7) was prepared by the two methods outlined in Scheme 3; from *o*-nitrophenylhydrazide in a four-stage synthesis, by the method of Sheng and Day [75], and in a much simpler alternative, by amination of the potassium salt of benzimidazole with HOS (90%).



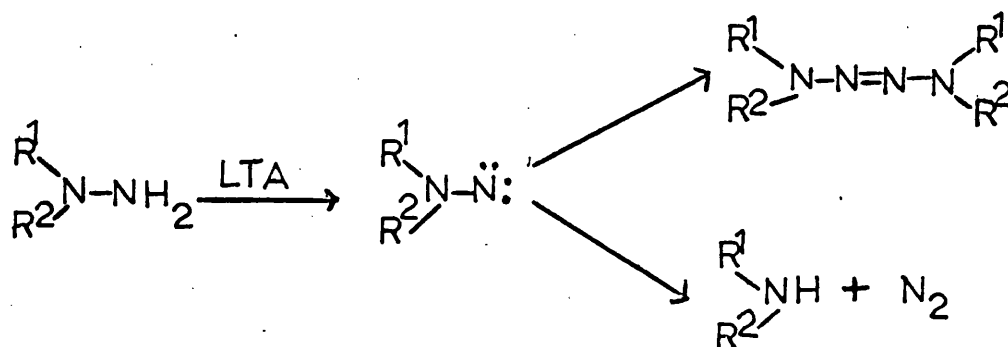
Scheme 3

Oxidation of Type A N-Amino Compounds (1-7)

The oxidation of the 1,1-disubstituted hydrazines (1-6) by lead

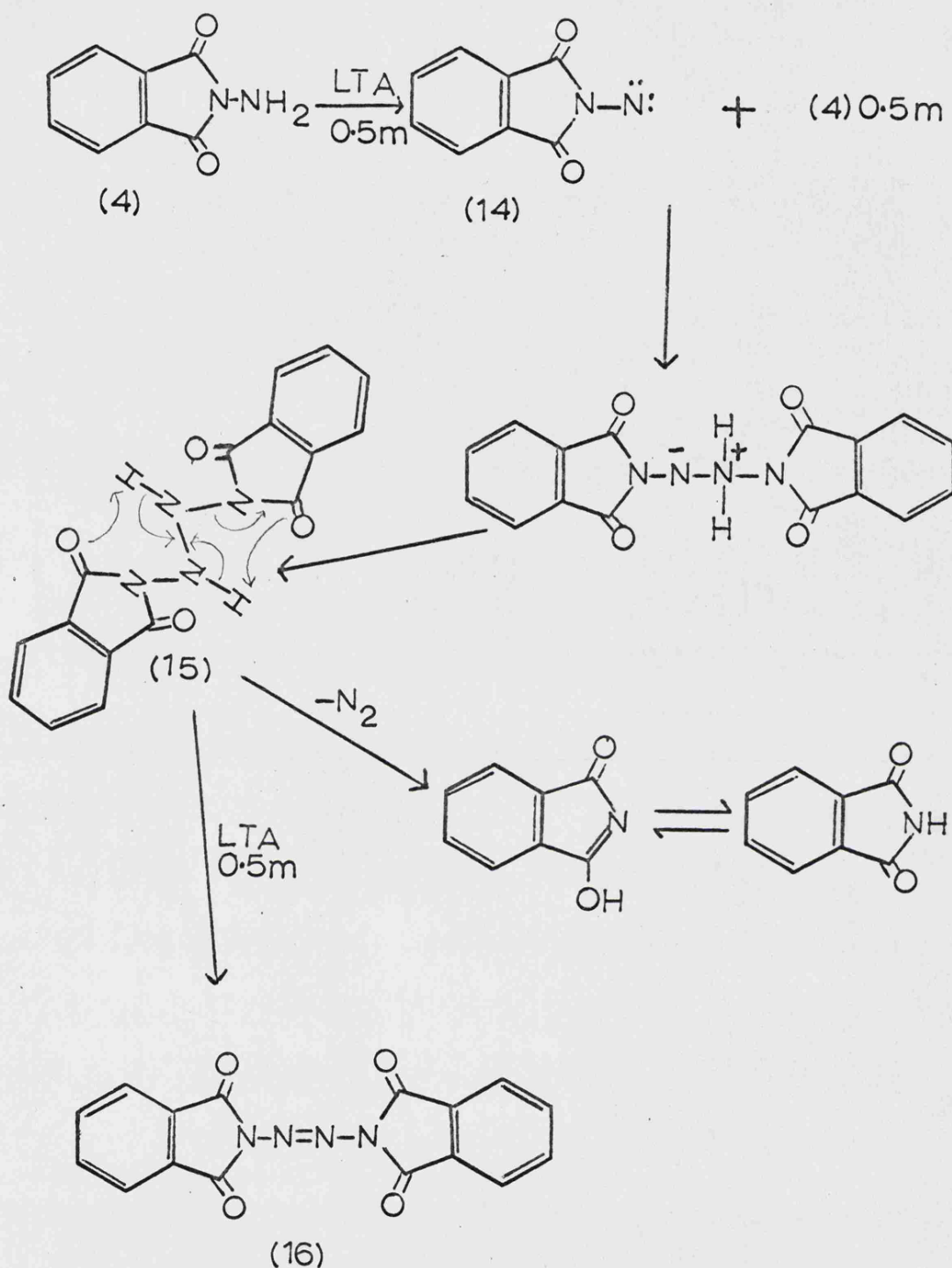
tetraacetate in methylene chloride at room temperature caused a vigorous evolution of nitrogen gas (identified by its mass spectrum in the case of 2a) and gave the corresponding deaminated compounds as the major products (50-70%). Trace amounts of tetrazenes (<5%) were found in the oxidations of 1-aminobenzoxazolinone (1) (which gave many other complex products, depending on reaction conditions [46]) and N-aminophthalimide (4) [76]. Tetrazene formation was also found on oxidation of (7), which is discussed separately later.

In general:



The mechanism of tetrazene formation and oxidative deamination by lead tetraacetate of N-aminophthalimide (4), a reaction studied by Anderson [76], has also been investigated by Dreiding [77], who proposed that the discrete nitrene (14) attacks N-aminophthalimide (4) to give the tetrazene (15). This can either lose nitrogen to give the deaminated product (phthalimide), via a concerted mechanism, or can be further oxidized to the tetrazene (16) as shown in

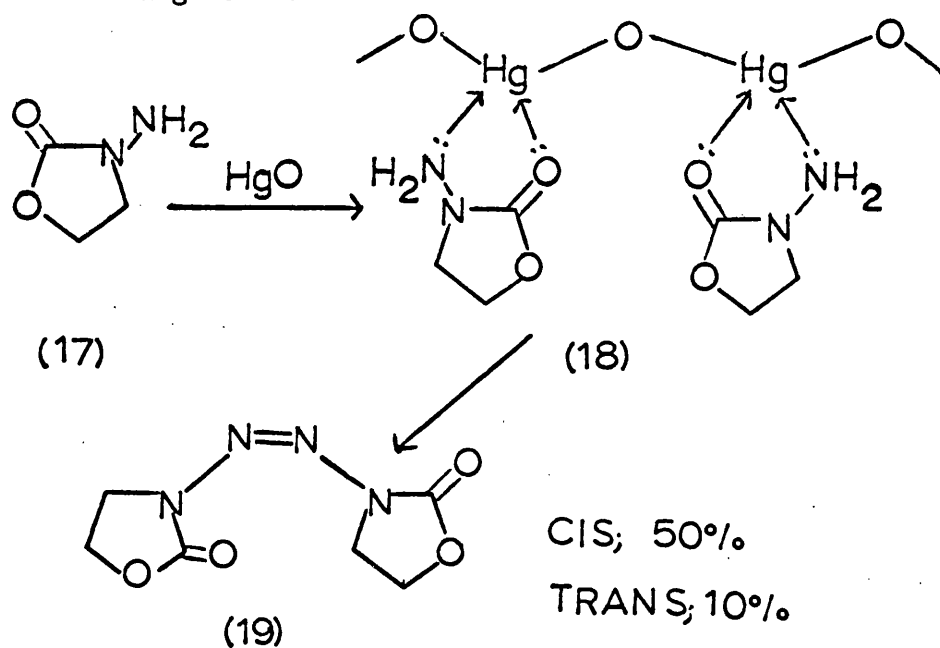
Scheme 4:



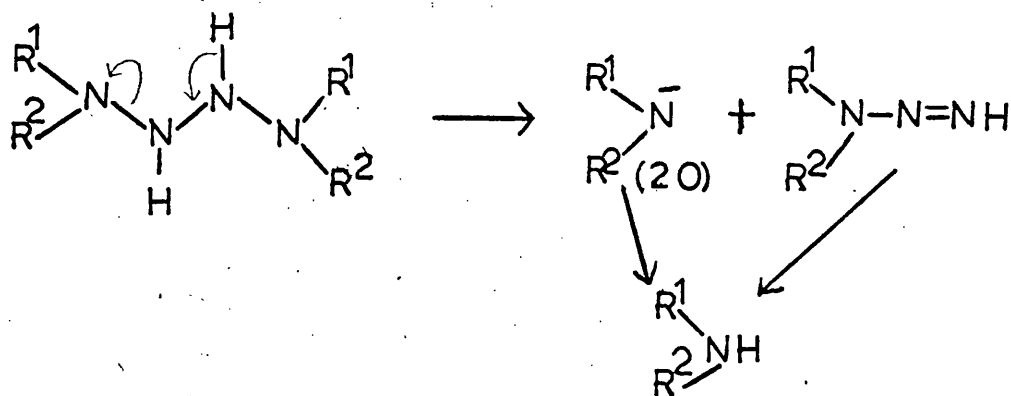
Scheme 4

This plausible mechanism can be applied to explain the formation of deaminated products from compounds (1-6). However, on oxidation of the 1,1-disubstituted hydrazine (17) by mercuric oxide the product via the intermolecular pathway is only the tetrazene (19), no deamination was observed [8i] (see Fig. 5, Introduction p. 8). The intermediate here is probably the highly ordered chelate (18), hence mainly cis-

tetrazene being formed:

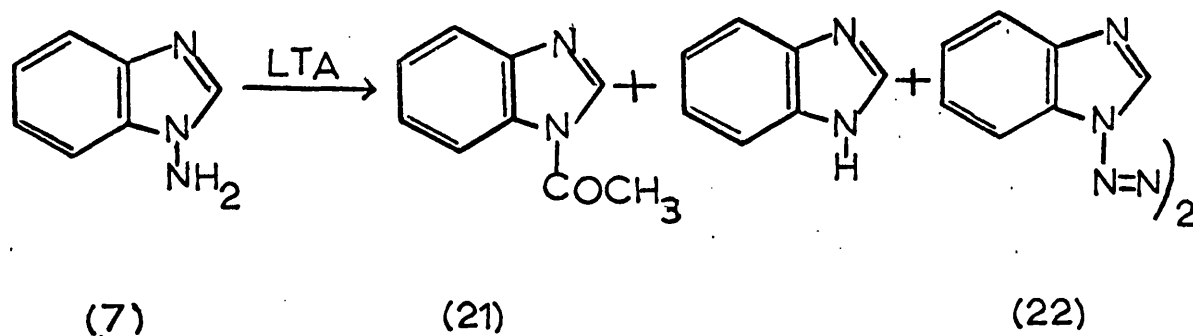


Presumably the driving force to predominant deamination in the oxidation of (1-6) is the high stability of the product, e.g. phthalimide. Alternatively, a non-concerted decomposition of the tetrazene (15), not involving the lactam carbonyl group of the phthalimide ring is also possible. Here, the driving force for deamination is the high stability of the intermediate nitrogen anion (20):

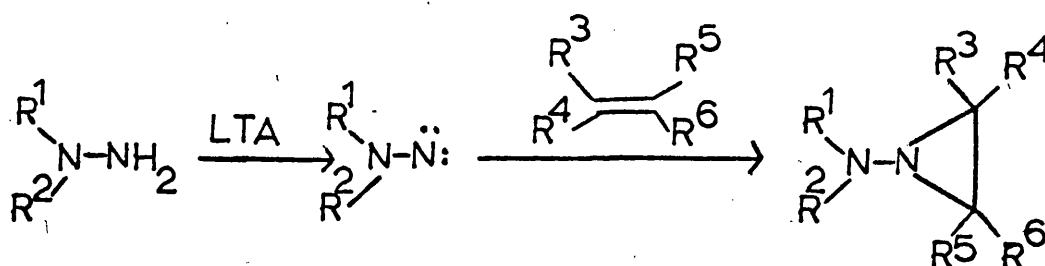


This latter mechanism is possibly better in explaining the three oxidation products of 1-aminobenzimidazole (7), which are N-acetylbenzimidazole (60%) (21), benzimidazole (trace yield) and the tetrazene

(2%) (22). It is possible that (21) is formed by acetylation of the anion of the primary product benzimidazole, which is formed as described above, via (20) where $R^1, R^2 = \text{benzimidazolyl}$. However, benzimidazole itself is not acetylated under the reaction conditions (see Experimental). Previous to this work, Abramovitch and Schofield also oxidized 1-aminobenzimidazole with K_3FeCN_6 to obtain benzimidazole as the only isolable product [78].



The oxidation of (1-7) by lead tetraacetate in methylene chloride in the presence of nucleophilic olefins, commonly used as carbene traps, gave the corresponding aziridines which could be isolated in fair to good yields (Scheme 5). The deaminated products and tetrazenes were also obtained in correspondingly reduced yields.

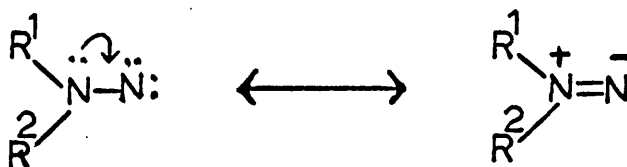


Scheme 5.

Olefins successfully used in this way (see Experimental) were cis and trans but-2-ene, cyclohexene, cyclooctene, indene, styrene and butadiene. The optimum amount of olefin was about 5 moles. Use of larger amounts did not improve the yield, but use of smaller amounts caused a corresponding reduction in yield of the aziridine. A few of the reactions failed unexpectedly; for example, no aziridine could be obtained from the oxidation of N-aminophthalimide in the presence of butadiene [76], although this may be result of the lability of the product, rather than a failure to react. The aziridines were isolated from the reactions either by column chromatography on deactivated basic alumina, or by evaporation of the filtrates and recrystallization of the residues. In general, column chromatography gave the pure aziridines directly, but the yields of the products were considerably reduced unless the retention time of the aziridines on the column was kept to a minimum. In two experiments with different aziridines, for example, only 20% could be recovered after adsorption on deactivated alumina for 2 hr. (not given in Experimental). In the preparations reported (see Experimental for details of olefins used with each N-amino compound), chromatography was often used to obtain pure materials for analysis and structure determination; so the yields do not usually represent the best obtainable.

The addition of the nitrenes formed by oxidation of 1-aminobenzoxazolinone (1) [46], 3-amino-2-methyl-4-quinazolone (2a) (see Experimental) and N-aminophthalimide (4) [76] to cis and trans but-2-ene were at least 95% stereospecific; an examination by PMR of the reaction mixtures failed to detect any of the non-stereospecific products. It is therefore reasonable to assume that the N-nitrenes are reacting in the singlet state, in accordance with Skell's hypothesis, as described in detail for ethoxycarbonyl nitrene in the Introduction,

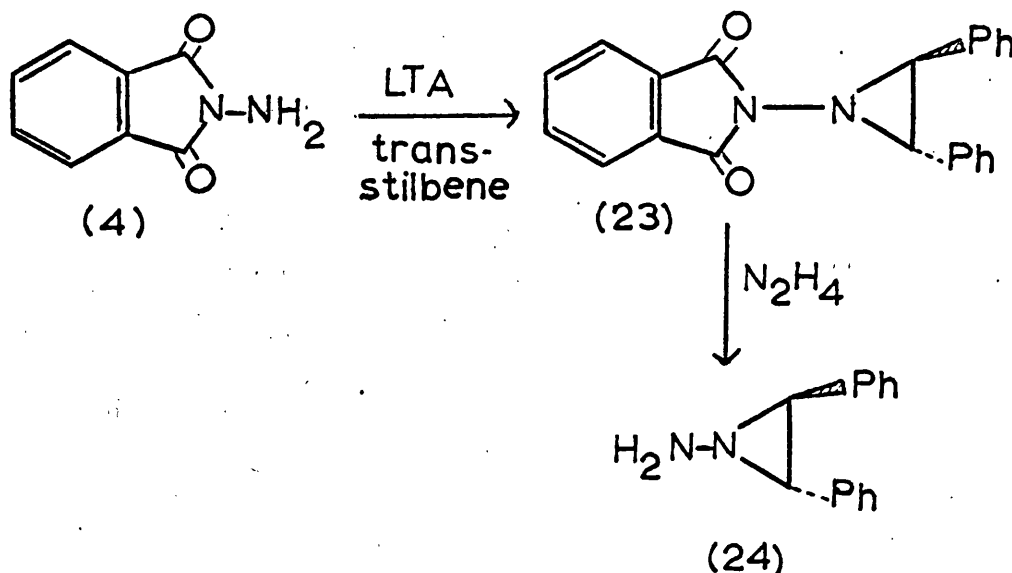
Section I. The singlet may even be the ground state. It can be stabilized by delocalization of the lone pair of the trivalent nitrogen into the vacant p orbital of the univalent nitrogen:



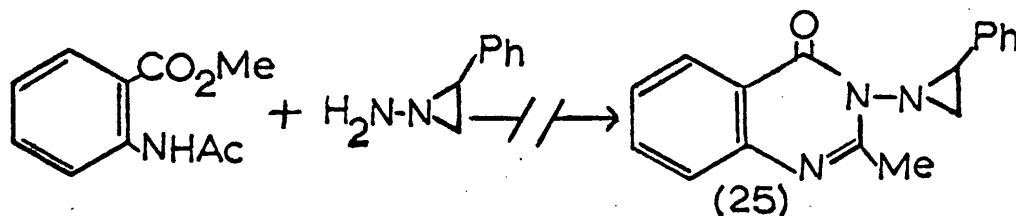
A consequence of such delocalization should be increased nucleophilic character of the intermediate. Evidence for this was sought by investigating the reactions of the N-nitrene with electrophilic olefins, such as acrylic esters, and similar olefins, in which the double bond is conjugated with an electron withdrawing group. These are usually rather poor traps for carbenes and nitrenes. In general, these did indeed give good yields of the aziridines. The carbenes which do add to these olefins readily are thought to have nucleophilic character [79]; this concept has been theoretically justified by Hoffmann [80]. Esters of acrylic, methacrylic and crotonic acids gave good yields of aziridines, and several halogenated olefins also reacted well. Again, some olefins failed unexpectedly to give aziridines; for example, trans dichloroethylene reacted to give the trans aziridine with 3-amino-2-methyl-4-quinazolone (2a) and N-aminophthalimide (4) [76] in ~ 60% yield, but cis dichloroethylene failed to give any aziridine with (2a) and (4); (not given in Experimental), the only product isolated being the deaminated compounds.

Thus, in general, the good yields obtained and the simplicity of the procedure make these reactions an attractive route to aziridines of this type. A simple clean method of removing the heteroaromatic

groups from the aziridine would increase the usefulness of this aziridine synthesis. However, a brief investigation of cleavage of the N - N bond by catalytic hydrogenation and by zinc in acetic acid gave only complex reaction mixtures on t.l.c. (not in Experimental). This was probably due to the lability of the expected aziridines. Carpino has oxidized N-aminophthalimide (4) in the presence of trans stilbene to give the trans aziridine (23) utilizing this aziridine synthesis. This aziridine was cleaved with ethanolic hydrazine in a Gabriel phthalimide synthesis to give 40% yield of the N-aminoaziridine (24) [81].

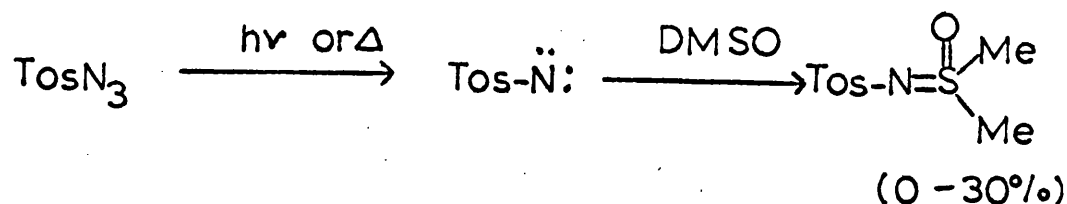
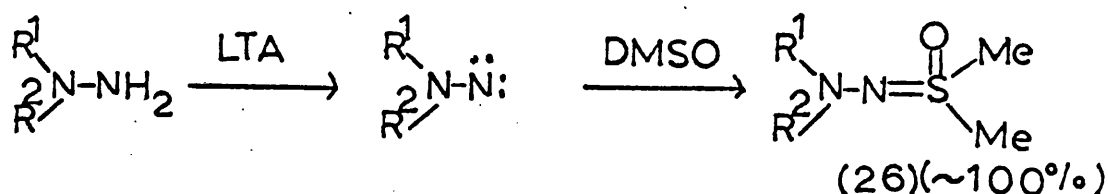


An attempt was made at an alternative synthesis of the aziridine (25), obtained on oxidation of (2a) in the presence of styrene, by condensation of N-amino-2-phenylaziridine, prepared by the method of Eschenmoser [82], with methyl-N-acetylanthranilate in a Niementowski synthesis in analogy to that of the synthesis of (2a) (see Scheme I, page 100):



However, the N-amino-2-phenylaziridine itself slowly decomposed under the reaction conditions to evolve a gas (possibly diimide [81]) and give styrene, presumably by an electrocyclic disrotatory ring opening reaction [14, 81].

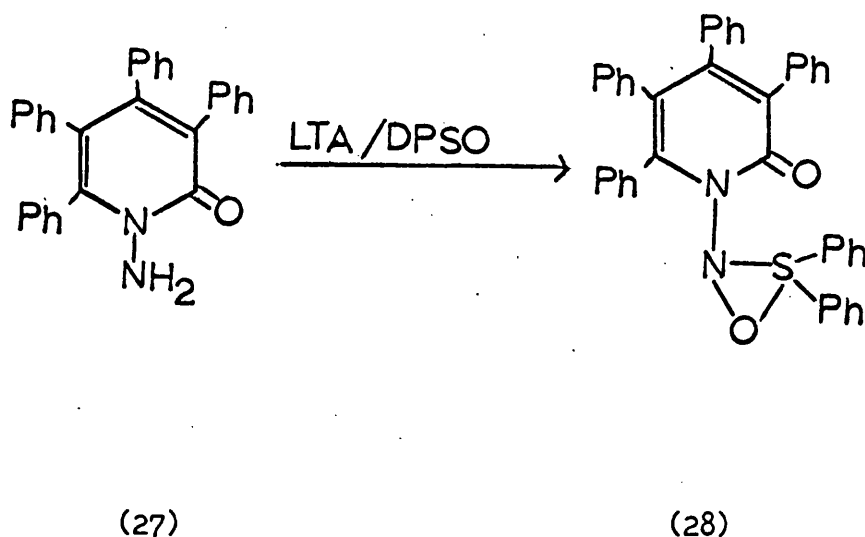
When the oxidation of compounds (1-7) was performed in dimethylsulphoxide as the solvent, high yields of the sulphoximines (26) were obtained (quantitative in the cases of 2a, 6 and 7). Their formation may be rationalized by involving the intermediary of the N-nitrenes, by analogy with the trapping of p-toluenesulphonylnitrene generated by thermolysis or photolysis of tosylazide [83]:



Other examples of the use of dimethylsulphoxide as a trap for nitrenes are known [84].

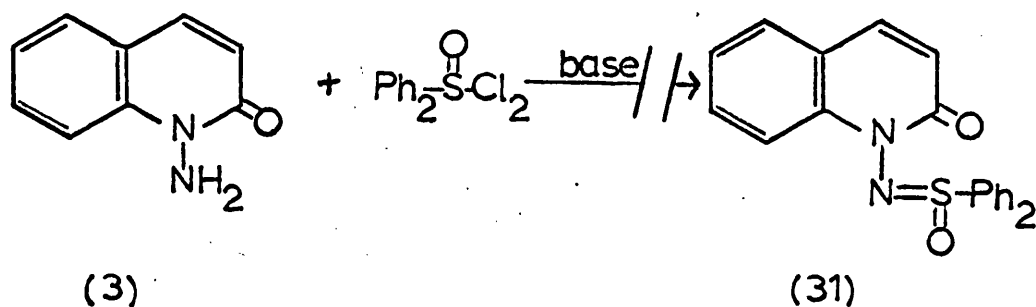
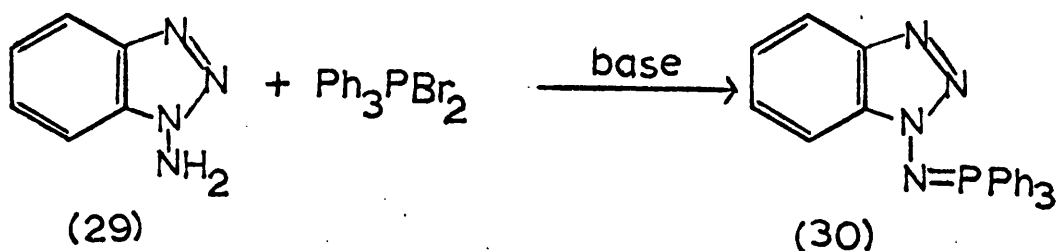
As well as dimethylsulphoxide (DMSO), diphenylsulphoxide (DPSO), methylphenylsulphoxide (MPSO) and dibenzothiophenesulphoxide (DBSO) were also shown to trap the N-nitrenes formed in the oxidation of (2a) and (3). All four of the sulphoxides show a strong S = O absorption in their i.r. spectrum in the range 1020-1000cm⁻¹; the sulphoximines derived from DMSO (26) also show this strong band in the range 1020-1100 cm⁻¹.

However, the sulphoximines derived from DPSO, MPSO and DBSO do not show this strong peak. Yelland tentatively assigned the structure of a sulphoximine, similarly obtained from the oxidation of 1-amino-3,4,5,6-tetraphenyl-2-pyridone (27) in the presence of DPSO as the oxathiaziridine (28) on steric considerations, hence the disappearance of the $S = O$ band [85]. However, the difference may be due to complex resonance with the aromatic ring of the sulphoximine substituents, such as Fermi resonance which is well known in sulphoxides [86]. Alternatively, it may be due to decrease in the $N = S = O$ absorption in this region, the absorption being transferred to its stronger mode in the $1200-1230\text{ cm}^{-1}$ region [87], where in fact a strong absorption does occur.



1-Aminobenzotriazole (29) and other N-amino compounds have been found to condense readily with triphenylphosphine dibromide to give the phosphineimine, e.g. (30) [9v]. By analogy with this it was hoped to be able to synthesise the above sulphoximines alternatively by condensation of the N-amino compounds with diphenylsulphoxide dichloride, generated in situ. For example, 1-amino-2-quinolone (3) should give

the sulphoximine (31). However, this reaction failed; only a foul-smelling red oil was obtained, probably due to the decomposition of the diphenylsulphoxide dichloride under the reaction conditions. This reaction was repeated several times under a variety of conditions to give the same result.

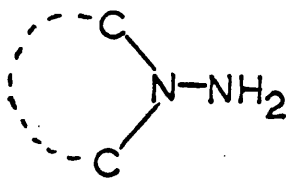


Thus, in conclusion, the N-nitrenes derived from oxidation of compounds (1-7) undergo intermolecular reactions, e.g. tetrazone formation and deamination, and are trapped readily by olefins to give aziridines stereospecifically and by sulphoxides to give sulphoximines. Accordingly, they can be classified as being Type A (see Introduction, Section I, Fig. 5, p.9).

Compounds of Type B

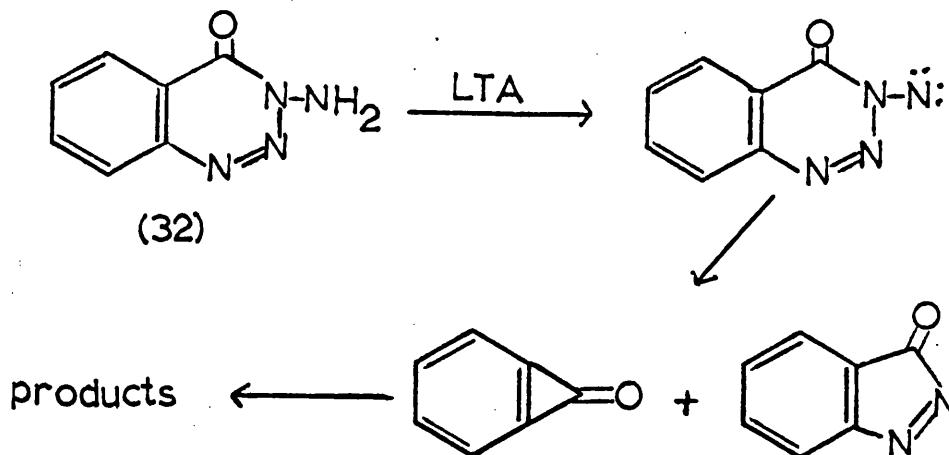
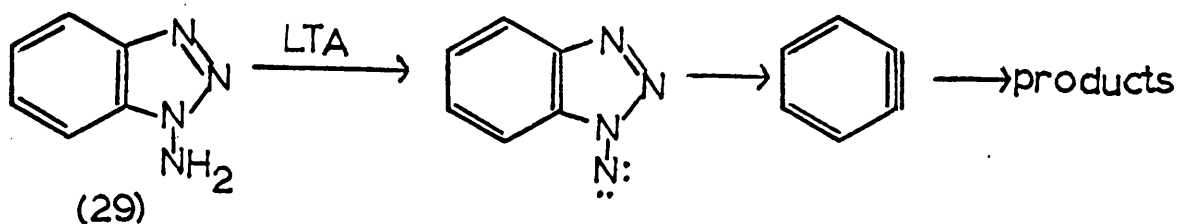
Attention was next focused on the nature of the heterocyclic ring which forms the 1,1-disubstituents of the hydrazine. We have

seen that the arrangement of atoms (8) in the compounds (1-7) produces intermolecular reactions of the N-nitrene.



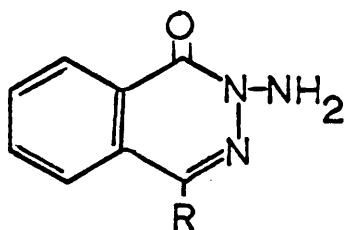
(8) TYPE "A"

However, intramolecular pathways are known to occur in similar molecules; e.g. where the N-amino group has one, or both, 1,1-disubstituents as another nitrogen atom. These were described in the Introduction, Section I. e.g.

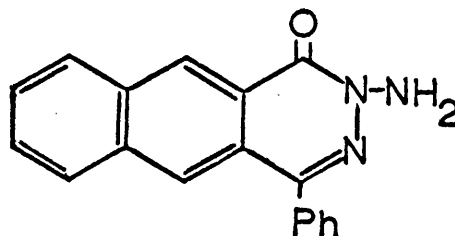


The N-aminobenzotriazinone (32) is, superficially, very similar in structure to 3-amino-2-methyl-4-quinazolone (2a) but reacts in this entirely different manner. Hence the closely related 3-aminophthalazones (33) were synthesized in order to determine their mode of reaction on oxidation. Compounds (34-36) were also prepared

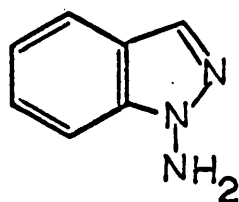
for this reason, all having in common the partial structure (37):



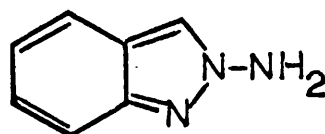
(33) a; R=H
b; R=Me



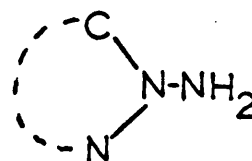
(34)



(35)



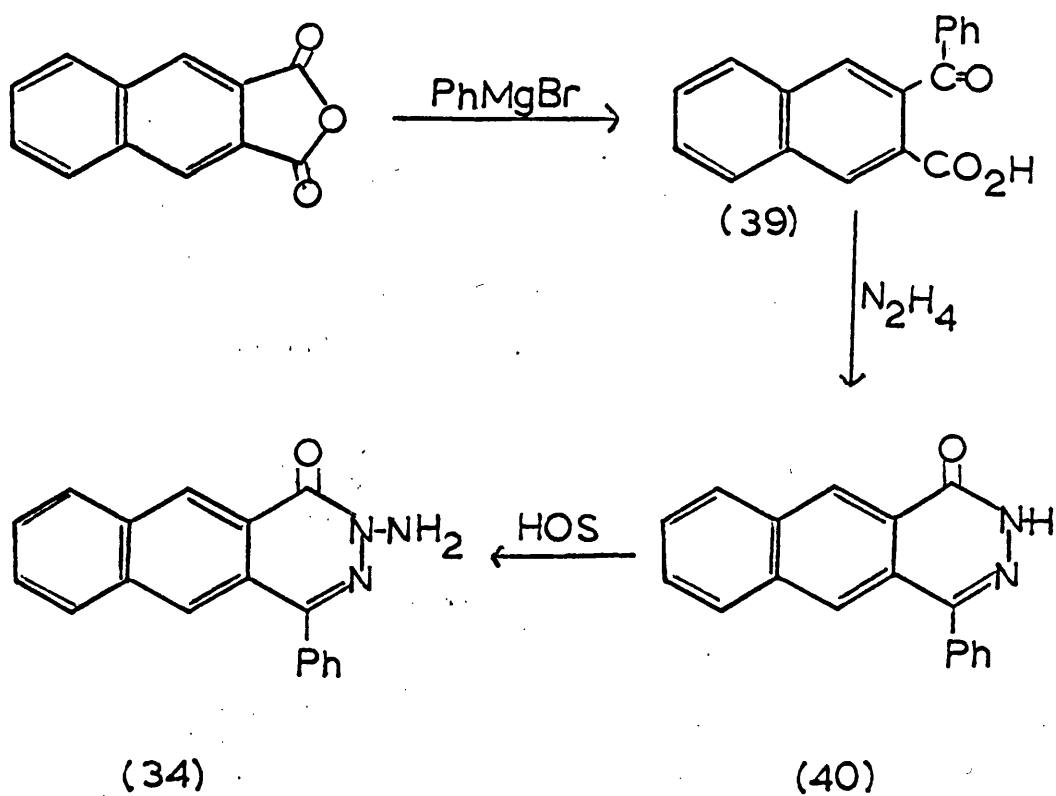
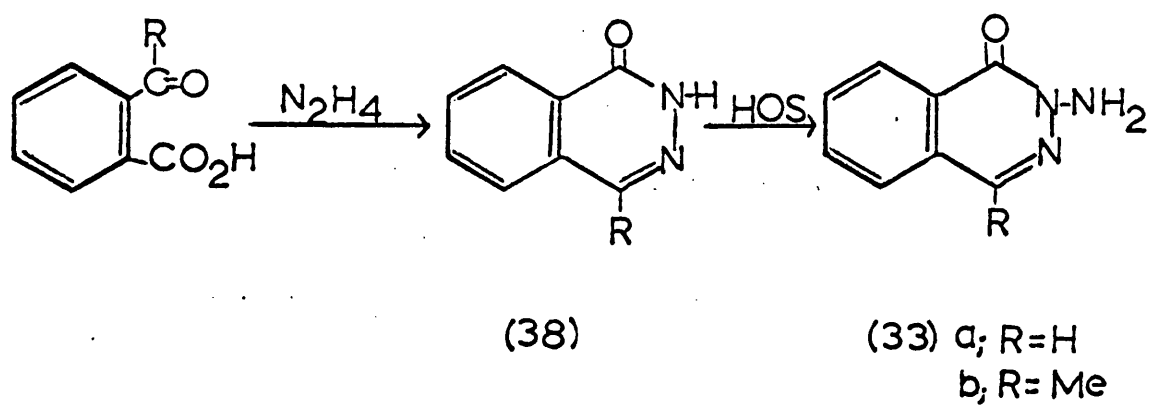
(36)



(37) TYPE "B"

Preparation of these N-amino compounds

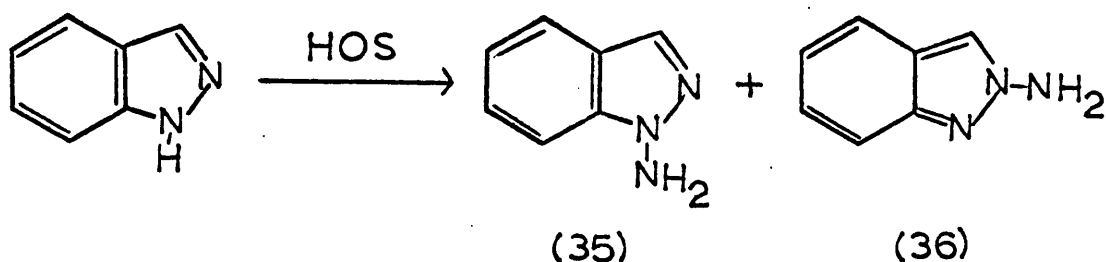
The 3H-4-phthalazones (38) were synthesized from the corresponding o-substituted phthalaldehydic acids and hydrazine hydrate, according to the method described by Vaughan [88]. They were then aminated in basic solution with HOS to give high yields (90%) of the N-amino compounds (33). In an analogous manner 3-amino-1-phenyl-6,7-benzphthalaz-4-one (34) was prepared from 2,3 naphthoic anhydride via the keto-acid (39), formed by the inverse Grignard reaction, according to the method of Weizmann [89]. The keto-acid (39) was converted into (40) on treatment with hydrazine hydrate, and this then aminated with HOS. The reaction sequences are summarized in Scheme 6:



Scheme 6

The 1- and 2-aminoindazoles (35 and 36) were prepared by amination of

indazole by HOS in basic solution, the ratio of the 1- and 2-amino compounds being 2 : 1 in a 90% overall yield:

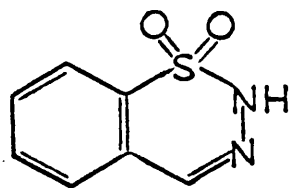


These isomeric structures were assigned on the following evidence that:

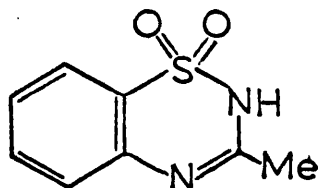
- 1) The u.v. spectra were directly comparable to the corresponding well established 1- and 2-methylindazoles [102]
- 2) The u.v. spectra were also comparable to the corresponding well established 1- and 2-aminobenzotriazoles [91]
- 3) The isomers are different compounds, forming different anisaldehyde derivatives.

The 1-aminoindazole appears to have a small impurity which could not be removed by repeated recrystallizations. It is not indazole (there is no secondary N - H peak in the PMR spectrum), and is unlikely to be the isomeric 3-aminoindazole (only one primary amine peak in the PMR spectrum). It was not possible to isolate the impurity.

Attempted amination with HOS and with chloramine of the sodium salts of the benzothiadiazine 1,1,dioxides (41) and (42), prepared by the literature methods (see Experimental), gave only a quantitative recovery of the sodium salts. A similar attempt to aminate the sodium salt of saccharin also failed [133].

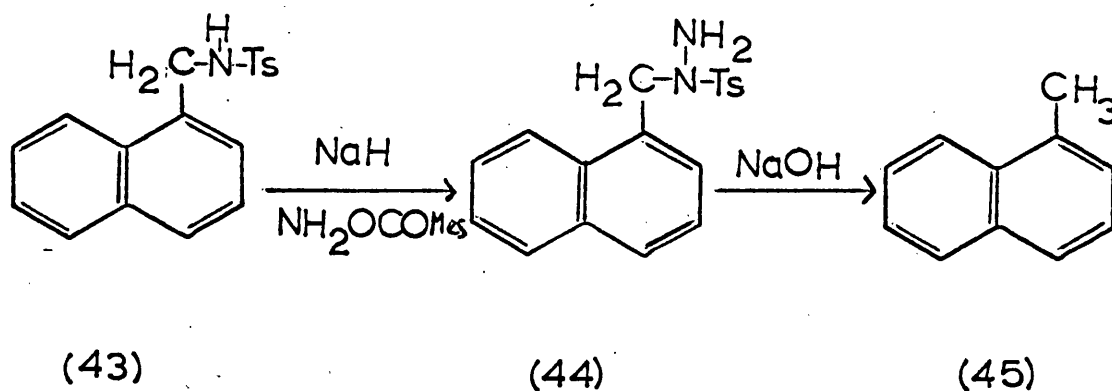


(41)



(42)

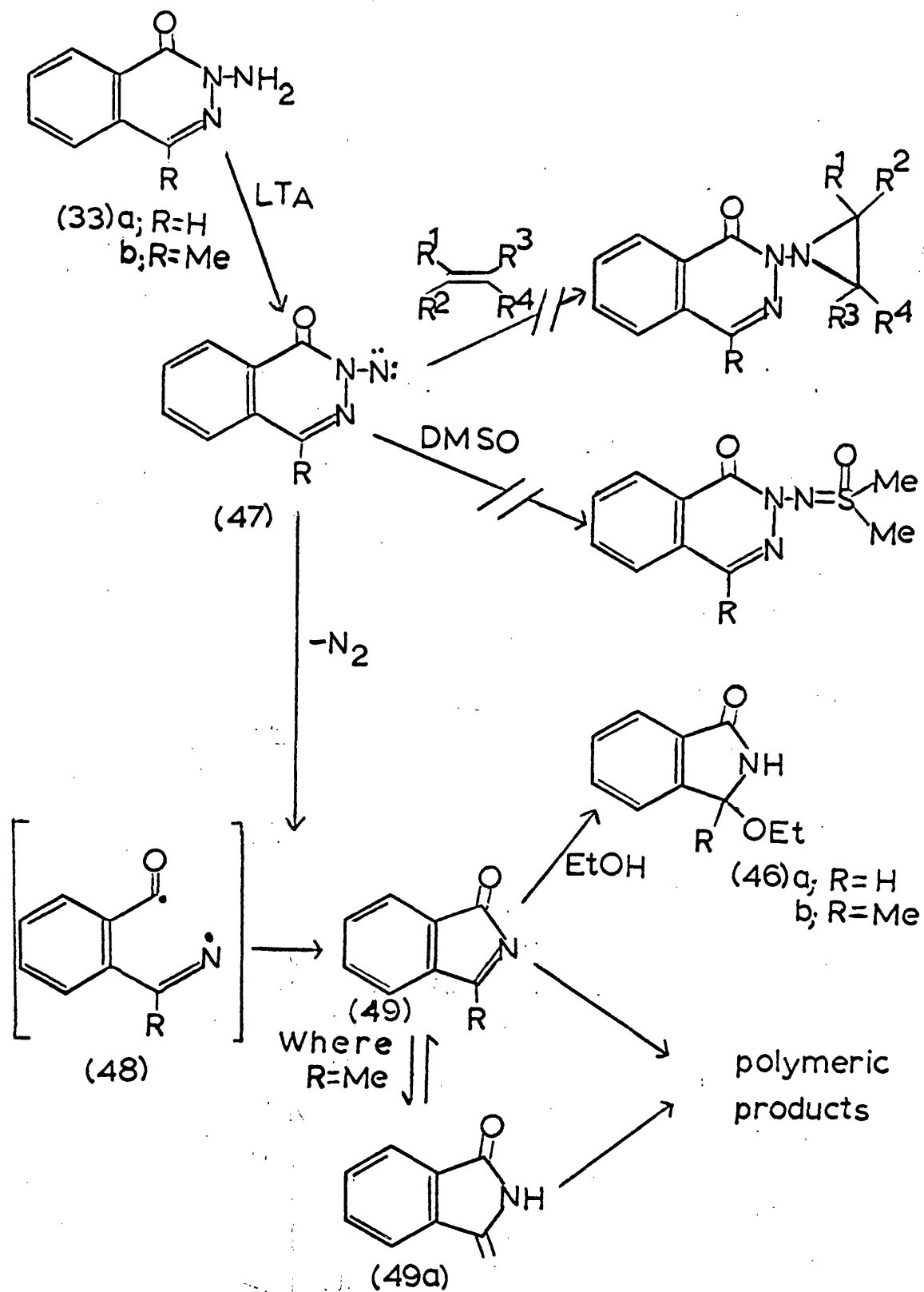
Mesitoxyamine has been used successfully to aminate a secondary sulphonamide (43), but the N-amino compound (44) is extremely labile to base, as shown by Carpino [122], in which it readily decomposes to (45).



The Oxidation of Type B N-amino Compounds (33-36)

The oxidation of 3-amino-1-methyl-4-phthalazone (33b) by lead tetraacetate in methylene chloride at room temperature led to a vigorous evolution of gas, presumably nitrogen. Chromatography of the

product on deactivated basic alumina gave only a series of oils which rapidly became a glassy solid, probably a polymer, especially on heating. Similar oxidation in the presence of the olefins styrene, butadiene and tetracyclopentadieneone, all good N-nitrene traps in the case of oxidation of (2a), gave no aziridines, only such glassy polymeric type substances. Even DMSO, a very efficient trap for the N-nitrenes from (1-7) gave no sulphoximine, again only these presumably polymeric substances were obtained. However, when the oxidation was performed in the presence of ethanol a good yield (64%) of 1-ethoxy-1-methylphthalimidine (46b) was obtained. Similarly, oxidation of (33a) in the presence of ethanol gave 1-ethoxyphthalimidine (46a), identical to a sample prepared by the method of Dunet [92]. These reactions are outlined in Scheme 7. (over page)

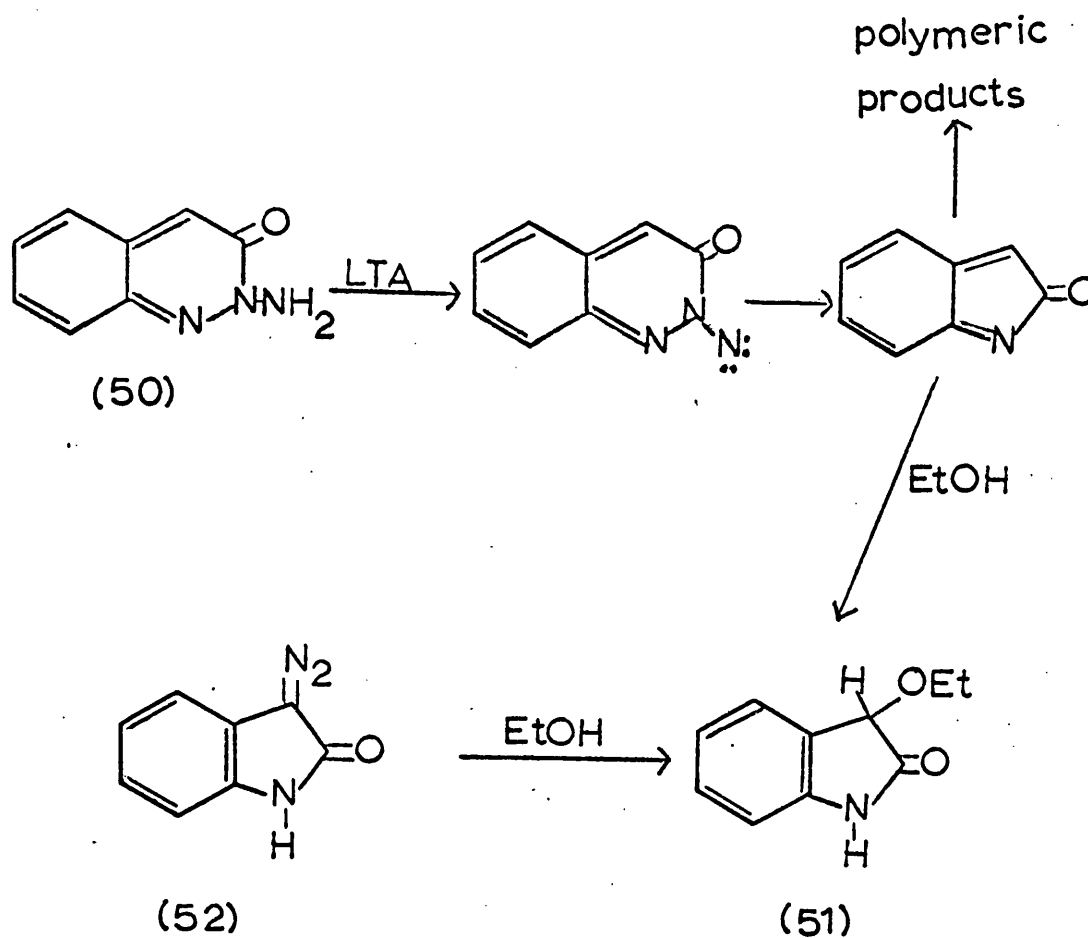


Scheme 7

The reactions may be rationalized by postulating that the nitrene (47) reacts in an intramolecular manner by extrusion of nitrogen, either by a cheletropic reaction [14] or via the diradical (48), in an analogous manner to the oxidation of the N-aminoisoindolines studied by Carpino (see Introduction, Section I, p.10-11), to give the product (49). This species is highly strained because it has an azacyclopentadienone structure, from which the polymeric substances are derived, or it is stabilized by being trapped by ethanol to give (46). In the case of (33b) the intermediate (49) could exist as the tautomeric form (49a) with an exocyclic methylene group. This compound is a known source of polymers on gentle heating in the presence of oxidizing agents, e.g. peroxides [93]; in this case the excess lead tetraacetate could be causing this polymerization.

Thus here is an efficient synthetic route to such 1-alkoxyl-1-alkyl-phthalimidines, which are not common. They have usually been prepared (when R = H only) by the reduction of phthalimide in the presence of the appropriate alcohol [92, 94].

This reaction was later extended by Sale [95] to the analogous oxidation of 2-amino-3-cinnolinone (50) in the presence of ethanol. This gave the ethoxyoxindole (51), the structure of which was verified by an alternative synthesis from 3-diazooxindole (52) and ethanol, as outlined in Scheme 8.



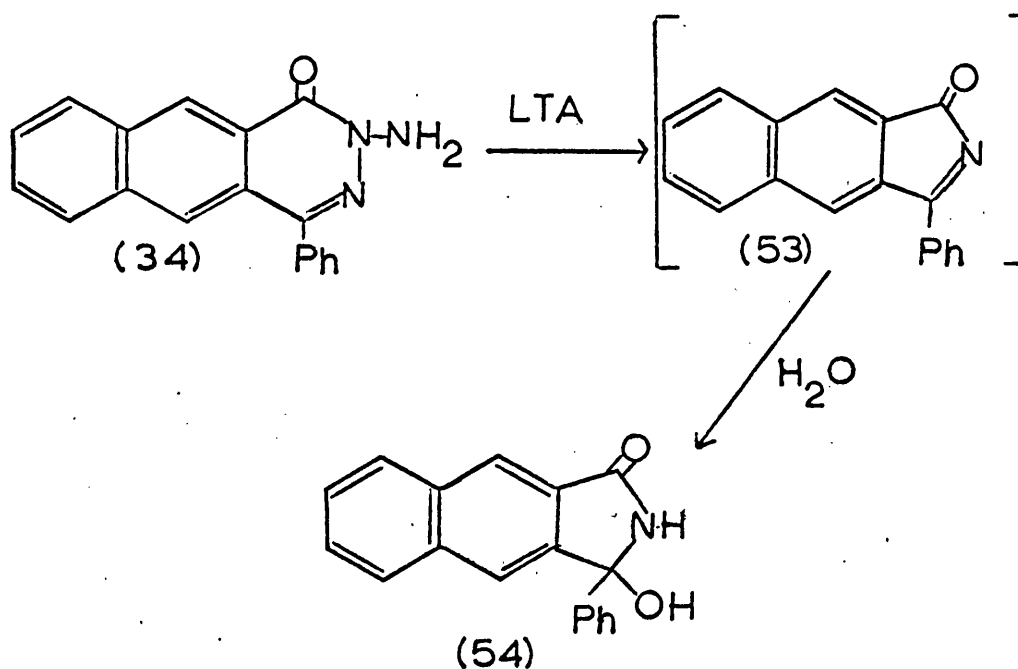
Scheme 8

This striking difference in reaction with lead tetraacetate of the N-aminoquinazolones (2a) and the reactions of the N-aminophthalazones (33) and N-aminocinnolinone (50) can be attributed to the difference in the bond dissociation energies [101]; C - N bond is $66 \text{ Kcal. mole}^{-1}$ and N - N bond is only $37 \text{ Kcal. mole}^{-1}$. Hence this accounts for the ready fragmentation of the nitrenes from (33) and (50), not observed at all with (2a).

The apparent polymerization of the product from oxidation of (33) and (50) is probably due to their strained azacyclopentadienone type part structure. This led to the study of the 6,7-benz²phthalazone (34). Here, the corresponding product (53) would presumably be more

stable as the bond order of the naphthalene 2,3 bond (fused to the heterocyclic ring) will be less than that of the corresponding benzene bond in (49); also the 1-phenyl substituent should help to stabilize the system by conjugation. However, oxidation of (34) in methylene chloride gave complex oils, the only isolable product after chromatography being (54), presumably by addition of water on work up to the labile (53). Oxidation of (34) in the presence of ethanol did not, however, give the anticipated ethoxy compound analogous to (54).

The probable sequence is outlined in Scheme 9.

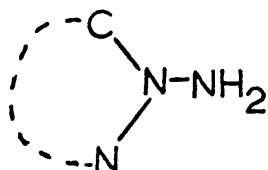


Scheme 9

The structure of (54) was based on the evidence that the u.v. spectrum showed almost identical shifts on comparing (34) with (54) and the phthalazones (33) with the phthalimidines (46). Also, the mass spectrum of (54) showed a small parent peak at 275 and a

large base peak at 257, corresponding to ready loss of water to give (53). The i.r. and PMR spectra were also consistent with this structure.

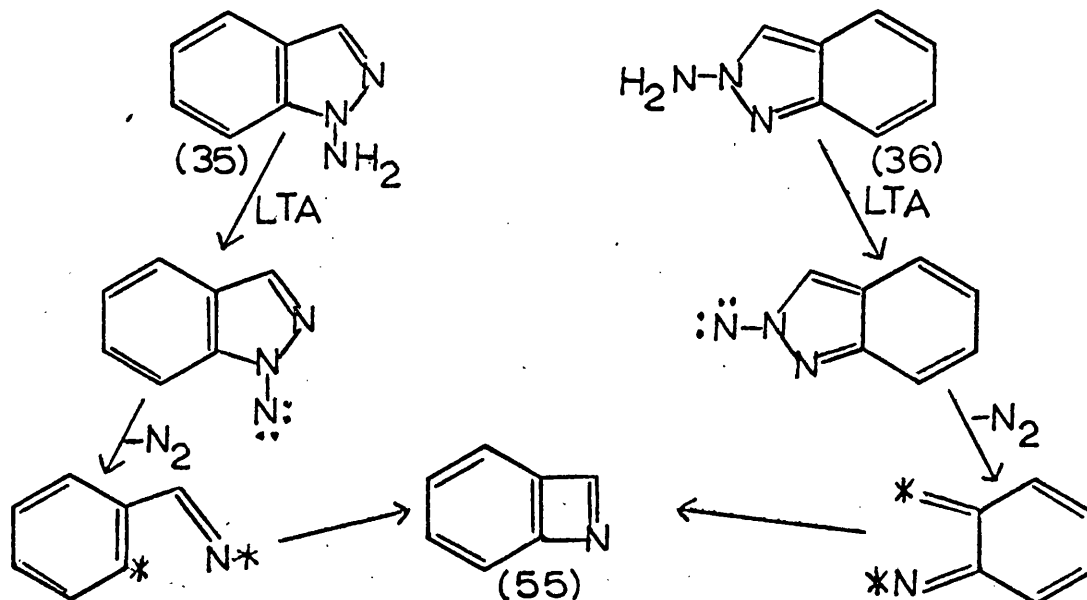
Thus the arrangement of atoms of Type B (37) i.e.



(37) TYPE "B"

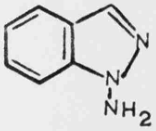
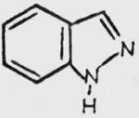
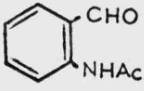
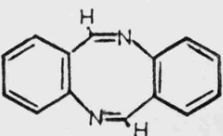
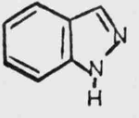
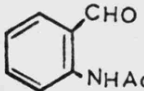
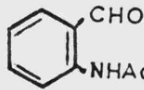
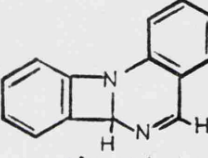
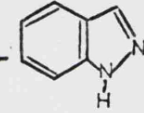
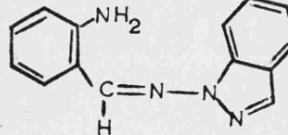
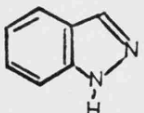
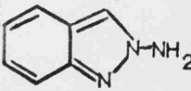
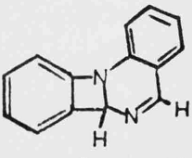
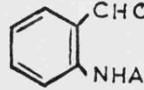
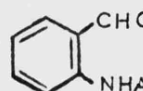
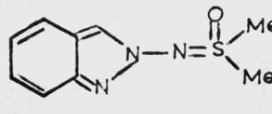
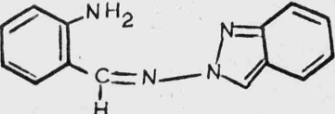
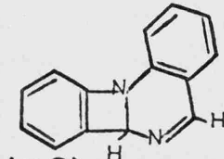
which is exemplified by compounds (32), (33), (34) and (50) causes intramolecular reaction of the N-nitrenes, and results in ring contraction. This pathway is also exemplified by other reactions investigated by Rees and coworkers (see Introduction, Section I, p.12-14).

The oxidation of 1-aminobenzimidazole (7) has already been discussed (see page 106); it is typical of its class in reacting in an intermolecular manner. However, if the theory postulated above, which is a central tenet of this thesis, the isomer of (7), the 1- and 2-indazoles (35) and (36) should fragment as outlined below, involving extrusion of nitrogen:



The product (55) can be compared with the oxidation products of the 2-aminoisoindolines, the benzocyclobutenes, as described in the Introduction, Section I, p. 10-11. This is a new anti-aromatic system, having 4 π electrons conjugated in a planar ring, being a 1-azabenzocyclobutadiene. Evidence was sought for the intermediary of (55). The products obtained from the oxidations are summarized in Table 1.

Table 1 over page.

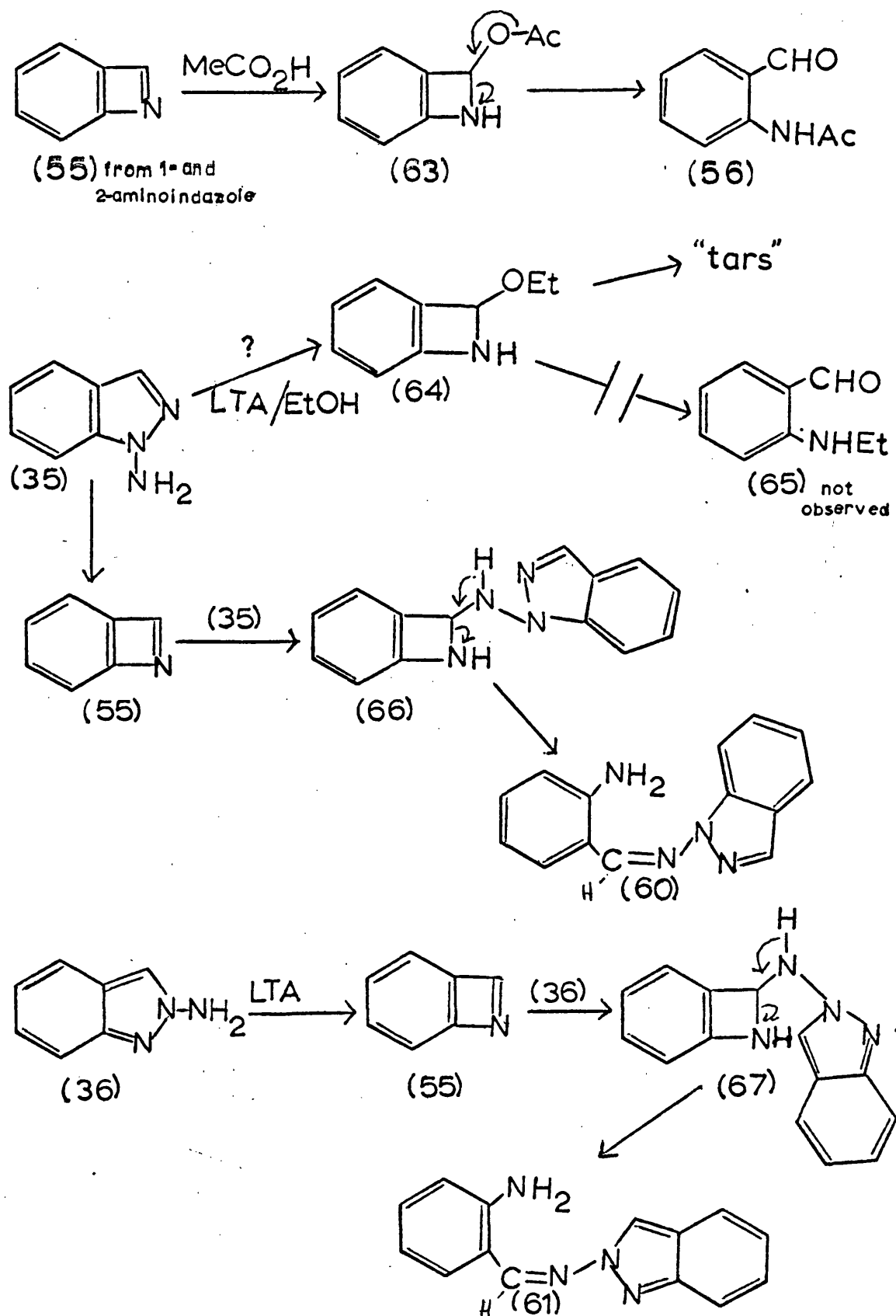
N-Amino Indazole	Reaction Conditions	TABLE 1	
		Products + yields	
	CH ₂ Cl ₂ /RT	 +  +  + "tars"	19% (56) 7% (57) 1.6%
"	DMSO RT	 + 	15% (56) 18%
"	DMF RT		(56) 70%
"	50% EtOH/CH ₂ Cl ₂ RT	 + "trimeric compound" + 	(58) 5% (59) "trace" 46%
"	EtOH -70°	 + 	(60) 10% 6%
	CH ₂ Cl ₂ /RT	 +  + "tars"	(58) 2.2% (56) 14%
"	DMSO RT	 + 	(56) 18% (62) 8%
"	CH ₂ Cl ₂ / cyclopenta- diene RT	 + 	(61) 34% (58) "trace"

Discussion of the results summarized in Table 1

Indazole, formed by oxidative deamination, and the sulphoximine adduct (62) result from intermolecular trapping of the nitrene. All the other products (56-61), some of which were formed in very small yield, can best be rationalized as being formed by the intermediary of (55) as follows:

The N-acetyl-o-aminobenzaldehyde (56) was formed by initial addition of acetic acid, of which 2 moles were generated in the oxidation, to the azabenzocyclobutadiene (55) to give (63), followed by an acyl shift to relieve the ring strain. High yields of this product were obtained in the aprotic polar solvents DMSO and DMF, which presumably promote the polar addition of acetic acid. Many examples of acid and thermal catalysis of acyl shifts are known, in particular those involving shift from an oxygen atom to nitrogen [136], as proposed here. It was hoped that ethanol would trap (55) to give compound (64), by analogy with the N-aminophthalazone oxidations described previously (see p. 148). However, in ethanol at -70° oxidation of 1-aminoindazole gave (60), and in methylene chloride-cyclopentadiene mixture at room temperature oxidation of 2-aminoindazole gave (61). In the latter case no adduct with cyclopentadiene was observed. These unusual products were identified by their spectral data, and by an alternative synthesis by condensation of o-aminobenzaldehyde [117] with the corresponding N-aminoindazole. Their formation can be explained by addition of the azabenzocyclobutadiene to the 1- and 2-aminoindazoles to give the benzoazetines (66) and (67) respectively, followed by a proton shift to open the ring, in direct analogy to the acyl shift postulated above. Presumably ethanol must add to (55) in the same manner to give (64) which must readily decompose; no product/as such (65) was observed, which would be formed only by an unfavourable ethyl shift. These mechanisms are summarized

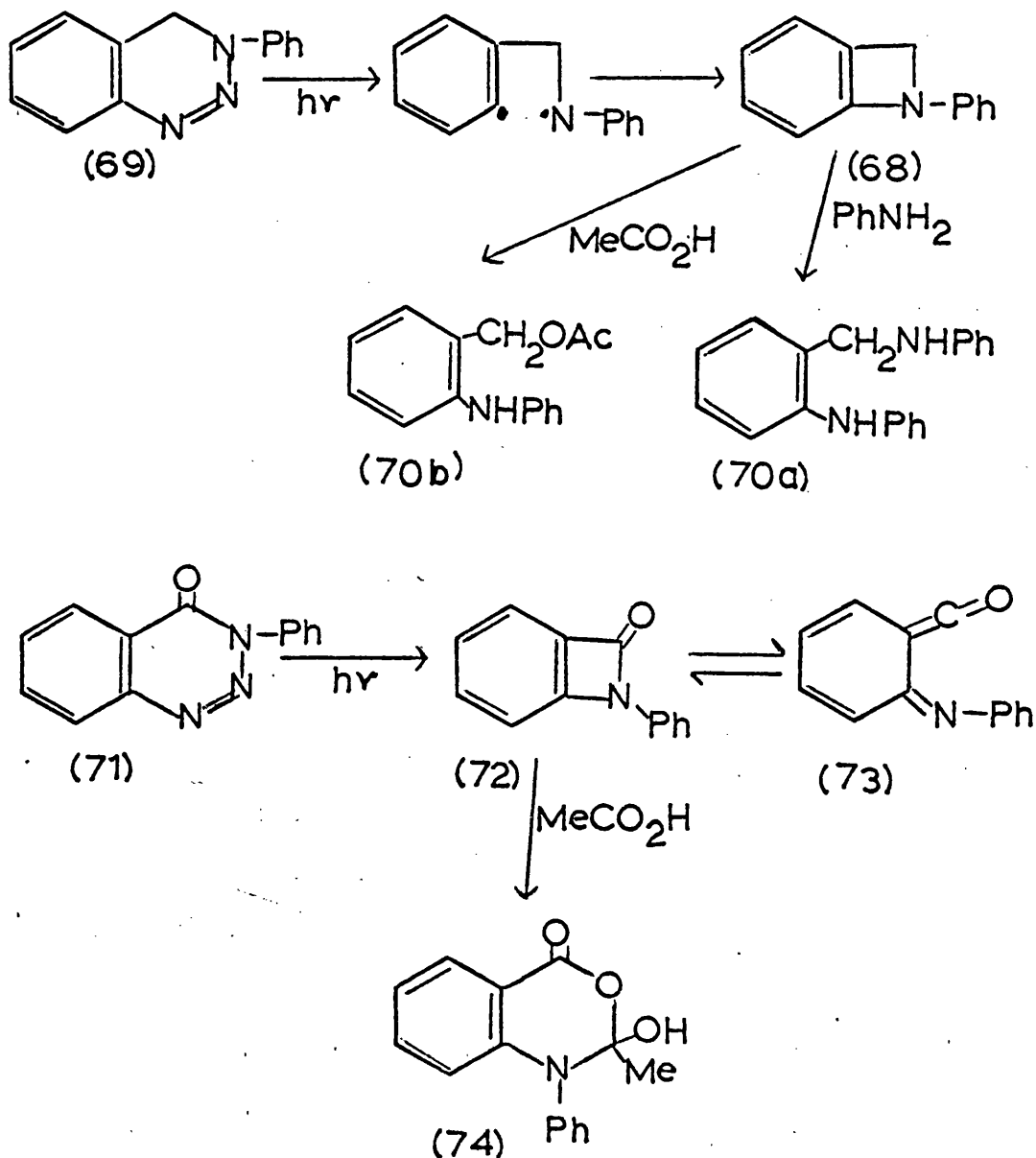
in Scheme 10.



Scheme 10.

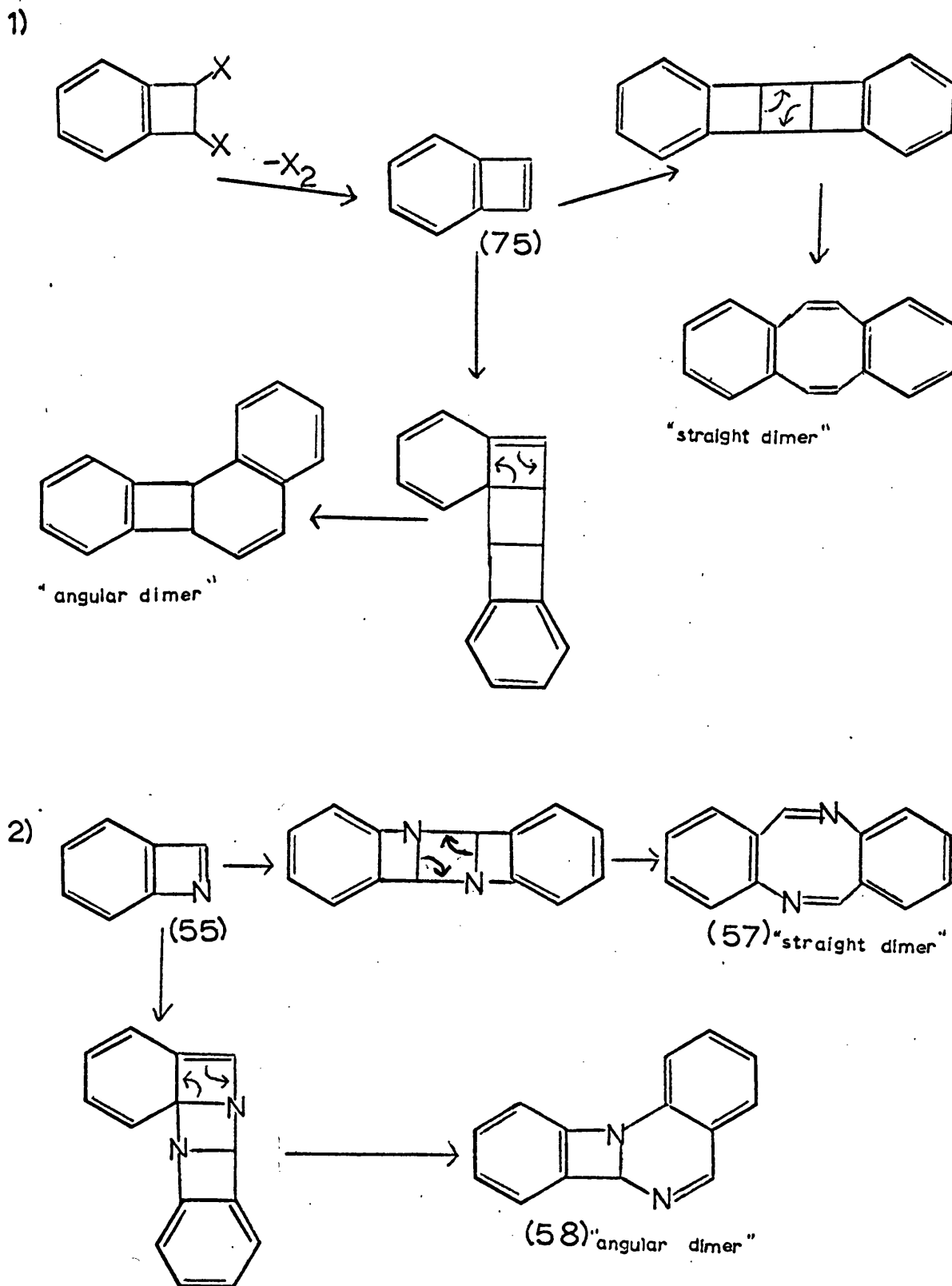
Support for the mechanism involving the proposed intermediate ring system, the benzoazetines (63), (64), (66) and (67), which is very labile

to nucleophiles, an internal nucleophilic attack in the above cases, is found in the findings of Burgess [96]. He found that the benzoazetine (68), produced on photolysis of the benzotriazine (69), is ring opened readily by aniline and acetic acid to give (70a) and (70b) respectively. Similarly, Ege photolysed the benzotriazinone (71) to give the benzoazetinone (72) which, possibly via its tautomer, the ketene (73), reacts with a range of nucleophiles, including acetic acid to give (74). These reactions are summarized in Scheme 11.



Scheme 11.

The dimers (57) and (58) were formed by a Diels Alder addition in an analogous manner to the dimerization of benzocyclobutadiene (75) [98], as outlined in Scheme 12.



Scheme 12.

The evidence for the structures (57) and (58) rests mainly on this analogy and the spectral data. Both dimers have an almost identical mass spectrum with $P^+ = 206$, followed by ready loss of two molecules of hydrogen cyanide, a fragment known to be very easily lost in the mass spectrum [99]. Both have simple i.r. spectra; (57) being assigned the "straight dimer" because it has a very weak $C = N$ stretch and very few "fingerprint" peaks, consistent with its highly symmetrical structure. The "angular dimer" (58) has a much stronger $C = N$ stretch.

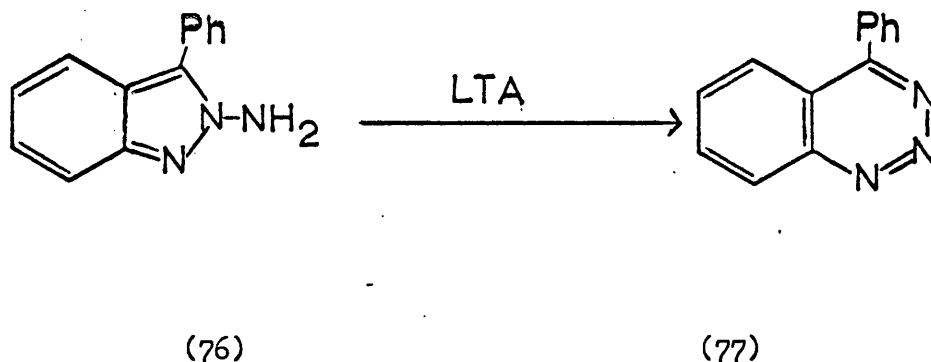
The trace amount of "trimeric compound" (59) has a mass spectrum with $P^+ = 382$; 355 (possibly loss of HCN), 309 (possibly loss of EtOH) (corresponds to trimer of (55)). Its structure is unknown.

It is interesting to note that the oxidation of 2-aminoindazole (36) did give a sulphoximine adduct (62) even though the yield was low. No such adduct could be isolated from 1-aminoindazole (35), even though the intermolecular pathway did occur as indicated by the formation of indazole, the deaminated product.

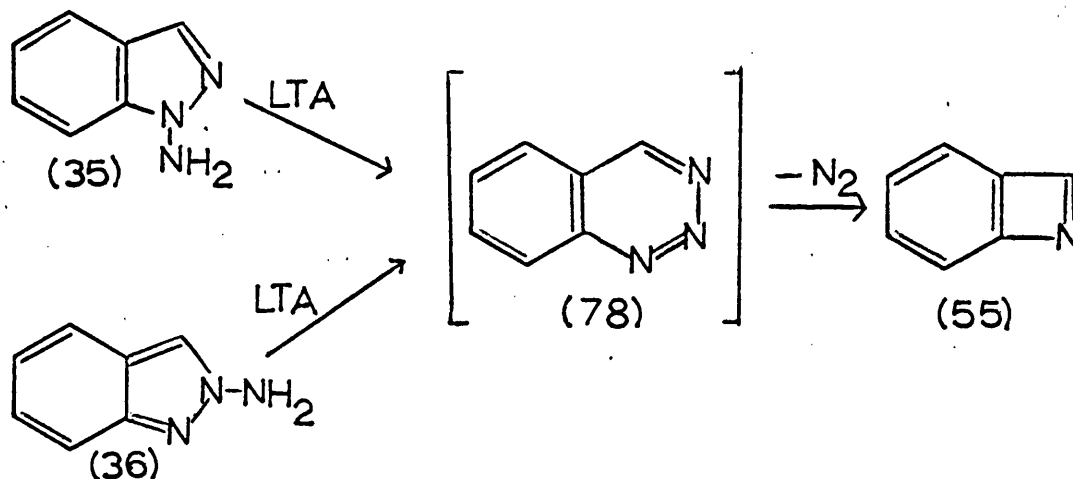
Hence, oxidation of 1- and 2-aminoindazoles proceed by intra- and intermolecular pathways simultaneously. The N-aminophthalazones (33) did not produce any isolable intermolecular products, presumably because the activation energy to extrusion of nitrogen is low, and the product is a favourable one. With the N-aminoindazoles the activation energy is presumably much higher, due to the unfavourable "anti-aromaticity" of the product (55). Hence the alternative intermolecular pathway can also occur.

Preliminary investigation by Bradbury has shown that oxidation of the amine assigned the structure 2-amino-3-phenylindazole (76), in contrast to 2-aminoindazole, undergoes the intramolecular insertion pathway (see Introduction, Section I, Fig. 5) to give the ring expanded

product benzotriazine (80%) (77). The 3-phenyl group presumably facilitates the required 1,2 shift [100].

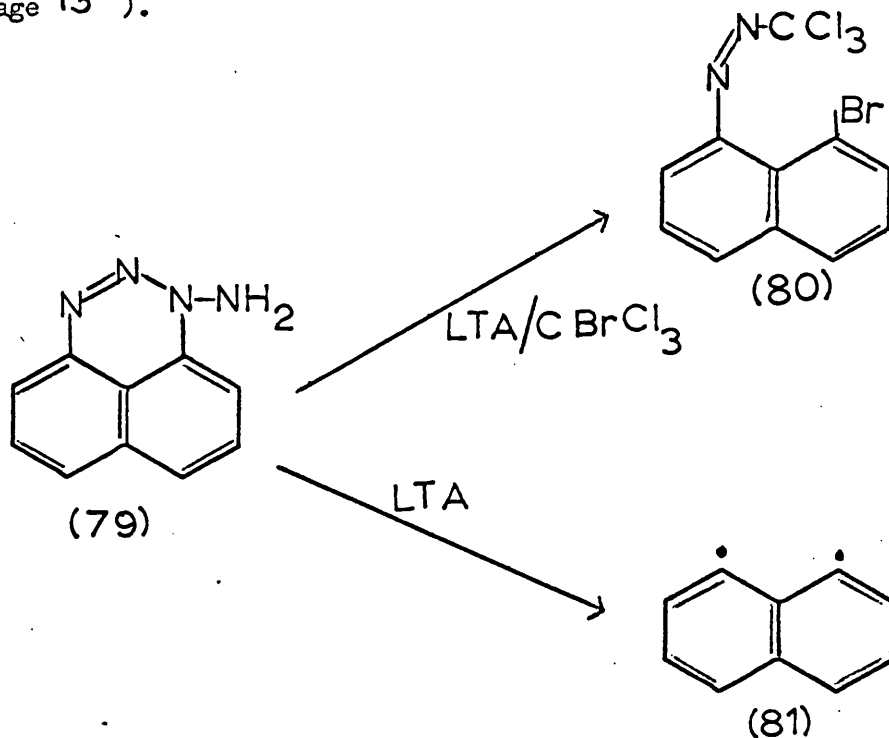


It is possible that formation of azabenzocyclobutadiene from the oxidation of 1- and 2-aminoindazoles could, in a similar manner, be via benzo-1,2,3-triazine (78) followed by rapid loss of nitrogen:



This parent compound (78) has not yet been described [103], although many 4-substituted derivatives are known, e.g. Ph [100], = O [9t], = S, -NH₂, -NHNH₂ [103]. Whether the mechanism of formation of azabenzocyclobutadiene is by direct extrusion of nitrogen or first via ring expansion by insertion is still open to further investigation. However, loss of nitrogen from (78) under the reaction conditions appears very unlikely. That direct extrusion first occurs is supported

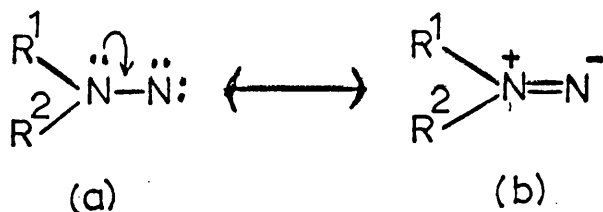
in the example of 1-aminonaphthotriazine (79). Oxidation by lead tetraacetate causes a similar extrusion of nitrogen, the resulting intermediate is trapped in the presence of bromotrichloromethane to give a small yield of the unstable compound (80)[91], as well as 1,8 dehydronaphthalene (81) as shown in the Introduction, Section I (page 13).



In conclusion, the different reaction pathways described in the Discussion, and those outlined in the Introduction, Section I, may all be conveniently rationalized in terms of the common intermediate, an N-nitrene. However, the discrete existence of such an intermediate is still open to question. For example, the low energy "nitrenoid" intermediate, proposed by Baumgarten on lead tetraacetate oxidation of the N-amino compound discussed (see Introduction, Section I, page 15), could account for the observed stereospecific addition to cis and trans butene by the oxidation of N-amino compounds (1), (2a) and (4). This is in analogy to the well known stereospecificity of the "carbenoid" intermediate in the Simmons-Smith reaction [104].

However, N-nitrenes themselves are much lower energy species

than their \underline{C} -nitrene counterparts, due to the resonance stabilization:

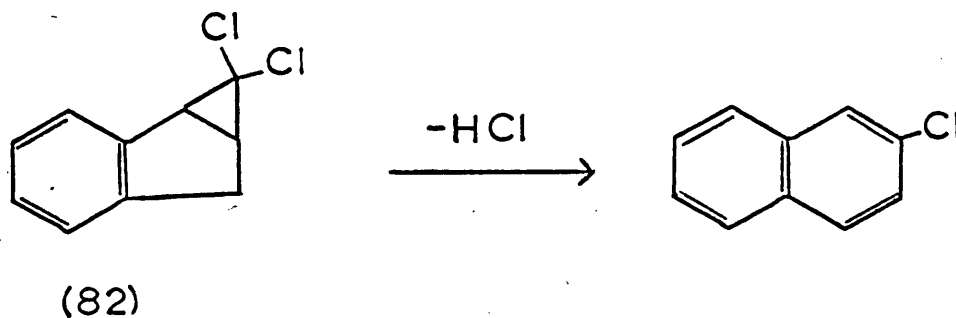


The form (b) has been isolated in some cases as its perchlorate salt [105].

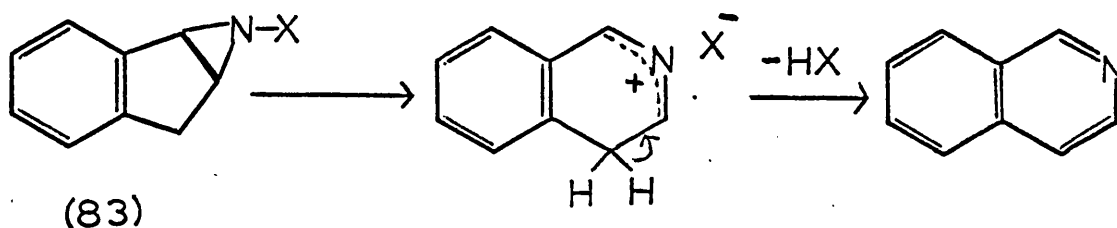
It is interesting to note that in acid solution (lead tetraacetate oxidation yields 2 moles of acetic acid) the nitrene in form (b) could be protonated to give its conjugate acid, which is in fact a nitrenium ion. This nitrenium ion is presumably in its singlet state, as resonance form (b) from which it is derived is only possible with the singlet nitrene (see Introduction, Section I, p. 1-9).

Section II: Fused Aziridine Ring Analogues of the Cyclopropyl to Allyl Cation Rearrangement

The conversion of 1,1-dichloro-1a,6a-dihydrocycloprop[*a*]-indene (82) into 2-chloronaphthalene in refluxing aqueous ethanol is known to be by a cyclopropyl to allyl cation rearrangement. This rearrangement has been discussed in the Introduction, Section II.



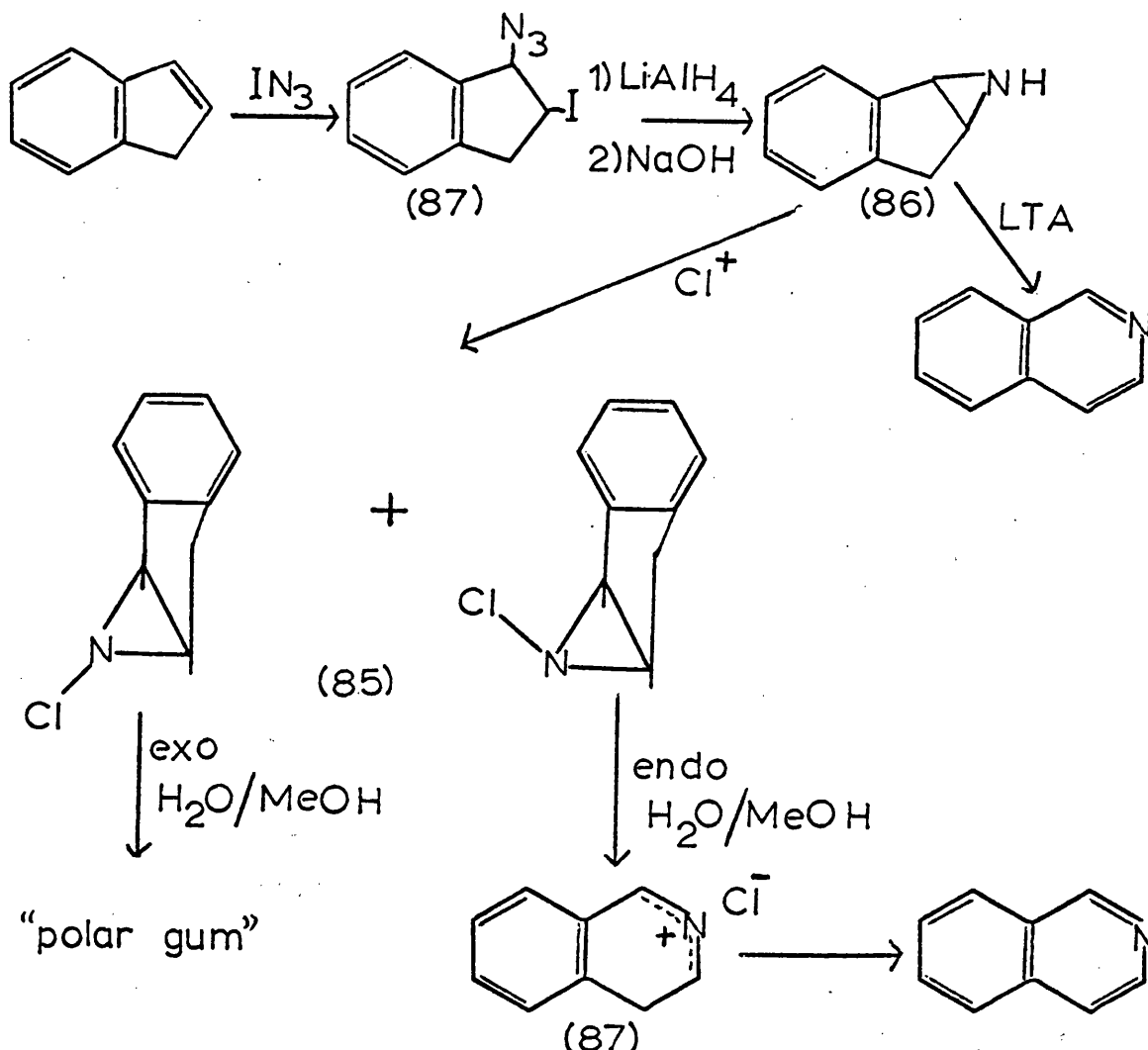
In this work the syntheses of aziridines of the type (83), where X was Qu, Cl and $\text{Pb}(\text{OAc})_3$, where Qu = (3,4-dihydro-2-methyl-4-oxoquinazolin-3-yl), were investigated in order to effect an aza-analogue of the above rearrangement, to give isoquinoline.



The endo conformer would not be present in a large proportion as the sterically favoured exo conformer is stereochemically stabilized due to the phenomenon of slow nitrogen inversion in aziridines when the aziridine nitrogen atom is substituted by an electronegative atom (nitrogen in this case) (see Introduction, Section III). However, it has recently been shown that thermolysis of (84) at 450° in a vacuum tube gives 2% isoquinoline [118]. Photolysis of (84) in quartz also failed to give any isoquinoline, again due to the formation of a tar. This would involve conrotatory opening of the abundant exo isomer.

(ii) where X = Cl

The N-chloro derivative of indano[1,2b]aziridine (85) was synthesized and solvolysed according to the procedure outlined in Scheme 13:



Scheme 13

Thus indene was converted in 90% yield into indano[1,2b]aziridine (86) by the addition of iodine azide in acetonitrile solution, to give trans 1-azido-2-iodoindane (87), followed by LiAlH_4 reduction and cautious treatment of the product with 2N sodium hydroxide solution, by analogy with the aziridine synthesis of Hassner [119]. The aziridine (86) is a colourless oil, picrate m.p. $240-245^\circ$ dec; which is very unstable, rapidly turning black on isolation, and decomposing completely in 48 hr. at room temperature. However, it is fairly stable in a cold dilute solution under nitrogen. Immediate treatment of (86) with sodium hypochlorite in methylene chloride at -70° or N-chlorobenzotriazole in methylene chloride at -70° gave the N-chloro derivative (85) as a colourless unstable oil, purified on Preparative t.l.c. Evidence for its structure was as follows:

it showed no N - H absorption in its i.r. spectrum, and its mass spectrum showed peaks at m/e 167, 165, 130 ($\text{P}^+ - \text{Cl}$) (base peak), 129 ($\text{P}^+ - \text{Cl} - \text{H}$). Thin layer chromatography showed the product to consist of two spots of nearly equal R_f value, in approximate ratio 4 : 1, the major spot of higher R_f presumably being the exo isomer, the minor spot of lower R_f being the endo isomer. These were inseparable on Preparative t.l.c. because of their rapid decomposition (a crude sample violently exploded on evaporation to dryness). After their isolation from the crude reaction mixture by Preparative t.l.c. the mixed N-chloro-aziridines were solvolysed in aqueous methanol at room temperature for 40 hour to yield isoquinoline in 10-15% after purification on Preparative t.l.c. The solvolysis was followed by t.l.c. The compound assumed to be the endo isomer disappeared rapidly to give the isoquinoline, the required disrotatory ring opening relieving the strain in the bicyclic system with this isomer. The other compound, assumed to be the exo isomer appeared to solvolysed in a different manner to

give a highly polar gum, possibly a polymer derived from its decomposition in the aqueous media.

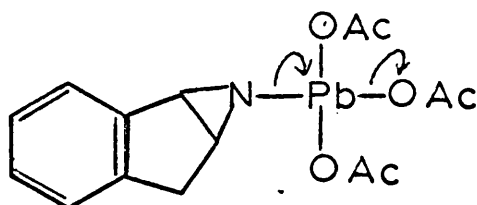
N-Chlorination with t-butyl hypochlorite was the cleanest reaction, the mixture of N-chloro compounds being easily separated from the reaction mixture, but not from each other, by Preparative t.l.c. Due to the instability of the mixture PMR assignments to each isomer were not possible. The N-chlorination by N-chlorobenzotriazole gave benzotriazole, which was difficult to separate from the isoquinoline formed. The sodium hypochlorite product mixture was very unstable, becoming black and polymeric in a short time.

Support for the proposed mechanism of solvolysis of the N-chloroaziridines is given by the kinetic data of Gassmann [1]. He has solvolysed a large number of N-chloroaziridines and shown these are electrocyclic processes with the same orbital symmetry control as the cyclopropyl to allyl cation rearrangement (see Introduction, Section II).

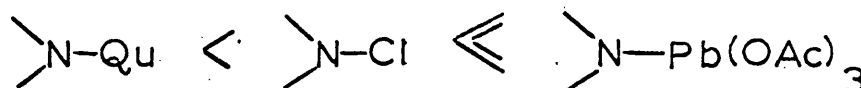
(iii) where X = Pb(OAc)₃

The removal of (H^+ , H^-) from indano[1,2b]aziridine (86), formally an oxidation process, gave isoquinoline in 50-60% yield directly. This was achieved by oxidation of (86) using lead tetraacetate in methylene chloride at -70° . This is a novel route to isoquinoline. The high yield in this case is probably due to the formation of the nitrogen-lead complex (88) where the N - Pb bond is so weak it cleaves much more readily than the N - N or N - Cl bonds in the cases described above. Possibly another important contribution is that nitrogen inversion is extremely rapid in this case, hence the N - Pb endo isomer being available to open in the required disrotatory mode with relief of strain in the bicyclic system. Low electronegativity aziridine N-substituents which can participate in $d\pi - p\pi$ overlap with the aziridine nitrogen lone pair, such as lead in this case, are known to enhance rapid nitrogen

inversion (see Introduction, Section III, p. 35). The highly electronegative substituents N and Cl in cases (i) and (ii) severely retard this inversion process. Thus the exo isomers, on steric ground, will be the most abundant, which will undergo the necessary disrotatory process only by introduction of severe strain in the bicyclic ring system, i.e. we have the series of ease of rearrangement as shown in (89).

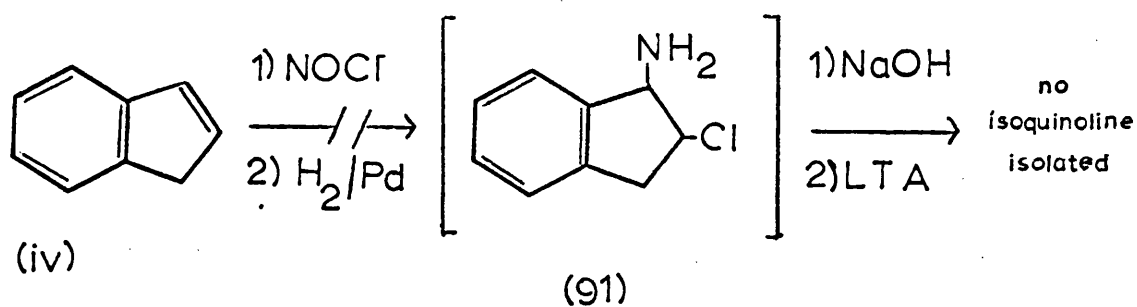
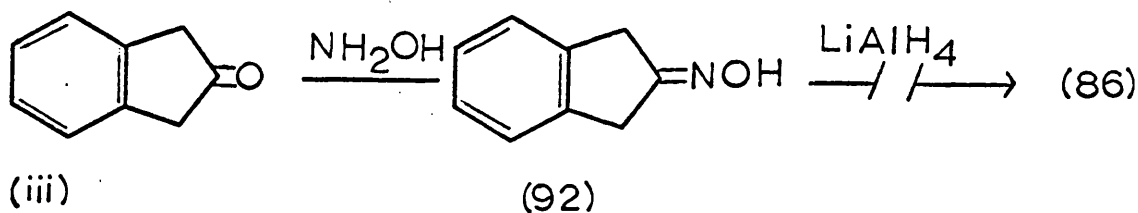
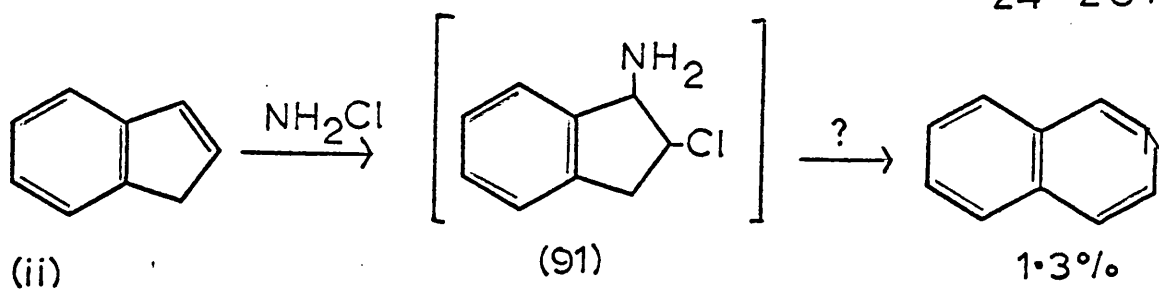
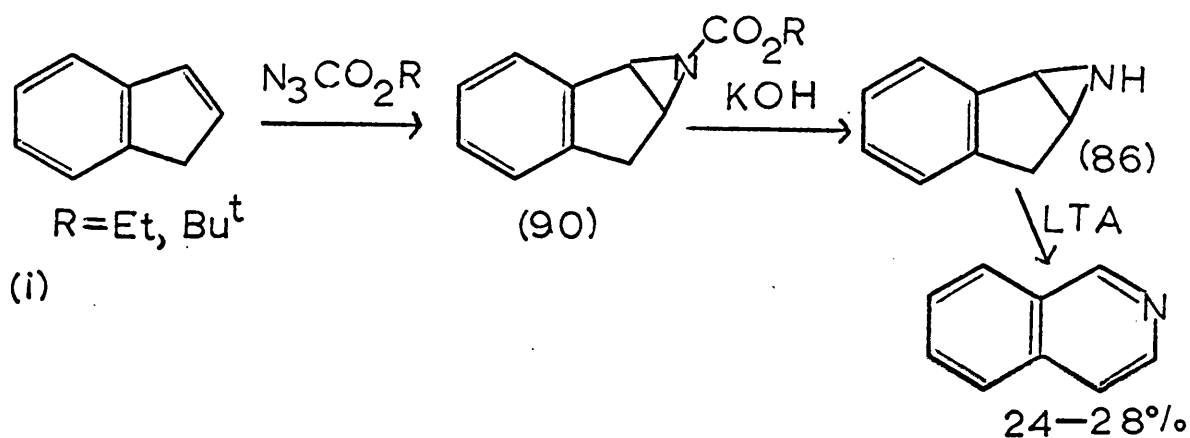


(88)



(89)

Other routes to the key intermediate, indano[1,2-b]aziridine (86) were attempted. These are outlined in Scheme 14.



Scheme 14

Route (i) involved addition to indene of the alkoxy carbonyl nitrene, derived from thermolysis of the azidoformates, giving the N-ethoxycarbonyl (R = Et) and N-t-butoxycarbonyl (R = Bu^t) aziridines (90),

by analogy with the aziridine synthesis of Lwowski [3]. The aziridines (90) were then treated with ethanolic potassium hydroxide solution to hydrolyse the ester. The resulting carbamic acid spontaneously decarboxylated to give (86) and a quantitative precipitate of potassium carbonate, by analogy with the method of Nozaki [120]. Oxidation of the crude aziridine (86) thus obtained by lead tetraacetate in methylene chloride at -70° , gave isoquinoline in 24-28% yield based on (90).

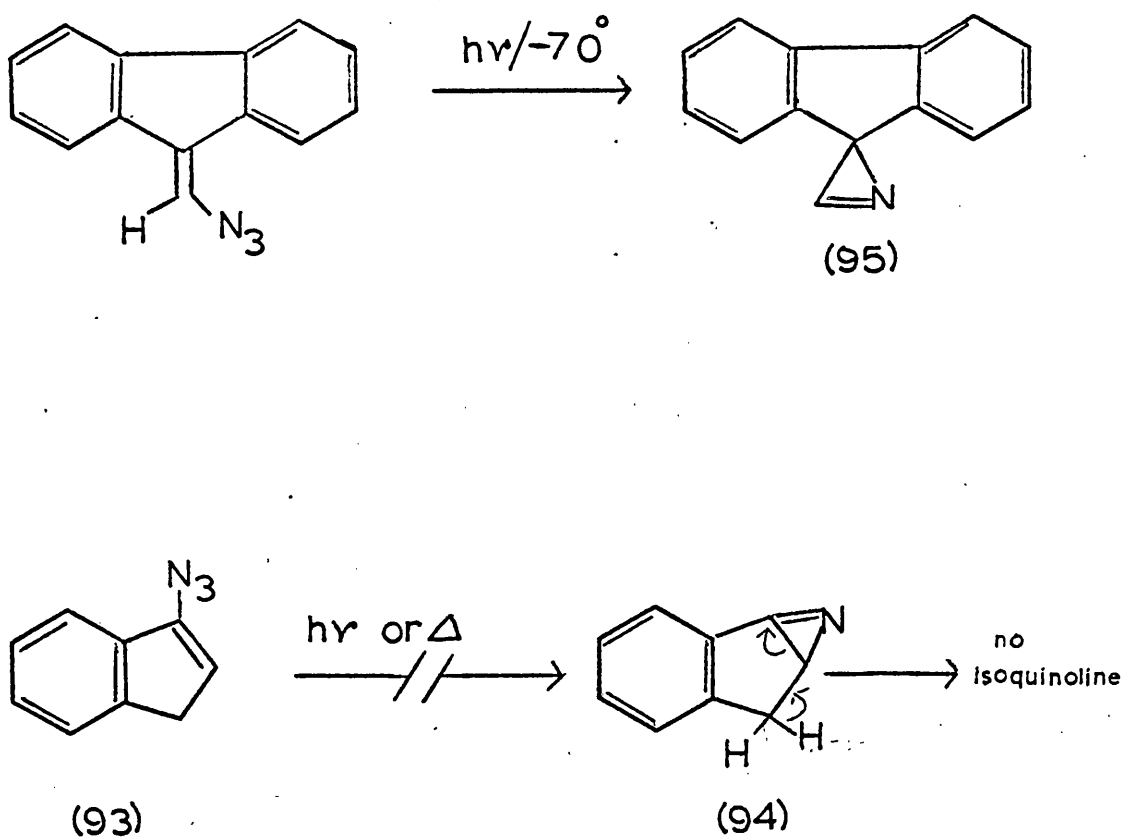
(ii) "Crude" indene was treated with a 9 molar excess of ethereal chloramine for 7 days to give 1.3% isoquinoline. Freshly distilled indene gave no isoquinoline. A possible mechanism involves addition of chloramine to indene to give (91) which ring closes to (86) possibly under catalysis by ammonia present in the ethereal chloramine; (86) was then oxidized to isoquinoline by excess chloramine, or more likely by indene hydroperoxide present in small amounts in the "crude" indene.

(iii) 2-Indanone was converted into its oxime (92) which on treatment with LiAlH_4 in refluxing THF gave no (86), but only a black gum. This method had previously been used in an aziridine synthesis [121].

(iv) Nitrosyl chloride was added to indene to give the dimeric adduct [123]. Attempted catalytic reduction, by analogy with the aziridine synthesis of Brois [124], gave only a black tar which on oxidation with lead tetraacetate gave no isoquinoline. This synthesis is known to work well only with highly substituted nitrosyl chloride adducts. The less substituted adducts, such as that from indene, unfortunately decompose on attempted reduction.

An interesting alternative approach considered was elimination of H I from the adduct (87), to give the vinylazide (93). This

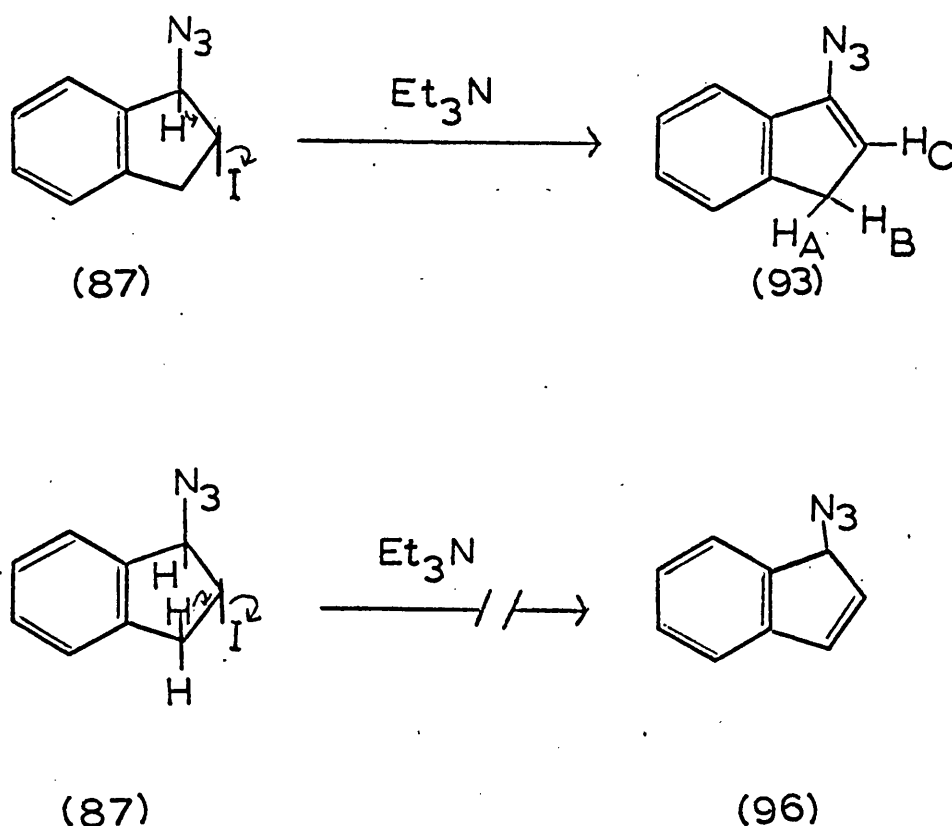
azidoindene could then decompose to the nitrene which could form the 2H-azirine (94) by analogy with the 2H-azirine (95) synthesis of Hafner [126]. Room temperature photolysis and thermolysis on sand at 200° of (93) gave an evolution of nitrogen but no isoquinoline was observed. These results are outlined in Scheme 15.



Scheme 15

It is interesting to note that the formation of the vinylazide (93) from trans 1-azido-2-iodoindane (87) on treatment with triethylamine involved a cis elimination of hydrogen iodide rather than trans elimination which would give the allylazide, 3-azidoindene (96). The PMR clearly shows the product to have the structure (93), with a doublet at $\delta = 3.0$ (H_A and H_B) and a triplet at $\delta = 5.62$ (H_C). Structure (96) would

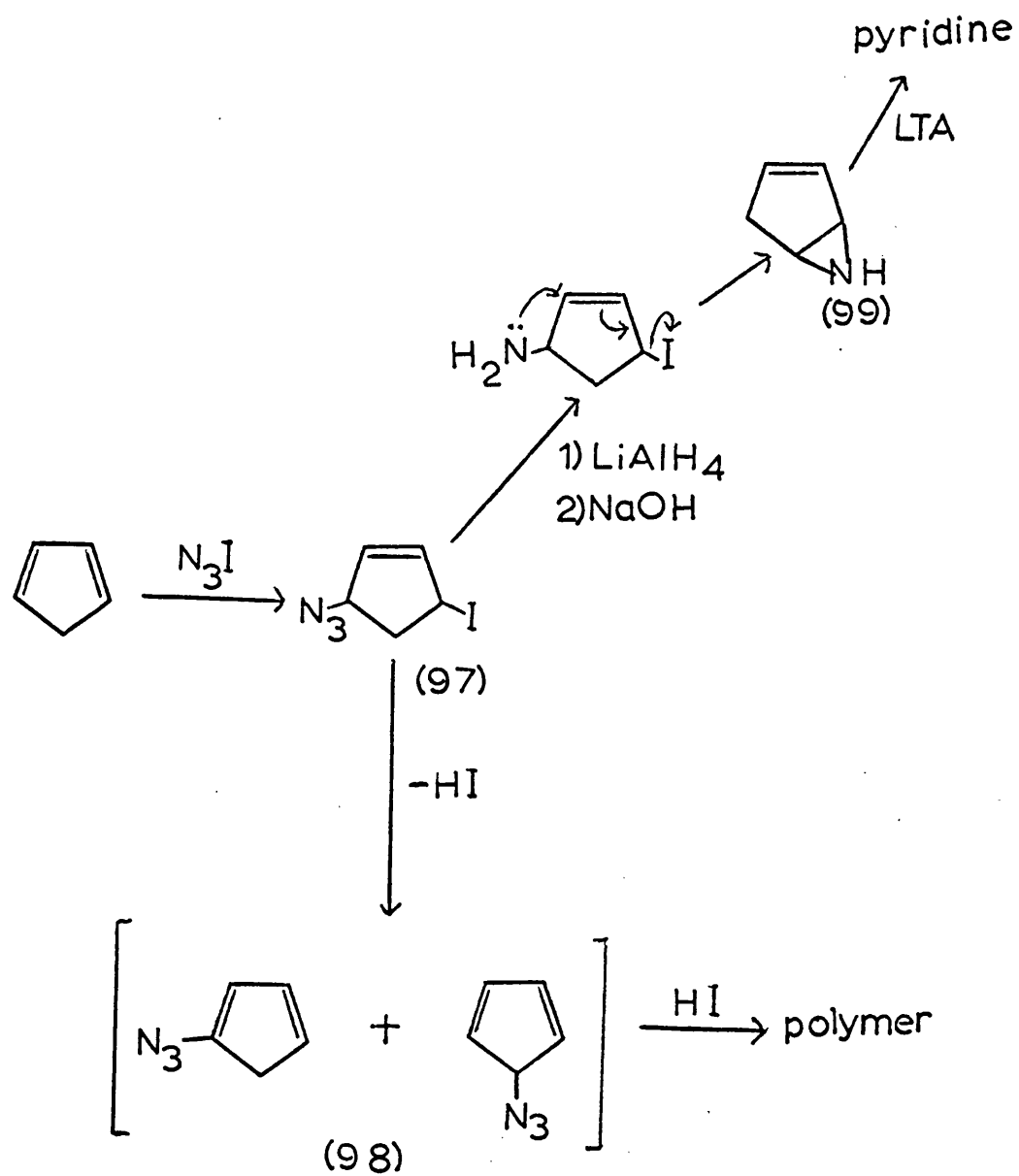
have three well separated proton signals. Presumably the azido group enhances the acidity of the 1-carbon hydrogen atom to make this the preferred elimination. This result has been independently confirmed by Hassner [125]. See Scheme 16.



Scheme 16

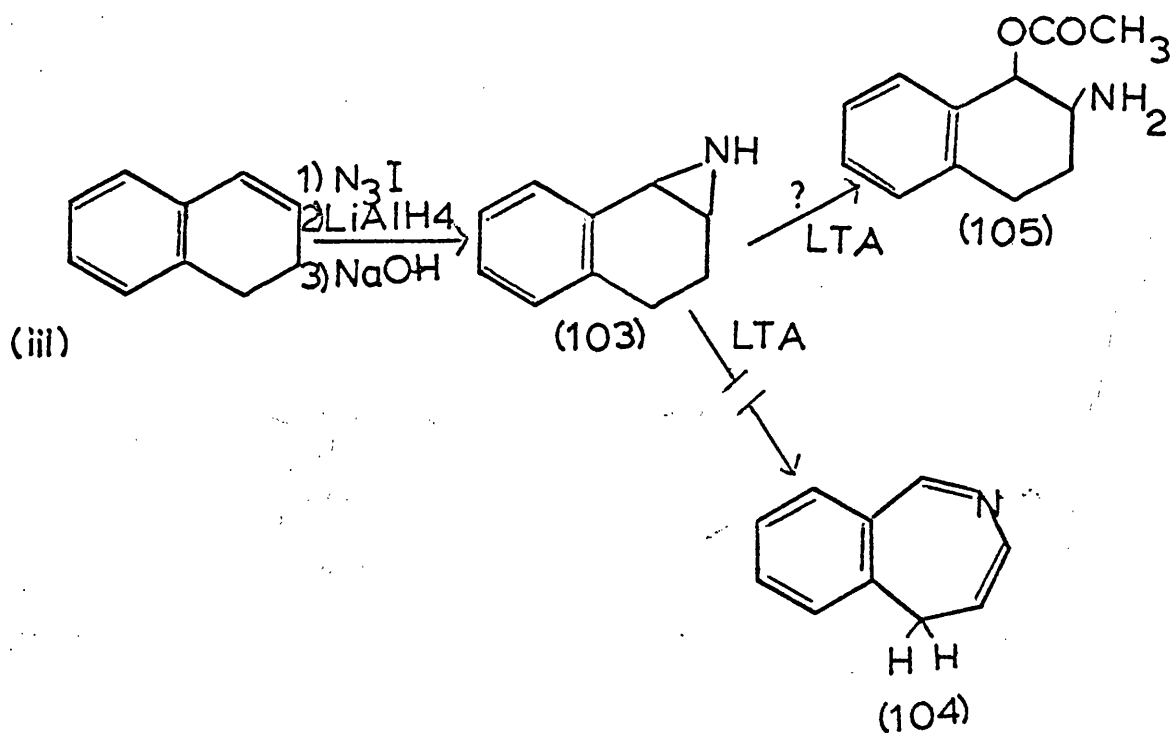
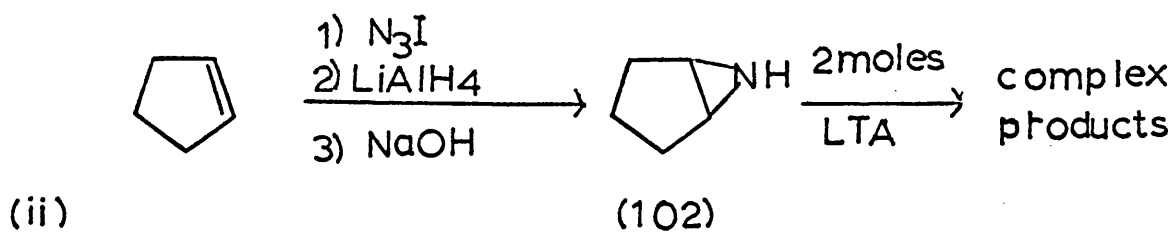
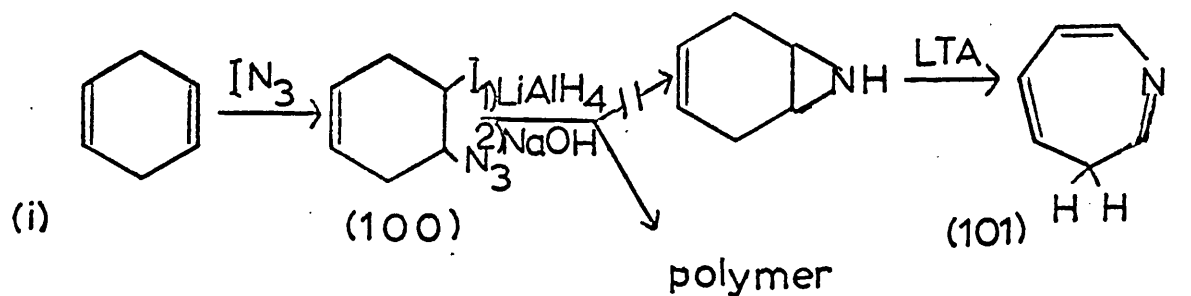
It was hoped to extend the oxidation reaction of fused aziridines to synthesize other nitrogen heterocyclic compounds, in particular the conversion of cyclopentadiene into pyridine. However, addition of iodine azide to cyclopentadiene presumably went 1,4 to give (97) rather than the required 1,2 adduct, by analogy with the well known 1,4 addition of HCl [127]. The unstable adduct (97) decomposed rapidly to a mixture of a red oil and a brown polymeric substance, the latter probably being formed by initial loss of HI, which catalysed the polymerization of the unsaturated azide (98). However (97) presumably gave some of the required aziridine (99) on reduction of the crude product with LiAlH_4 followed by treatment with

2N sodium hydroxide, because oxidation of the crude unstable reaction product gave 1% pyridine, purified by Preparative t.l.c. and characterized as its picrate. These reactions are summarized in Scheme 17



Scheme 17

Other similar syntheses attempted are outlined in Scheme 18.



(i) 1,4-Cyclohexadiene gave a low yield of the trans iodoazide (100), which polymerized on standing, presumably by a mechanism similar to that for (97) above. The attempted sequence to give the azepine (101) failed because of complete polymerization on attempted reduction of (100). An expansion of a 1,4-cyclohexadiene, via an aziridine to an azepine has been achieved by Paquette [128].

(ii) Cyclopentene gave a reasonable yield (30%) of the aziridine (102) which has been prepared only once before in low yield by a Wenker synthesis, as described by Fanta [129]. This compound gave no reaction with 2 molar equivalents of lead tetraacetate at -70° , presumably as the α -hydrogen atoms are not as acidic as those benzylic hydrogens which are readily removed in the indanoaziridine (86). Only complex products, containing no pyridine, were obtained on subsequent reflux of the mixture in methylene chloride for 5 hr. It was hoped that the use of 2 molar equivalents of lead tetraacetate would simultaneously oxidize the aziridine and dehydrogenate the ring, to give pyridine.

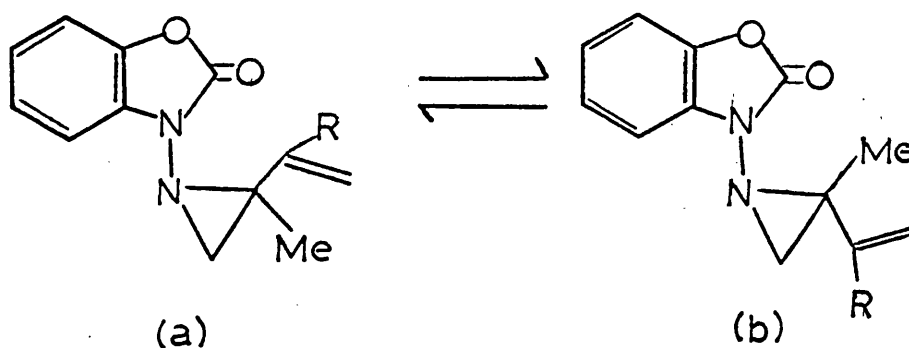
(iii) The aziridine (103) was prepared in 90% yield from 1,2-dihydronaphthalene. It also gave no reaction with lead tetraacetate at -70° . On refluxing in methylene chloride a complex reaction mixture resulted. The PMR of the black oil isolated after chromatography showed the 1,2-(4H)-multiplet of the A_2B_2 system present, hence the required oxidation had not occurred to give (104). I.r. and PMR showed that a component of the product contained the $-NH_2$ and $-COCH_3$ functions, probably due to the compound (105) formed by ring opening of the aziridine by acetic acid.

Thus, in conclusion, the isoquinoline synthesis (Scheme 13) appears to be the most favourable case in all these attempted aziridine ring expansions. The driving force of the oxidation of (86) to give isoquinoline presumably being the relatively high acidity of the benzylic

hydrogen atoms, and the aromaticity of the product. This 2π electrocyclic reaction follows a disrotatory mode of ring opening in concert with an endo leaving group. Steric hindrance and retarded nitrogen inversion in the aziridines make the exo conformer the stabilized predominant one. Only in the case where the leaving group X is $\text{Pb}(\text{OAc})_3$, where rapid interconversion of the exo to endo conformers can occur, is a high yield of isoquinoline obtained.

Section III: Substituent Interactions in Slowly Inverting Aziridines

An example where the slow inversion phenomenon in aziridines has been used as a probe for the measurement of relative sizes of groups is due to Atkinson and Rees, who found the ratio of invertomers $a : b$ was 1.4 : 1 for (106) and 1 : 11 for (107) from the measurement of the peak areas of the respective invertomers in the PMR spectrum [46]. Thus it was concluded that the vinyl group is less sterically demanding than the methyl group; a result in agreement with a conformational analysis in substituted cyclohexanes [131]. These values are only valid in such cases as above, where the substituents being compared lack any attractive or repulsive electronic interactions:

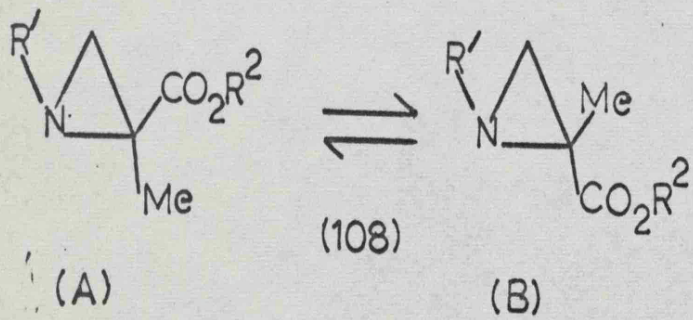


(106); R=H

(107); R=Me

The lead tetraacetate oxidation of 1-aminobenzoxazolinone, 3-amino-2-methyl-4-quinazolone, 1-amino-2-quinolone and N-aminophthalimide in the presence of methacrylate and acrylate esters gave good yields of aziridines (108) and (109) respectively (see Discussion, Section I). These aziridines exist as an equilibrium between the two invertomers (A) and (B):

LOOSE COPY OF ACRYLATE AND METHACRYLATE DERIVED AZIRIDINES
STUDIED BY PMR.



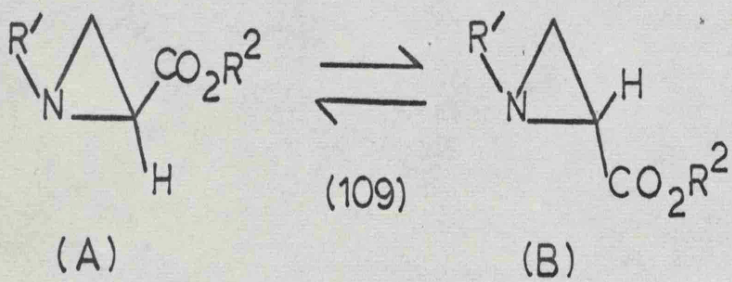
Where:

a; $R^2 = \text{Me}$

b; $R^2 = \text{Et}$

c; $R^2 = \text{Pr}^i$

d; $R^2 = \text{Bu}^t$



Where:

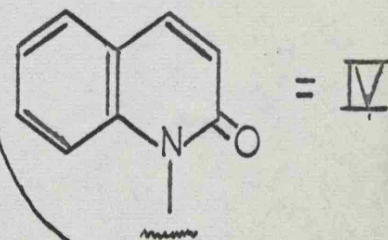
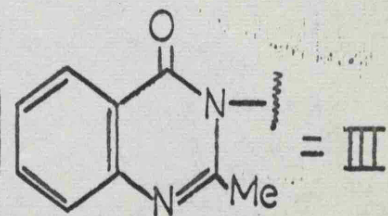
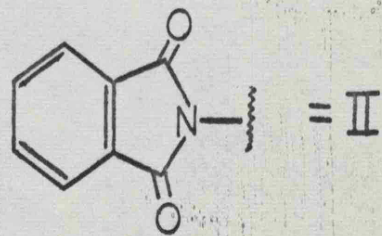
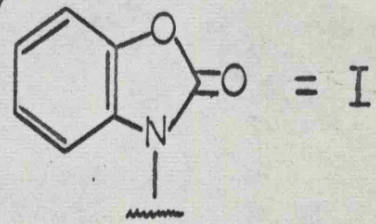
$R' = \text{I II,}$

e; $R^2 = \text{Me}$

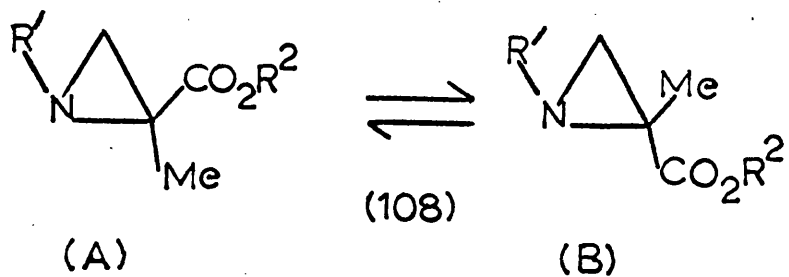
f; $R^2 = \text{Bu}^t$

$R' = \text{III IV,}$

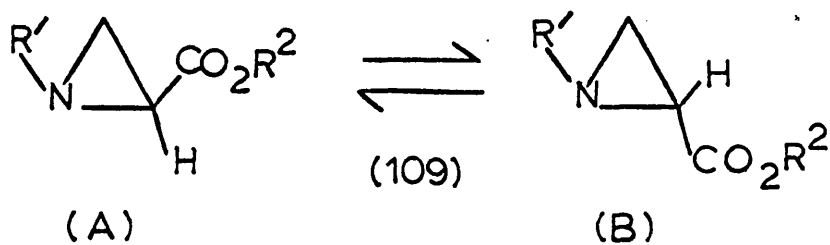
$R^2 = \text{Me only.}$



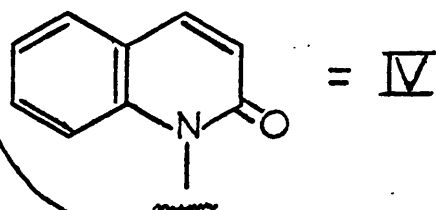
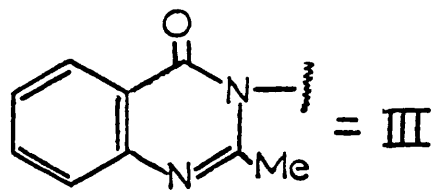
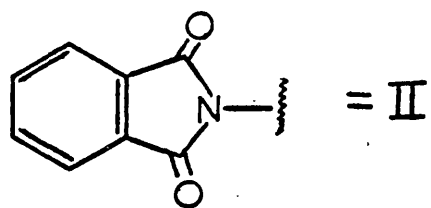
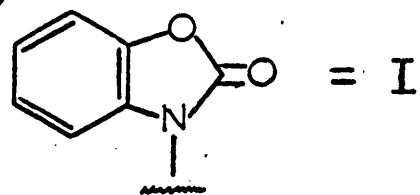
and $R' =$



Where:

a; $R^2 = \text{Me}$ b; $R^2 = \text{Et}$ c; $R^2 = \text{Pr}^i$ d; $R^2 = \text{Bu}^t$ 

Where:

 $R' = \text{I II,}$ e; $R^2 = \text{Me}$ f; $R^2 = \text{Bu}^t$ $R' = \text{III IV,}$ $R^2 = \text{Me only.}$ and $R' =$

The signals due to both invertomers in all these compounds are clearly seen in the PMR spectrum at room temperature, hence they are convenient to use to study invertomer ratios, by simple integration of the respective peak areas. The factors enabling this to be so, as indeed in the cases of (106) and (107) are:

- (i) the process of nitrogen inversion is greatly retarded in aziridines,
- (ii) an electronegative N-aziridine substituent, nitrogen in this case, greatly enhances the retardation of the process of inversion,
- (iii) each invertomer is present in approximately equal amounts so that peaks due to both invertomers are seen in the PMR spectrum,
- (iv) the anisotropic effects of the N-substituent of the aziridines enhance the separation of corresponding signals of the two invertomers, which facilitates the integration.

The reason for the observed effects (i) - (iii) listed above are discussed in detail in the Introduction, Section III.

The detailed spectra of the methacrylate derived aziridines (108) are given in Table II, signals for invertomers with ester cis (A) and trans (B) to the N-heterocyclic substituent are given separately. The spectra of the acrylate derived aziridines (109) from N-aminobenzoxazolinone and N-aminophthalimide i.e. where R' is I and II respectively, are likewise presented in Table III.

The nature of the interactions which lead to the observed invertomer ratios, which are given in Table IV for the methacrylate derived aziridines and in Table III for the acrylate derived aziridines (e) and (f), will be discussed in this Section.

Examination of Table II leads to the following conclusions:

- (i) the aziridine ring methyl groups are shielded when cis to the N-heterocyclic substituent. This effect, which is common to R' being (I - IV) varies in magnitude between the N-heterocyclic substituents,

TABLE II

N.m.r. data (δ values; solution in $CDCl_3$) of methacrylate-derived aziridines

152

A

ester (CO_2R^1) and heterocycle (R^1) *cis*

B

ester (CO_2R^2) and heterocycle (R^1) *trans*

	A				B				aromatic H	QUINAZOLONE RIMS METHYL GROUP
	H <i>cis</i> to R^1	H <i>trans</i> to R^1	CO_2R^2	CH_3	H <i>cis</i> to R^1	H <i>trans</i> to R^1	CO_2R^2	CH_3		
I	a	3.95, d, J 2	2.69, d, J 2	3.51, s	1.72, s	3.76, d, J 2	3.07, d, J 2	3.85, s	1.53, s	7.15, 7.18 (2 lines)
	b	3.98, d, J 2	2.67, d, J 2	0.97, t, J 7 3.93, q, J 7	1.70, s	3.70, d, J 2	3.05, d, J 2	1.35, t, J 7 4.30, q, J 7	1.51, s	7.08, 7.14 (2 lines)
	c	4.05, d, J 2	2.64, d, J 2	0.95, 0.92, 2xd, J 6.5 4.72, h, J 6.5	1.67, s	3.68, d, J 2	3.02, d, J 2	1.32, d, J 6 5.12, h, J 6	1.48, s	7.06, 7.12 (2 lines)
	d	4.06, d, J 2	2.62, d, J 2	1.12, s	1.66, s	3.67, d, J 2	3.00, d, J 2	1.55, s	1.47, s	7.10, 7.16 (2 lines)
II	a	3.42, d, J 2	2.69, d, J 2	3.68, s	1.69, s	3.09, s	3.09, s	3.84, s	1.54, s	7.6 - 7.8, m
	b	3.44, d, J 2	2.66, d, J 2	1.16, t, J 7 4.07, q, J 7	1.68, s	3.07, s	3.07, s	1.32, t, J 7 4.27, q, J 7	1.53, s	7.6 - 7.8, m
	c	3.45, d, J 2	2.64, d, J 2	1.11, 1.15, 2xd, J 6 4.86, h, J 6	1.67, s	3.05, s	3.05, s	1.31, d, J 6 5.12, h, J 6	1.52, s	7.6 - 7.8, m
	d	3.44, d, J 2	2.61, d, J 2	1.33, s	1.63, s	3.02, s	3.02, s	1.53, s	1.47, s	7.6 - 7.8, m
III	a	3.32, d, J 2	2.81, d, J 2	3.58, s	1.76, s	3.51, d, J 3	~ 3.35	3.83, s	1.40, s	8.0 - 8.3 } 7.2 - 7.8 } ^m
	b	3.40, d, J 2	2.83, d, J 2	1.02, t, J 7 4.01, q, J 7	1.77, s	3.53, d, J 3	~ 3.35	1.34, t, J 7 4.30, q, J 7	1.40, s	8.0 - 8.3 } 7.2 - 7.8 } ^m
	c	3.45, d, J 2	2.81, d, J 2	0.95, 1.10, 2xd, J 6 4.79, h, J 6	1.73, s	3.53, d, J 3	3.33, d, J 3	1.30, d, J 6 5.12, h, J 6	1.36, s	8.0 - 8.3 } 7.2 - 7.8 } ^m
	d	3.42, d, J 2	2.79, d, J 2	1.22, s	1.70, s	3.50, d, J 3	3.32, d, J 3	1.53, s	1.33, s	8.0 - 8.3 } 7.2 - 7.8 } ^m
IV	a	~ 3.4	2.93, d, J 2	3.41, s	1.85, s	~ 3.4	~ 3.4	3.87, s	1.22, s	7.0 - 7.7, m, 4H 6.60, d, 2H, J 9.5
	b	3.48, d, J 2.5	2.99, d, J 2.5	0.90, t, J 7 3.82, q, J 7	1.82, s	3.39, s	3.39, s	1.30, t, J 7 4.36, q, J 7	1.22, s	7.0 - 7.7, m, 4H 6.62, d, 2H, J 9.5
	c	3.55, d, J 2.5	2.95, d, J 2.5	0.84, 0.86, 2xd, J 6 4.60, h, J 6	1.82, s	3.30, s	3.38, s	1.34, d, J 6 5.20, h, J 6	1.19, s	7.0 - 7.7, m, 4H 6.64, d, 2H, J 9.5
	d	3.60, s, broad	2.97, d, J 2	1.03, s	1.80, s	3.39, s	3.39, s	1.50, s	1.18, s	7.1 - 7.8, m, 4H 6.67, d, 2H, J 9.5

TABLE III

N.m.r. data (δ values, solutions in $CDCl_3$) of acrylate derived acrylamides.

153a

A ester (CO_2R^2) cis to heterocycle (R^1)		B ester (CO_2R^2) trans to heterocycle (R^1)					aromatic H	Invertomer Ratio (A/B)
CO_2R^2	CO_2R^2	H cis to R^1	H trans to R^1	H to CO_2R^2				
3.56, s	3.85, s	3.54, dxd, J 8 x 1	2.78, dxd, J 4.5 x 1	3.60, dxd, J 8 x 4.5	7.0 - 7.3, m	1 : 14		
1.19, s	1.56, s	3.25, d, J 7.5	2.73, d, J 4.5	3.43, dxd, J 7.5 x 4.5	7.0 - 7.3, m	1 : 8.8		
3.70, s	3.85, s	2.83, dxd, J 7 x 1.5	2.82, dxd, J 6 x 1.5	3.21, dxd, J 7 x 6	7.7 - 7.8, m	1 : 5.8		
1.38, s	1.56, s	2.75, d, J 8	2.78, d, J 4.5	3.1, dxd, J 8 x 4.5	7.7 - 7.8, m	1 : 3		

I { e
fII { e
f

TABLE IV
Ratio of ester cis/trans (A/B) to heterocycle for aziridines in Table II

	a	b	c	d
I	0.7	0.9	1.1	1.5
II	1.8	2.2	2.8	3.5
III	2.1	2.4	2.9	3.3
IV	1.9	2.2	2.5	3.1

Errors estimated to be ± 0.1 units.

Fig. 40 N.m.r. spectrum (CDCl₃, 60 M Hz) of (2-t-butoxy-carbonyl-2-methylaziridin-1-yl)benzoxazolin-2-one (Id). The broadening of the doublet at δ 3.00 is N¹⁴-C-H coupling.

153c

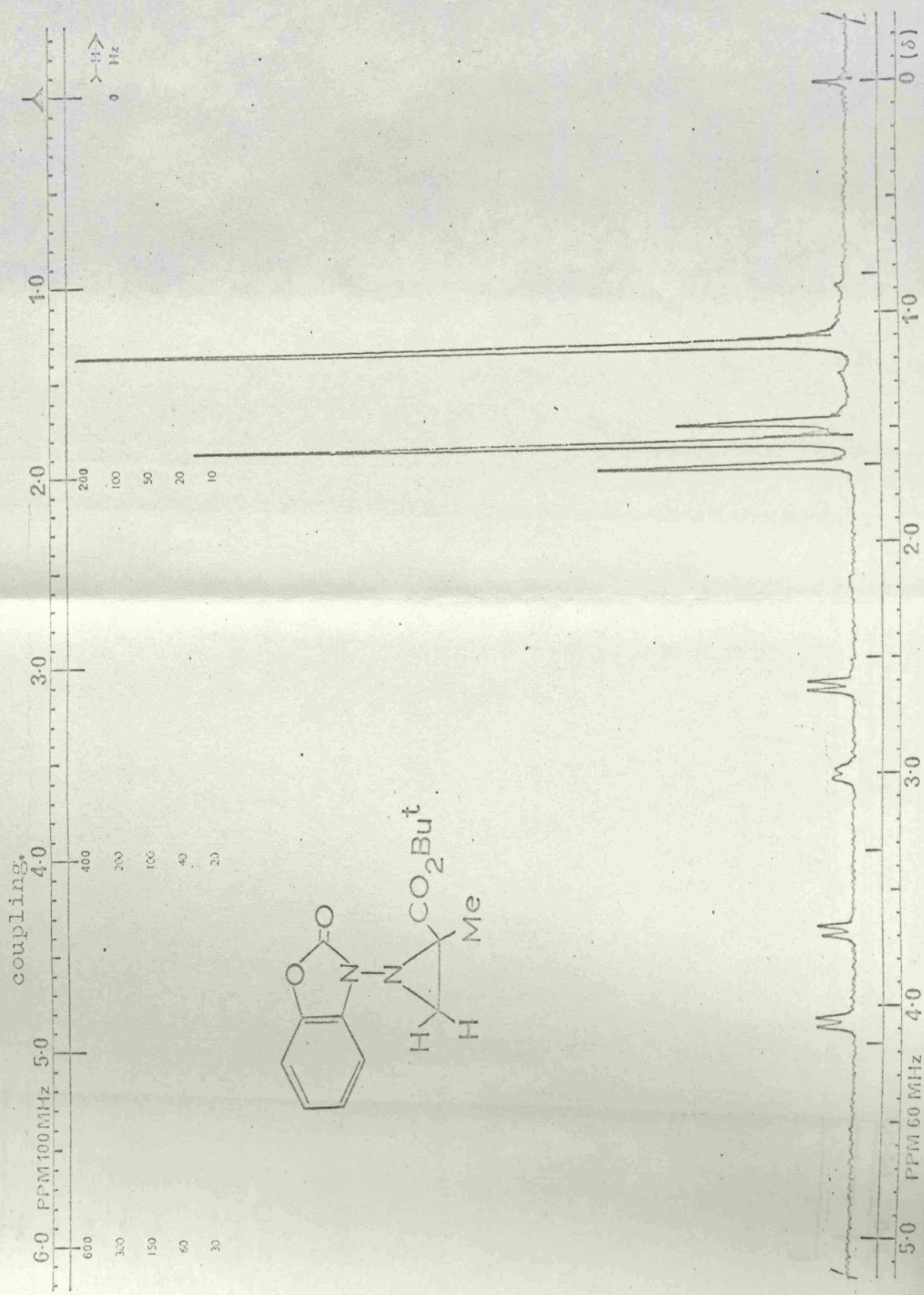
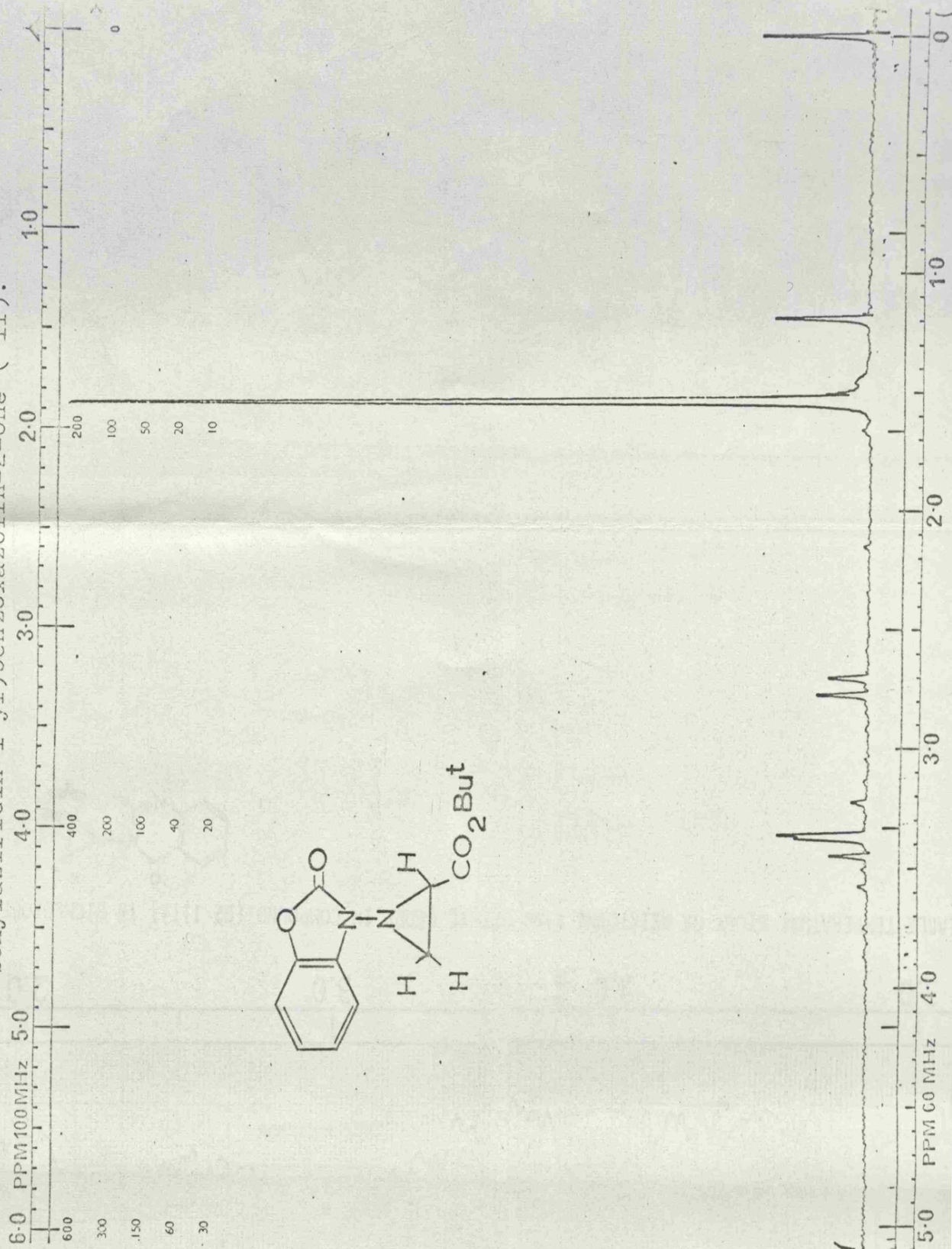


Fig. 41 N.m.r. spectrum (CDCl₃, 60 M Hz) of (2-t-butoxycarbonylaziridin-1-yl)benzoxazolin-2-one (If). 153d



being the greatest when the substituent is 2-quinolin-1-yl (IV).

Along with this effect goes a smaller deshielding of the trans aziridine ring methyl groups.... continued on p. 155

This is of lesser magnitude presumably because these methyl groups are more remote and hence less influenced by the anisotropic effects of the heterocyclic groups.

(ii) similarly, all protons of the ester alkyl groups are shielded when cis to the N-heterocyclic substituent.

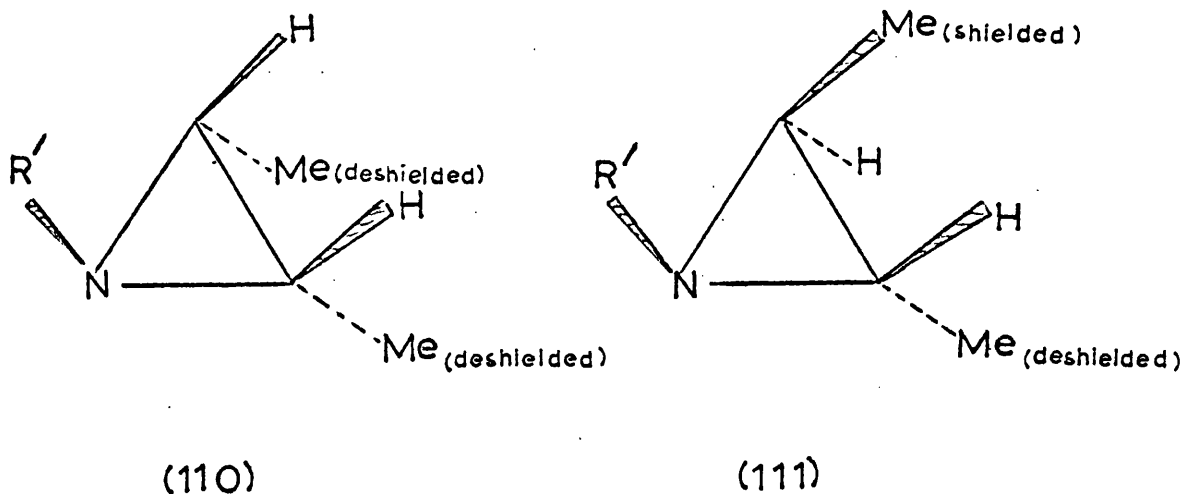
(iii) aziridine ring protons are deshielded when cis to the N-heterocyclic substituents, the magnitude of this being greatest in invertomer (A), where the ester group which exerts a deshielding effect on the aziridine ring protons, is also cis to the N-heterocyclic substituent. This effect is the reversal of that noted by Brois. He found that with N-alkyl aziridine ring substituents, aziridine ring protons are shielded, except where the alkyl group is t-butyl, which is so bulky that it distorts the electron cloud about the ring protons, causing deshielding (see Introduction, Section III, p. 32). Presumably the high π -electron density associated with the N-heterocyclic substituents is responsible for a similar distortion, hence deshielding of the aziridine ring protons.

The validity of these conclusions depends upon the initially correct assignments of chemical shifts of the invertomer peaks. Evidence for this is as follows:

The aziridine (110, where R' = III) formed on oxidation of 3-amino-2-methyl-4-quinazolone in the presence of cis-butene would, on steric considerations, have the two aziridine ring methyl groups trans to the N-heterocyclic substituent, which appear as a doublet at

$\delta = 1.40$ and 1.49 (at 60°C). The corresponding trans-butene derived aziridine (111) has two different aziridine methyl groups, which appear as two doublets; one at $\delta = 1.49$ and 1.59 (which must be trans to the N-heterocyclic substituent as the chemical shifts are approximately the same as assigned above), and another doublet which is shielded, at $\delta = 1.09$ and 1.19 (which is cis to the N-heterocyclic substituent).

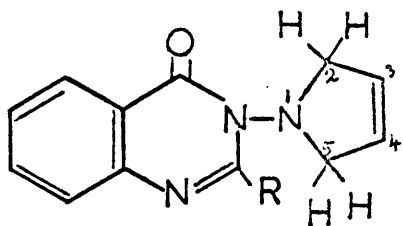
These assignments are further supported where $R' =$ benzoxazolinone (I) and phthalimide (II) [76]



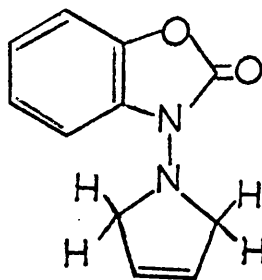
Hence cis aziridine ring methyl groups to the N-heterocyclic substituent are shielded. Further evidence supporting this is provided by examination of the PMR spectrum of the acrylate ester derived aziridines (109). Even in these cases, where it would be expected on steric grounds alone that the invertomer (B), with ester trans to the N-heterocyclic substituent, would be the only invertomer to be seen in the PMR, both invertomers clearly give peaks (for example, see Fig. 41). If the reasonable assumption is made that (B) is indeed the major invertomer in the acrylate series, then the observed good correlation of assignments in the acrylate and methacrylate derived aziridines supports the conclusions mentioned above (compare Figs. 40 and 41, and Table II with the chemical shifts presented in Table III). In addition, the magnitude of the coupling constants found in the acrylate derived aziridines (109), where for cis, $J \sim 8$ c.p.s.; for trans, $J \sim 4.5$ c.p.s.

and for gem, $J \sim 2.0$ c.p.s.; agree well with the values obtained by Brois [135] for other aziridines.

When the N-heterocyclic substituent is the quinazolone-3-yl group (III) the methyl group in the 2-position of the quinazolone ring also appears as two peaks, presumably due to each invertomer, thus providing another check on the invertomer ratios. It is possible that the latter observation is due to restricted rotation about the N - N bond. However, such rotational energies are considerably smaller than the energy involved in the inversion process in such aziridines [28]. Hence restricted inversion, rather than rotation is more likely to cause the presence of the two signals due to the quinazolone ring methyl group. However, in the case of the quinazolonyl-pyrroline (112b) the 2,5-pyrroline ring protons appear as a complex multiplet at room temperature, which coalesces into a singlet at 100° [133], whereas the corresponding benzoxazolonyl-pyrroline (113) shows a sharp singlet for the 2,5-pyrroline protons even at room temperature [132]. The barrier to nitrogen inversion in pyrrolines is much smaller than in aziridines [28], in this case the observations are possibly due to hindered rotation, rather than retarded inversion of the pyrroline group by the quinazolonyl-2-substituent. This is because the pyrroline group is much more bulky than an aziridine. Preliminary observations by Stanton [133] show that as the 2-substituent increases in size the coalescence temperature (T_c) does indeed increase (compare 112 a and b)

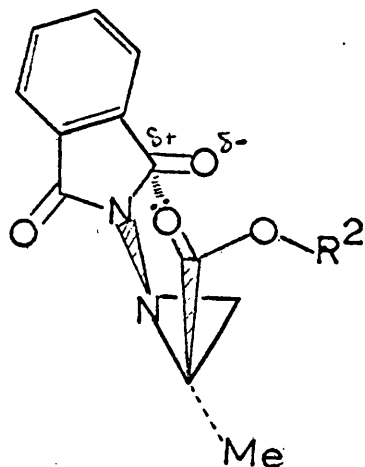


(112) a; R = H, $T_c = -60^\circ$
 b; R = Me, $T_c = +100^\circ$



(113)

The invertomer ratios in the methacrylate derived aziridines (see Table IV) indicate, rather surprisingly, that as the size of the ester alkyl group (R^2) increases the proportion of the ester cis to the N-heterocyclic substituent also increases. This is contrary to the trend that would be expected in terms of steric hindrance, where the larger the group the proportion of the trans invertomer would increase. There is little evidence in the literature on conformational energy preferences of esters in substituted cyclohexanes [134] (but see later). These observations can be explained in terms of dipolar attractions between the ester carbonyl oxygen lone pairs and the electrophilic carbon of the lactam carbonyl functions present in all the N-heterocyclic substituents studied e.g. (114).

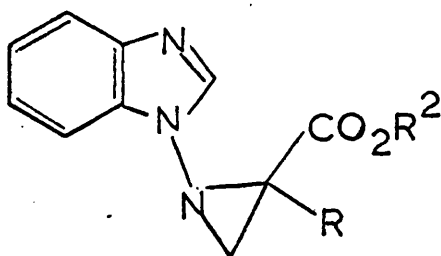


(114)

Thus in the cis invertomer (A) the rotation of the aziridine ring-ester C - C bond will occur in such a way as to favour those rotamers where the bulky group R^2 is farthest away from the N-heterocyclic substituent, hence the ester carbonyl group will become nearer to the attracting lactam electrophilic carbonyl carbon atom on a time averaged basis. This effect is, as expected, the most pronounced where $R^2 = Bu^t$ (see Table IV; I - IV,d). The invertomer ratio is largest in the phthalimide case (IIId) ($^{cis}/^{trans} = 3.5$) because there are two such attracting lactam carbonyl carbon atoms (114). The smallest ratio is found in the benzoxazolinonyl case (Id) ($^{cis}/^{trans} = 1.5$) where the electrophilicity of the carbonyl carbon atom is diminished by the mesomeric effect of the lone pair on the adjacent oxygen atom. This latter effect is so pronounced that the major invertomer in the methyl and ethyl methacrylate esters of the benzoxazolinonyl case (I a and b) is where the ester is trans to the N-heterocyclic substituent (see Table IV). Further support for this proposal is supplied by the invertomer ratios of the acrylate derived aziridines. Here, the cis ester conformation is more strongly preferred where $R^2 = Bu^t$ than where $R^2 = Me$, even though

in both cases the trans conformation is the predominant one (see Table III, e and f). Further evidence is also given when there is a lack of such an attracting lactam carbonyl function in the N-heterocyclic substituent, i.e. with the benzimidazolyl-aziridines (115). These aziridines show the same conformation preference in both the acrylate and methacrylate derived aziridines with the major invertomer having the ester trans to the N-heterocyclic substituent.

The invertomer ratios are given in Table V.



(115)

Compound (115)	Ratio of ester $\frac{\text{cis}}{\text{trans}}$ to the <u>N</u> -benzimidazolyl substituent.
$R^2 = \text{Me}, R = \text{H}$	0.13
$R^2 = \text{Me}, R = \text{Me}$	0.48
$R^2 = \text{Et}, R = \text{Me}$	0.62

Table V

The proportion of ester cis to the N-benzimidazolyl substituent still increases as R^2 becomes more bulky due to the similar, but weaker attraction of the benzimidazole 2-carbon atom. Here, the sterically controlled trans preference now outweighs the electrostatically controlled cis preference of the ester to the N-benzimidazolyl substituent. The methacrylate ester derived aziridine (where $R^2 = \text{Bu}^t$, $R = \text{Me}$) was not studied, but its invertomer ratio could well be greater than unity if the observed trend in Table V is followed.

These observations may also be explained by the increased repulsion between the aziridine ring nitrogen lone pair and the ester group as the size of the ester increases. However, the observed invertomer ratios can be qualitatively correlated with the anticipated electrophilicity of the N-heterocyclic substituent lactam carbonyl atom (and that of the 2-carbon atom in the benzimidazolyl case), as described above. If the aziridine ring nitrogen lone pair to ester interactions played a great part in influencing the invertomer ratios, the correlation above would not be expected.

The variable temperature PMR spectra of the methyl methacrylate derived aziridines (108; IIa [76] and IIIa) were studied in order to determine their coalescence temperatures. These were found to be $\sim 130^\circ$. The variation with temperature of the signals due to the aziridine ring methyl group of (108; IIIa) is shown in Fig. 42. This relatively low value for coalescence makes the separation of the two invertomers at room temperature impossible (see Introduction, Section III).

Hence, in conclusion, the aziridines derived from the acrylate and methacrylate esters (108) (109) and (115) illustrate the phenomenon of retarded nitrogen inversion in aziridines, both invertomers being clearly seen in the PMR spectra at room temperature. These particular

aziridines cannot be used to give quantitative information about the sizes of groups because of the attractions present between the N-heterocyclic group and the aziridine ester substituents; but they do offer a convenient method of studying in detail such attractive and repulsive forces that exist between groups in organic molecules.

It is interesting to note that using the relationship $\Delta G = -RT \ln K$, where $K = \text{cis}/\text{trans}$ invertomer ratios, the average values for K of all the methyl methacrylate derived aziridines gives a value for ΔG for the -Me and -CO₂Me groups as $\Delta G = -0.43 \text{ Kcal.mole}^{-1}$. In fact, the value obtained from averaging the values obtained by various techniques in cyclohexane conformational studies is also exactly $\Delta G = -0.43 \text{ Kcal.mole}^{-1}$ [134].

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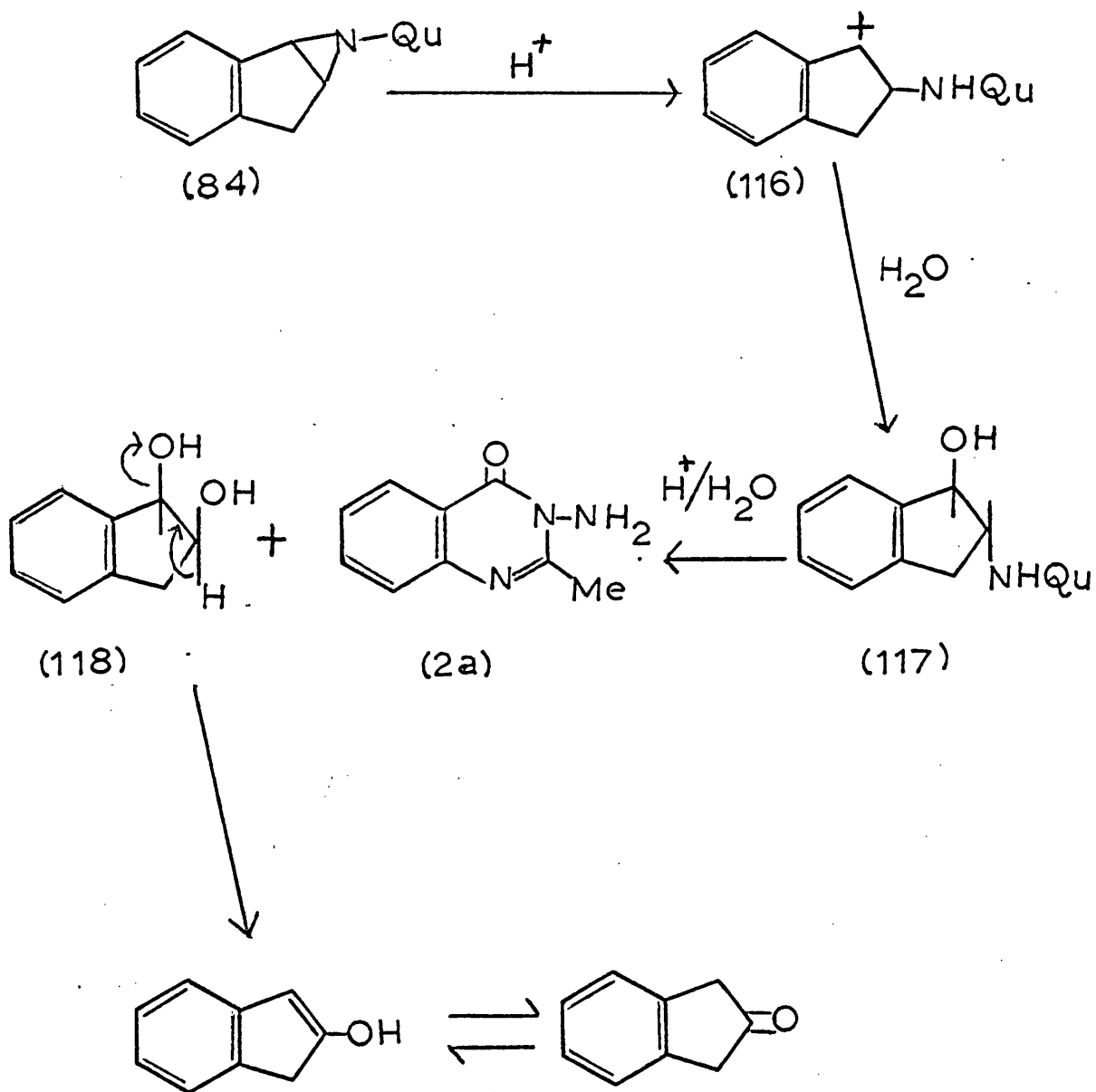
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APPENDIX1. Acid hydrolysis of the quinazolone-indene adduct (84)

An interesting reaction of the aziridine (84), involving aziridine ring C - N bond fission was found on treatment with refluxing 2N hydrochloric acid. This gave a quantitative yield of 2-indanone and 3-amino-2-methyl-4-quinazolone (2a). The formation of 2-indanone can be explained by the mechanism outlined in Scheme 19. Here, the aziridine (84) is ring opened on protonation of the aziridine ring nitrogen to give the stable benzylic carbonium ion (116). This is attacked by water to give, on steric considerations, the trans isomer (117). This is further hydrolysed to the cis diol (118). Trans elimination of water, involving the benzylic carbonium ion gives the enol form of 2-indanone. The possible alternative elimination of water from (118) to give the enol form of 1-indanone would involve a less stable non-benzylic carbonium ion.

Scheme 19 over/

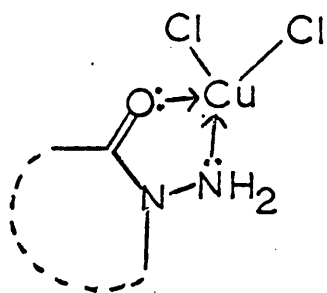


Scheme 19

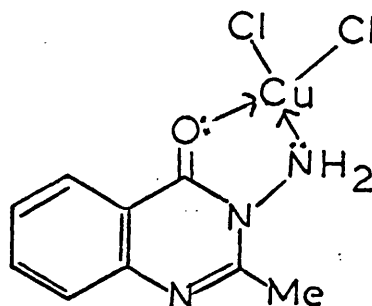
2. Aqueous hydrolysis of quinazolinone $Cu^{II}Cl_2$ complex (120)

Treatment of the N-aminoamides described in this thesis with $CuCl_2 \cdot 2H_2O$ in methanol gave green coloured highly crystalline 1 : 1 chelates,

of general structure (119). These complexes are tabulated in the Experimental, page 97



(119)

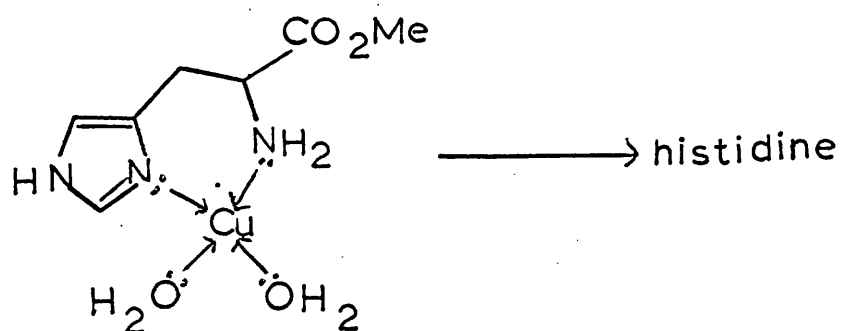


(120)

The complex (120) hydrolysed readily in cold water to the N-amino compound (2a). Similarly, the complexes from (2b) and (2c) also hydrolysed to the N-amino compounds. However, the complex from (3) was stable even to warm water. All complexes in dilute NaOH gave a blue precipitate of copper hydroxide and the N-amino compound.

However, the complex (120) only, hydrolysed to a different product in hot water. On cooling, the solution deposited long needles of presumably compound (121). The i.r. spectrum showed a primary amine doublet and a further N - H stretch. The PMR spectrum in D_6 DMSO also showed a primary and secondary amine peak. The third secondary amine peak was not seen. Compound (121) in refluxing benzene was converted into (2a). The sequence is outlined in Scheme 20.

The mechanism of the hydrolysis of (120) to (121) involving Cu^{II} ion catalysis of hydrolysis of the quinazolone C = N bond is proposed (see Scheme 21). Here, there is no interaction between the Cu^{II} ion and the labilized C = N group, this catalysis is mainly due to electrostatic effects. This is also the conclusion of Hay and Morris in a related Cu^{II} ion catalysis where the complexed histidine methyl ester (122) hydrolyses 500 times faster than the free ester [137]. The nature of the active labile metal complexes in solution is uncertain.



(122)