

AZIDOCINNAMATES IN HETEROCYCLIC SYNTHESIS

A THESIS PRESENTED BY

DEIRDRE M.B. HICKEY B.SC.

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DEGREE OF DOCTOR OF PHILOSOPHY,

UNIVERSITY OF LONDON

Hofmann Laboratory,
Department of Chemistry,
Imperial College of Science and Technology,
London, SW7 2AY.

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To my parents, Paddy and Therese,

with love and gratitude.

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ABSTRACT

The reactions of various types of nitrenes to give heterocyclic products is reviewed.

A series of vinyl azides, mostly *ortho*-substituted azidocinnamates, was prepared and their decomposition reactions studied.

The thermal decomposition of *ortho*-alkyl azidocinnamates gave 2,4-disubstituted indoles, 1,3-disubstituted isoquinolines, 1,3-disubstituted -1,2-dihydroisoquinolines, and enamines, the amounts of each varying with the *ortho*-group and the conditions used, iodine having a marked effect on the product ratios.

Azidocinnamates with *ortho*-unsaturated groups were thermolysed and it was found that, in addition to small amounts of indoles, a variety of heterocyclic products was formed which could be rationalised by interaction of the vinyl azide and vinylnitrene with the unsaturated substituent.

Treatment of *ortho*-carbonyl azidocinnamates with triethylphosphite gave isoquinolines, often in high yield, presumably *via* iminophosphorane derivatives. Not all of the vinyl azides so treated were converted to isoquinolines however. Thermal decomposition of *ortho*-carbonyl azidocinnamates gave 2,4-disubstituted indoles in varying yields. An exception was an *ortho*-carboxy azidocinnamate which gave a novel fused aziridine. There is scope for further investigation of *ortho*-carbonyl azidocinnamates, in particular their reactions with trivalent phosphorus reagents.

The photolysis of *ortho*-alkyl azidocinnamates gave unusual azirine trimers, whilst an *ortho*-allyl azidocinnamate gave a dimer on photolysis. The formation of these products is rationalised and a common mechanism, involving azirine dimerisation followed by ring opening to give an azo-methine ylide intermediate, is proposed. Vinyl azides containing unsaturated or nucleophilic groups were also irradiated and the intermediate nitrile ylides trapped intramolecularly by the unsaturated group or nucleophile.

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ABBREVIATIONS

i.r.	:	infra red
n.m.r.	:	nuclear magnetic resonance
n.O.e.	:	nuclear Overhauser effect
u.v.	:	ultra violet
DMF	:	dimethylformamide
E	:	CO ₂ Et
FVP	:	flash vacuum pyrolysis
MCPBA	:	3-chloroperbenzoic acid
TEP	:	triethylphosphite
THF	:	tetrahydrofuran
DMSO	:	dimethylsulphoxide

PART 1

CHAPTER ONE

INTRODUCTION: NITRENES IN
HETEROCYCLIC SYNTHESIS

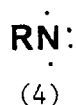
CHAPTER ONE. INTRODUCTION: NITRENES IN HETEROCYCLIC SYNTHESIS

1.1. INTRODUCTION

Nitrenes (1) ($R = \text{acyl}$) were first proposed by Tiemann in 1891¹ as short-lived intermediates in the Lossen rearrangement. The nitrene mechanism was also adopted by Stieglitz and Curtius for the Curtius reaction,² although there is now considerable evidence against nitrenes being involved in these reactions.³ The electronic absorption band at 366 nm of the parent nitrene (2) was first observed in 1892, and was assigned to N-H (2) by Frank and Reichardt in 1936, and by Keyser in 1960.⁴



Nitrenes are defined as derivatives of the neutral molecule N-H (imidogen or nitrene). They are uncharged, electron deficient, reactive intermediates, in which the nitrogen atom possesses a sextet of electrons in its outer shell. Two of these are located in a covalent bond, two in a lone pair orbital, and the remainder may be arranged in either a spin paired configuration in a non-bonded orbital giving rise to an electrophilic singlet nitrene (3), or alternatively, orthogonally and unpaired giving the biradical triplet nitrene (4).



In general nitrenes have triplet ground states. E.s.r. signals, obtained from HN, alkylnitrenes and ethoxycarbonylnitrene upon irradiation of the corresponding azides at low temperature, indicate that they have a triplet ground state (or at least a triplet state a few cm^{-1} above ground state).⁵ Similarly, paramagnetic resonance spectra of aryl- and arenesulphonylnitrenes generated by photolysis at 4 K indicate that these also have triplet ground states.⁶ Theoretical calculations have also predicted triplet ground states for many nitrenes. A singlet nitrene has also been spectroscopically observed: nanosecond laser photolysis of 1-azidopyrene gives the S_0 nitrene (λ_{max} 450 nm) which decays to the triplet ground state T_1 (λ_{max} 415 nm).⁷

Nitrenes are often generated by thermal or photochemical decomposition of the corresponding azides. The thermal reaction gives a singlet nitrene initially because of spin conservation. Photolysis can give both singlet and triplet nitrenes.

While nitrenes can be observed as described above, in most of the reactions which will be presented in this work no direct observation of an intermediate nitrene is claimed. The intermediacy of nitrenes is inferred from a study of the reaction kinetics (first order reaction, solvent independent, *etc.*), by showing that several possible nitrene precursors give the same product or product mixtures, and by a study of the types of products, and by comparison with similar reactions in which nitrenes are believed to be involved. Sometimes, when a given precursor gives two sets of products, depending on the mode of decomposition, a nitrene mechanism is logically proposed for one reaction. The claim that nitrenes are intermediates in many reactions of nitro compounds with deoxygenating reagents is based on the similarity of the product mixtures to those produced by decomposition of the corresponding azides.

Whether a singlet or triplet nitrene is involved in a particular reaction is often hard to determine. Singlet nitrenes are believed to undergo concerted reactions and reactions with nucleophiles, whereas triplet nitrenes undergo stepwise reactions *via* radicals. Speculation on which type of nitrene is involved is often based on the reactions products and their stereochemistry, and on the method of generation.

The reactions of nitrenes can be subdivided in many ways, and in this review each type of nitrene will be dealt with separately.

The types of reactions which nitrenes undergo include the following:

- (1) Hydrogen abstraction to give amines. This is usually a triplet reaction.

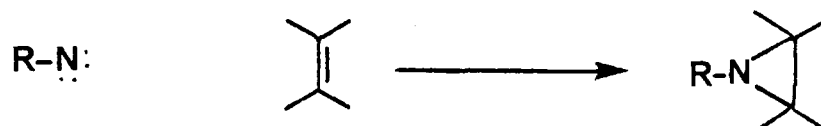


- (2) Insertion into a R-H bond. This can be either a triplet or singlet nitrene reaction. The singlet nitrene inserts in a concerted manner and any chirality in R' is maintained. A triplet nitrene probably inserts in a stepwise manner and optical activity at the point of insertion is often lost.

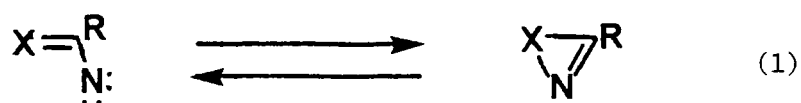


- (3) Addition to multiple bonds, including aromatic rings. Addition of singlet nitrenes is stereospecific and that of triplet nitrenes is often non-stereospecific.

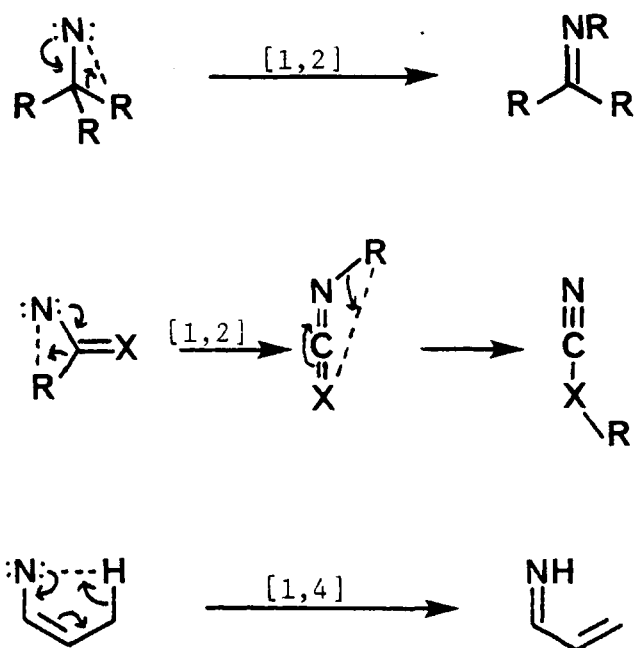
e.g.,



(4) Isomerism as shown in equation (1) is thought to occur for some singlet nitrenes.



(5) Rearrangement of nitrenes can occur as shown in Scheme 1.

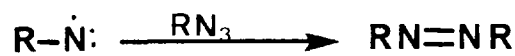


SCHEME 1

(6) Electrocyclic reactions. Electrocyclic ring closures (*e.g.*, equation 2) are considered to be singlet nitrene reactions.



(7) Dimerisation.



This is usually observed in triplet nitrenes.

(8) Reaction with nucleophiles.



This is considered to be characteristic of singlet nitrenes.

The material presented in sections 1.2-1.9 is summarised in section 1.10 in terms of the relationship between the structures of nitrenes and the types of reactions they undergo.

In the last thirty years the generation and reactions of nitrenes have been widely investigated both for mechanistic studies and synthetic applications. This introduction is intended to illustrate the use of nitrenes to prepare heterocyclic products. The generation of nitrenes and their reactions to give non-heterocyclic products will only be briefly mentioned, as will reactions of nitrene precursors *via* non-nitrene pathways. This review is not intended to be comprehensive but will give representative examples of the many heterocyclic compounds of various ring sizes which can be formed from nitrenes.

Reviews of the literature on nitrenes include those by Lwowski,^{8,9} and Wentrup,¹⁰ the annual review contained in the Organic Reaction Mechanism series,¹¹ and more specialised reviews on the formation of five-membered heterocyclics.^{12,13}

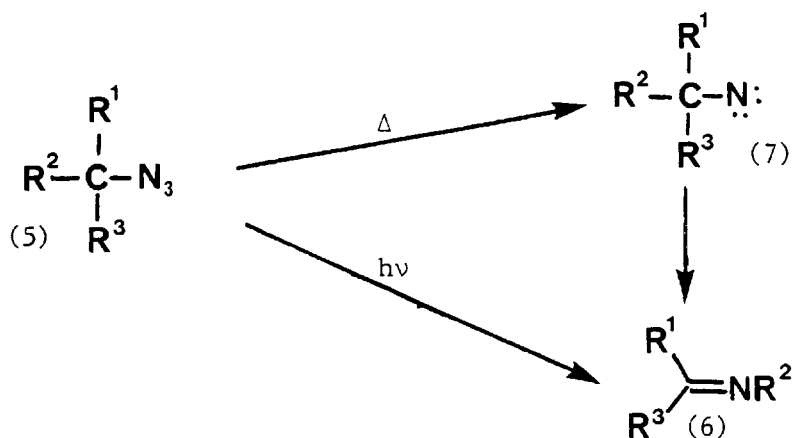
1.2. ALKYL NITRENES

1.2.1. Generation.

Alkyl nitrenes are usually generated from the corresponding azides by photolysis or thermolysis.¹⁴ They are highly reactive species.

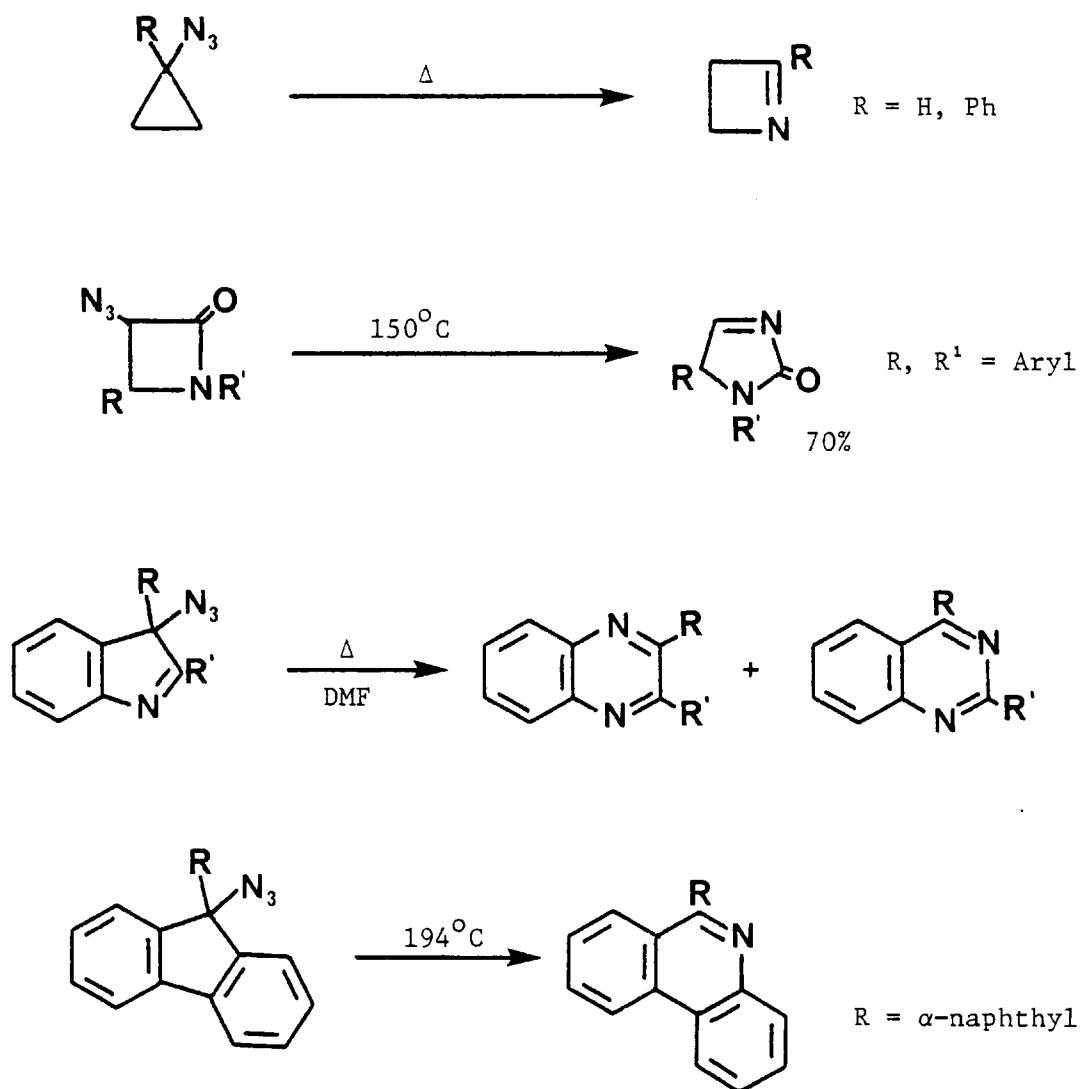
1.2.2. Imine formation.

The most common reaction of alkyl azides (5) is decomposition with rearrangement to give imines (6). There is strong evidence to suggest that alkyl azides rearrange thermally *via* the nitrene (7) but that the photolytic reaction is a non-nitrene process.¹⁵



If two of the groups in nitrene (5) (*e.g.*, R¹ and R²) form part of a ring, then migration of R¹ or R² leads to heterocycle formation.

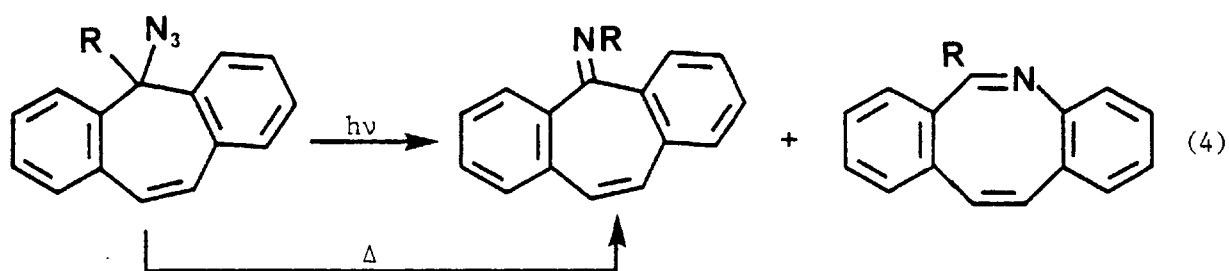
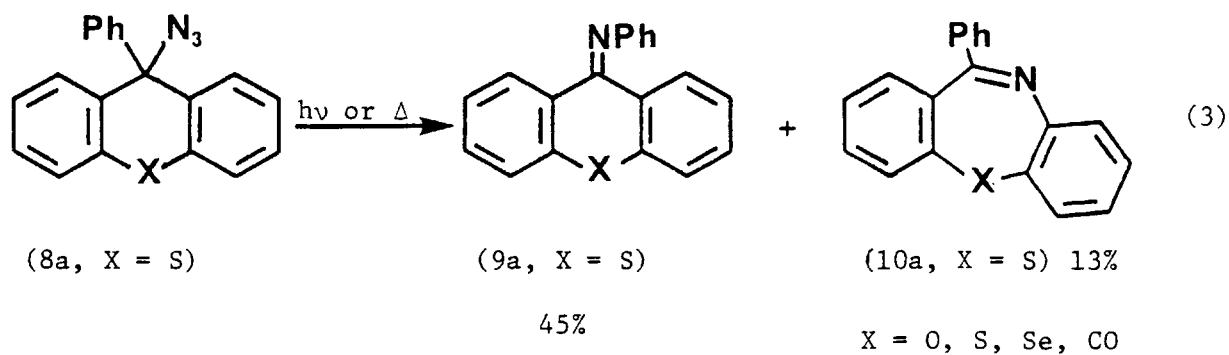
Examples of formation of four-,¹⁶ five-,¹⁷ and six-membered^{18,19} rings are shown in Scheme 2.



SCHEME 2

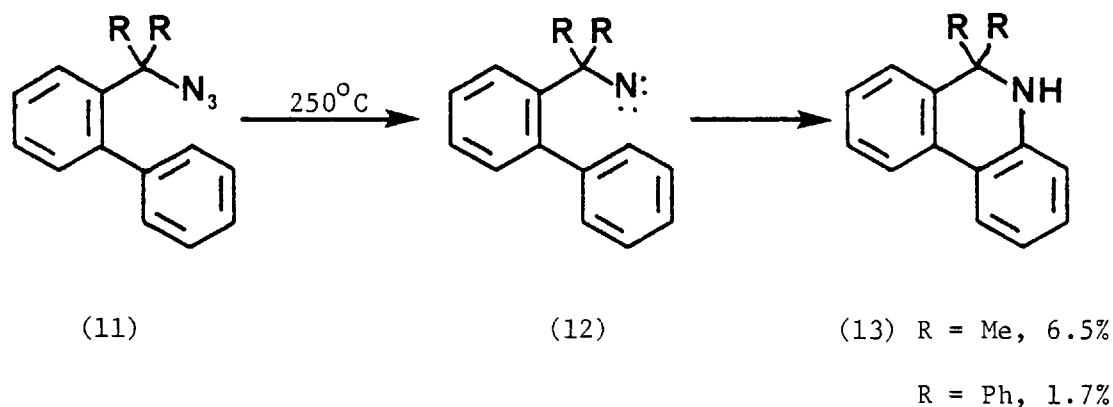
Ring expansion to seven-membered rings^{20,21} is less favourable as demonstrated by the relative amounts of thiazepine (10a) and phenyl imine (9a)²¹ formed on decomposition of (8a) (equation 3). An eight

membered heterocycle was similarly prepared, though the pathway may not involve a nitrene (equation 4).²²

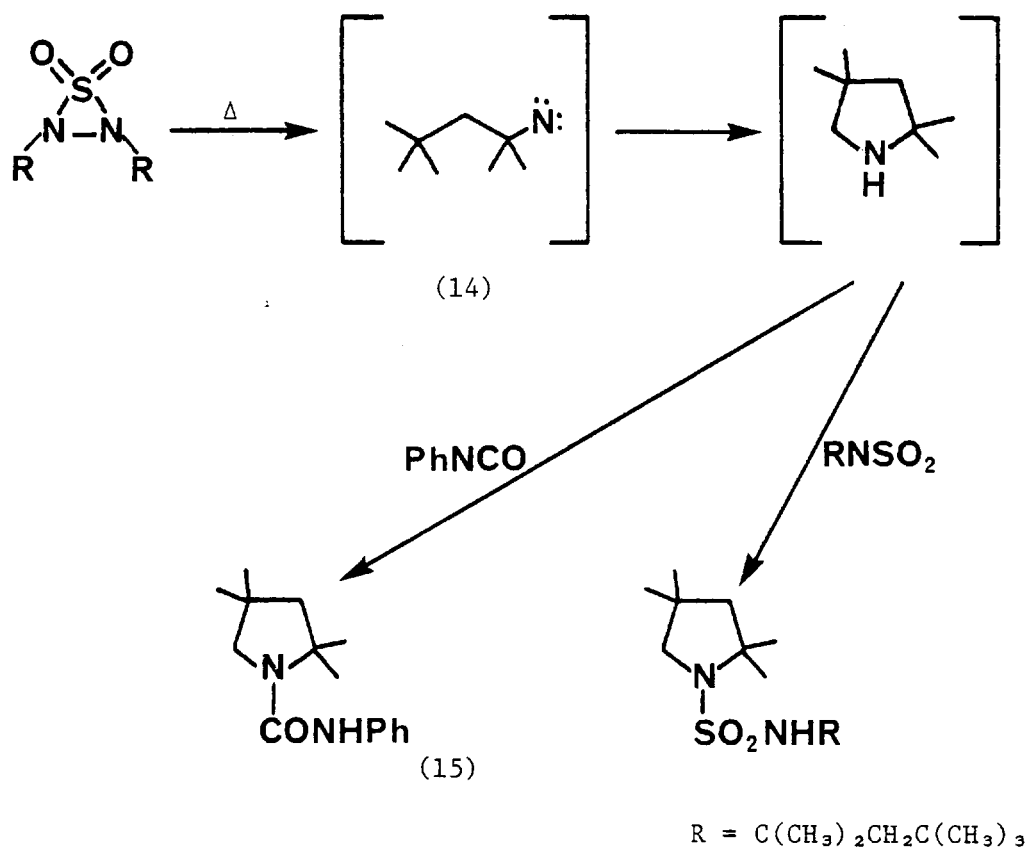


1.2.3. Insertion reactions.

Some alkylnitrenes were sufficiently long lived to react intramolecularly with aromatic C-H bonds to give 9,10-dihydrophenanthrenes (13) in low yields.^{15,23} Other products arose from loss of HN_3 from the azide (11) and by 1,2-shifts to give imines from the nitrene (12).



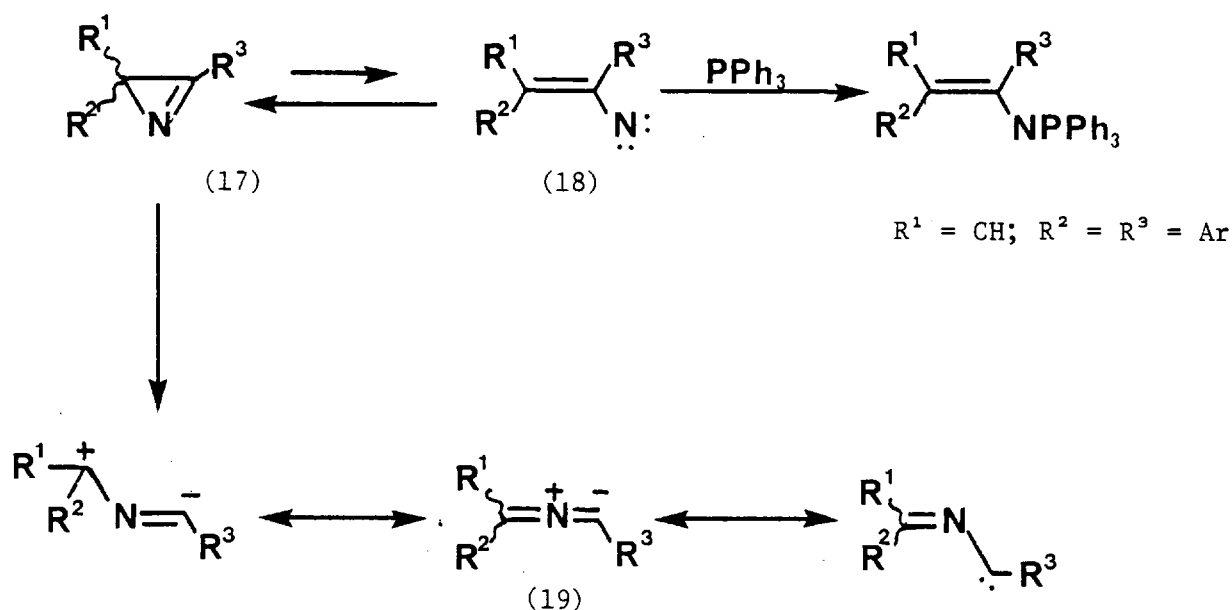
Pyrrolidines have been reported as products of photolysis of *n*-butyl azide and other long chain azides, but the authors could not reproduce their results.^{24,25} More recently *t*-octylnitrene (14) was proposed as an intermediate in the formation of some substituted pyrrolidines (15).²⁶ Aziridine (16) is formed in moderate yields (35-46%) on pyrolysis of ethyl azide in the gas phase.^{15,27}



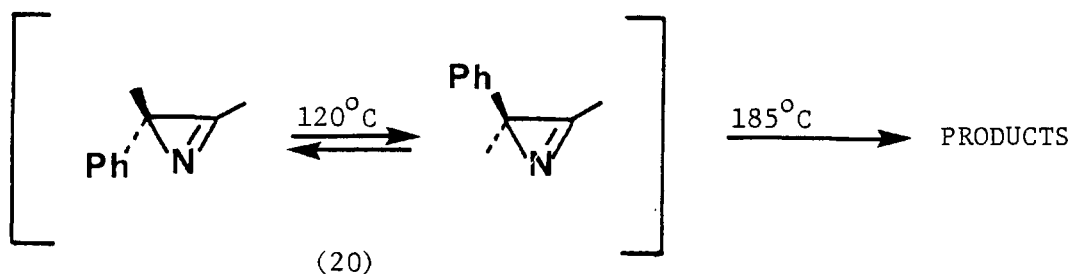
1.3. VINYLNITRENES

1.3.1. Generation; Azirine involvement.

Vinylnitrenes (18) are considered to be in thermal equilibrium with azirines (17). The thermolysis products of azirines are usually those of the corresponding vinylnitrene (formed *via* C-N bond cleavage). Nitrenes have been trapped by trivalent phosphorus reagents in reactions known to involve azirines.¹⁸⁻³¹



Further evidence for this equilibrium is provided by the fact that a chiral azirine (20) racemises 2039 times faster than it reacts to give products, presumably *via* a vinylnitrene intermediate.³²



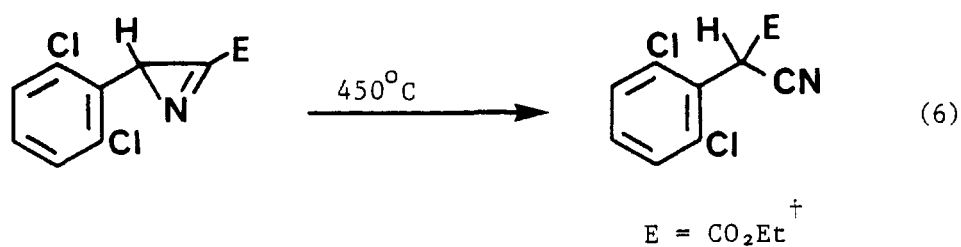
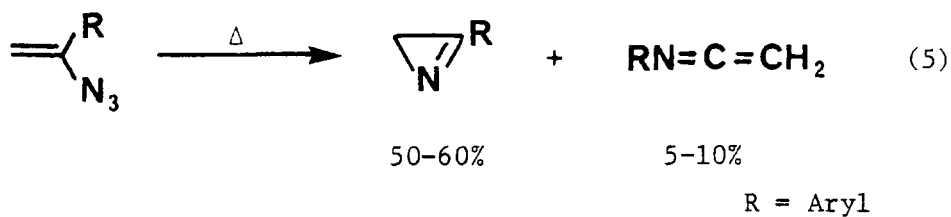
Azirines have been found to undergo C-C bond cleavage, on pyrolysis in the gas phase, to give nitrile ylides (19), the normal products of photolysis of azirines.¹⁰ Such nitrile ylides undergo inter- and intramolecular cycloadditions to give a variety of heterocyclic products.^{10,11,33-35}

The synthesis of azirines has been well reviewed.³⁶⁻³⁸ The most common methods are the Neber reaction and its modifications,³⁶ and the thermolytic and photolytic decomposition of vinyl azides.^{37,38} Vinylnitrenes have also been proposed as intermediates in the reactions of nitroalkenes with trivalent phosphorus compounds, and in the photolysis of vinyl isocyanates.³⁹ The decomposition of vinyl azides to give azirines is believed to be a concerted reaction which does not involve vinylnitrenes.^{38,40,41}

1.3.2. Reactions not leading to heterocyclic products.

If other reactions are not open to them, or are disfavoured, then vinylnitrenes will rearrange to ketenimines and nitriles.³⁶ Some examples are shown in equations (5)⁴² and (6).⁴³ † The ability of vinylnitrenes to equilibrate with azirines, thus making them relatively stable, means that such rearrangement reactions take place far less readily than in the case of alkylnitrenes. High temperatures are often required. The absence of a 3-substituent renders an azirine less stable and rearrangement occurs more readily. It is possible that rearrangement to ketenimines and nitriles does not involve a discrete nitrene species but is a concerted reaction of the azirine.

† Throughout this text E will be used to denote CO₂Et.

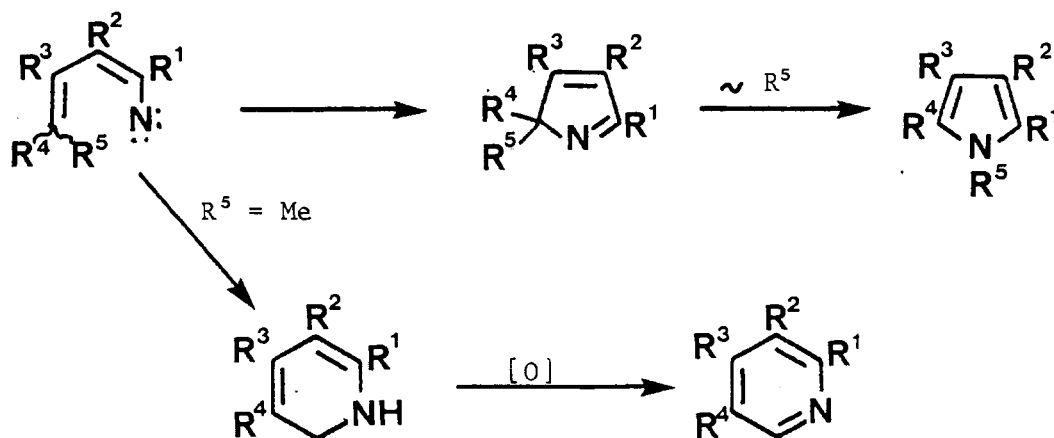


When either R¹ or R² in the azirine (17) is unsaturated then other reactions are possible (Sections 1.3.3.-1.3.5.).

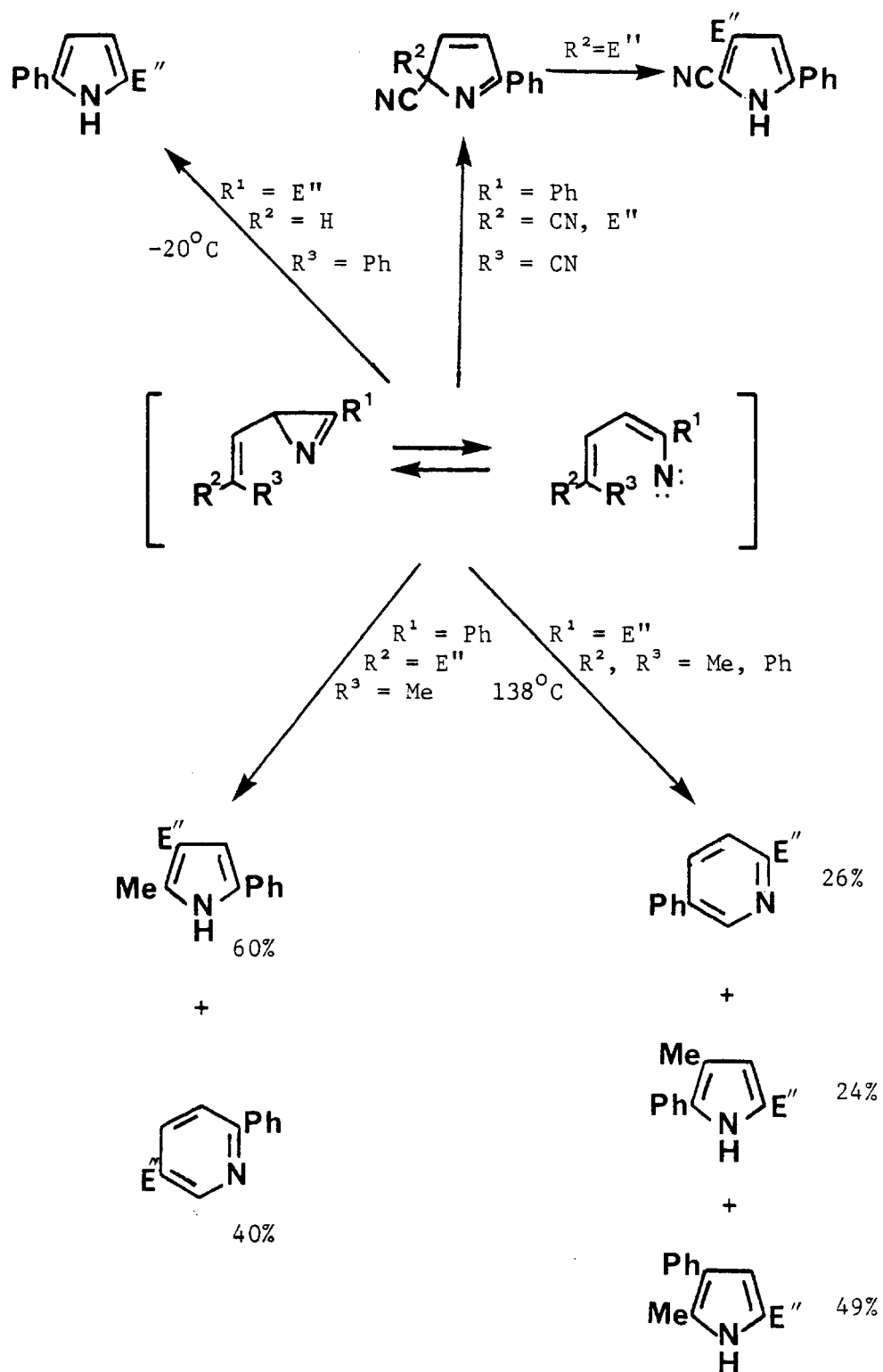
1.3.3. Reactions of 1-nitrenobutadiene derivatives and analogues.

(a) Acyclic.

Pyrroles and pyridines are the thermolysis products of 1-butadienyl-nitrenes (Scheme 3).⁴⁴⁻⁵⁰ Some examples are shown in Scheme 4.



SCHEME 3



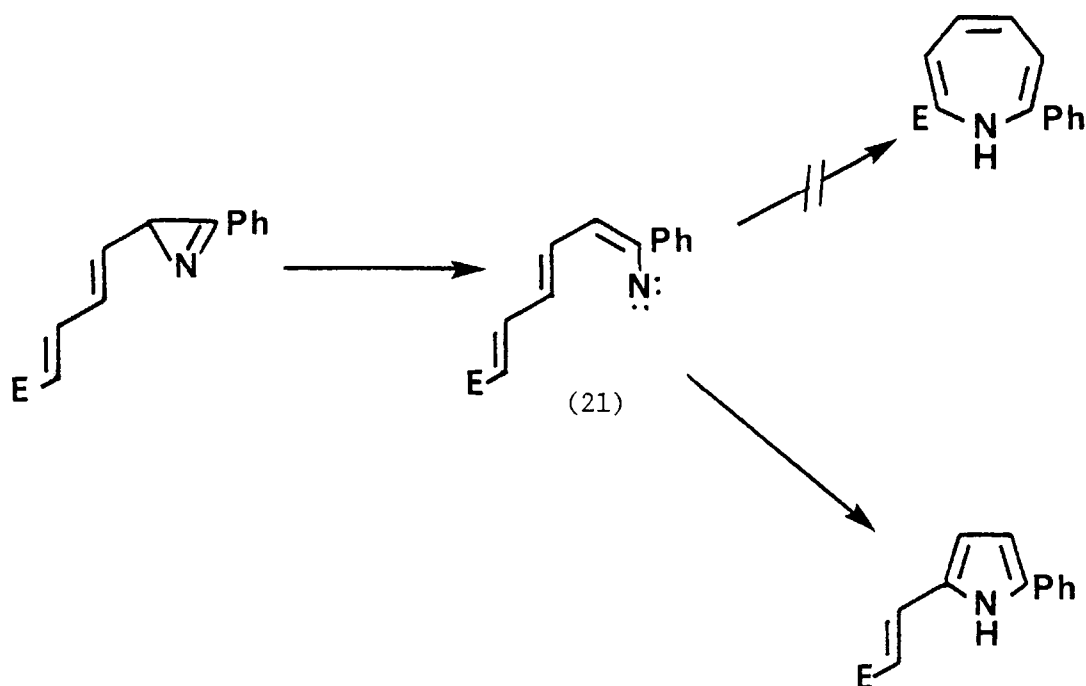
$\text{E}'' = \text{CO}_2\text{R}, \text{R} = \text{Me}, \text{Et}$

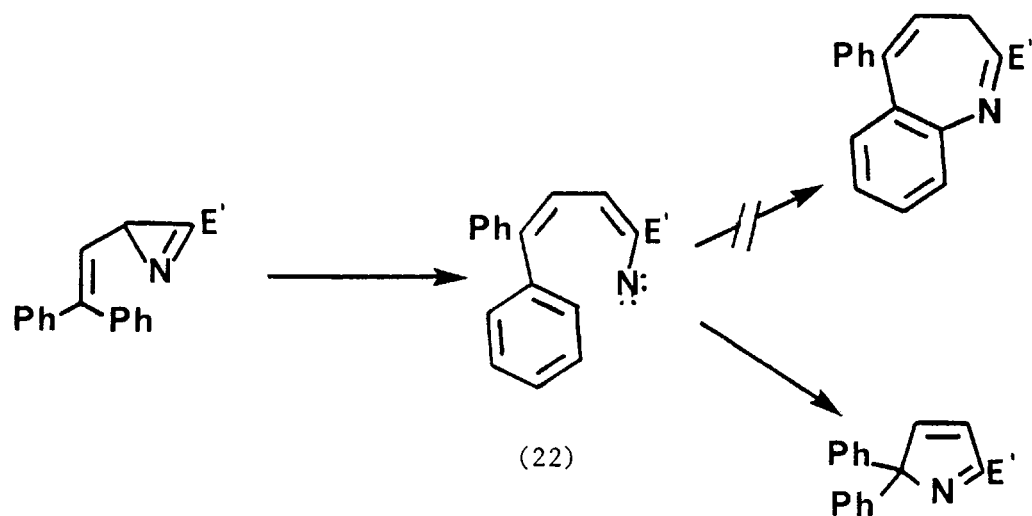
SCHEME 4

The pyrroles are probably formed by electrocyclic ring closure of a singlet nitrene; the pyridines by insertion of a singlet or triplet nitrene into the C-H bond, or by a [1,6]H shift followed by an electrocyclic ring closure. Evidence for the latter pathway will be presented later [Section 1.3.3.(b)].⁵¹

In many of the cases where the azirine was derived from a vinyl azide, the vinyl azide was shown to give the same products as thermolysis of the azirine.

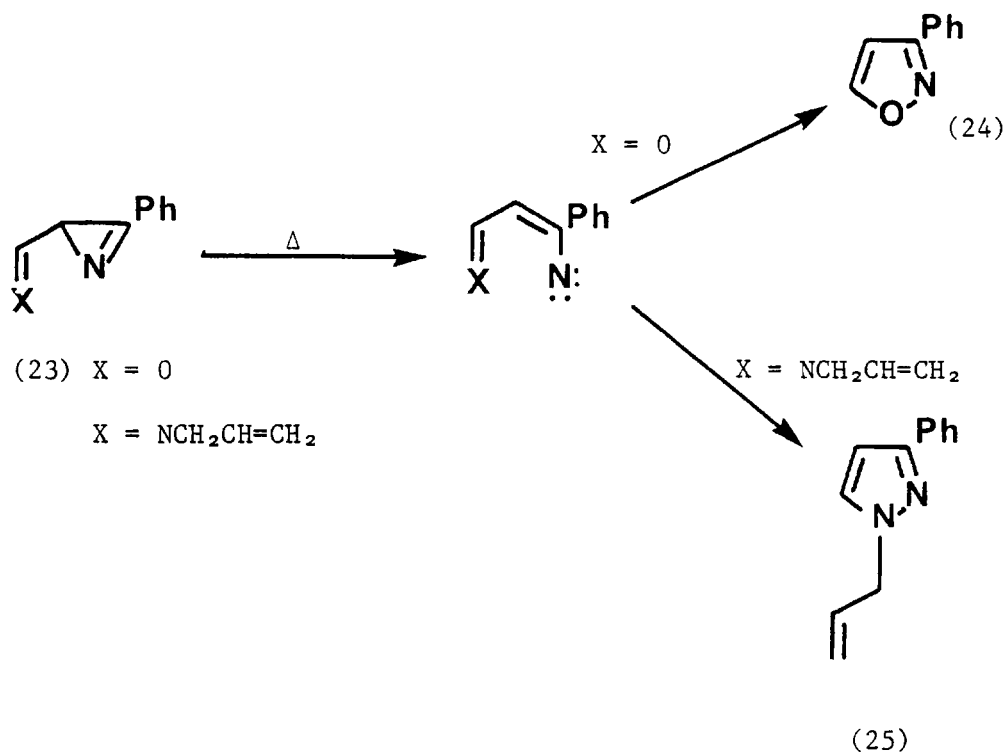
Trienylnitrenes such as compound (21) do not cyclise to give an azepine ring as once reported,³⁰ but give the corresponding vinyl pyrroles.⁵² Similarly phenyl-substituted butadienylnitrenes such as (22) do not give benzazepines but phenyl-substituted pyrroles.⁴⁵



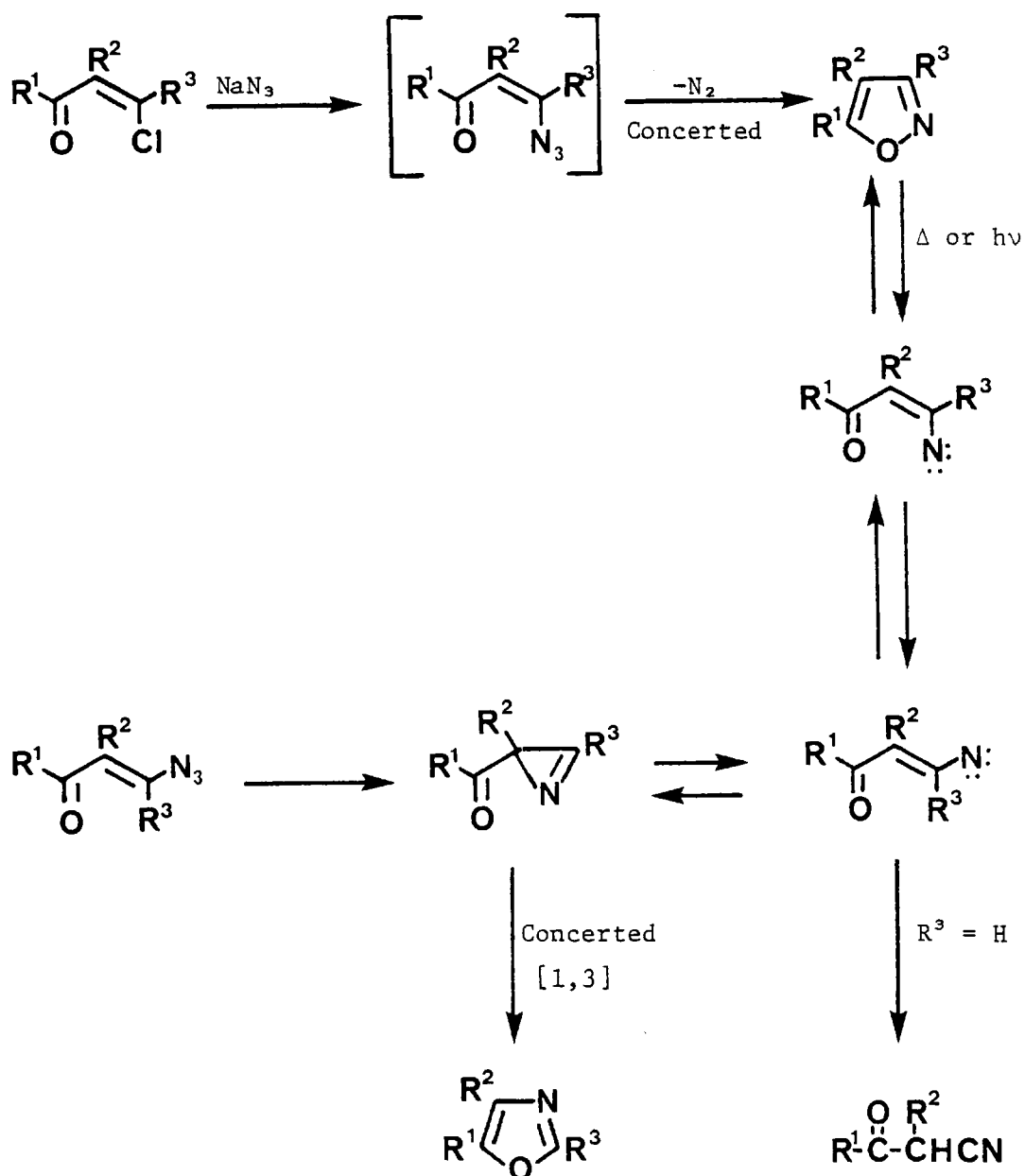


$E' = \text{CO}_2\text{Me}$

Heteroanalogues of the above systems, (23) ($X = \text{NR}$, O) undergo cyclisation to give isoxazoles ($X = \text{O}$), *e.g.*, (24),⁵³ or pyrazoles ($X = \text{NR}$) *e.g.*, (25).³⁰



The formation of isoxazoles from *cis*- β -ketovinylazides is probably a concerted (*i.e.*, non-nitrene) process. The *trans* isomers decompose to give azirines and while these are converted to oxazoles *via* a concerted, irreversible process, they give isoxazoles in a reversible nitrene reaction (Scheme 5).¹⁰

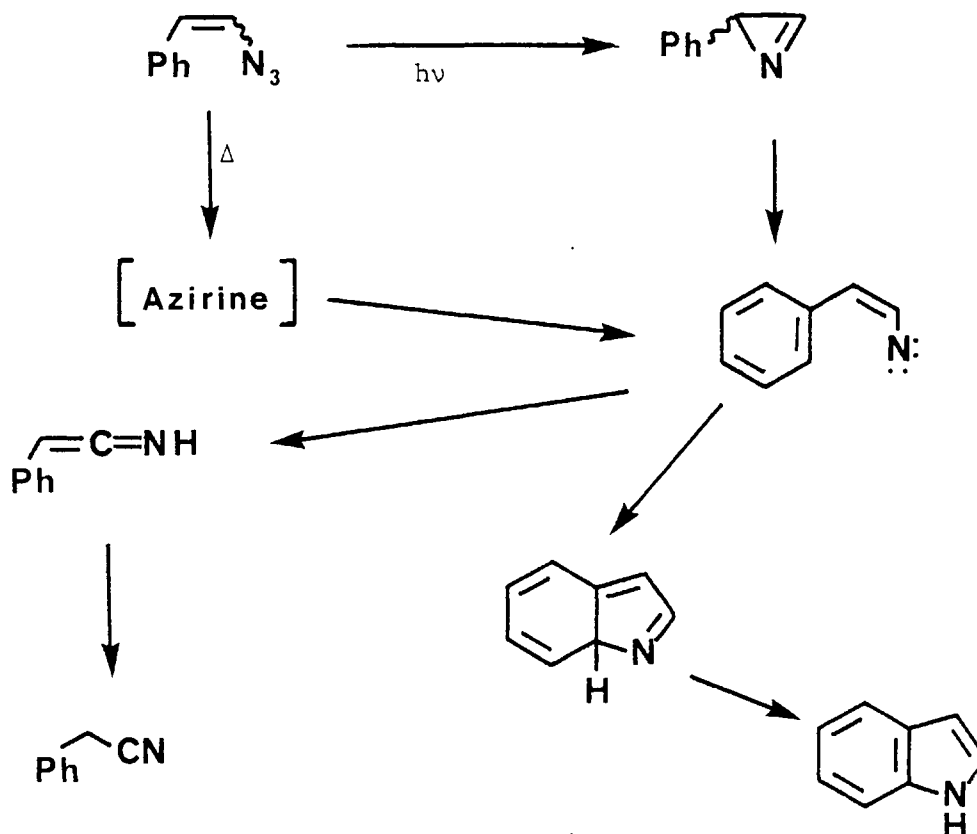


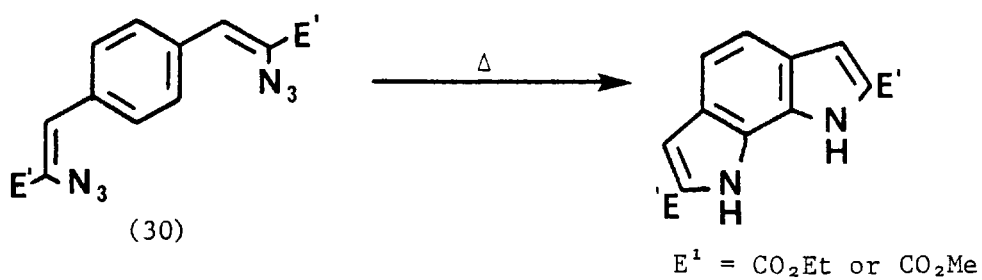
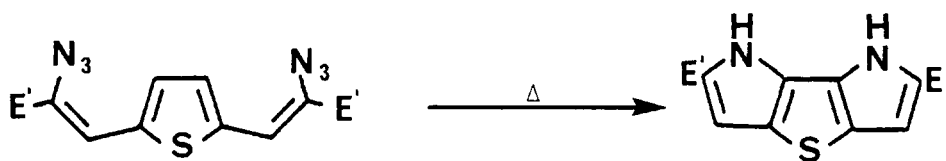
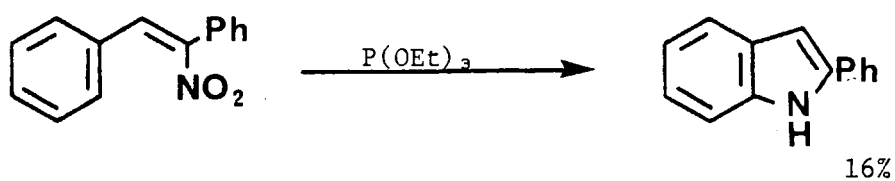
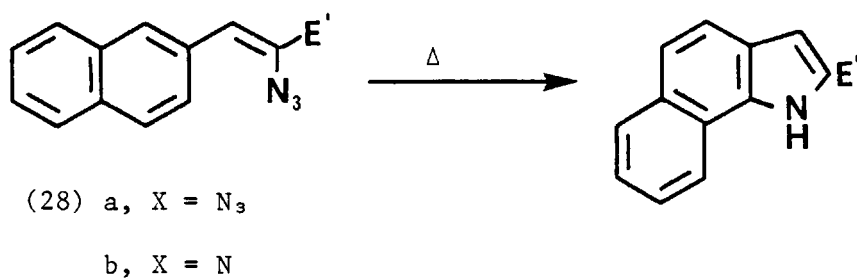
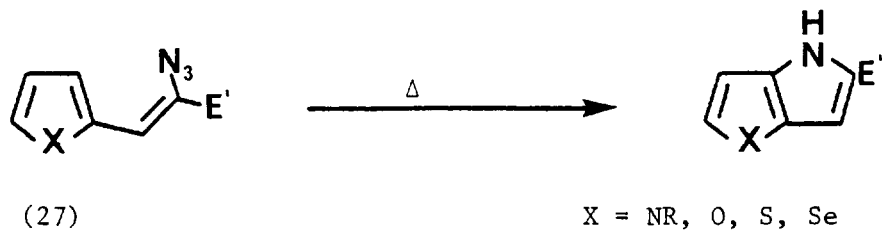
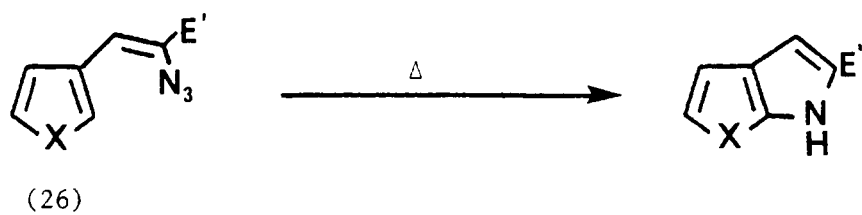
SCHEME 5

The rearrangement of azirines with 2-vinyl, 2-imino or 2-keto groups occurred at room temperature in the presence of Mo(CO)_6 to give high yields of the corresponding pyrroles, pyrazoles and isoxazoles. Such reactions probably proceed *via* complexed nitrenes.⁵⁴

(b) Annelated.

Vinyl nitrenes derived from 2-aryl-azirines behave in a manner similar to the non-annelated butadienylnitrenes discussed above. Fused five-membered nitrogen heterocycles, such as indoles result from closure of the nitrenes onto the *ortho*-position of the aryl group. This reaction was first discovered by Isomura and co-workers.⁵⁵ As in the non-annelated cases, the intermediate azirines have been isolated and shown to give the same products as the vinyl azides which are their precursors.^{55,56}

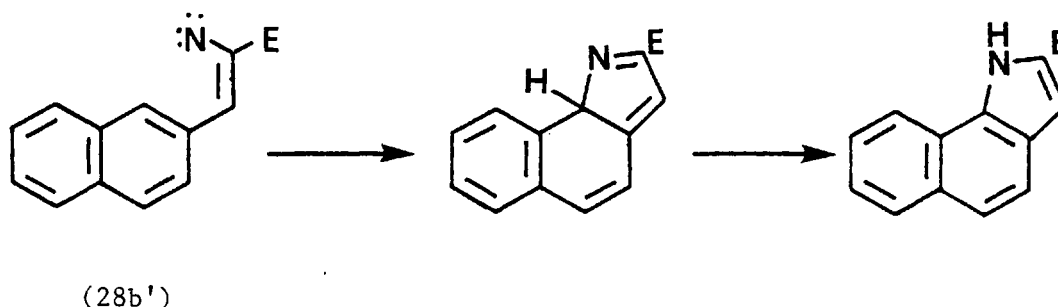




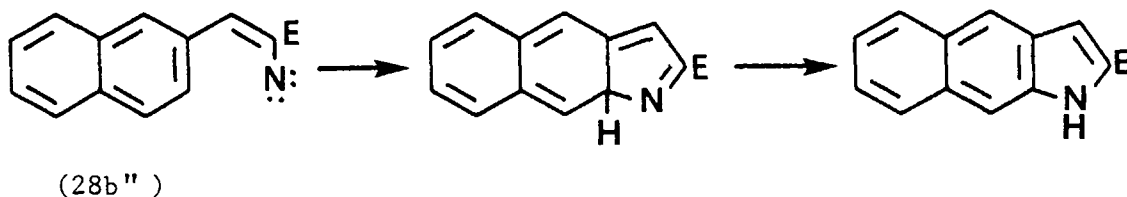
SCHEME 6

This reaction has found wide application in the synthesis of pyrroles fused to other aromatic rings (Scheme 6).⁵⁵⁻⁶⁵ The yields of such reactions are usually very high. Substituents in the 3-position of the azirine stabilise it, and decrease the amounts of nitriles formed. 3-Ketoazirines are exceptions, however, giving nitrenes readily on heating.⁶⁶

In the decomposition of vinyl azides (26), (28), and (30), only one product was formed in each case, even though two isomeric products are possible. One explanation for this is that the electrophilic nitrene cyclises onto the position of highest electron density (*i.e.*, the 1-position in the naphthalene (28) rather than the 3-position). In terms of valence bond theory this selectivity is the result of "bond-fixation" in the nitrene *e.g.*, hybrid (28b') is considered to contribute much more than hybrid (28b'') to the structure of the naphthalene and thus reaction occurs *via* (28b') to give the observed product (Scheme 7). This is also the case in the cyclisation of the second vinylnitrene in the decomposition of the bis-azide (30), and in the decomposition of vinyl azide (26).

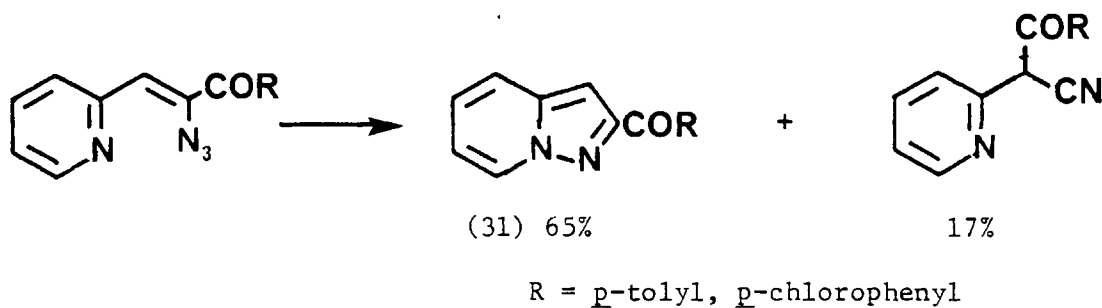


SCHEME 7 (continued overleaf)

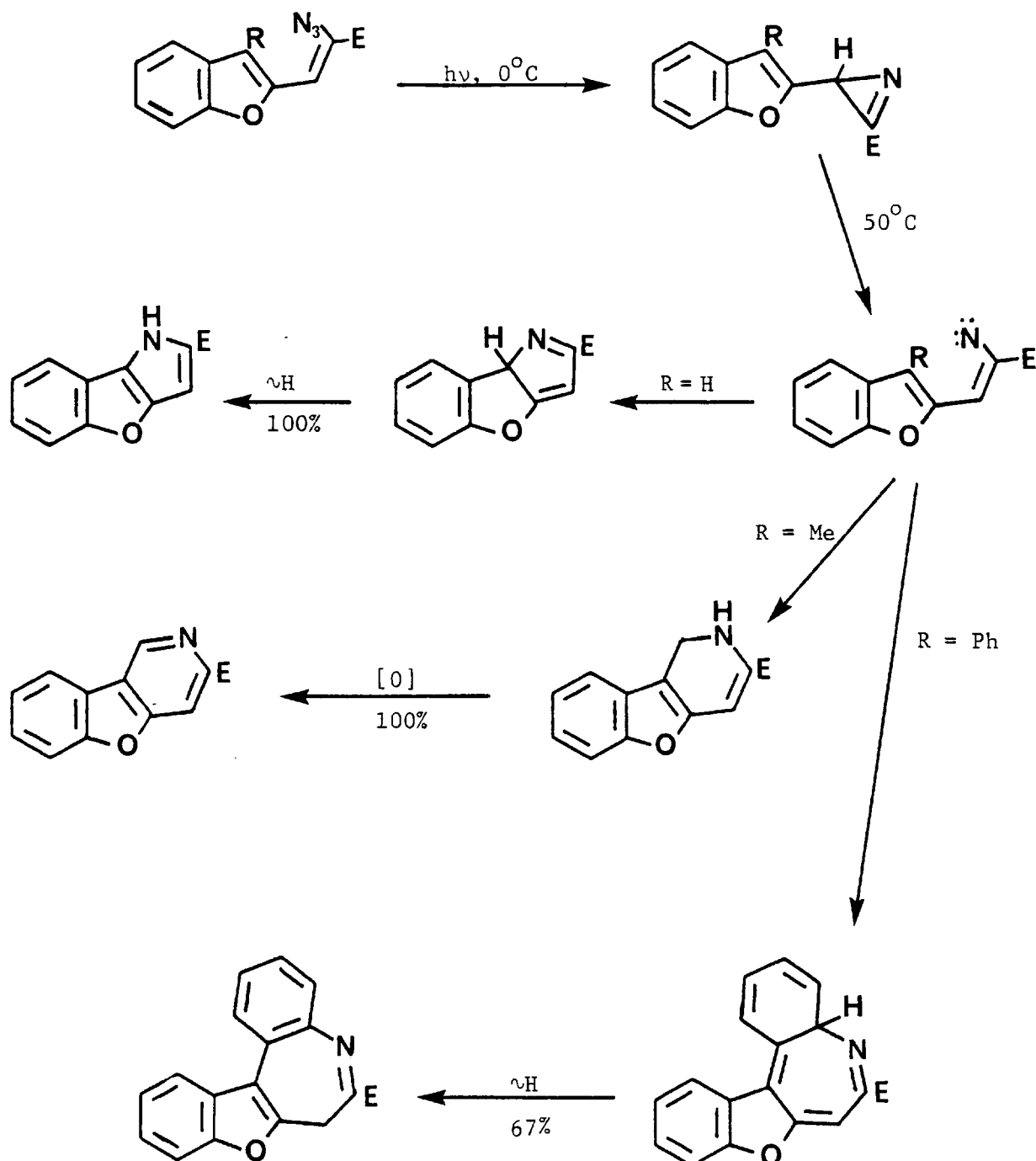


SCHEME 7

Cyclisation of the nitrene onto the heteroatom X does not occur in the decomposition of vinyl azides (27) and (29). However, this may be just the result of reversible ylide formation. The nitrene can, however, cyclise onto a heteroatom if the product is thermally stable, as in the formation of the pyrazolopyridine (31).⁶⁰ As before the nitrene cyclises to the position of greatest electron density. This is an unusual reaction of α -ketovinyl azides which usually rearrange rapidly to nitriles.

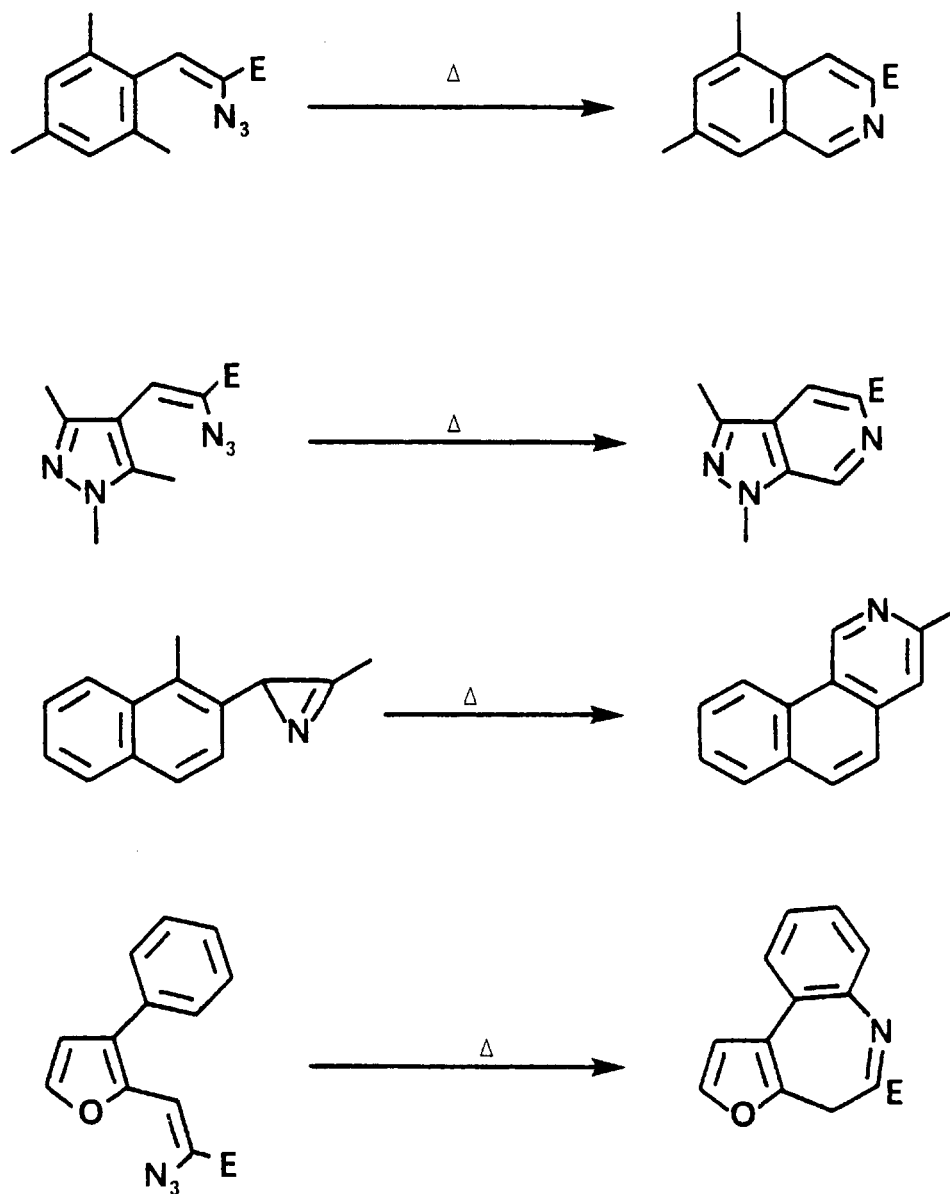


The whole range of vinylnitrene reactivity was observed in the case of some benzofuranylvinyl azides (Scheme 8). The formation of fused pyridines parallels the reactions of the butadienylnitrenes shown in Scheme 3. A new type of reaction was observed with the formation of a condensed azepine.⁶⁵



SCHEME 8

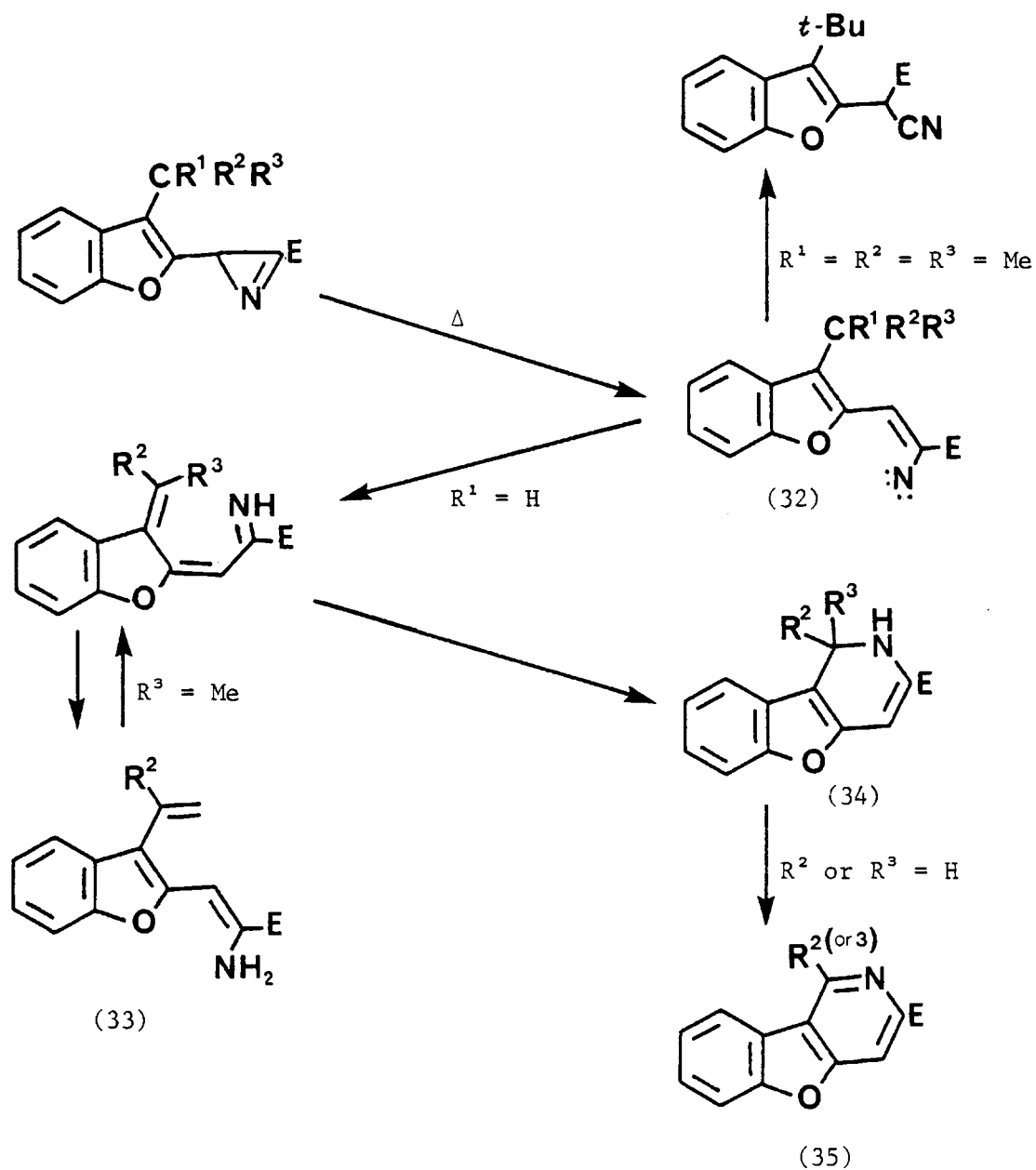
Other examples of fused pyridine and azepine formation are shown in Scheme 9.^{43,64,67}

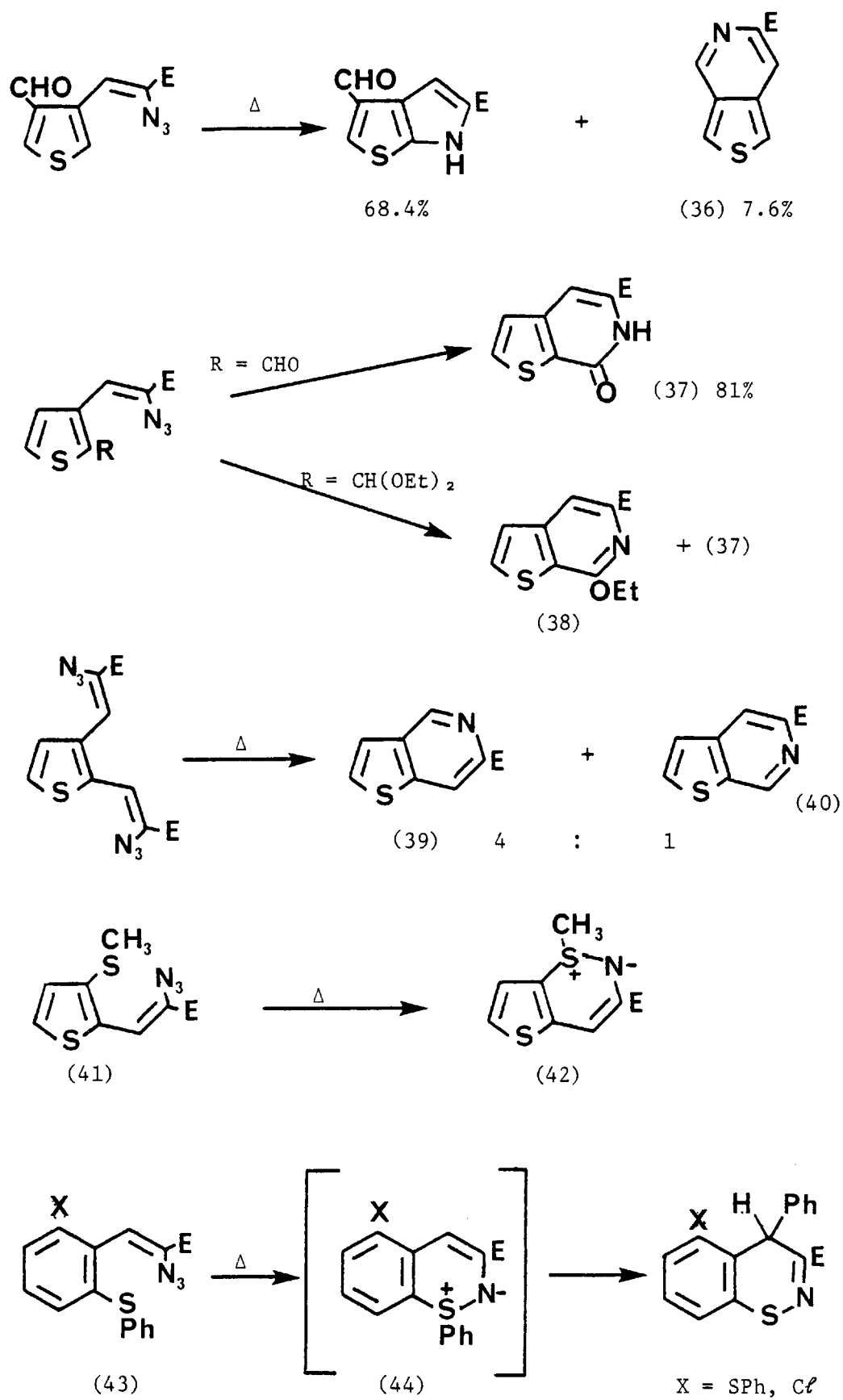


SCHEME 9

It has been proposed that the reaction of the nitrenes (32) to give fused pyridines is not an insertion but occurs *via* sigmatropic hydrogen shifts and an electrocyclic ring closure.⁵¹ Enamines (33)

have been isolated by thermolysis at 350°C and have been converted into the dihydrobenzofuropyridines (34) and benzofuropyridines (35) at higher temperatures.⁵¹



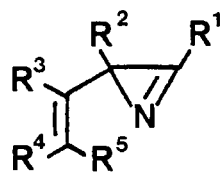


SCHEME 10

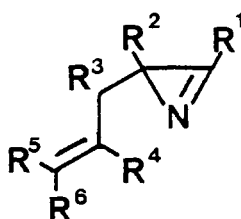
Other reactions in which vinylnitrenes form six-membered nitrogen-containing rings include the formation of fused pyridones (36) and (37) and the fused pyridines (38), (39), and (40) [by formal insertion into C-H bonds] (Scheme 10).^{63,68} Intramolecular trapping of a nitrene by a sulphur nucleophile gave the ylides (42) and (44) from vinyl azides (41) and (43) (Scheme 10).⁶⁹

1.3.4. Reactions of 1-nitreno-1,4-pentadiene derivatives and analogues.

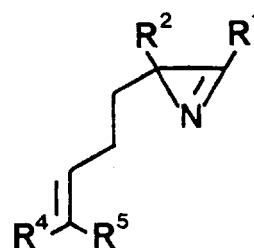
The thermolysis of 2-alkenylazirines (45)-(47) has been widely studied.^{30,47,70,71}



(45)

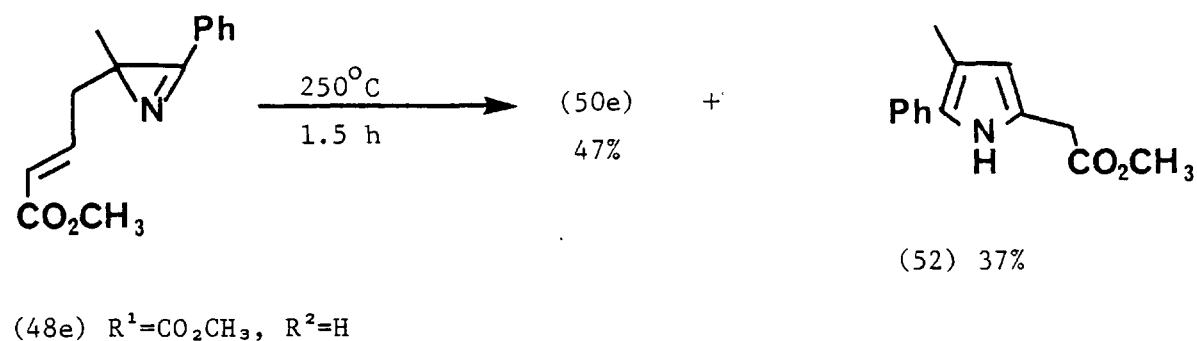
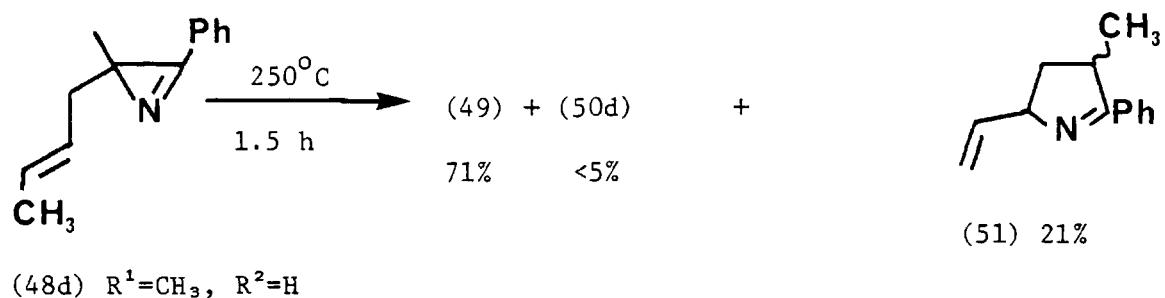
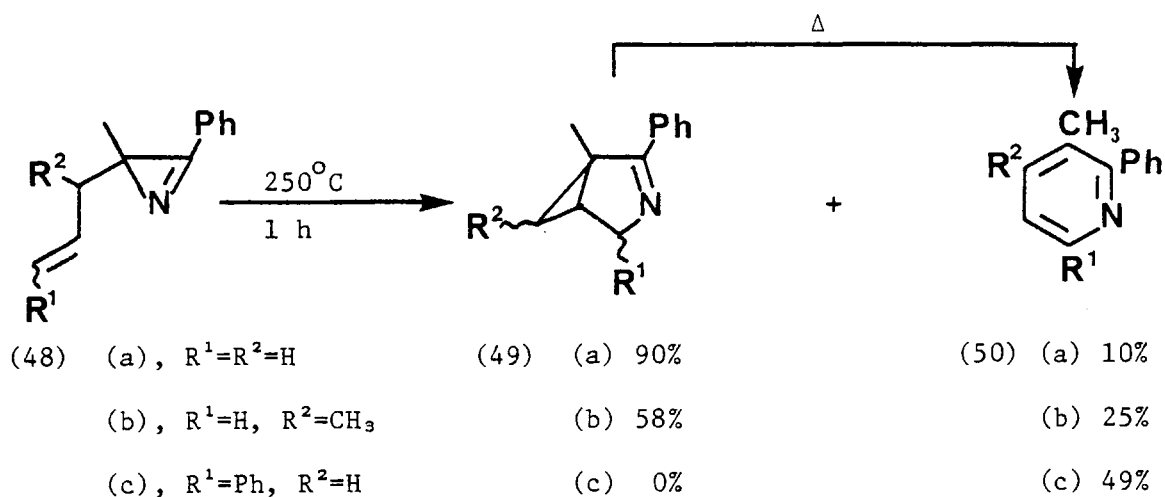


(46)

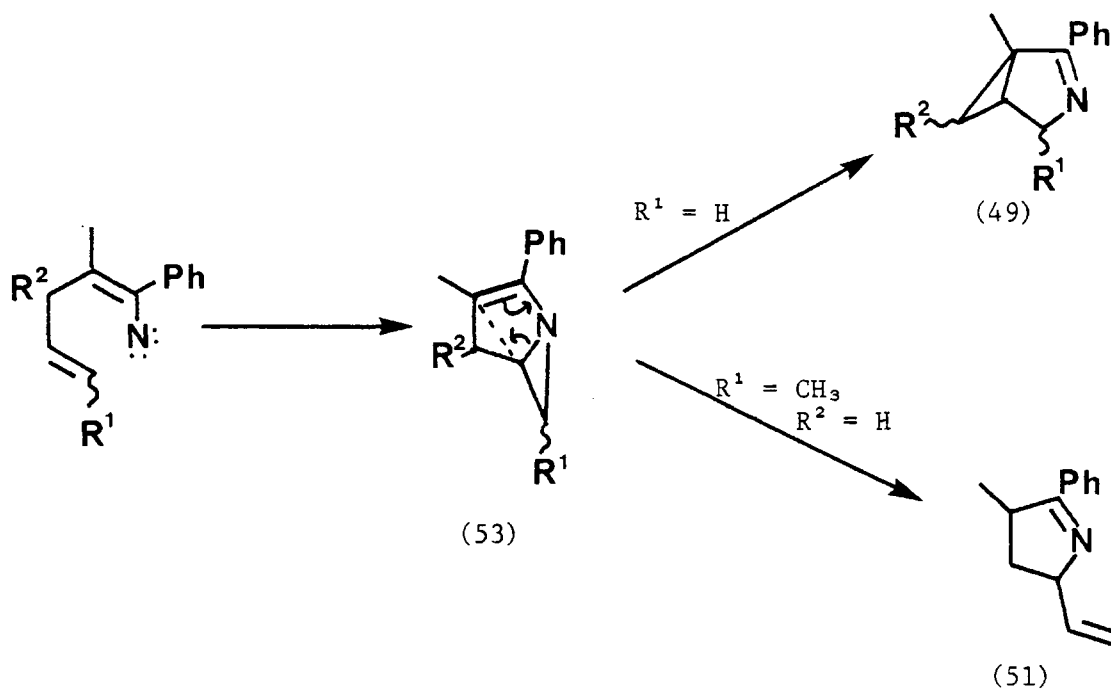


(47)

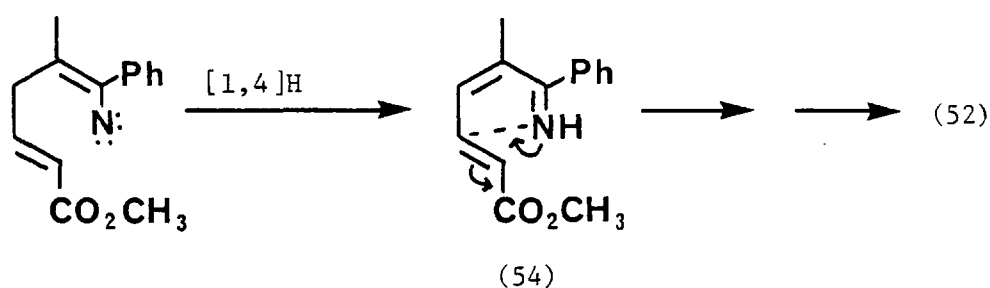
Azirines (45) have been discussed in the previous section [1.3.3.(a)] and azirines (47) will be discussed in the next section (1.3.5.). The allyl-substituted azirines (48) reacted *via* 1-nitreno-1,4-pentadienes to give a variety of products, depending on the substituents.⁷⁰ The 3-azabicyclo[3,1,0]hex-2-enes (49) formed were cleanly converted to pyridines (50) on further heating. Thermolysis of (48d) ($R^1 = \text{CH}_3$, $R^2 = \text{H}$) gave a new product, the pyrroline (51). The azirine (48e) ($R^1 = \text{CO}_2\text{CH}_3$, $R^2 = \text{H}$) gave pyridine (50e) in 47% yield and pyrrole (52) in 37% yield.



The formation of the cyclic products (49)-(51) can be rationalised as proceeding *via* a bicyclic aziridine (53) which is formed by addition of the nitrene to the C=C bond. Subsequent rearrangement of (53) gives the observed products.

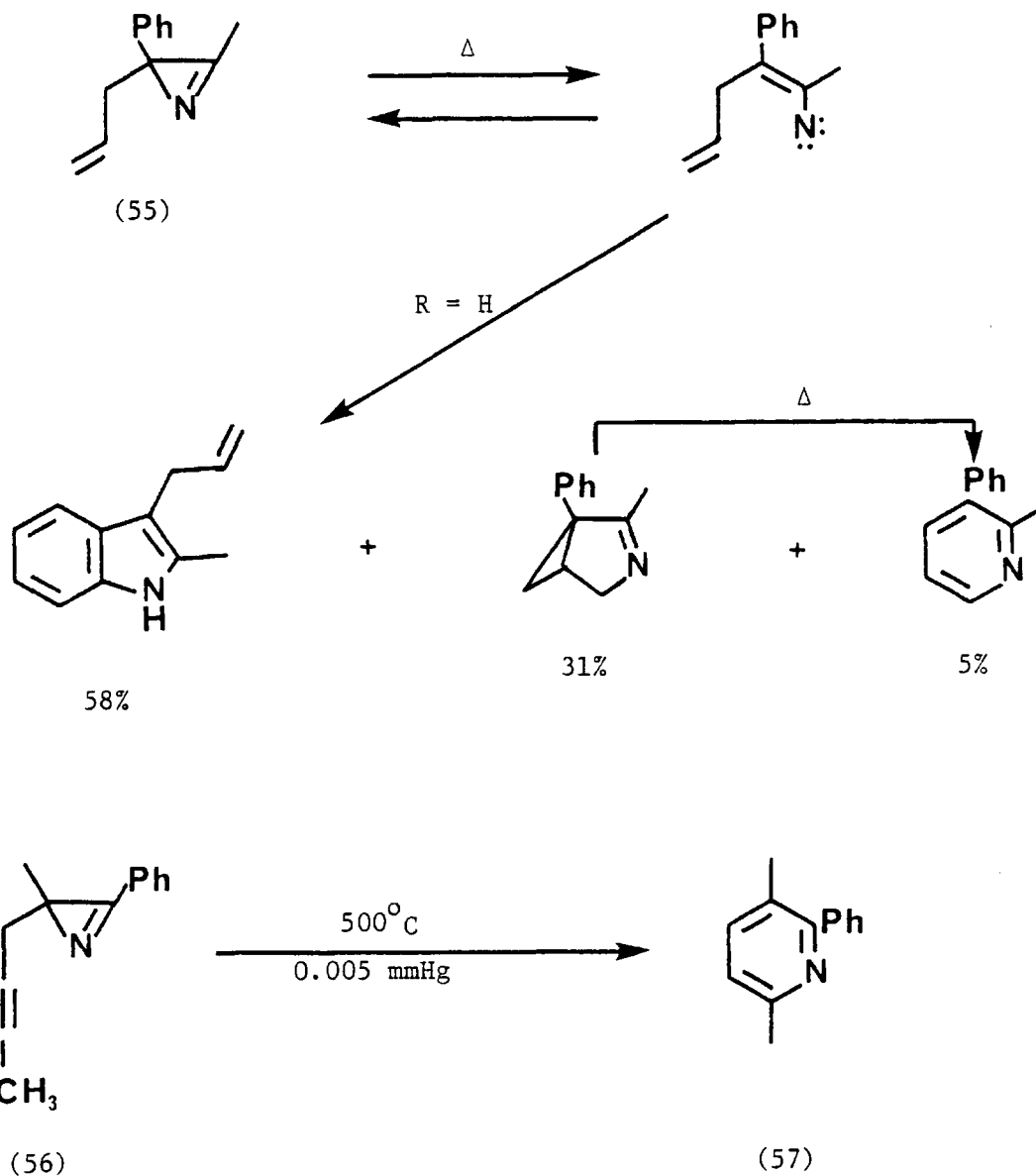


It was proposed⁷⁰ that the pyrrole (52) was formed by a [1,4]H shift to give the imine (54) which cyclised *via* a Michael addition.



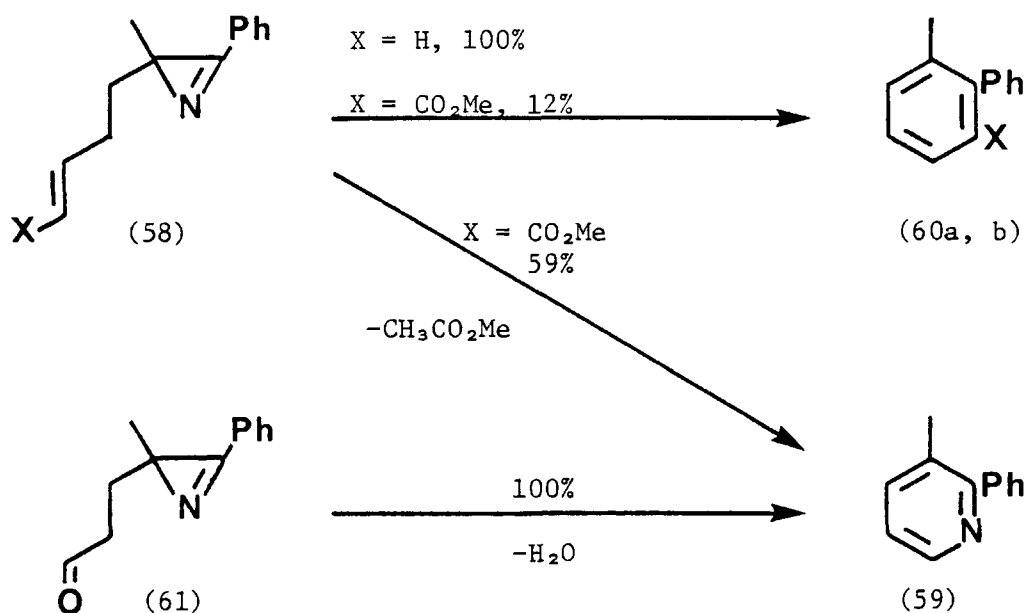
The vinylnitrene derived from azirine (55) gave products resulting from addition of the nitrene to the double bond and cyclisation of the nitrene onto the phenyl group.

Flash vacuum pyrolysis of the acetylene (56) gave the pyridine (57) in 34% yield as the only characterisable product.⁷⁰



1.3.5. Reactions of 1-nitreno-1,5-hexadiene derivatives and analogues.

Thermolysis of the azirines (58) (a, X = H ; b, X = CO₂Me) gave pyridine (59) and/or the substituted benzenes (60a,b). Similar treatment of the analogous aldehyde (61) afforded the pyridine (59) in quantitative yield.⁷¹



These reactions occur by a series of hydrogen shifts followed by cyclisation.

1.3.6. Intermolecular reactions.

The trapping of vinylnitrenes with phosphorus reagents is the only known intermolecular reaction of such nitrenes. Azirines do, however, undergo intermolecular reactions and there is a large volume of literature on these reactions.

The reactions of azirines by non-nitrene pathways are summarised in recent reviews.^{38,72,73}

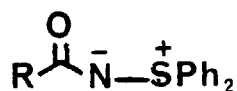
1.4. CARBONYLNITRENES

1.4.1. Generation. Isocyanate formation.

The preparation and reactions of acyl nitrenes are well reviewed.^{10,13,74,75} As mentioned previously the Curtius and related rearrangements to give isocyanates are not thought to involve nitrenes.³

Wentrup, however, presents evidence favouring the intermediacy of nitrenes in some cases at least.¹⁰

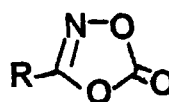
Acylnitrenes are produced by photolysis of acyl azides and have been shown not to undergo the Curtius rearrangement. Other precursors include sulphimides (62), nitrile oxides (63), and the heterocyclics (64) and (65).¹⁰



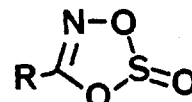
(62)



(63)



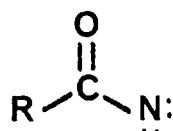
(64)



(65)

Alkoxycarbonylnitrenes can be prepared by thermolysis or photolysis of the corresponding azides¹³ and by α -elimination. Neither these nitrenes nor their precursors undergo the Curtius reaction.

1.4.2. Insertion reactions.



(66)

(66) (a), R = alkyl

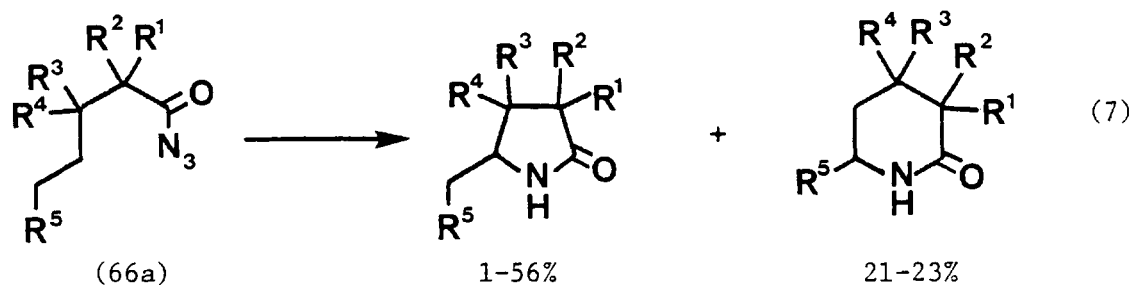
(b), R = aryl

(c), R = O alkyl

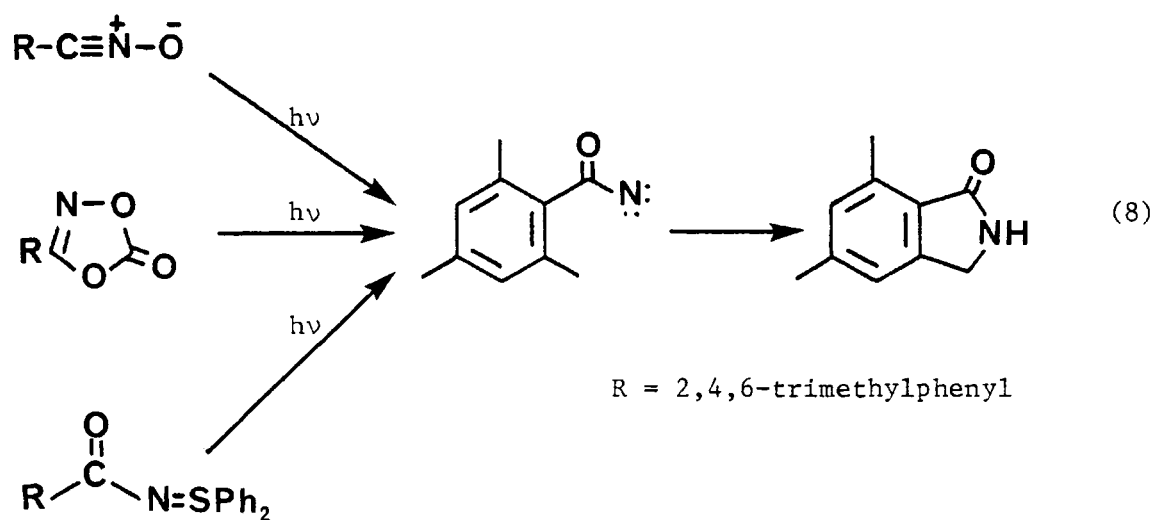
(d), R = O aryl

(e), R = NRR¹

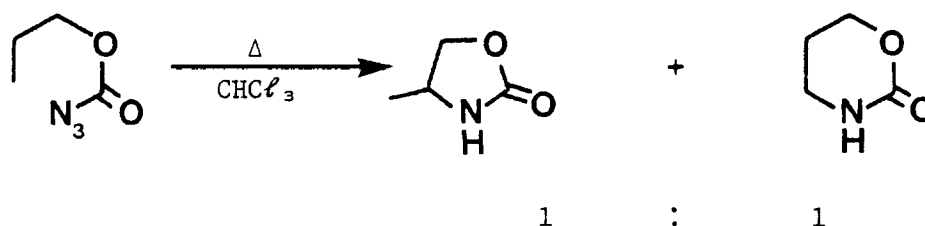
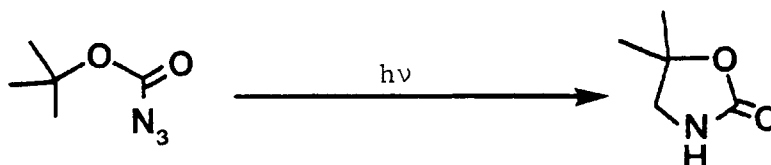
Acylnitrenes (66a) undergo intramolecular insertion into saturated C-H bonds to give 2-pyrrolidones and 2-piperidones (equation 7). Such reactions are thought to occur *via* singlet nitrenes because insertion



at a chiral centre occurs with retention of stereochemistry.⁷⁶ Suitably substituted aroylnitrenes (66b) give benzofused pyrrolidones (equation 8).⁷⁷⁻⁷⁹



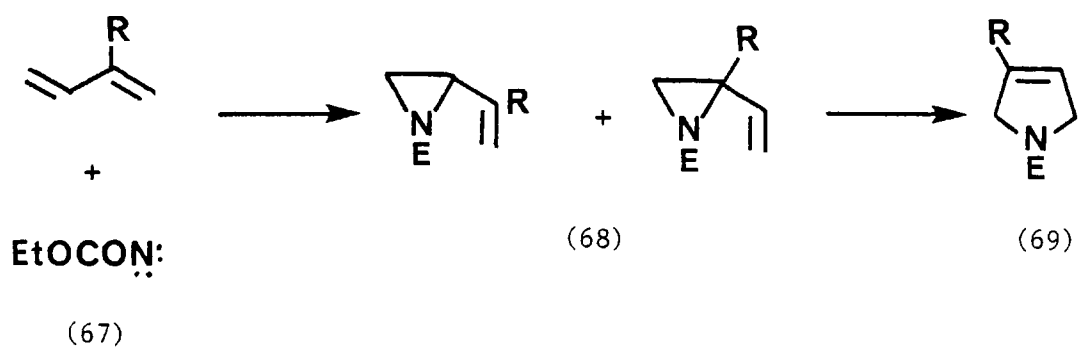
Alkoxy carbonylnitrenes (66c) also inserted, *via* the singlet species, into C-H bonds to give 2-oxazolidines and 2-oxotetrahydro-1,3-oxazines. Examples are shown in Scheme 11.⁸⁰⁻⁸²



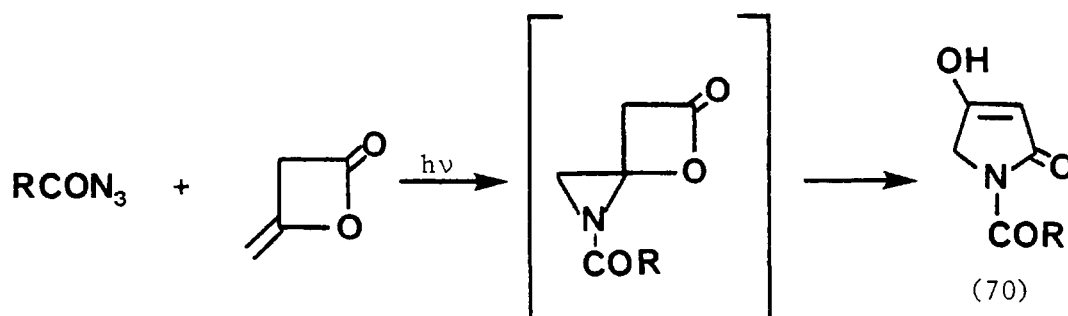
SCHEME 11

1.4.3. Reaction with alkenes.

Ethoxycarbonylnitrene (67) can add to carbon-carbon double bonds to give aziridines (68) which, if part of a 1,3-diene system, can isomerise to pyrrolines (69), the apparent 1,4-addition products.⁷⁴ However, no initial 1,4-addition is observed.

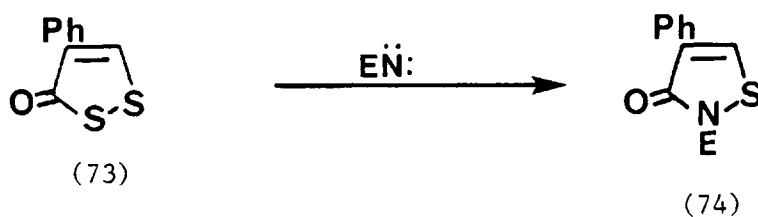
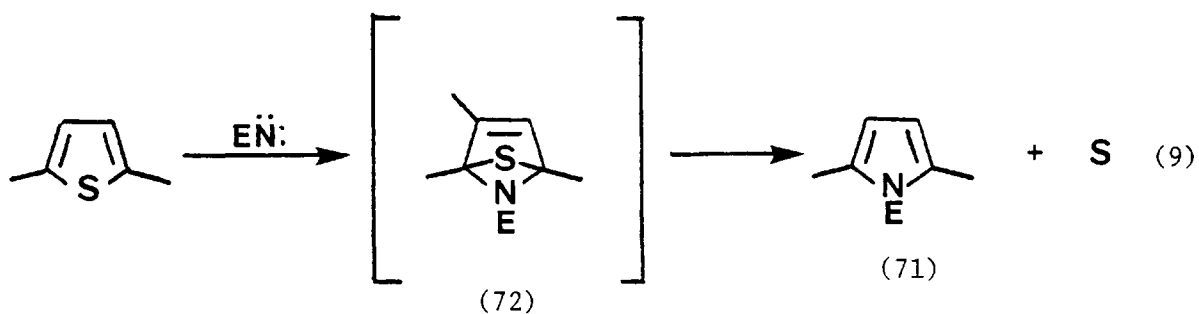


The addition is stereospecific for singlet nitrenes and non-stereospecific for triplet nitrenes. Acylnitrenes also add to alkenes, both inter- and intramolecularly.^{74,75} Addition of acylnitrenes to diketene gave the rearranged product (70).⁸³



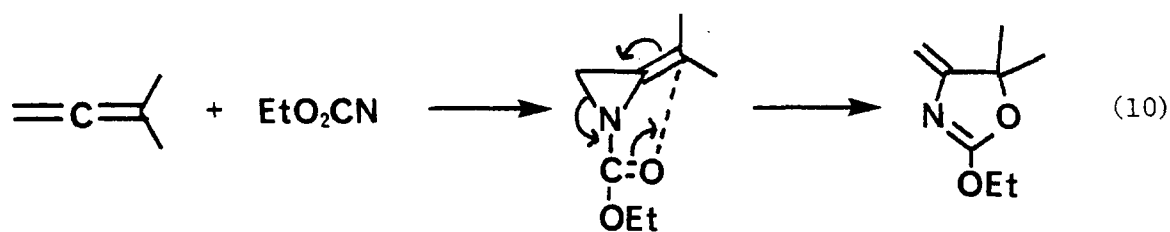
The reaction of 2,5-dimethylthiophene with ethoxycarbonylnitrene gave 2,5-dimethyl-*N*-ethoxycarbonylpyrrole (71).⁸⁴ Pyrroles react in the same way. It was proposed that this reaction proceeds *via* a bridged thiophene (72) (equation 9), which was formed by the same mechanism as led to the pyrroline (69).⁷⁴ The mechanism may, however, involve electrophilic attack of the nitrene on the aromatic ring followed by ring opening (see Section 1.4.6. and 1.4.7.). A similar reaction is the formation of the 3-oxothiazoline (74) from the dithiolone (73).⁸⁵

The reaction of acyl azides with alkenes is often complicated by the formation of triazolines by 1,3-dipolar cycloaddition of the azido group to the alkene. These triazolines can then decompose to give aziridines.



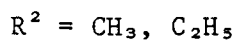
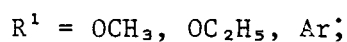
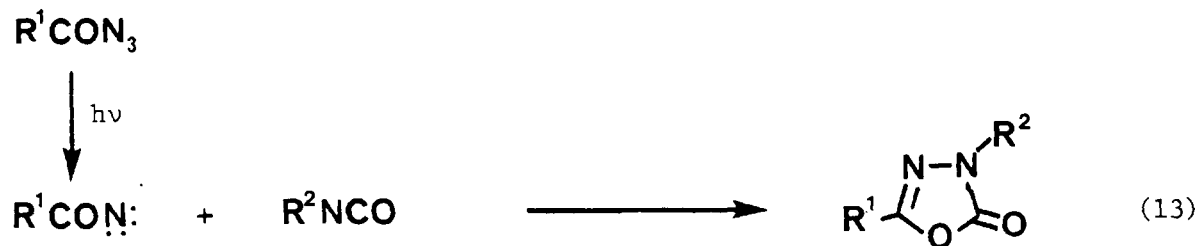
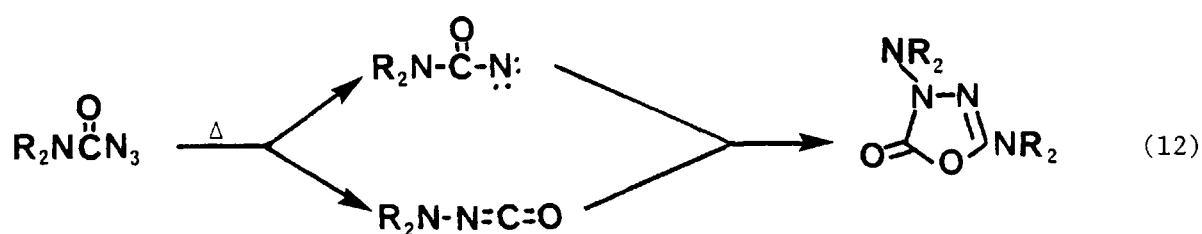
1.4.4. Reaction with cumulenes.

Ethoxycarbonylnitrene generated by azide photolysis⁸⁶ or α -elimination⁸⁷ added to the least substituted double bond of allenes to give aziridines which rearranged to give oxazolines (*e.g.*, equation 10).^{86,87} They are



also known to react with ketenimines (equation 11).⁸⁸ Carbonylnitrenes reacted with isocyanates to give 1,5-disubstituted-1,3,4-oxadiazol-5-ones (equations 12 and 13).^{89,90} This reaction may be considered to be

nitrene addition to a double bond followed by rearrangement, or, more probably, 1,3-addition of the carbonylnitrene to the isocyanate C=N bond.

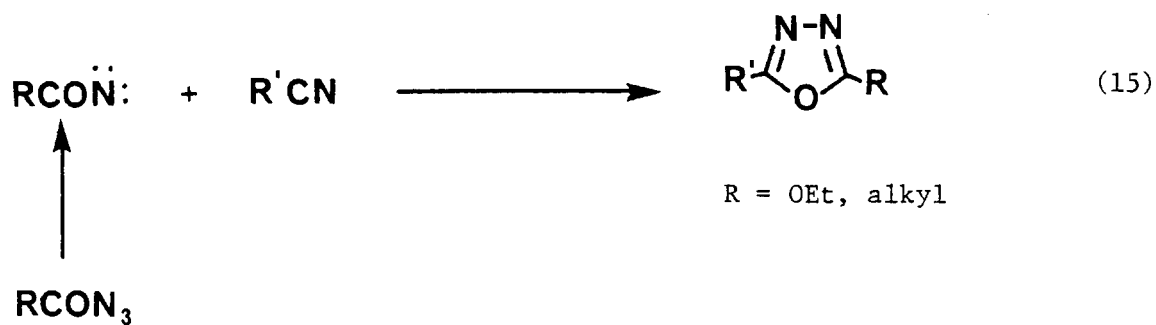
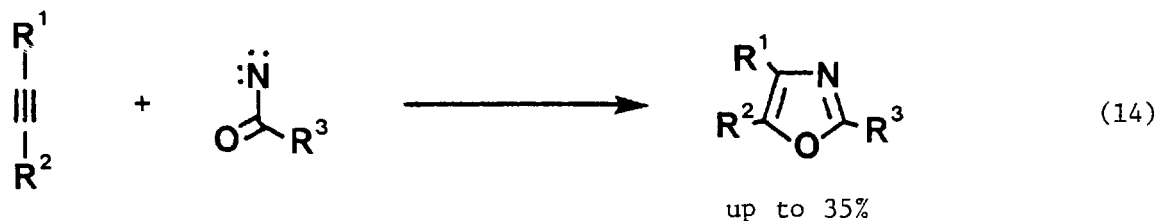


1.4.5. Reaction with acetylenes and nitriles.

A general method of synthesis of oxazoles is the addition of acylnitrenes to acetylenes (equation 14).^{13,74} This is regarded as a 1,3-cycloaddition of the carbonylnitrene to the triple bond.

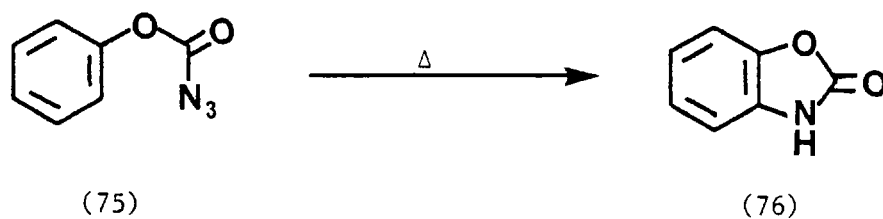
1,3,4-Oxadiazoles are formed by addition of acylnitrenes to nitriles

(equation 15).^{13,74,81,91,92} In competition experiments nitriles were less reactive towards carbonylnitrenes than were alkenes.

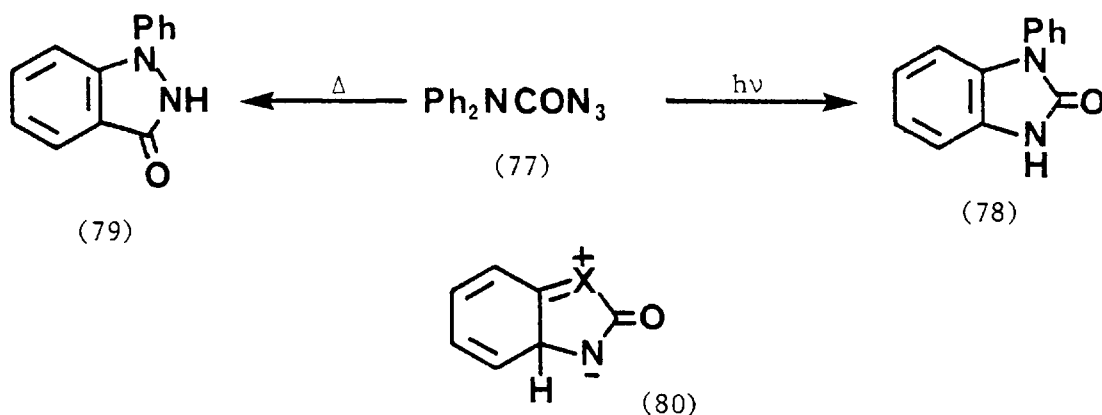


1.4.6. Reaction with aromatics.

Benzofused five-membered heterocycles are formed by decomposition of arylcarbonyl azides and aroyl azides. Thermolysis of the aryl-oxycarbonyl azide (75) gave the benzoxazoline (76).⁸² Photolysis of

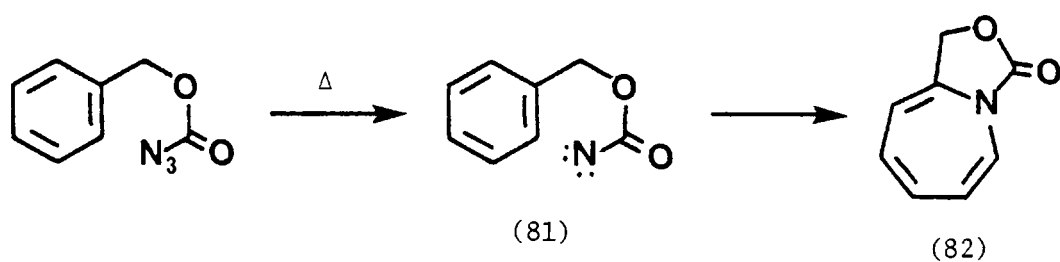
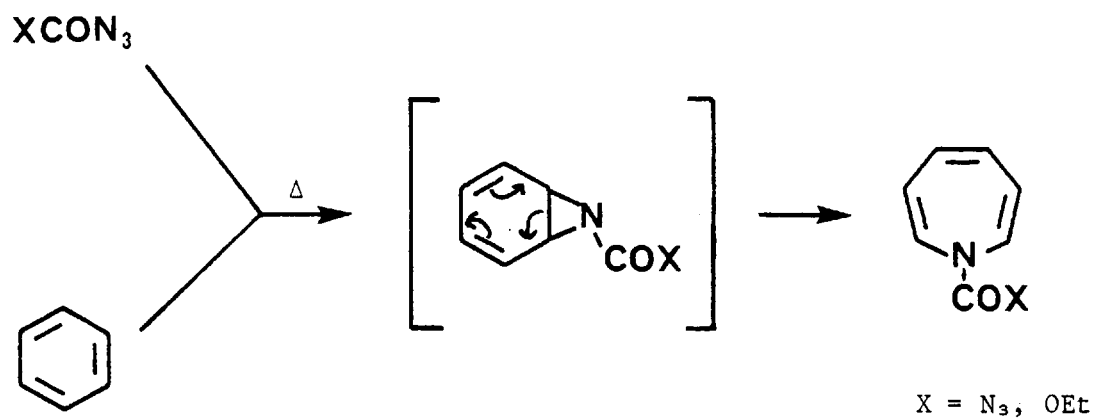


diphenylcarbonyl azide (77) gave benzimidazolin-2-one (78). Thermolysis gave a 90% yield of the indazolone (79) *via* the isocyanate.⁹³ Other benzimidazolin-2-ones have been prepared in the same way.^{89,94} These



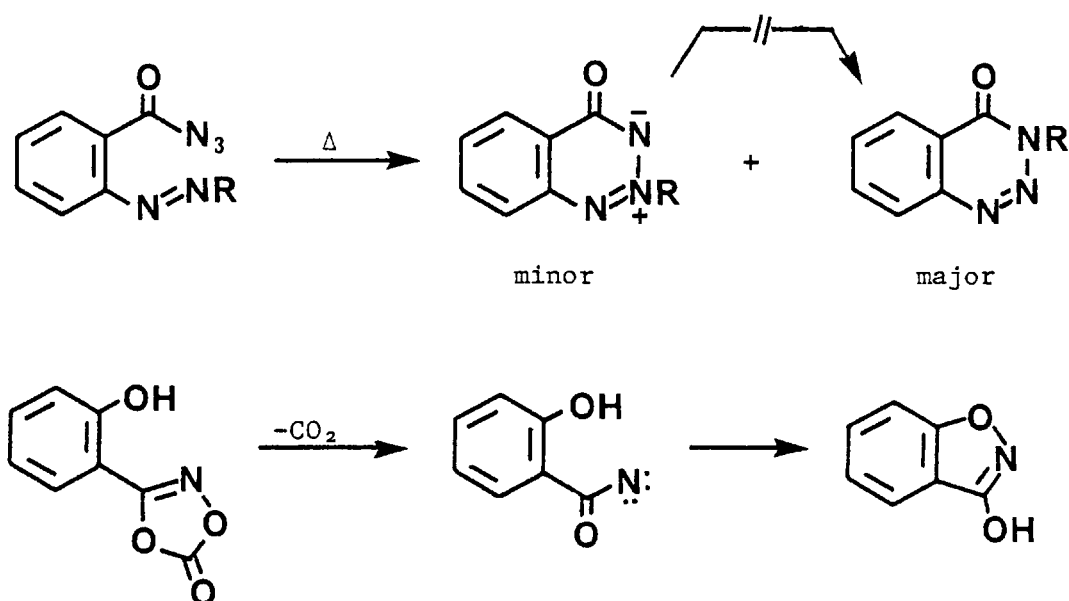
reactions may occur by insertion of the nitrene into the C-H bond or by cyclisation of the nitrene onto the ring followed by rearrangement. Intermediates such as (80) can be envisaged.

Azidocarbonylnitrene and ethoxycarbonylnitrene reacted intermolecularly with benzene to give *N*-azidocarbonylazepine⁹⁵ and *N*-ethoxycarbonylazepine⁹⁶. Similarly intramolecular addition of the carbonylnitrene (81) onto a benzene ring gave the azepine (82) which dimerised under the reaction conditions.⁹⁷ Such reactions are thought to proceed by initial addition of the nitrene to the aromatic ring to give an azanorcaradiene (a reaction analogous to the addition of nitrenes to alkenes) followed by ring opening to give the observed azepines. The intermolecular reactions of ethoxycarbonylnitrenes with thiophenes and pyrroles have already been presented (section 1.4.3.).



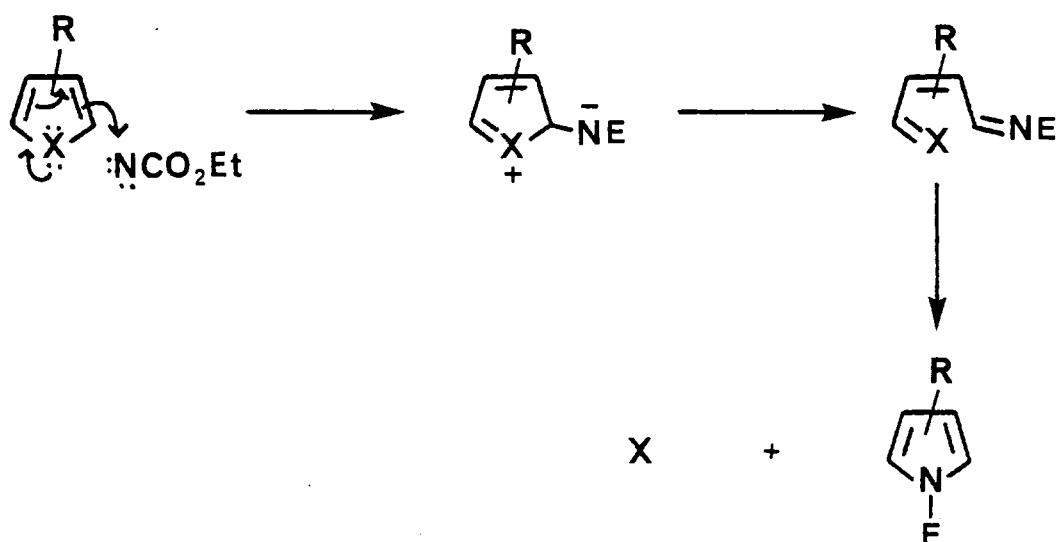
1.4.7. Reaction with nucleophiles.

Substituted benzoylnitrenes can react intramolecularly with nucleophiles. Some examples are shown in Scheme 12.^{98,99}



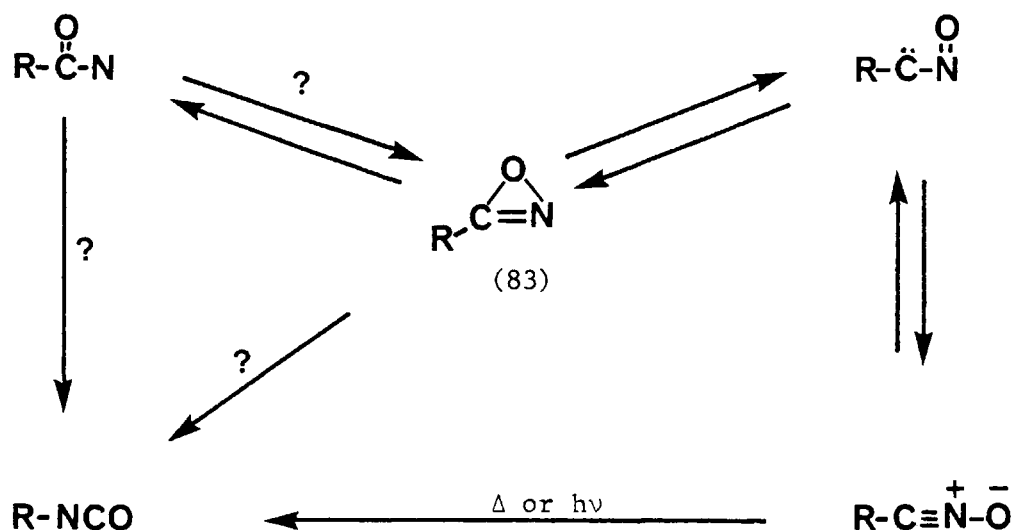
SCHEME 12

The first step in the reaction of ethoxycarbonylnitrene with thiophenes (equation 9) and pyrroles and in the reactions of the carbonylazides (75) and (77) can be considered to be an electrophilic addition of the nitrene to the aromatic ring. In the case of thiophenes and pyrroles, the species generated could then undergo ring opening and ring closure to give the observed ethoxycarbonylpyrroles.



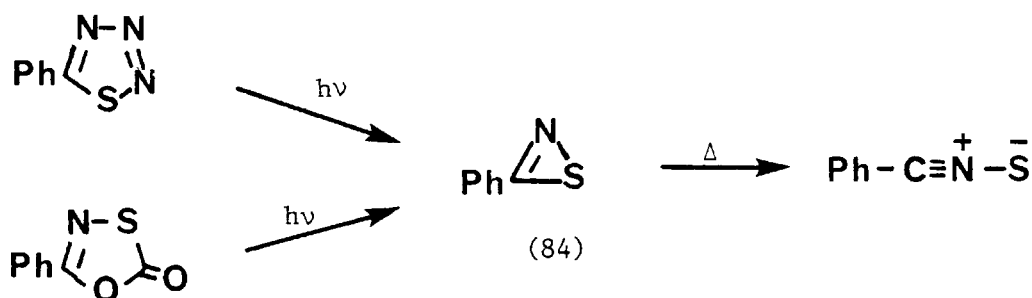
1.4.8. Isomerisation.

There is no evidence for the formation of the potentially antiaromatic oxazirine (83) from carbonylnitrenes. Such a reaction would be analogous to the vinylnitrene - azirine equilibrium. It is possible, however, that such a species is involved in the well known thermal and photochemical rearrangement of nitrile oxides to isocyanates (Scheme 13).¹⁰⁰



SCHEME 13

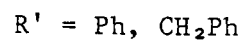
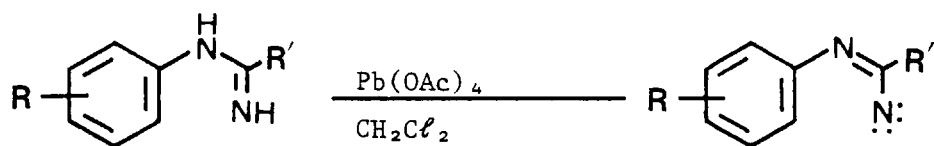
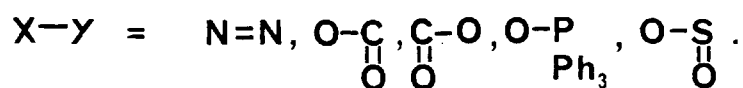
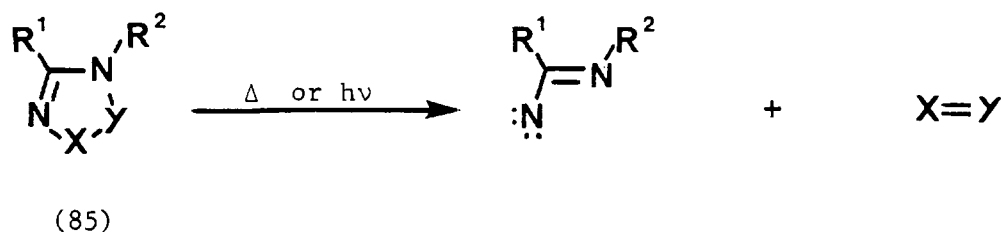
The analogous 3-phenylthiazirine (84) was formed by photolysis of a variety of precursors at 10-15 K but no evidence for the initial formation of thioacylnitrenes was obtained.¹⁰¹ The thiazirine (84) rearranged to benzonitrile sulphide on warming above 20 K.¹⁰²



1.5. IMIDOYLNITRENES.

1.5.1. Generation.

Imidoynitrenes can be generated by thermal or photochemical fragmentation of compounds of the general structure (85), as well as by photolysis of sulphimides,^{10,13} and by oxidation of *N*-arylbenzamidines.¹⁰³

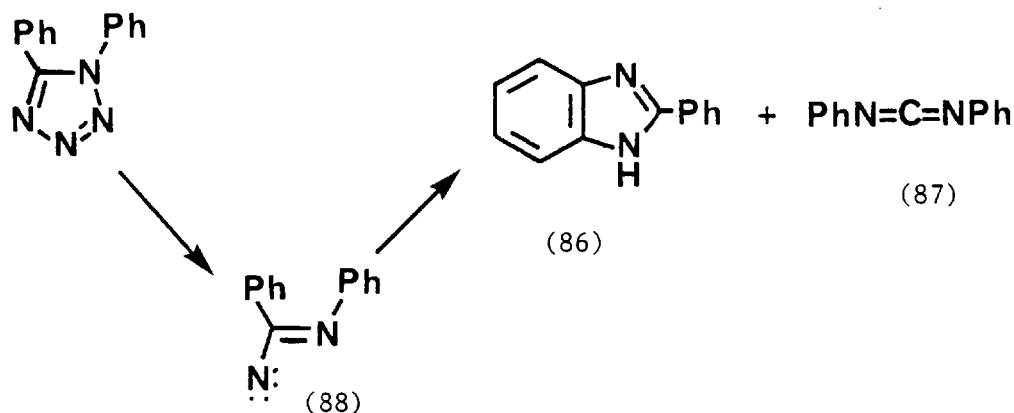


1.5.2. Acyclic imidoynitrenes.

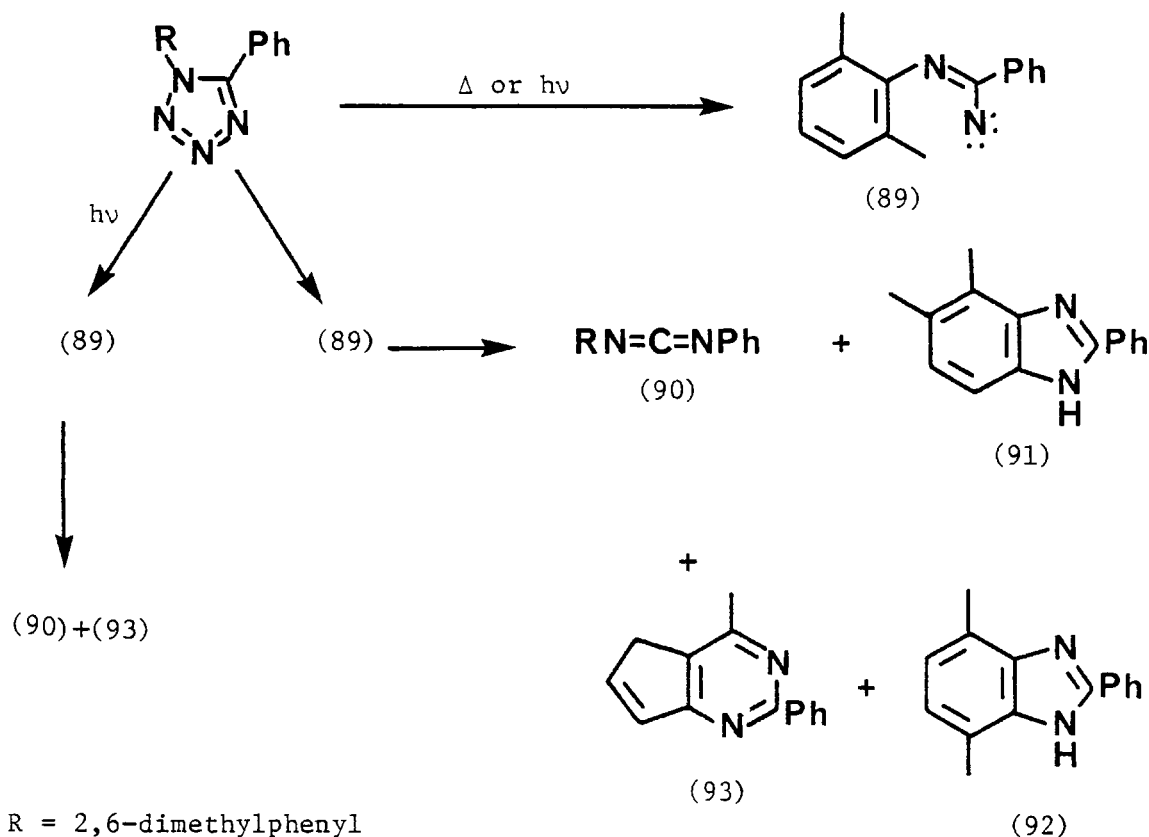
(a) Reactions of diarylimidoynitrenes.

Imidoynitrenes can be considered as aza analogues of both vinyl-nitrenes and acylnitrenes, and they exhibit analogous reactions.

1,5-Diphenyltetrazole formed a mixture of 2-phenylbenzimidazole (86) (23%) and diphenylcarbodiimide (87) (76%) on thermolysis above 200°C.¹⁰⁴ Photolysis gave only the benzimidazole (86).¹⁰⁵



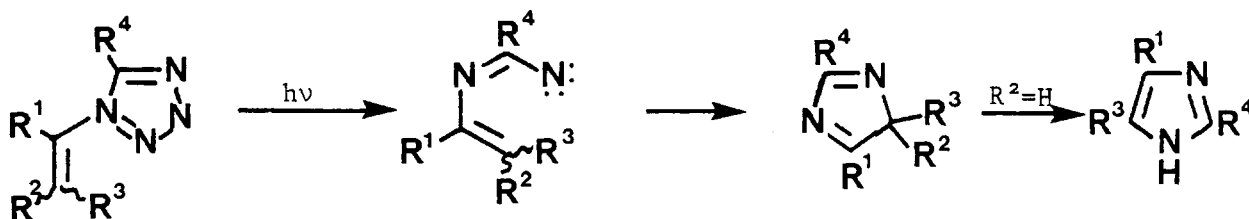
Generation of the imidoylnitrene (88) from a variety of precursors under different conditions gave varying amounts of the benzimidazole and carbodiimide.¹⁰ When the *N*-phenyl group in the imidoylnitrene (88) is substituted in the *o*-position other reactions are possible. The relative amounts of each of the products (90)-(93) depended on the conditions used (Δ or $h\nu$) and on the imidoylnitrene precursor.¹⁰⁶ Other examples of this reaction have been reported.^{106,107}



Cyclisation onto the blocked position of the ring followed by rearrangements occurred. The reactions of imidoynitrenes differ in this respect from those of vinylnitrenes and carbonylnitrenes. Both vinylnitrenes and carbonylnitrenes can formally insert into adjacent methyl groups and do not cyclise to a blocked aromatic position. Direct mechanistic comparison with carbonylnitrene reactions is not possible as the ring closure reaction cannot be an electrocyclic one. The reason for this difference in behaviour between vinyl- and imidoynitrenes is not obvious. Under the conditions necessary to generate the imidoynitrene (89) ($h\nu$ or high temperatures), azirines often, but not always, undergo C-C bond cleavage, or rearrangement to ketenimines or nitriles.⁷² No cyclisation of the vinylnitrene onto a blocked position is observed.

(b) Reactions of *N*-alkenylimidoynitrenes.

A variety of 1,5-disubstituted tetrazoles have been prepared, which on photolysis give rise to *N*-alkenylimidoynitrenes. These nitrenes behave analogously to the *N*-arylimidoynitrenes (88) in that they cyclise giving imidazoles in good yields. No carbodiimides were observed, however. This method of preparation of imidazoles appears to be quite general.¹⁰⁸



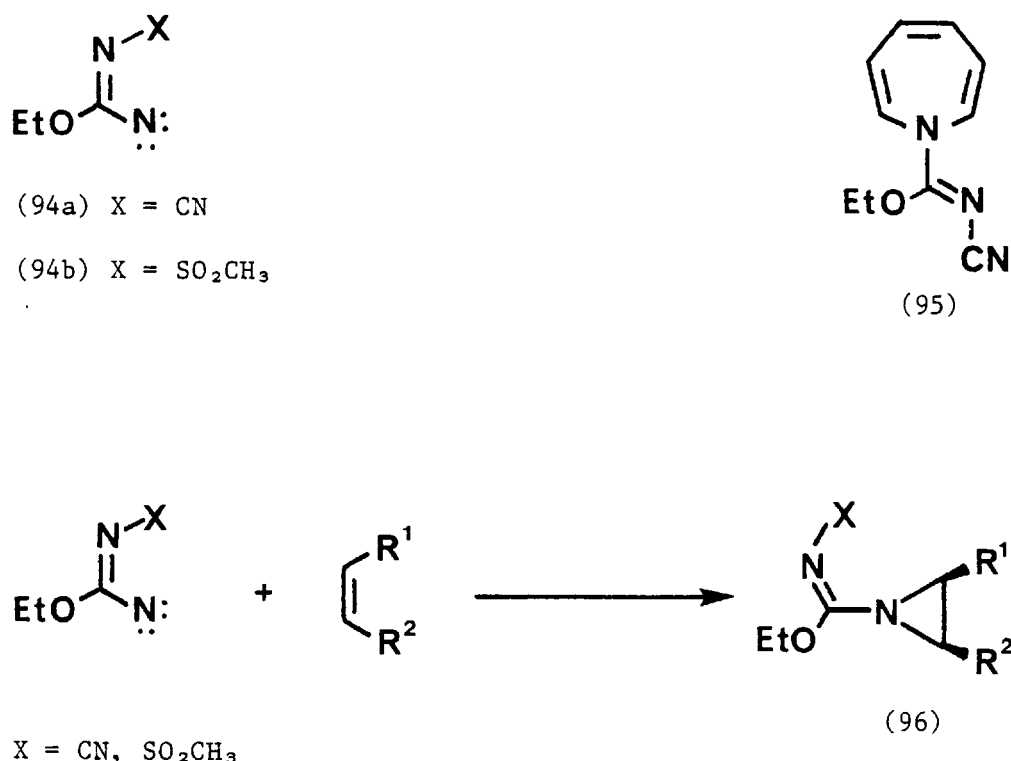
$R^1, R^2, R^3 = H, Me, (CH_2)_4, Ph, CO_2Me;$

$R^4 = H, Me, Ph$

(c) Reaction with aromatics and alkenes.

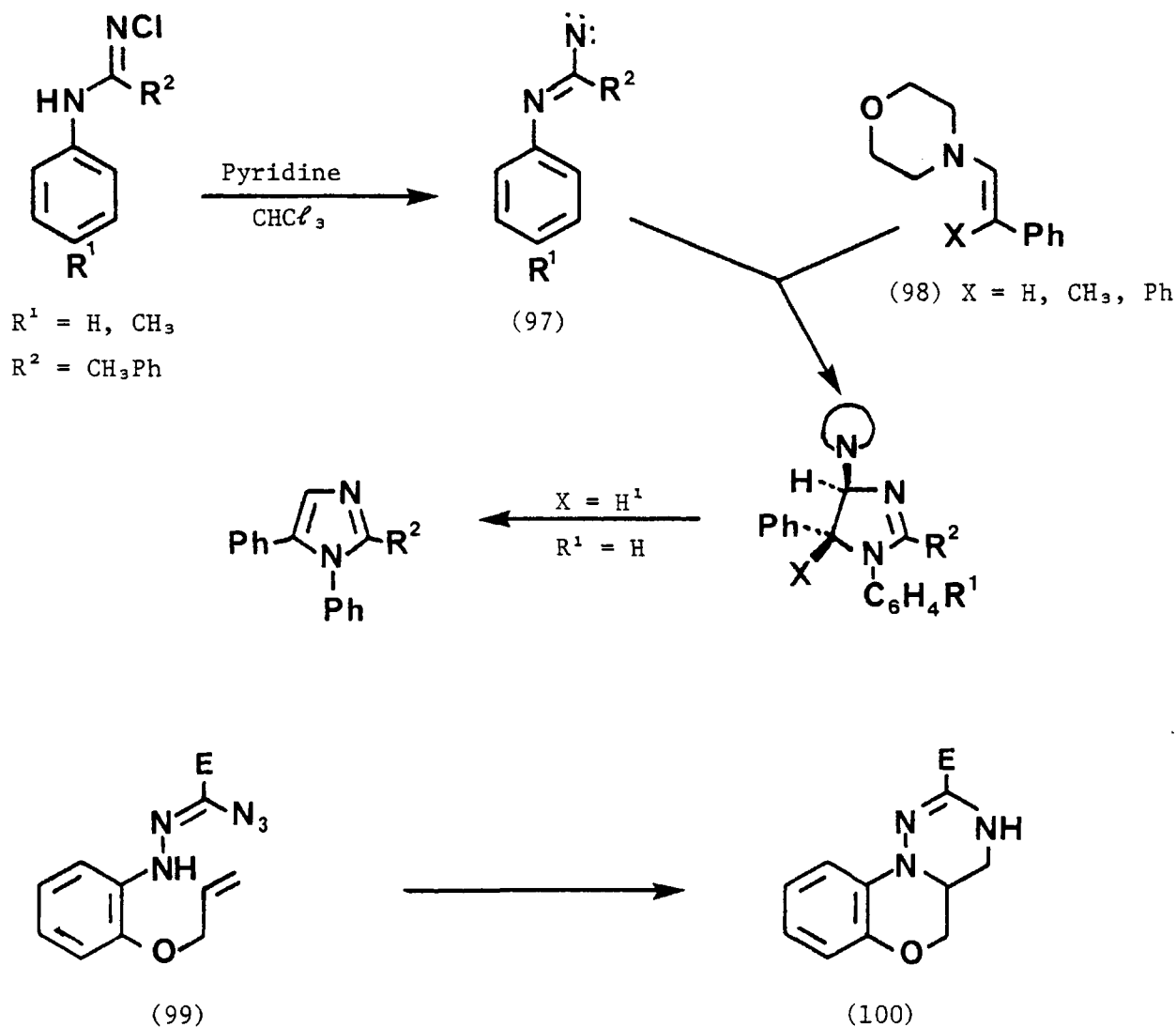
Intermolecular reactions of imidoynitrenes include addition to a benzene ring to give azepines,⁹⁶ addition to alkenes to give aziridines⁹⁶ and a formal 1,3-dipolar cycloaddition to alkenes to give imidazoles and dihydroimidazoles.¹⁰⁹

The imidoynitrenes (94a) and (94b) were generated by thermolysis or photolysis of the corresponding azides. Generation of (94a) in benzene gave a 60% yield of the azepine (95). The nitrene (95b) did not react with benzene. Both nitrenes added stereospecifically to olefins to give aziridines (96).⁹⁶



The reaction of imidoynitrenes (97) with enamines (98) to give dihydroimidazoles and/or imidazoles was rationalised as a 1,3-dipolar cycloaddition, or by an initial addition of the nitrene to the double

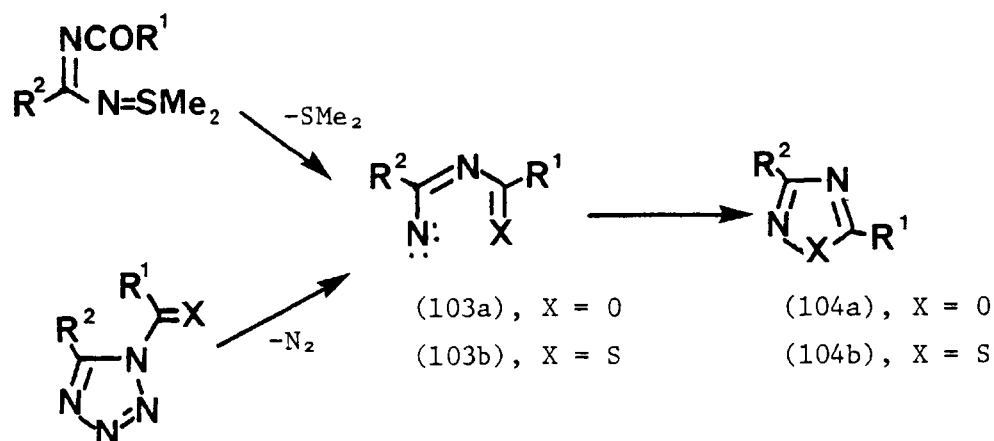
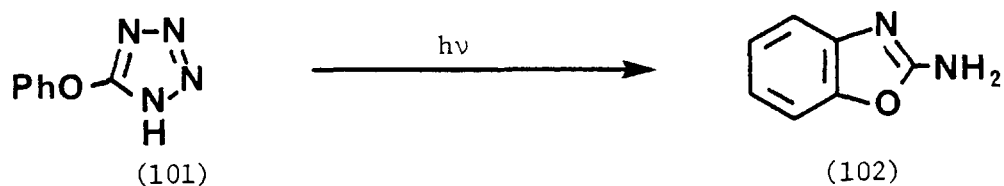
bond followed by rearrangement.¹⁰⁹ Intramolecular 1,4-addition of an imidoynitrene is thought to be responsible for the formation of the triazine (100), by thermal decomposition of azide (99).



(d) Miscellaneous reactions.

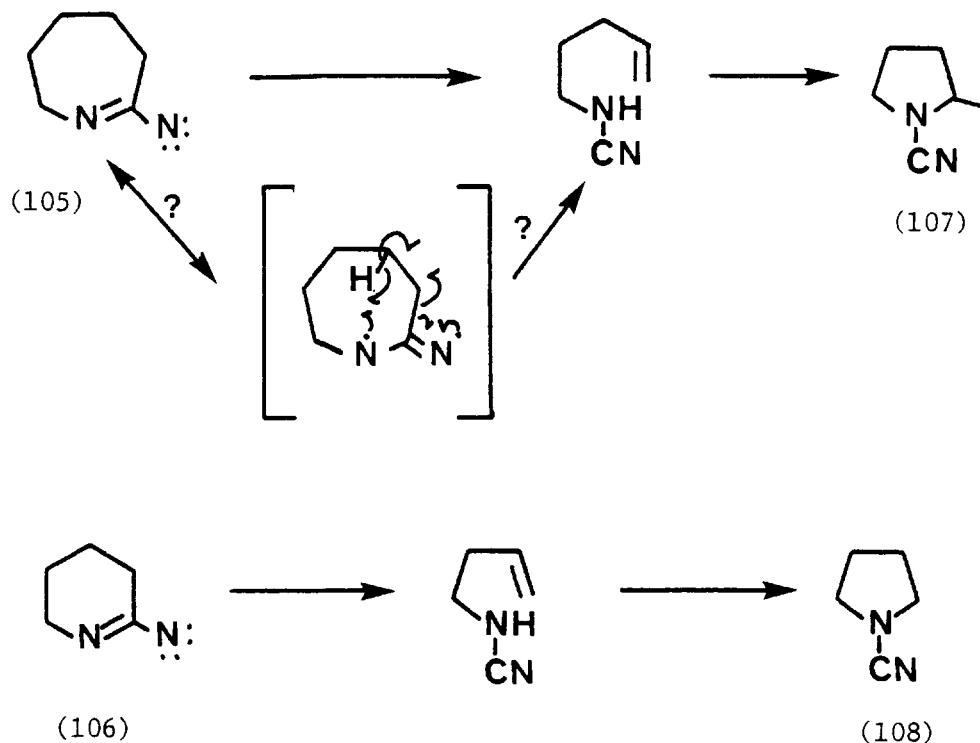
Photolytic decomposition of 4-phenoxy-tetrazole (101) gave a high yield of 2-aminobenzoxazole (102) (90%).¹¹¹ *N*-Acylimidoynitrenes (103a) were found to cyclise to 1,2,4-oxadiazoles (104a) in yields of up to 70%.¹¹²⁻¹¹⁴ *N*-Thioacylimidoynitrenes (103b) behaved in the

same way.¹¹⁵ These reactions are analogous to the cyclisation of *N*-alkenylimidoynitrenes to imidazoles.



1.5.3. Annelated imidoynitrenes.

Imidoynitrenes that are part of an aromatic system will be dealt with in section 1.6. The annelated imidoynitrenes (105) and (106) which are generated by flash vacuum pyrolysis of the corresponding tetrazoles were found to undergo ring cleavage and re-closure to give the *N*-cyanopyrrolines (107) and (108) respectively.¹¹⁶



1.6. ARYLNITRENES.

The early work on the generation and reactions of arylnitrenes has been reviewed by Smith¹⁰³ and Boyer,¹¹⁷ and the recent review by Wentrup¹⁰ includes a discussion on the generation and intramolecular reactions of arylnitrenes.

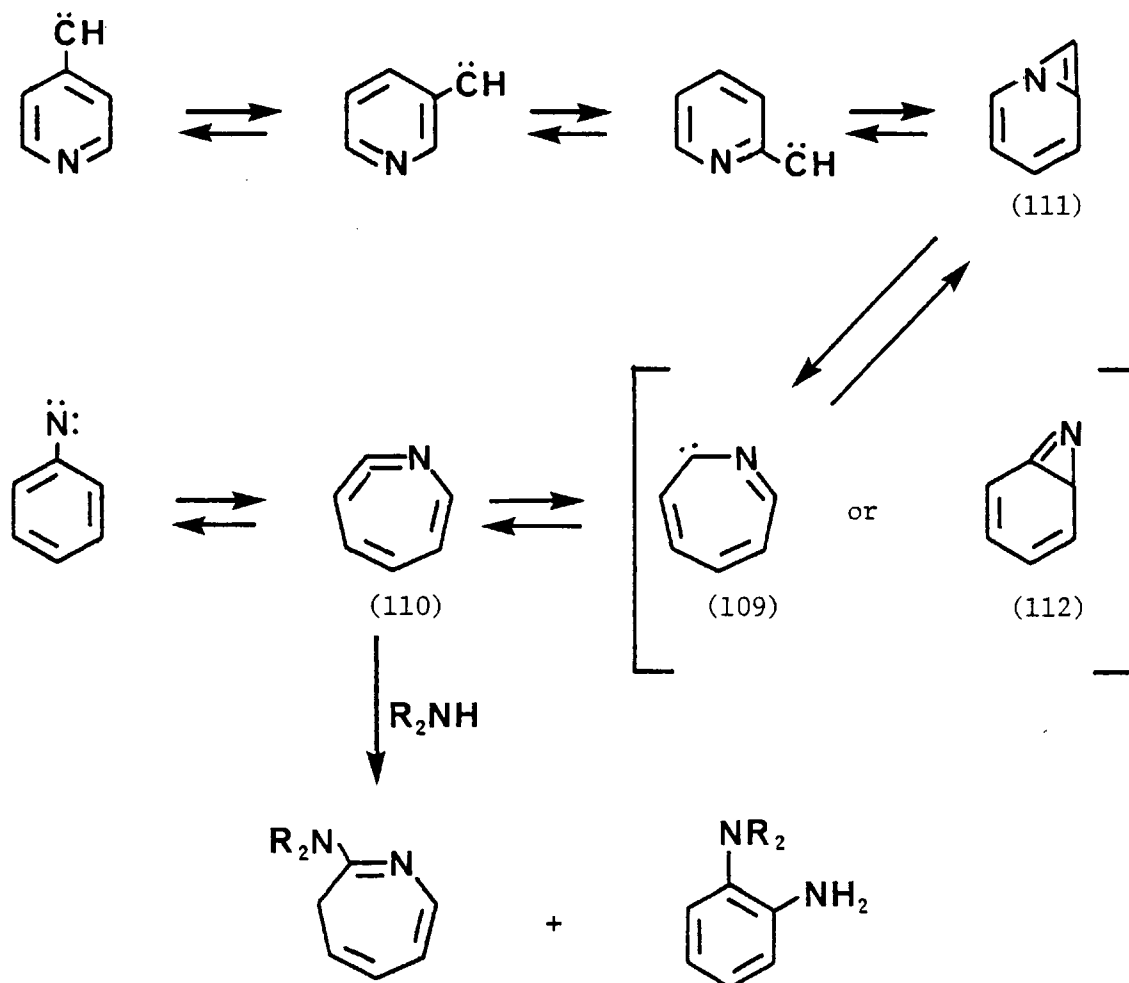
1.6.1. Generation.

Arylnitrenes have been widely studied, primarily because they are easily obtainable from a wide range of precursors and react to form many useful products. Much mechanistic investigation into their reactions has also been carried out. Arylnitrenes can be produced by thermolysis and photolysis of aryl azides, by deoxygenation of aryl nitroso- and nitro- compounds, by rearrangements of carbenes, by ring opening of anthranils and indazoles, and by α -elimination from *N*-arylhydroxylamine derivatives.^{10, 118-127}

1.6.2. Intramolecular reactions.

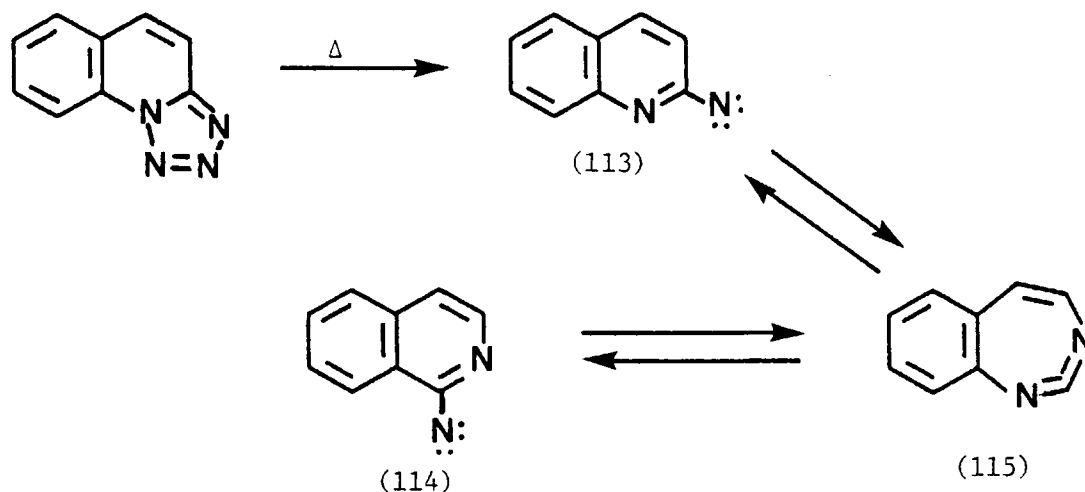
(a) Carbene-nitrene, nitrene-nitrene interconversions. Formation of azepines, 1,2-diamines and pyridines.

As mentioned above, nitrenes can interconvert with carbenes. This reaction is thought to occur *via* azacycloheptatrienylidenes (109), and/or azacycloheptatetraenes (110), and/or benzazirines (111) and (112). Wentrup¹⁰ presents the evidence for and against these intermediates, and concludes that an equilibrium probably exists between (110) and (109) or (112), (110) being the most stable of the three structures. Aza analogues of cycloheptatetraene can be detected.

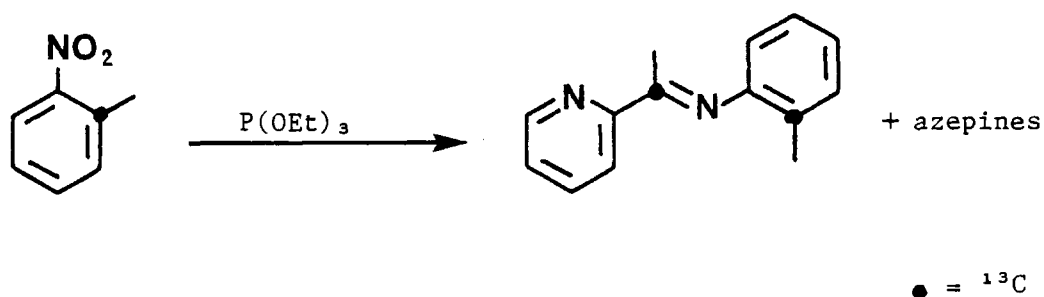
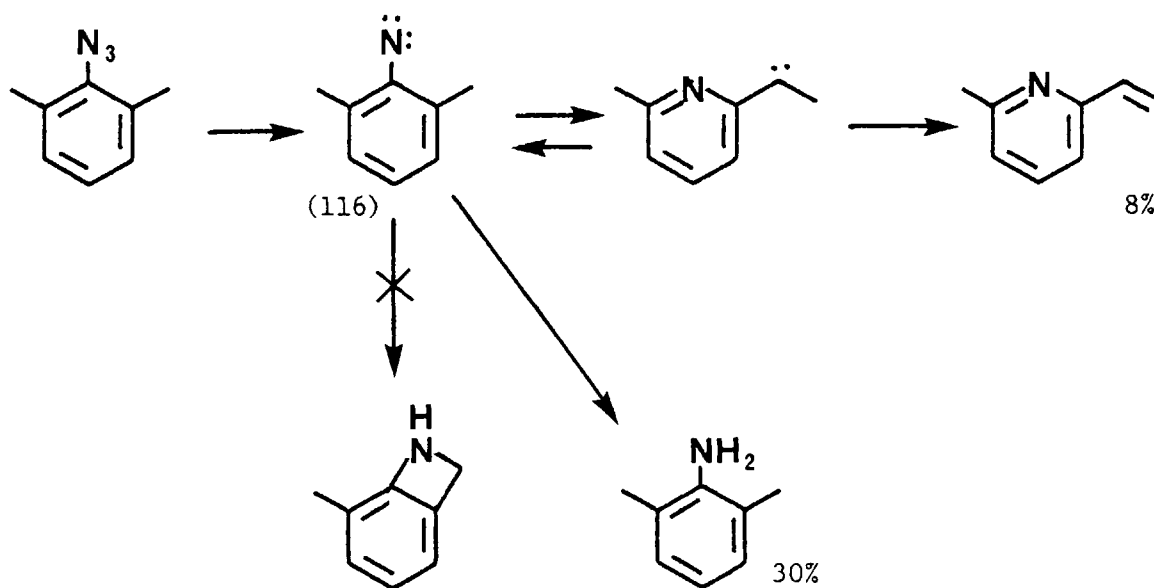


The postulated equilibrium between arylnitrenes and benzazirines (112) is analogous to the equilibrium between vinylnitrenes and azirines. The reaction of (112) [or (109) or (110)] with nucleophiles is analogous to the facile reaction of azirines with nucleophiles. The ring opening reaction to give the seven-membered rings (110) or (109) (and hence the 2-aminoazepines) while not typical of thermal reaction of azirines, is typical of photochemical reactions of azirines and led many workers to propose intermediate (112) in the conversion of arylnitrenes to azepines and 1,2-phenylenediamines.

The arylnitrenes (113) and (114) can interconvert and the intermediate cyclic carbodiimide (115) was detected at -196°C .¹²⁸

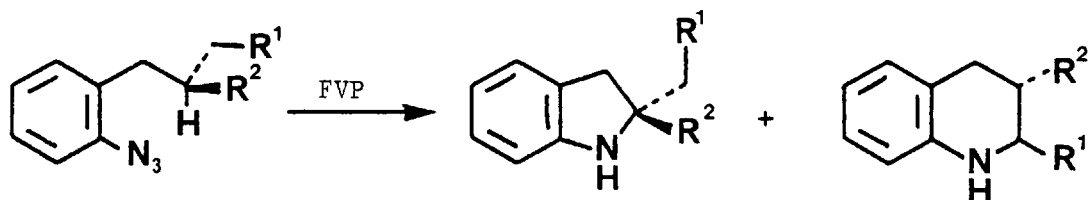


Arylnitrenes such as (116) with an *ortho*-methyl group do not undergo insertion to give a four-membered ring. Instead, rearrangement to carbenes can occur, giving pyridines.^{10,129,130}

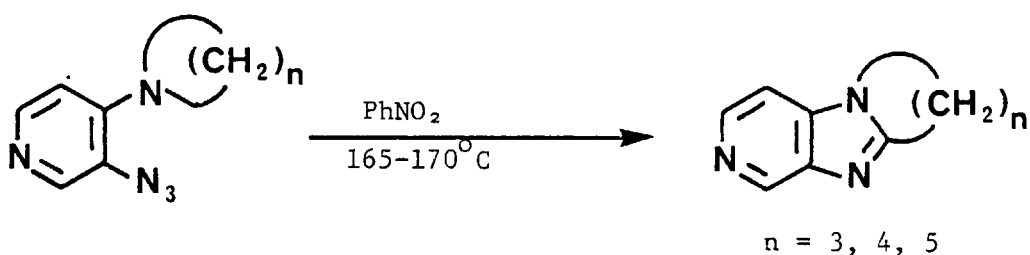
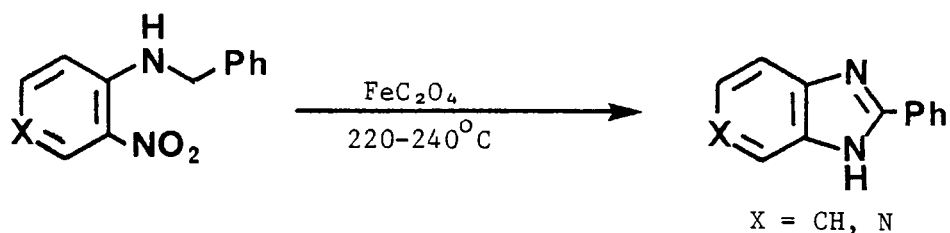


(b) Reaction with saturated side chains.

The thermolysis of aryl azides or the deoxygenation of nitrobenzenes with alkyl side chains leads to indoline derivatives and small amounts of tetrahydroquinoline derivatives. The reaction is often regiospecific giving indolines only. When the precursor is an azide high stereospecificity occurs on flash vacuum pyrolysis, but solution thermolysis leads to lower stereoselectivity (60% retention of configuration) due to the formation of triplet nitrenes.^{12,103}



N-Alkyl- or *N*-cycloalkyl-*o*-aminophenylnitrenes give the side chain insertion products benzimidazolines and benzimidazoles.^{13,103} Benzimidazoles substituted in the 1- and/or 2-positions are the isolated products of this reaction, but the intermediate benzimidazolines were trapped under non-oxidative conditions.¹⁰³ Some examples are given in Scheme 15.

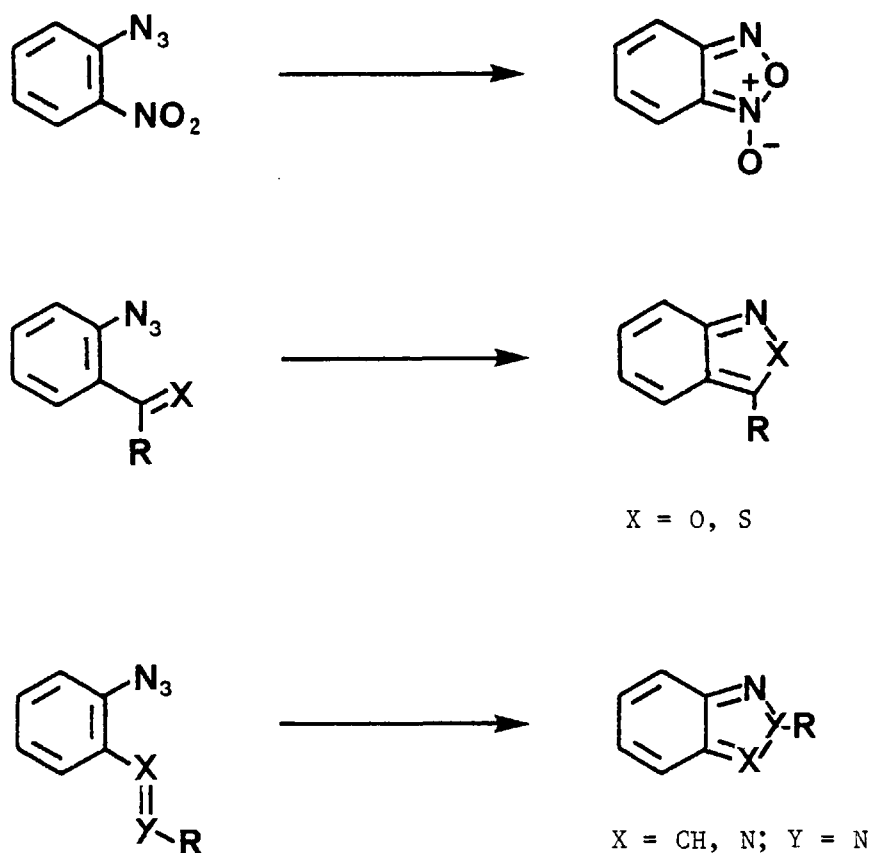


SCHEME 15

(c) Reaction with unsaturated side chains.

Aryl azides with an unsaturated group at the *o*-position often decompose at relatively low temperatures, *via* a concerted pathway which does not involve nitrenes. Thus, aryl azides with *o*-nitro,

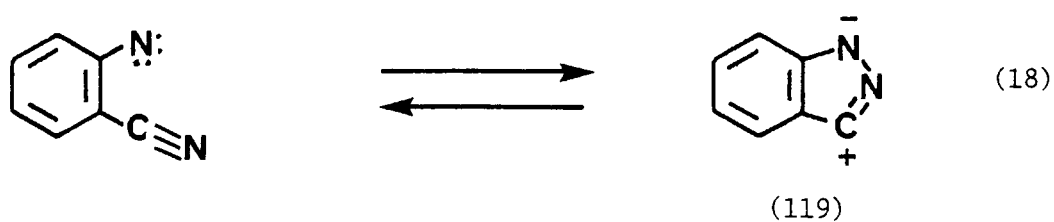
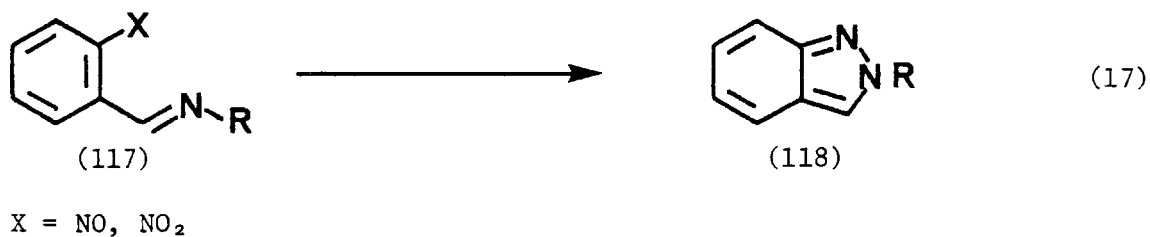
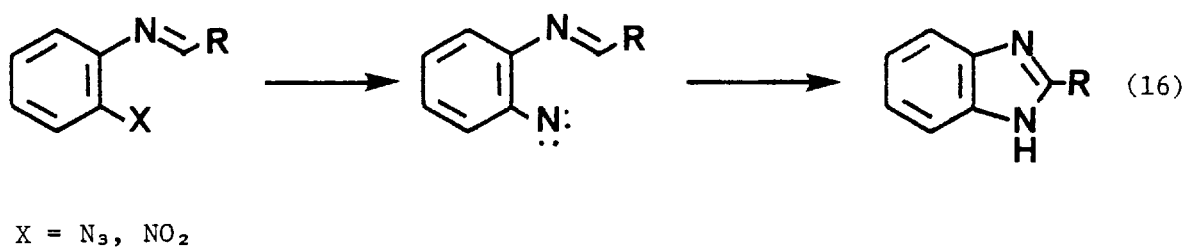
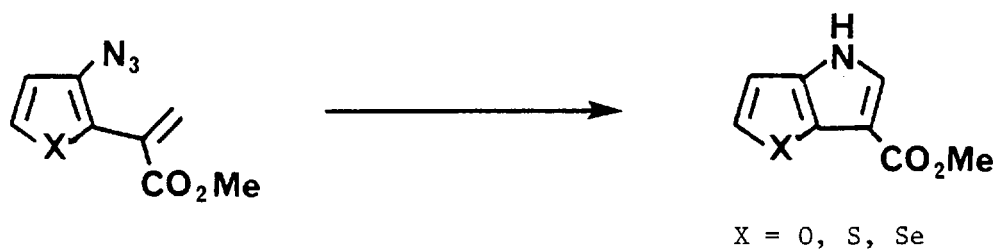
acyl and thioacyl groups gave benzofuroxans, anthranils and thioanthranils respectively, and *o*-imidyl and azo groups gave 2*H*-indazoles and 2*H*-benzotriazoles respectively (Scheme 16).¹⁰



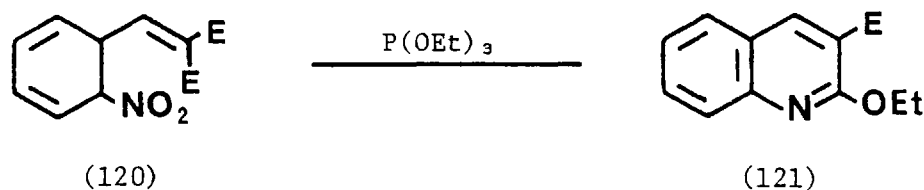
SCHEME 16

Reactions of azides in which the *o*-group is $-\text{CR}=\text{CR}_2$ or $-\text{N}=\text{CR}_2$ usually occur *via* nitrenes (equations 16 and 17) as do some reactions in which a nitro group is the nitrene precursor.^{10,13} Deoxygenation of *o*-nitroso or *o*-nitrobenzaldimines (117) gave 2-aryl-2*H*-indazoles (118) (equation 17).¹³ Similarly, it has been proposed that

o-cyanophenylnitrene is in equilibrium with the cyclic compound (119) (equation 18).¹³¹ This reaction seems far less likely than those shown in Scheme 16 due to the linear structure of the nitride.



Treatment of the nitrocinnamate derivative (120) with triethyl phosphite did not produce an indole, but rather the quinoline derivative (121). It was proposed that this reaction occurred *via* the corresponding nitrene.¹³²

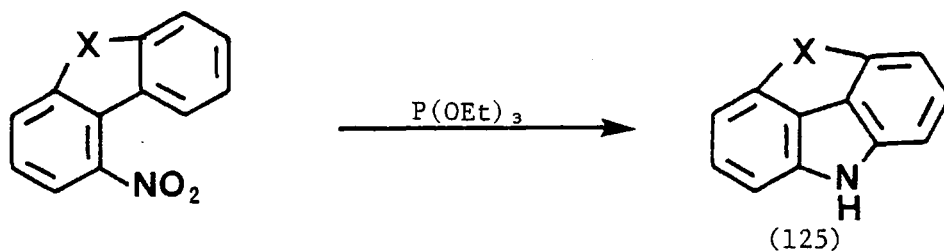
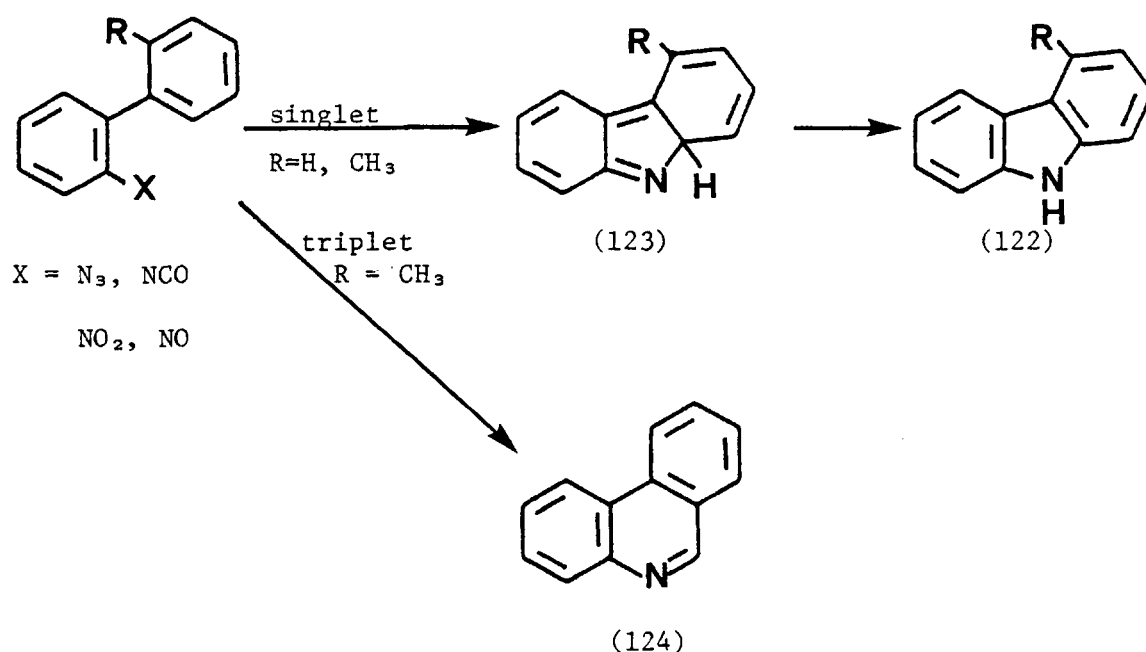


(d) Cyclisation onto an adjacent ring.

In the previous section [1.6.2.(c)] cyclisation onto *o*-unsaturated side chains gave rise to fused five-membered heterocycles. Cyclisation of nitrenes onto adjacent rings leads to the formation of both five- and six-membered heterocycles.

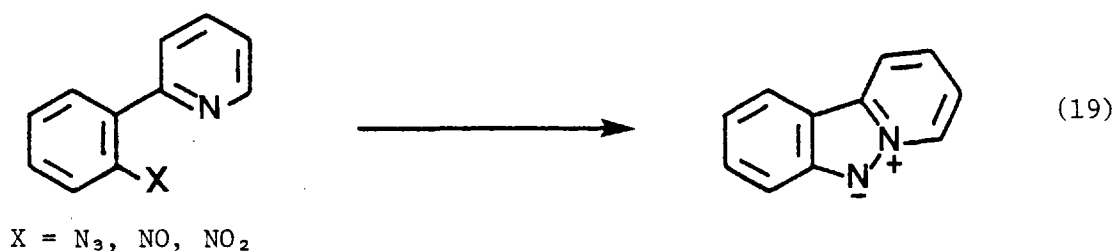
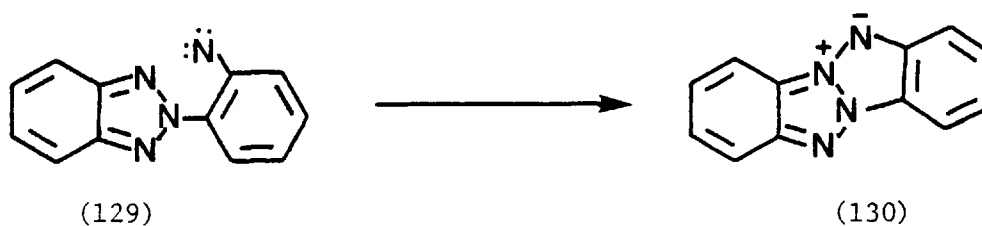
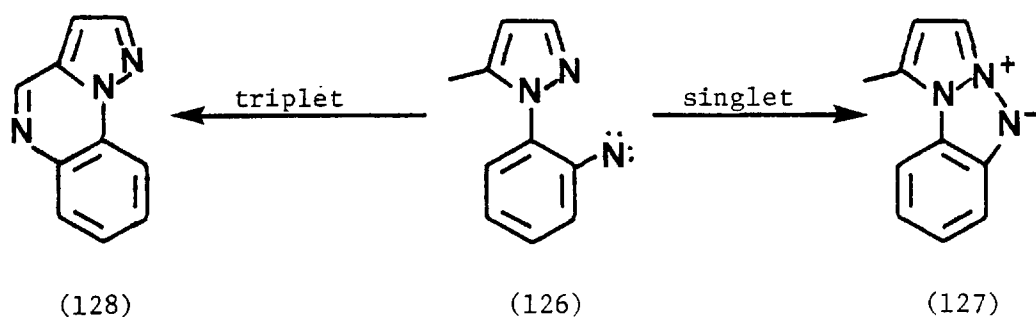
Carbazoles (122) are formed from singlet 2-nitrenobiphenyls, probably *via* electrocyclic ring closure to an intermediate 4aH-carbazole (123).¹⁰ Triplet nitrenes gave amines and azobiphenyls *via* hydrogen abstraction and nitrene dimerisation, respectively. Triplet nitrenes are also responsible for the formal insertion reaction leading to phenanthridines (124).¹³³ The tetracyclic ring systems (125) have been prepared in the same way.¹³⁴

Cyclisation can also take place onto five- and six-membered heterocyclic rings to give a variety of fused nitrogen-containing heterocyclics. This reaction has been reviewed.¹³⁵ When the heterocyclic ring



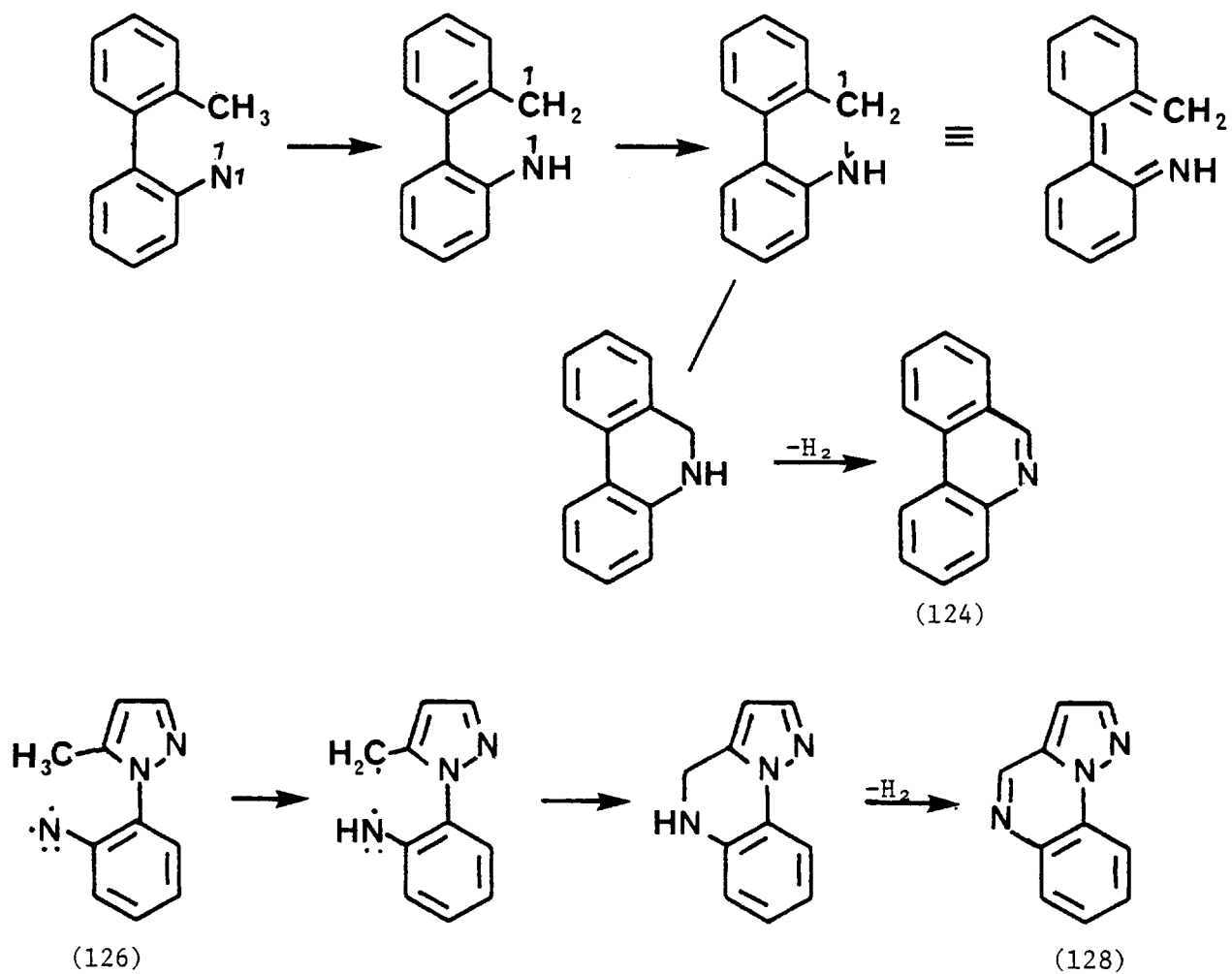
$X = C(CO_2Et)_2, NMe, NCH_2Ph, O, S, SO_2, S-S, CH_2-O, C(OMe)=CH, C(OMe)=N.$

was attached *via* the heteroatom as in (126) and (129), singlet nitrenes gave mesoionic structures (127) and (130) whereas triplet nitrenes reacted with alkyl groups to give six-membered rings [e.g., (128)]. Mesoionic heterocycles of this type have been made by photolysis of 2-(2'-azidoaryl)pyridines and by deoxygenation of 2-(2'-nitroaryl)pyridines and 2-(2'-nitrosoaryl)pyridines with triethyl phosphite (equation 19).

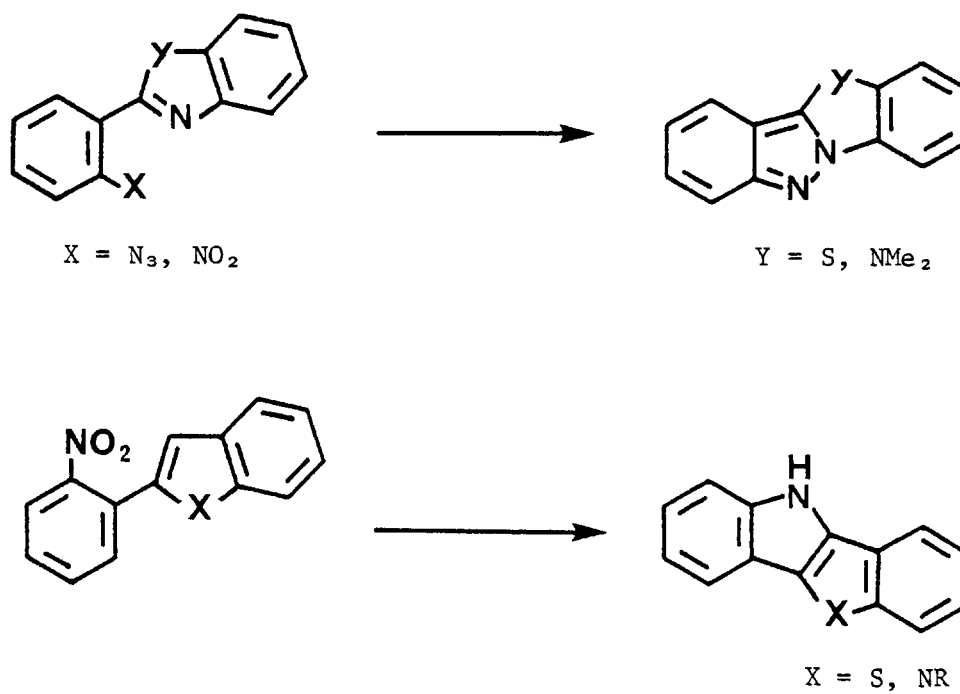


Triplet nitrenes cannot insert into adjacent methyl groups in a concerted manner. The mechanism is most likely to be stepwise by initial H[•] abstraction, followed by spin pairing of the diradical, which then cyclises. Dehydrogenation then gives the observed products (124) and (128) (Scheme 17).

When the adjacent heterocycle is attached *via* carbon then the nitrene cyclises to give fused indole and indazole derivatives, or if it is a heteroarylnitrene, fused pyrrole derivatives (Scheme 18).¹⁰



SCHEME 17

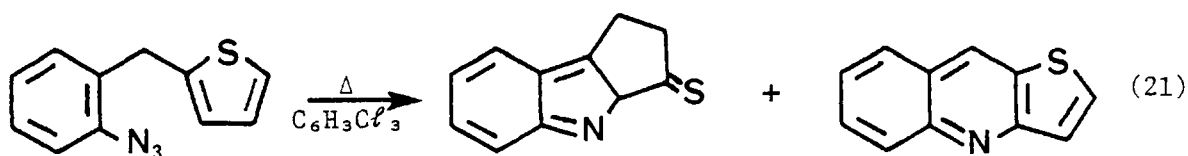
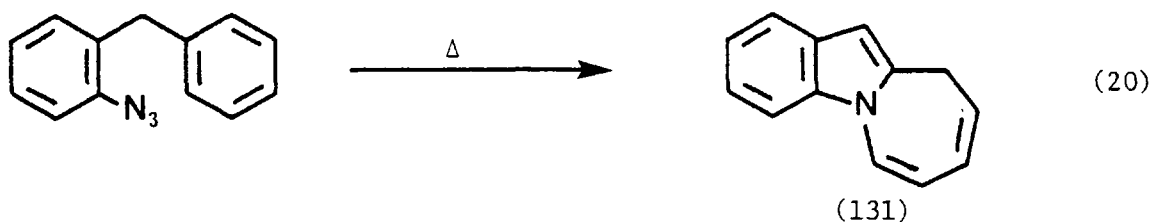


SCHEME 18

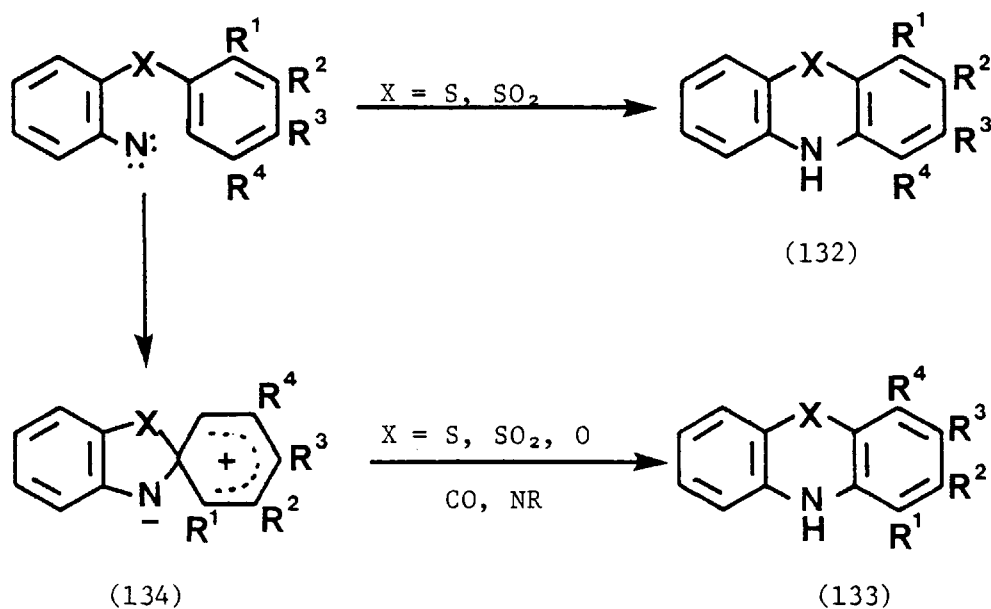
As was the case with vinylnitrenes [Section 1.3.3.(b)], aryl-nitrenes cyclise onto positions of highest electron density (equation 19), and onto the positions which give the most stable products (Scheme 18). Many more examples of the above reactions are described in recent reviews.^{10,12,13,132,136} The arylnitrenes of the type described above can also be formed by carbene-nitrene rearrangement.

(e) Cyclisation between bridged rings.

2-Azidodiphenylmethane gave the 10*H*-azepino[1,2-*a*]indole (131) in 56% yield on pyrolysis in the liquid phase.¹³⁶ This reaction is analogous to the reactions of carbonylnitrenes with aromatic rings (section 1.4.6.), and to the intermolecular reaction of imido-yl-nitrenes with benzene [section 1.5.2.(b)]. This intramolecular reaction of arylnitrenes (equation 20) has recently been observed for electron deficient aromatic rings.¹³⁷ The presence of pyrrol, furyl and thienyl rings on the methylene bridge led to substitution and rearrangement products which contained five- and six-membered nitrogen-containing rings.¹⁰ An example is shown in equation 21.



When the bridging group is S, O, NR, SO₂ or CO then the major products were the fused six-membered heterocyclics (132) and (133) (Scheme 19).¹⁰ Cyclisation with rearrangement *via* a spiro intermediate (134) gave (133), whereas cyclisation without rearrangement gave (132).

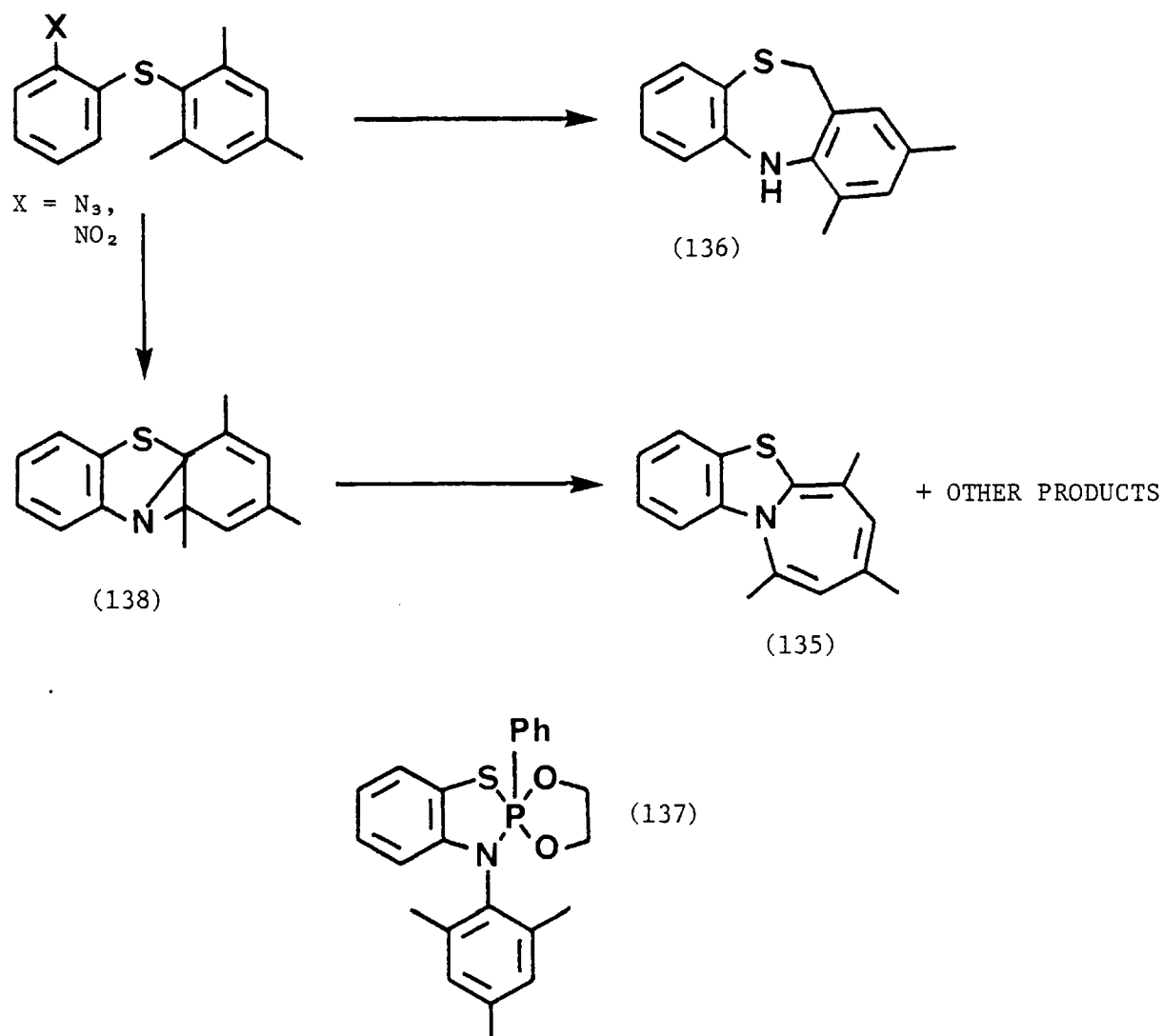


SCHEME 19

The above reactions (equation 20, Scheme 19) are examples of electrophilic attack of a nitrene on an aromatic ring and are analogous to the mechanisms proposed for the intermolecular reaction of ethoxy-carbonylnitrene with thiophenes and pyrroles (section 1.4.7.), and the intramolecular reactions of arylcarbamoynitrenes and aroyl-nitrenes (section 1.4.6.).

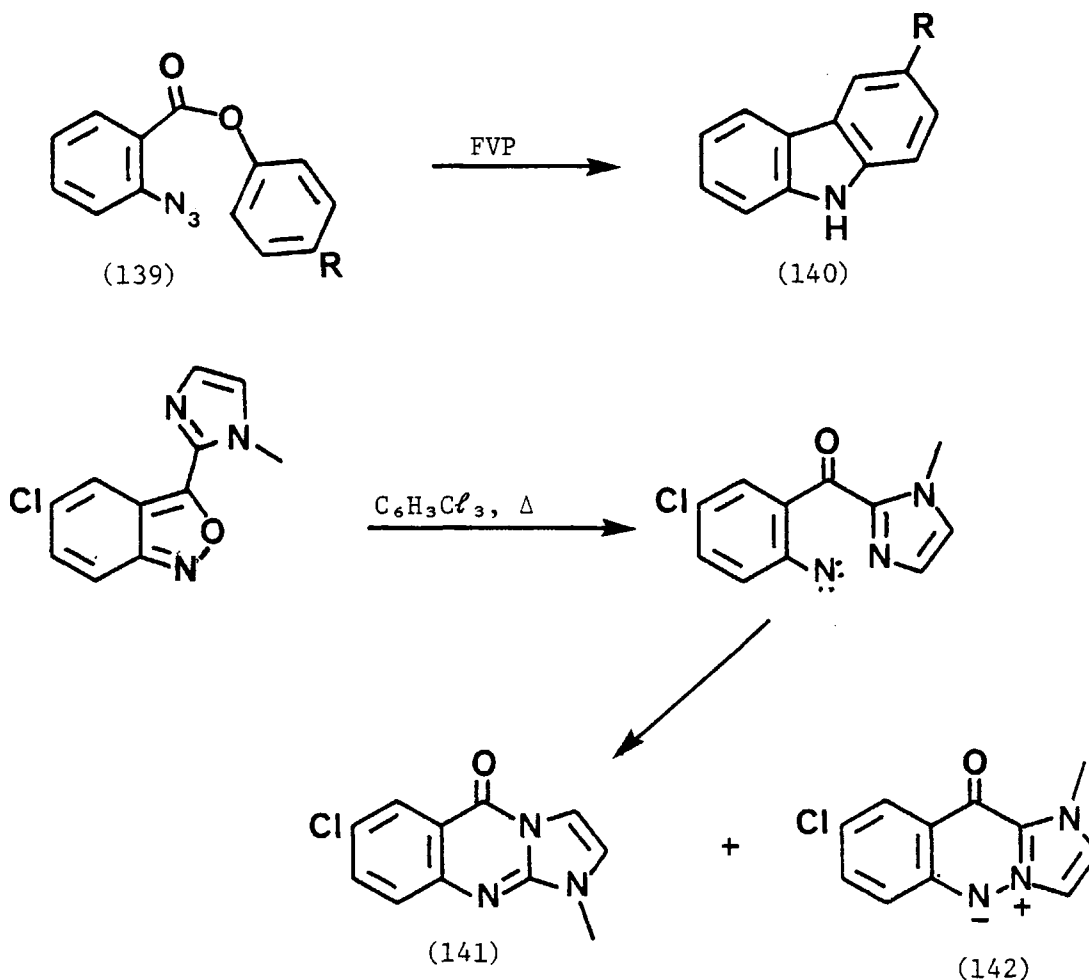
The system which has been most studied is that with a sulphur bridging group.¹³⁸ When the S-aryl chain has *o*-methyl groups then rearrangement gives the azepine (135) and thiazepine (136). Thio-

aminophosphoranes, *e.g.*, (137) were isolated when the nitrene was generated by deoxygenation of nitro groups by trivalent phosphorus reagents. The proposed azepine (135) precursor, a benzaziridine (138) could be formed from the spiro intermediate (134) ($X = S$) or could conceivably be formed directly from the nitrene by addition to the aromatic ring.



Unexpectedly, the *ortho*-azidobenzoate (139) gave carbazoles (140) on flash vacuum pyrolysis.¹³⁹ Cyclisation onto an imidazole ring proceeded *via* rearrangement to give the imidazopyrimidine (141),

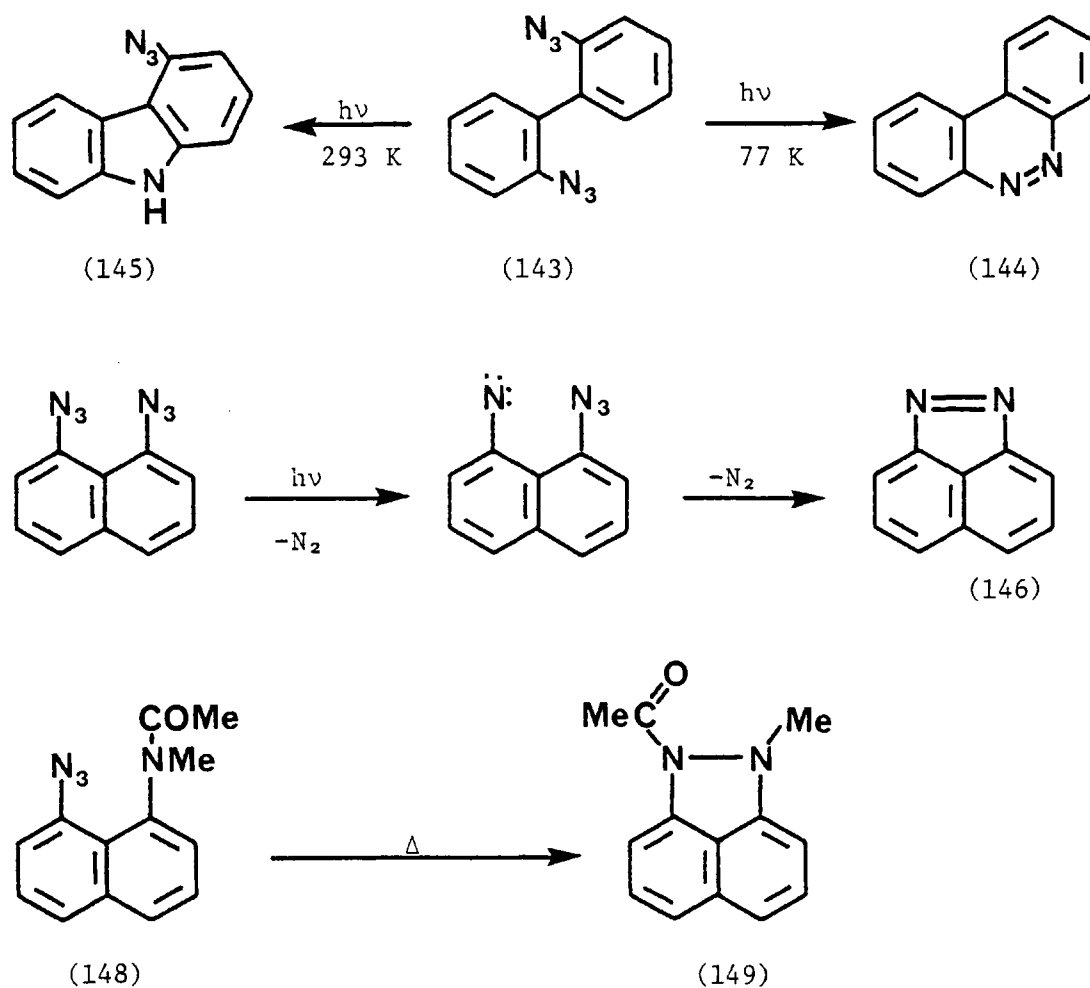
together with small amounts of the product of direct cyclisation onto nitrogen (142).¹⁴⁰ Again, a mechanism involving electrophilic attack of the nitrene onto the hetero-ring can be invoked.



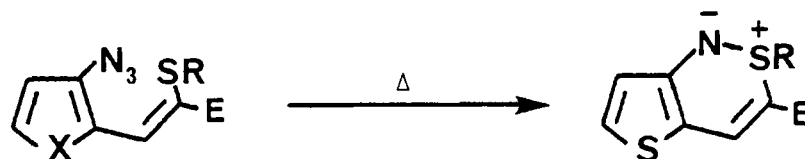
(f) Reaction with nucleophiles.

Arylnitrenes can react intramolecularly with nucleophiles to give a variety of heterocyclic products. The reaction with the heteroatom on an adjacent heterocycle to form mesoionic compounds can be considered as examples of this type of reaction [section 1.6.2.(d)] as can the reactions described in the previous section [1.6.2.(e)] to give spiro

intermediates. Arylnitrenes also react with azido groups, amines and azo groups. Examples of this include the photolysis of the bis-azide (143) at 77 K to give benzo[*c*]cinnoline (144),¹⁴¹ the formation of benzo[*cd*]indazole (146) by irradiation of 1,8-diazido-naphthalene in a matrix at 77 K,¹⁴² and the formation of the dihydro-benzindazole (149) by thermolysis of the azide (148).¹⁴³ Photolysis of the bisazide (143) at room temperature gave the azidocarbazole (145).¹⁴¹



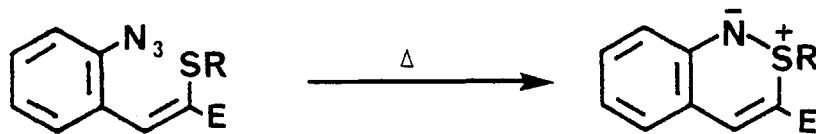
The nitrenes derived from 3-azidothiophenes (150), -furan (151) and arylazides (152) were intercepted by sulphur nucleophiles to give cyclic sulphur-nitrogen ylides, analogous to those described in section 1.3.3.(b).^{69,144}



(150) X = S, R = Me, Ph

80-85%

(151) X = O, R = Ph



(152)

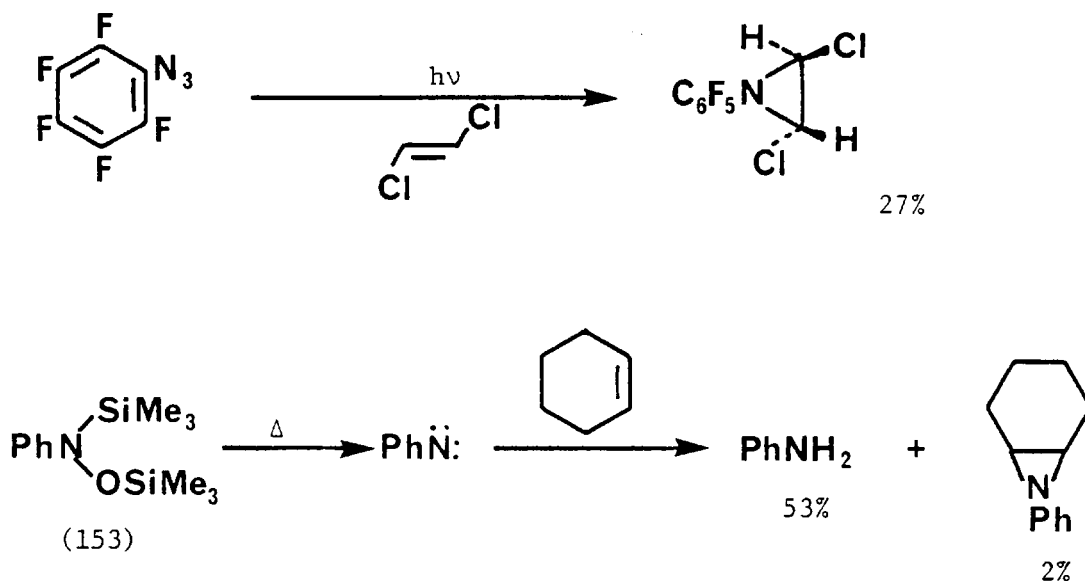
R = Ph, Me

1.6.3. Intermolecular Reactions.

(a) Reactions with alkenes.

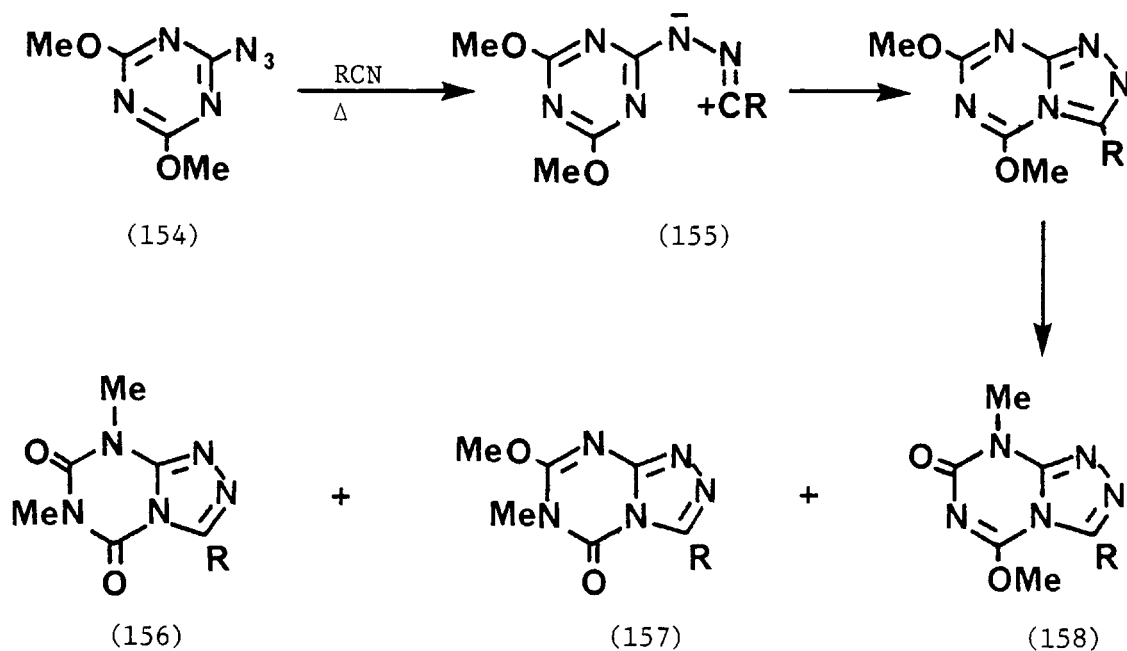
There are few examples of addition of an aryl nitrene to alkenes to give aziridines. Many of the early attempts to generate a nitrene in the presence of an alkene were complicated by the fact that azide precursors added to the alkene to give triazolines at temperatures lower than those required for nitrene formation. Photolysis of pentafluorophenylazide and deoxygenation of nitropentafluorobenzene gave pentafluorophenyl nitrene which added stereospecifically to a variety of alkenes giving aziridines.¹⁴⁵ Similarly phenyl nitrene, generated

by α -elimination of the hydroxylamine derivative (153), added to cyclohexene to give a low yield of the corresponding aziridine.¹⁴⁶



(b) Reaction with nitriles.

The nitrene generated from the azidotriazine (154) reacted with nitriles to give the fused 1,2,4-triazoles (156)-(158), probably in

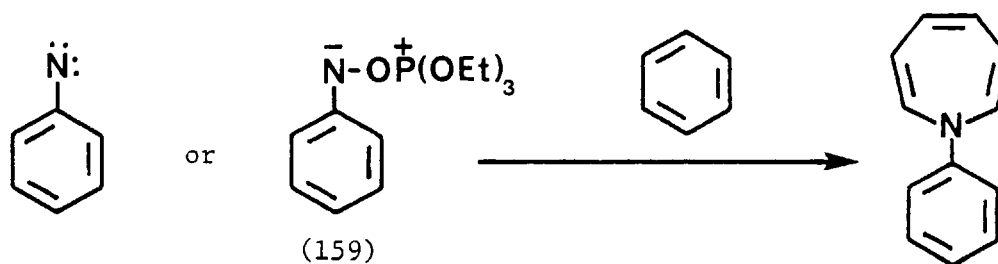


R = Me, Et, Ph

a stepwise manner *via* (155).¹⁴⁷ This reaction is analogous to the reaction of carbonylnitrenes with nitriles (section 1.4.5.).

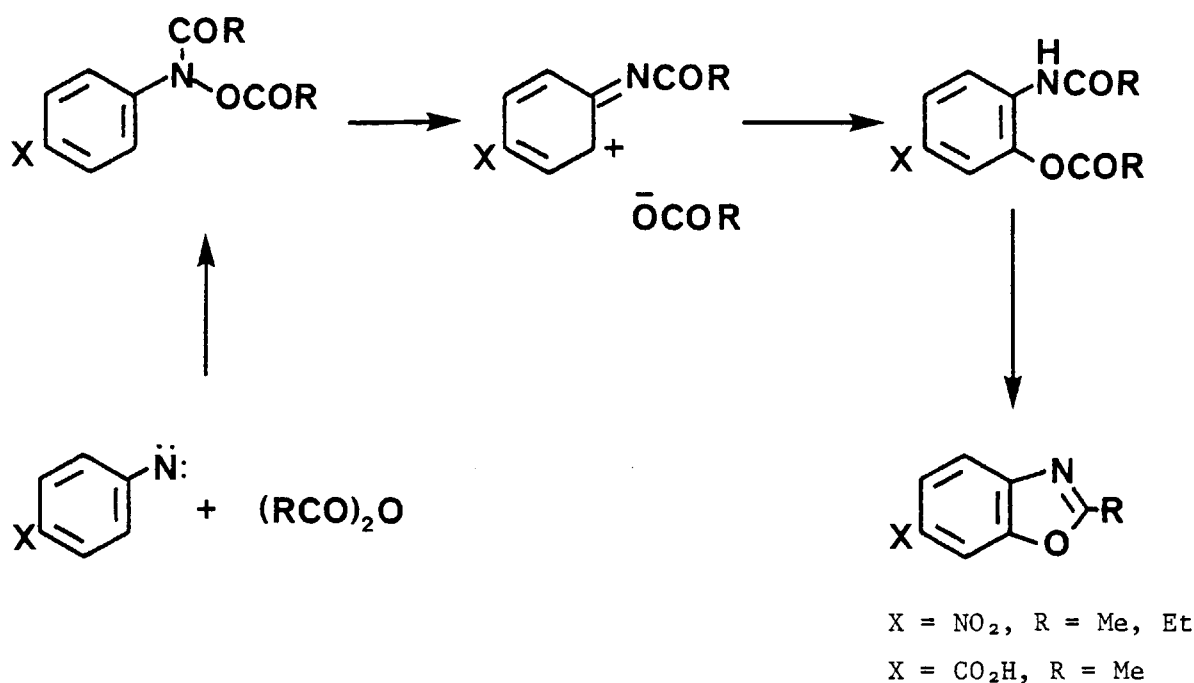
(c) Reaction with benzene.

Intramolecular examples of the addition of nitrenes to benzene rings have already been discussed. The formation of *N*-phenylazepine by deoxygenation of nitrosobenzene in benzene may be an intermolecular example of this reaction.¹⁴⁸ The authors, however, believe that a nitrenoid (159) may be the species involved in the reaction.



(d) Reaction with anhydrides.

Derivatives of phenyl azide substituted by electron-withdrawing groups and with the *p*-position blocked give high yields of 2,6-disubstituted benzoxazoles when decomposed in the presence of anhydrides. The method of decomposition may be either thermal or photochemical, and the anhydride may be preformed or generated in situ by the action of polyphosphoric acid on carboxylic acids. Aryl azides other than phenyl azides have also been used to give a variety of annelated benzoxazoles.^{135,147,148} Representative examples are shown in Scheme 20.



SCHEME 20

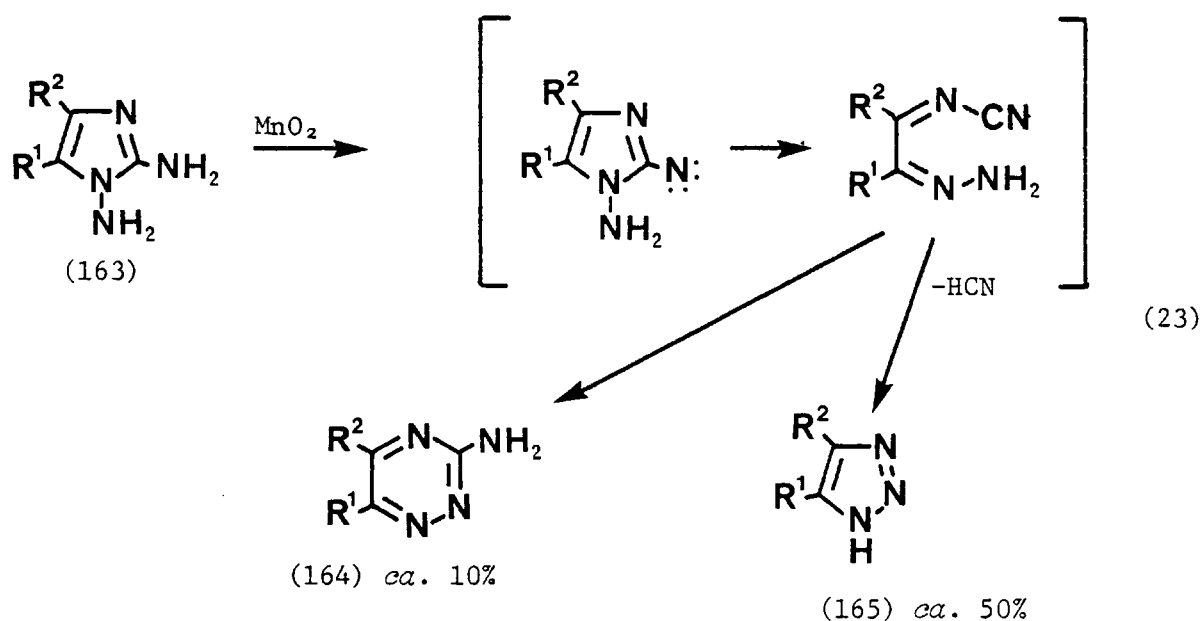
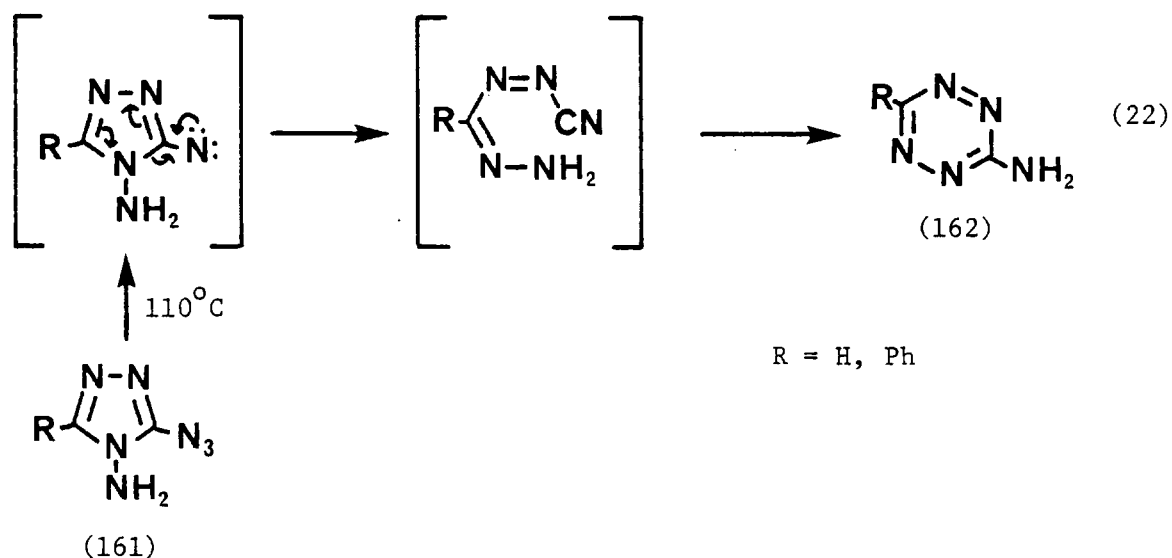
1.6.4. Ring Contraction or Ring Opening.

When no other inter- or intramolecular pathway is available arylnitrenes will undergo ring contraction to a five-membered ring or will ring open. Many five-membered nitrogen-containing rings can be formed in this way (Scheme 21).¹⁰ These reactions are formally analogous to the rearrangements of vinylnitrenes to nitriles (section 1.3.2.), and the ring contraction reactions of annelated imidoaryl nitrenes (section 1.5.3.), though different mechanisms may be involved.

1.6.5. Five-Membered Heteroaryl nitrenes.

The most common reaction of five-membered heteroaryl nitrenes is ring opening.¹⁰ 2-Substituted-3-azidothiophenes (160) ($X = SMe, SPh$), have been described which do not ring open but such thiophene azides

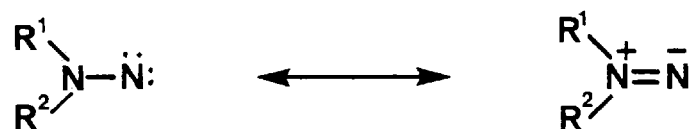
Ring opening reactions were postulated to account for the transformation of the azides (161) into tetrazines (162) (equation 22) and for the formation of triazoles (165) and triazines (164) from diamines (163) (equation 23).¹⁰



1.7. AMINONITRENES (1,1-DIAZENES).

1.7.1. Generation.

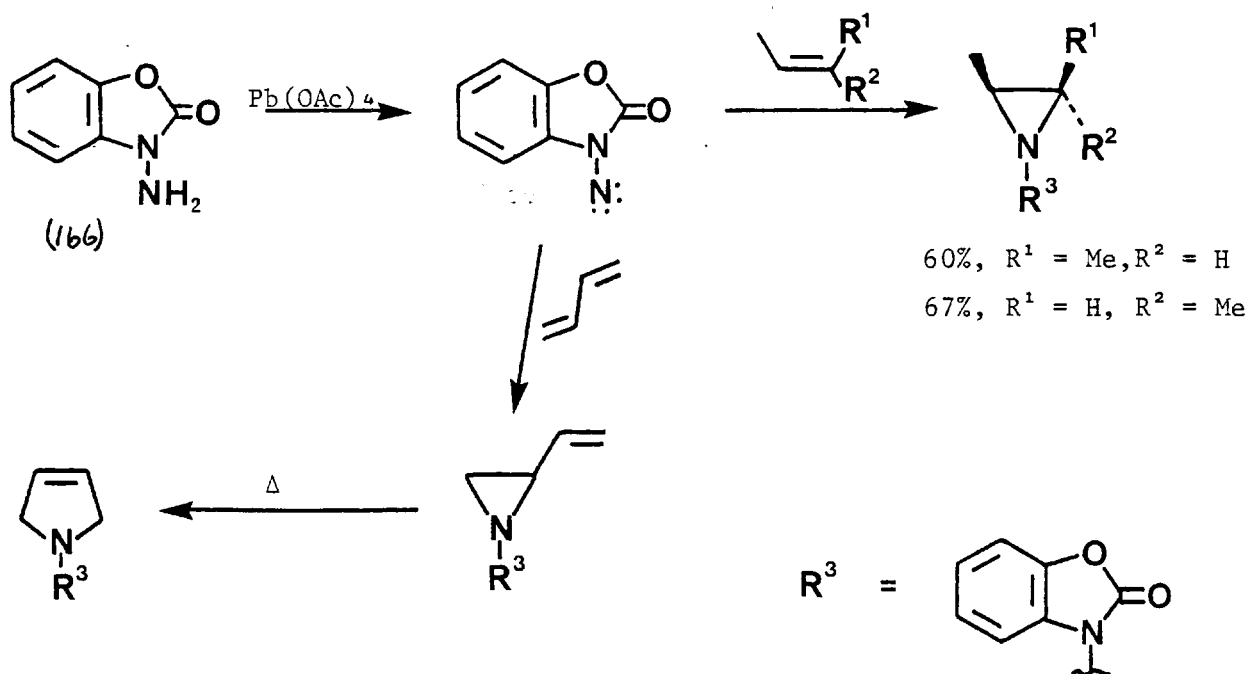
Aminonitrenes are relatively stable, having a resonance stabilised 1,1-diazene form. The ground state is probably a singlet nitrene.



Details of the generation and general reactions of aminonitrenes are contained in several reviews.¹⁵¹⁻¹⁵³ The reactions of cyclic aminonitrenes are similar to those of heteroarylnitrenes in that fragmentation reactions are common.¹⁰

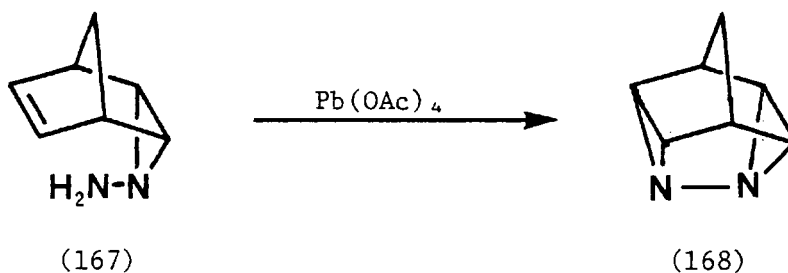
1.7.2. Reaction with alkenes.

Lead tetraacetate oxidation of 3-aminobenzoxazoline in the presence



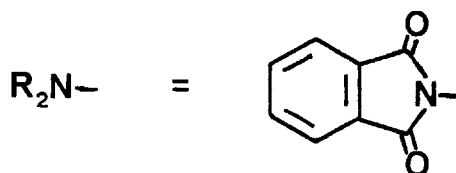
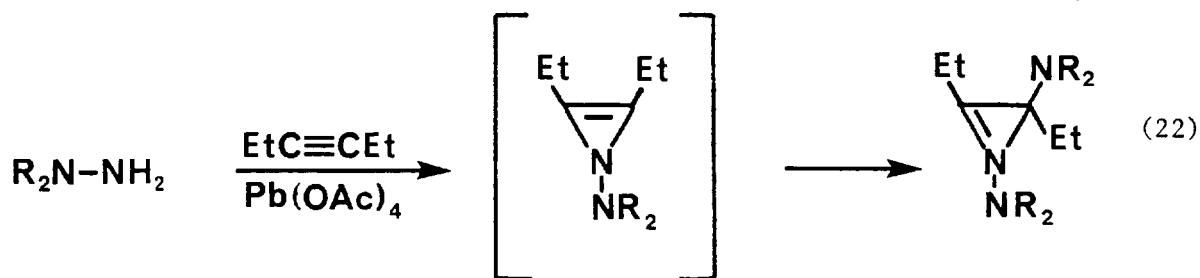
of alkenes and dienes led to aziridine formation, stereospecifically, and in high yield.¹⁵⁴ 1,4-Adducts were not formed but could be prepared from the 1,2-adducts by thermal rearrangement.¹⁵⁵

An intramolecular example of the addition of aminonitrenes to alkenes is the formation of the cage compound (168) by oxidation of the hydrazine (167).¹⁵⁶ Other examples of inter- and intramolecular addition of aminonitrenes to alkenes are contained in the literature.¹⁵⁷



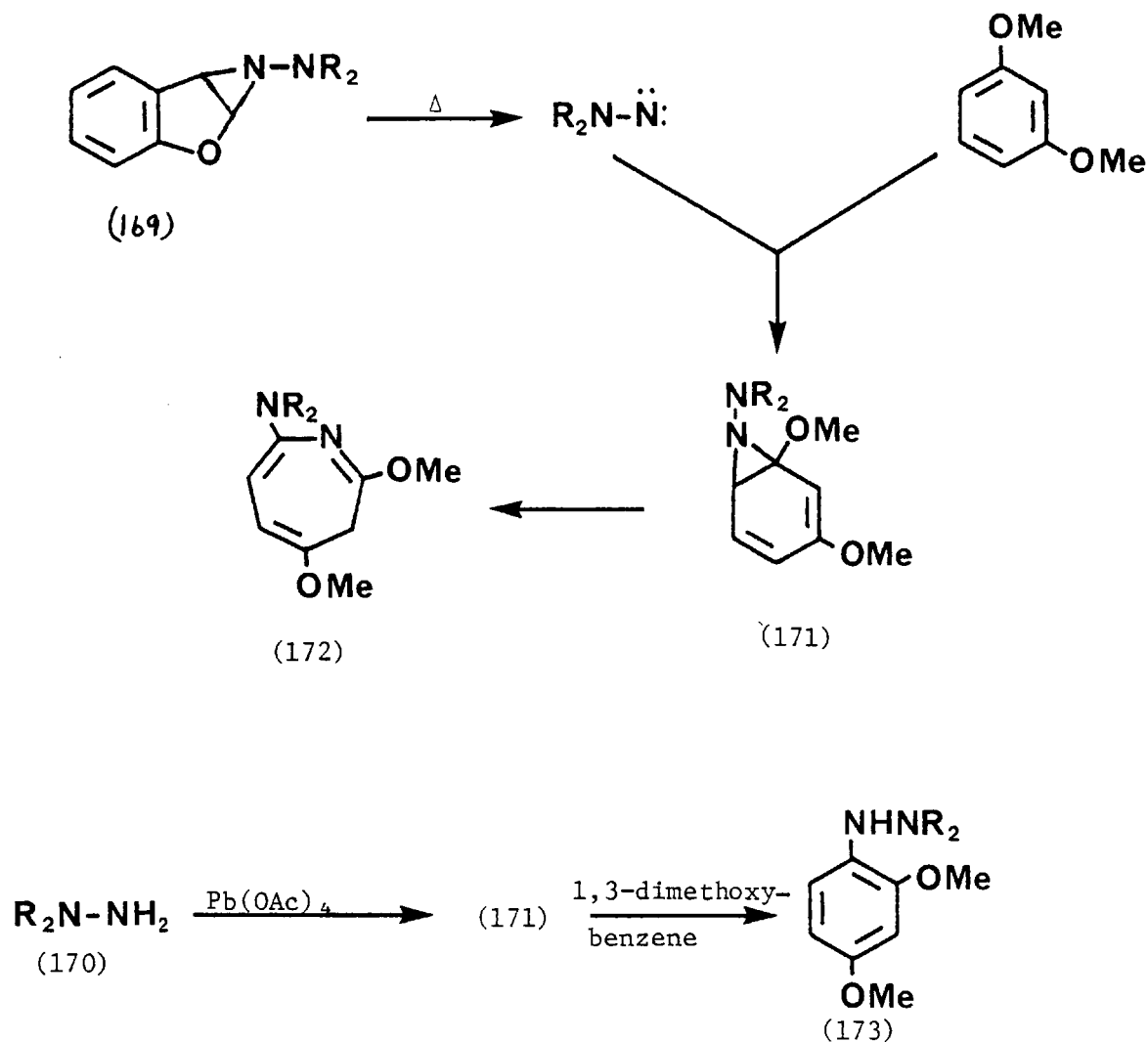
1.7.3. Reaction with acetylenes.

The addition of an aminonitrene to acetylenes initially gave antiaromatic 1*H*-azirines which rapidly isomerised to 2-amino-2*H* azirines (equation 22).¹⁵⁸



1.7.4. Reaction with aromatics.

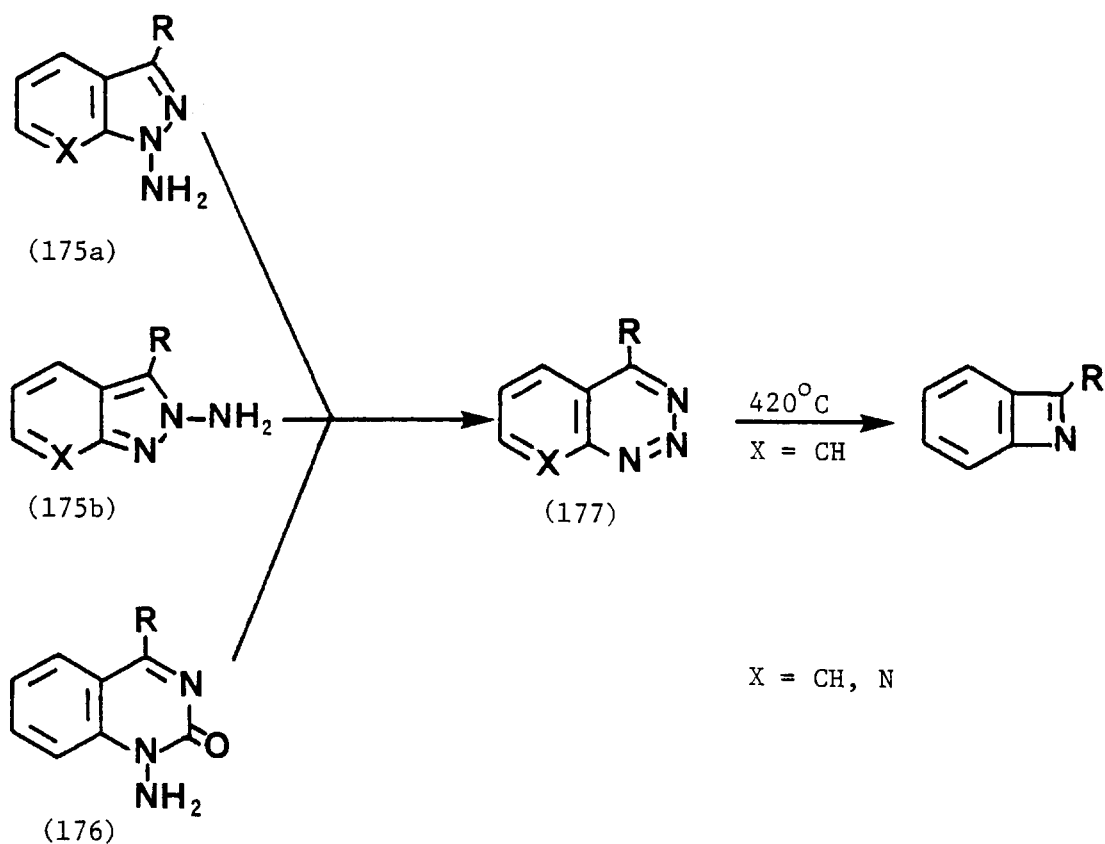
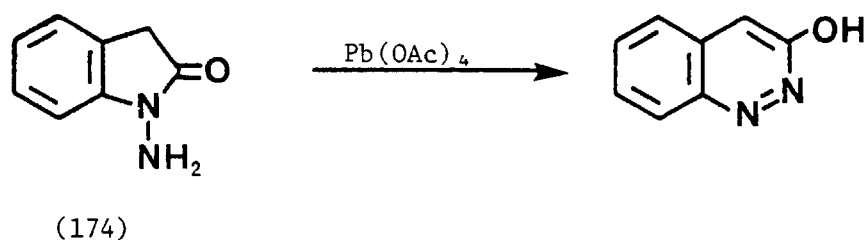
The aminonitrene generated by extrusion from (169), or by lead-tetraacetate oxidation of the hydrazine (170) as before, added to *m*-dimethoxybenzene to give the bicyclic aziridine (171) which rearranged to the azepine (172) or the aniline (173) depending on the method of formation.¹⁵⁹ When the aminonitrene and the aromatic ring were linked then an intramolecular reaction analogous to the formation of aniline (173) occurred.¹⁶⁰



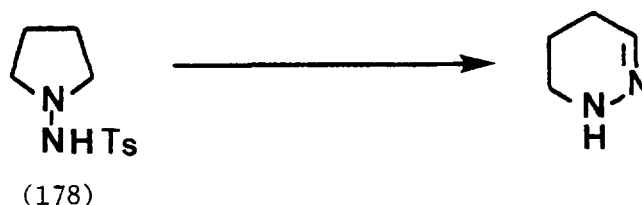
$\text{R}_2\text{N} = \text{Phthalimido}$

1.7.5. Ring expansion.

The major reaction of five- and six-membered cyclic aminonitrenes is to ring open or to fragment. Some five-membered aminonitrenes can rearrange to six-membered heterocyclics. The nitrene derived from 3-aminobenzoxazoline (166) did not fragment whereas the analogous 1-aminoindazole (174) ring expanded on oxidation.¹⁵⁵ Similarly, oxidation of 1- and 2-aminooxindazoles (175 a,b) gave the ring expanded 1,2,3-triazines (177). These were also formed by oxidation of 1-aminoquinazol-2-ones (176).¹⁶¹ Flash vacuum pyrolysis or photolysis of triazines (177) (X = CH) gave benzazetes.¹⁶²



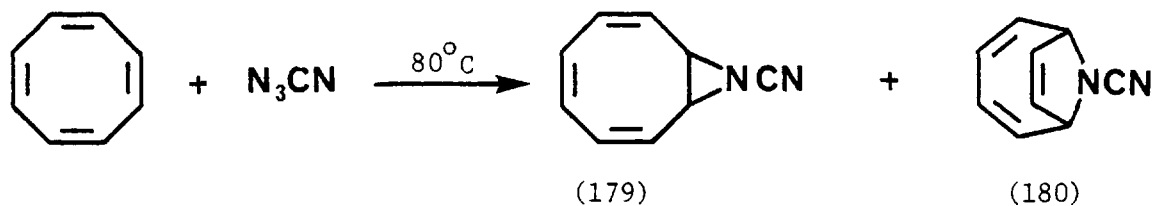
On treatment of the sulphonyl hydrazine (178) with sodium methoxide in methanol 1,4,5,6-tetrahydropyridazine was formed, presumably *via* the aminonitrene.¹⁵²



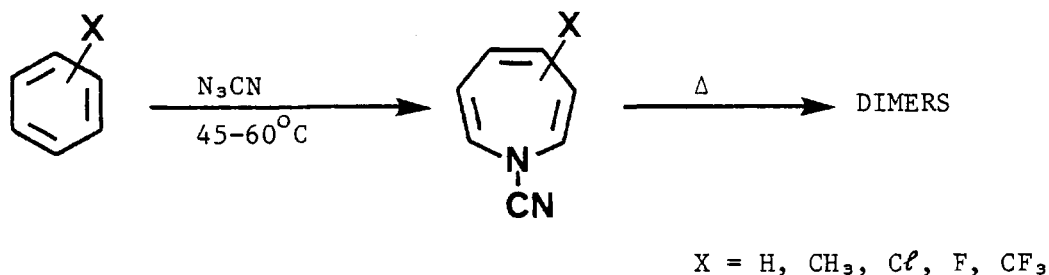
1.8. CYANONITRENE.

1.8.1. Generation and reactions.

Thermal decomposition of cyanogen azide in cyclooctatetraene gave a mixture of products (179) and (180) derived from 1,2- and 1,4-addition of the nitrene. It was shown that (180) is not derived from (179) and it was proposed that (179) was formed from a singlet nitrene and (180) from a triplet nitrene.¹⁶³ The 1,4-addition reaction is very rare.



Cyanogen azide reacted readily with aromatic substrates to give *N*-cyanoazepines.¹⁶⁴



1.9. SULPHONYLNITRENES.

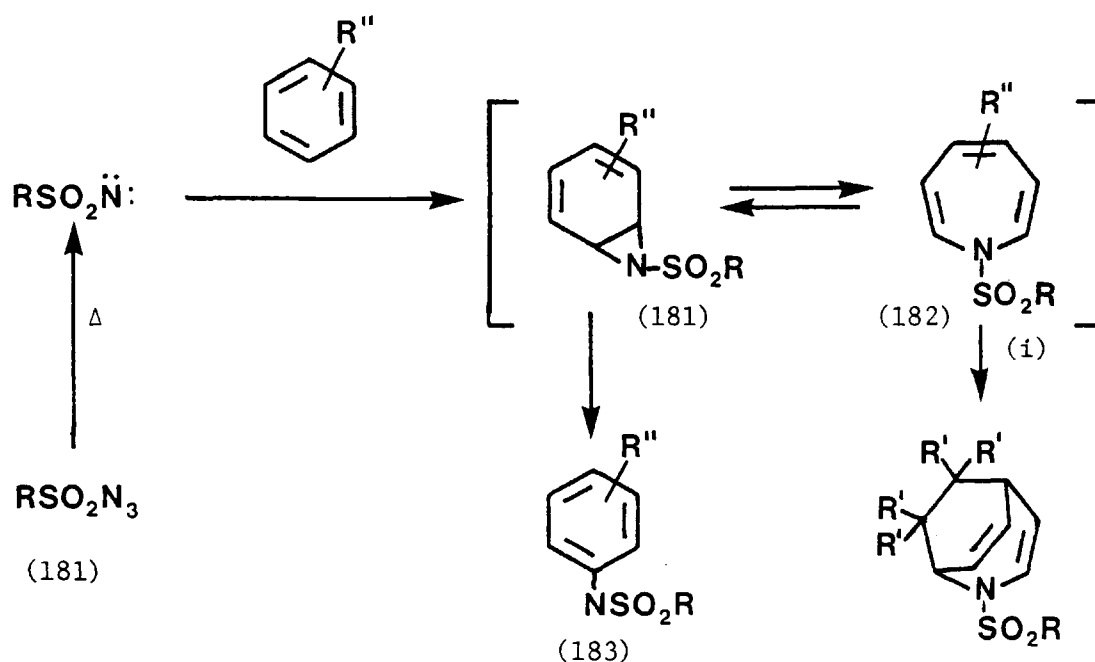
1.9.1. Generation and properties.

Sulphonylnitrenes are usually prepared by thermolysis of the corresponding azides.¹⁶⁵ They rarely undergo a Curtius type rearrangement, but such a rearrangement has been reported in at least one case.¹⁶⁶ The reaction of sulphonyl azides with alkenes to give aziridines is thought not to involve nitrenes. A triazoline may be involved.¹⁶⁵

1.9.2. Reaction with aromatics.

Sulphonyl azides (181) are known to react with aromatic compounds to give azepines (182) which may be trapped by dienophiles. The product of this reaction is usually a sulphonanilide (183) which is formally the result of insertion into an aromatic C-H bond.¹⁶⁵ This is analogous to the reaction of ethoxycarbonylnitrene and imido-yl-nitrenes with aromatics [sections 1.4.6. and 1.5.2.(b)].

Intramolecular reactions of this sort gave six- and seven-membered heterocycles (Scheme 22).¹⁶⁷⁻¹⁶⁹ The reaction of the sulphonylnitrene (184) with the benzene ring did not proceed by rearrangement *via* a spiro intermediate of the type described in section 1.7.2.(e).¹⁶⁷



(i) $\text{R}^1_2\text{C}=\text{CR}^1_2$

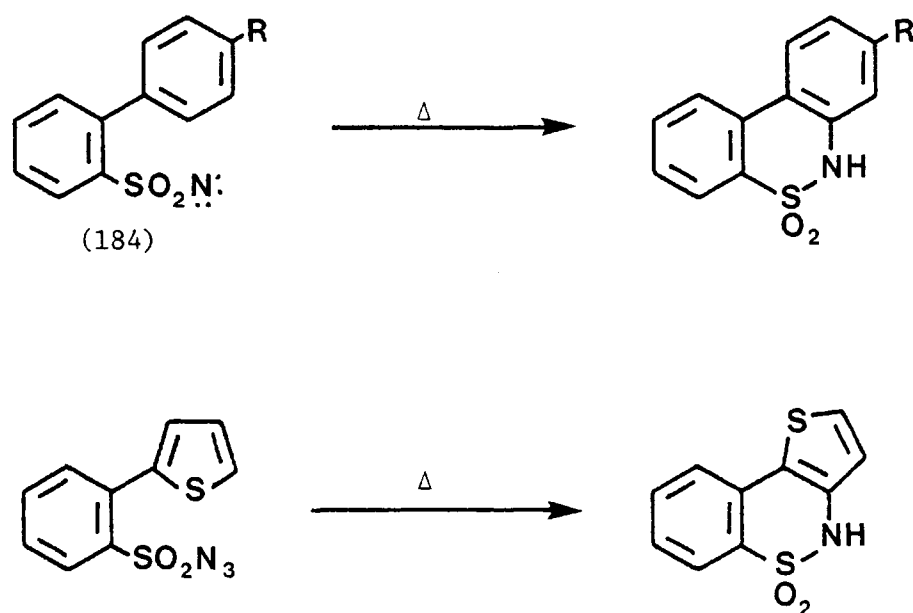
R = alkyl, aryl; $\text{R}^1 = \text{CN}$

Thermolysis of azides (185a,b) gave seven-membered heterocycles

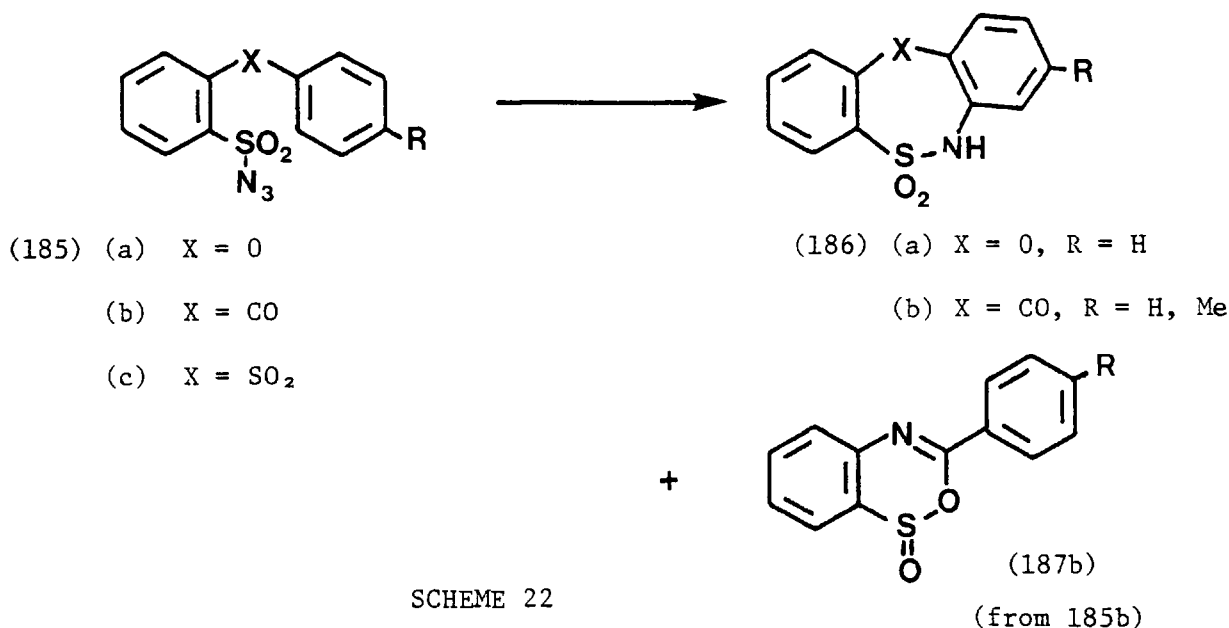
(186a,b), the six-membered heterocycle (187b) by rearrangement, and

products derived from hydrogen abstraction and nitrene insertion into the solvent.¹⁶⁸ Thermolysis of (185c) ($\text{X} = \text{SO}_2$) gave no cyclic

products. See also section 1.9.3.



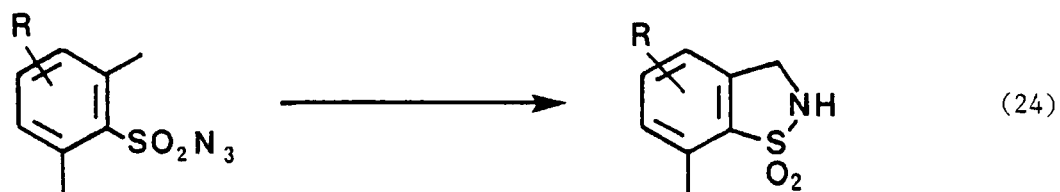
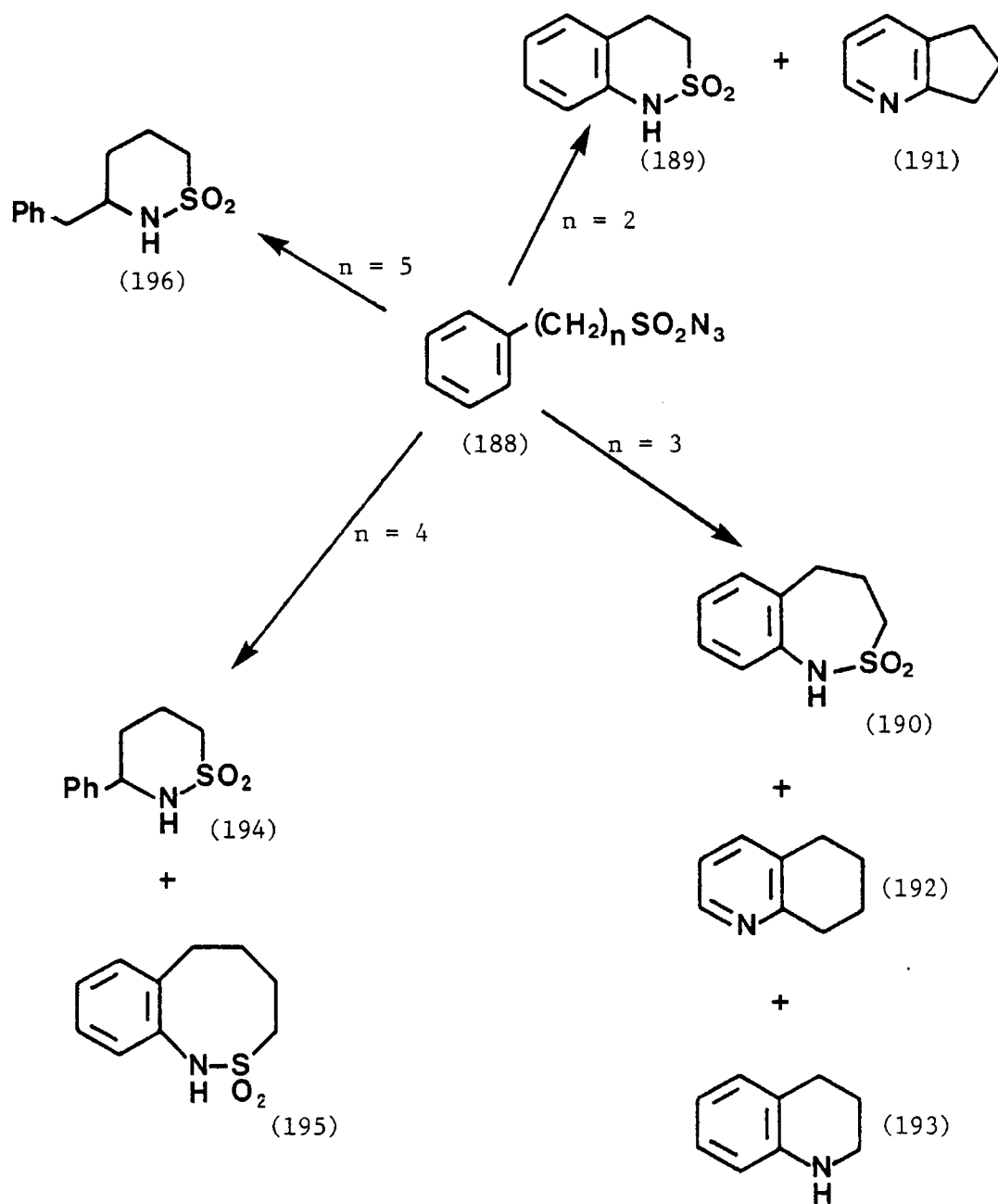
SCHEME 22 (continued overleaf)



1.9.3. Insertion into alkyl C-H bonds.

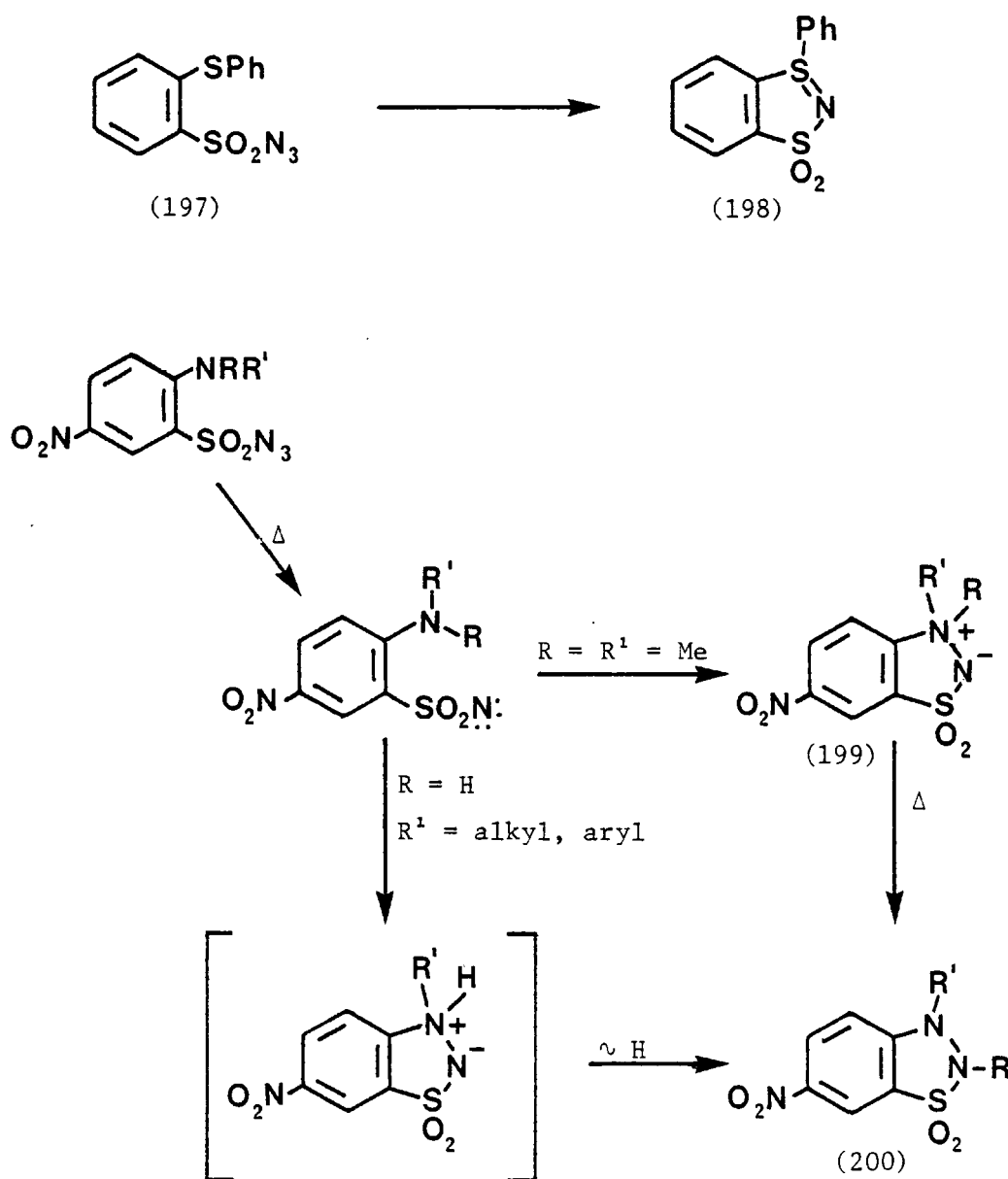
The decomposition of sulphonyl azides (188) ($n = 2-5$) provided more examples of the above reaction, as well as examples of insertion into hydrocarbon C-H bonds, a well known intermolecular reaction of sulphonyl nitrenes.¹⁶⁹ The sulphonyl azides (188) ($n = 2,3$) gave the corresponding sultams (189) and (190) as well as the rearrangement products (191) and (192), and, in the case of (188) ($n = 3$), the tetrahydroquinoline (193), formed at the expense of the sultam at higher temperatures. The pyridines (191) and (192) are thought to be formed *via* nitrene addition to the benzene ring, followed by SO_2 extrusion and ring opening *via* a diradical intermediate.¹⁷⁰ The sulphonyl azide (188) ($n = 4$) gave both the eight-membered sultam (195) as the major product and the six-membered sultam (194) by insertion into the alkyl chain. When $n = 5$ the only observable reaction was side chain insertion leading to the six-membered sultam (196).¹⁷¹

A further example of intramolecular insertion into a saturated C-H bond is the reaction of 2,6-dimethylphenylsulphonylazides to give 2,3-dihydro-1,2-benzisothiazole-1,1-dioxides (equation 24).^{165,166}



1.9.4. Cyclisation onto adjacent heteroatoms.

Unlike its oxygen analogue (185a), in which the nitrene reacted with the adjacent aromatic ring, *o*-(phenylthio)phenylsulphonylazide (197) gave a nitrene which attacked the bridging sulphur atom to give 3-phenylbenzo-1,3,2-dithiazole 1,1-dioxide (198) in 28% yield.¹⁶⁷ Arylsulphonylnitrenes with *o*-amino groups underwent addition to the amino nitrogen atom giving cyclic aminosulphamidates (199) or 2,3-dihydrobenzothiazole dioxides (200).¹⁷²



1.10. SUMMARY.

A variety of cyclic compounds are produced in nitrene reactions. Five- and six-membered rings are those most frequently formed, thus giving a wide range of nitrogen-containing heterocyclics, particularly aromatics. The three-membered rings, azirines and aziridines, and the seven-membered azepines and their analogues can also be formed in good yields. Four- and eight-membered nitrogen-containing rings are rarely, if ever, made by nitrene reactions.

The different types of reactions outlined in section 1.1 will now be considered briefly and their utility or otherwise in heterocyclic synthesis discussed.

(1) Hydrogen abstraction.

This reaction leads to cyclic products only when it is the first step in the insertion of a triplet nitrene into a C-H bond.

(2) Insertion reactions.

The most useful applications of this reaction are the formal insertion of vinylnitrenes into adjacent methyl groups to give pyridines, the insertion reactions of carbonylnitrenes to give five- and six-membered rings, and the insertion reactions of arylnitrenes into saturated sidechains to give indolines, benzimidazoles, and benzimidazolines. Formal insertion of triplet arylnitrenes into alkyl groups on adjacent rings is a potentially useful reaction but few examples are known. Sulphonylnitrenes also insert intramolecularly but often the yields of insertion products are not synthetically useful. Insertion

reactions have not been observed for aminonitrenes or imidoynitrenes, nor do vinylnitrenes insert intermolecularly. Low yields of insertion products are obtained from alkylnitrenes. This is possibly due to the fragmentation and rearrangement reactions which are open to these nitrenes, and which compete successfully with insertion reactions.

The formal insertion of many nitrenes into aromatic C-H bonds may proceed *via* initial addition to the ring and thus will not be discussed in this section. [1,X]H shifts followed by cyclisation can also give the products of formal insertion [c.f., vinylnitrenes, section 1.3.3.(b)]. This may not always be the case however, as for example, highly reactive alkylnitrenes may insert directly. The reaction of arylnitrenes with anhydrides has been postulated to occur *via* initial insertion of the nitrene into a C-O bond of the anhydride.

(3) Addition to multiple bonds, including aromatic rings.

This is a general reaction of nitrenes, though it does not always occur both inter- and intramolecularly. Vinylnitrenes do not appear to react with aromatics by addition to the aromatic ring; however, addition to double bonds has been observed. The usual products of addition to C=C bonds are the synthetically useful aziridines. and, by rearrangement, five-membered rings such as pyrrolines.

Addition of nitrenes to aromatic rings followed by ring expansion is probably the most general method of making these seven-membered rings. Both inter- and intramolecular examples of this reaction are known, the intramolecular process being particularly useful in that it yields azepines which would be difficult to obtain by other methods. If ring expansion does not occur then aromatic amino compounds are formed - the products of formal insertion into an aromatic C-H bond.

Nitrene additions to triple bonds such as acetylenes and nitriles are not quite as common. The reaction with nitriles is thought either to be a stepwise process involving initial nucleophilic attack of the nitrile N on the nitrene N, or cycloaddition of the nitrene onto the nitrile.

(4) Isomerism.

The isomerism described in section 1.1 between nitrenes and azirines or their analogues is known only for the vinylnitrene-azirine equilibrium. It is quite likely that such an equilibrium exists between arylnitrenes and benzazirines, but such benzazirines cannot be isolated. While equilibria have been proposed to exist between imidoynitrenes and diazirines, and acylnitrenes and oxazirines, there is as yet no concrete evidence for such intermediates.

(5) Rearrangement of nitrenes.

This can be the most facile reaction of some nitrenes. Alkyl-nitrenes rearrange so fast that few other inter- or intramolecular reactions occur. It is also an important reaction for some vinyl- and imidoynitrenes. The imines, ketenimines, and carbodiimides formed are synthetically useful, in particular the carbodiimides which can be trapped to give a variety of heterocyclic products.¹⁰ The rearrangement of carbonyl azides to isocyanates is not thought to occur *via* nitrenes but is a convenient synthesis of isocyanates. Sulphonylnitrenes rarely rearrange, but certain cyclic aminonitrenes rearrange in good yield to six-membered rings.

(6) Electrocyclic reactions.

Electrocyclic reactions are not possible for alkyl-, carbonyl-, amino-, cyano-, and sulphonylnitrenes. They are confined to vinyl-, imido-, and aryl nitrenes, and they are often the major reactions of these species. Phenyl nitrenes with *o*-vinyl, imido, and phenyl groups cyclise readily to give indoles, benzimidazoles, and carbazoles respectively. Analogous compounds can be made with other aryl nitrenes. Various nitrene precursors can be used, and the reactions are usually high yielding.

High yields of 1,2,4-oxadiazoles, 1,2,4-oxathiadiazoles, imidazoles, and benzimidazoles can often be obtained by cyclisation of *N*-acyl-, *N*-thioacyl-, *N*-alkenyl-, and *N*-arylimidoynitrenes respectively. Cyclisation of 8-substituted vinylnitrenes gives isoxazoles, pyrazoles, pyrroles, indoles and azepines.

(7) Dimerisation.

This is usually an intermolecular reaction of triplet aryl nitrenes which does not give rise to heterocyclic products.

(8) Reaction with nucleophiles.

Vinyl-, aryl-, and sulphonylnitrenes can be trapped intramolecularly by sulphur and nitrogen nucleophiles. Carbonylnitrenes can be trapped intramolecularly by oxygen and nitrogen nucleophiles. Heteroaryl-nitrenes can also react as electrophiles with nitriles. Further examples include the intermolecular trapping of vinylnitrenes with trivalent phosphorus reagents, of acylnitrenes with sulfoxides, and of imidoynitrenes with sulfoxides and phosphorus reagents, though these reactions do not lead to the formation of new rings. The

reactions of arylnitrenes and carbonylnitrenes with aryl groups to which they are not conjugated can be considered to occur by electrophilic attack of the nitrene on the aromatic ring. Carbonylnitrenes can react intermolecularly in a similar manner with thiophenes and pyrroles.

Alkylnitrenes and aminonitrenes appear not to react with nucleophiles. The unsubstituted N atom of an aminonitrene is nucleophilic, protonating easily, unlike all other nitrenes. Cyanogen azide reacts with Lewis bases to give ylides, but such reactions do not appear to involve cyanonitrene.¹⁷³

The most useful nitrenes for heterocyclic synthesis appear to be aryl-, carbonyl-, imido-, and vinylnitrenes. The major use of alkylnitrenes is the formation of cyclic imines. The synthetic usefulness of amino-, cyano-, and sulphonylnitrenes is limited, although fragmentation reactions of aminonitrenes are useful in non-heterocyclic synthesis (*e.g.*, benzyne formation).

PART II

RESULTS AND DISCUSSION

CHAPTER TWO

PREPARATION OF ALDEHYDES AND VINYL AZIDES

CHAPTER TWO: PREPARATION OF ALDEHYDES AND VINYL AZIDES

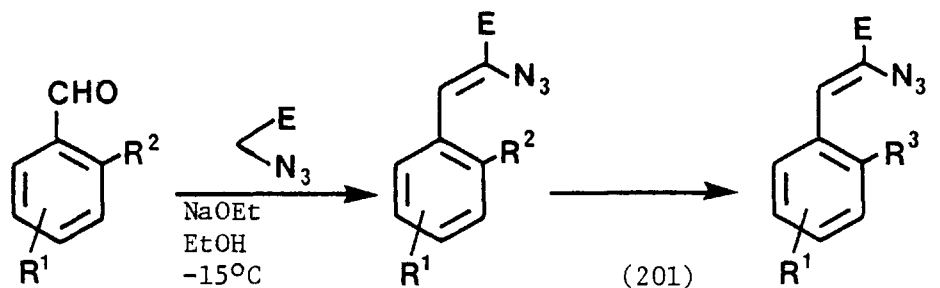
2.1. INTRODUCTION

The purpose of this investigation was to examine the thermal and photochemical decomposition reactions of some *o*-substituted azido-cinnamates (201). The thermal reactions of azidocinnamates with *o*-alkyl groups are described in Chapter 3, those of the azidocinnamates with *o*-alkenyl groups in Chapter 4 and those of the azidocinnamates with *o*-carbonyl groups in Chapter 5. The photochemical work undertaken is described in Chapter 6.

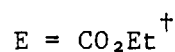
The reason why particular azidocinnamates were chosen will be explained in each of the Chapters. This Chapter will deal solely with their preparation, and will also describe some of the difficulties encountered in the attempted preparation of some aldehydes and vinyl azides.

Most of the vinyl azides were prepared by condensation of the appropriate aldehyde with ethyl azidoacetate in ethanolic sodium ethoxide solution.^{46,174} The yields of these reactions will be detailed in section 2.3. . Some of the vinyl azides were prepared from other vinyl azides by modification of the *o*-substituent (section 2.4.).

The stereochemistry about the vinyl bond is not known but is assumed to be *Z*, as written in Scheme 23, the thermodynamically more stable isomer. This is based on analogy with α -azidovinylketones which have the *Z*-configuration, and on consideration of the instability of certain vinyl azides which have two bulky groups (*e.g.* phenyl and



SCHEME 23



ester) *cis* to one another.³⁷ Throughout this work vinyl azides will be written in the *Z*-form.

2.2. PREPARATION OF ALDEHYDES

The precursors which were found to be most useful in aldehyde synthesis were aryl halides and aryl carboxylic acids, the former by formation of the corresponding Grignard reagent followed by reaction with DMF, and the latter by reduction to the corresponding alcohol, followed by oxidation to the required aldehyde.

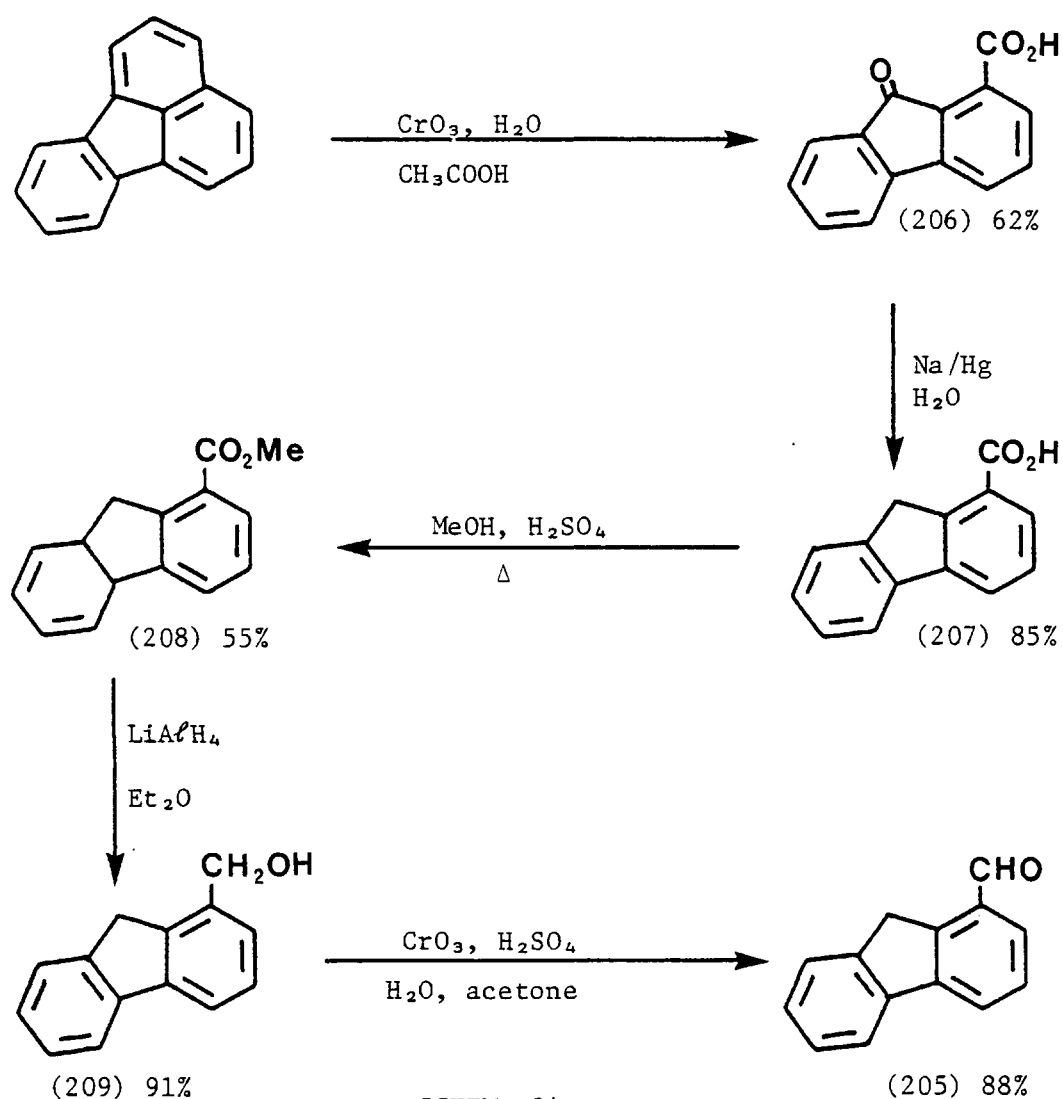
(a) The following aldehydes were purchased:- pyridine-2-carbaldehyde (203), 2-tolualdehyde (211), 2-formylbenzoic acid (228), and benzaldehyde (230).

(b) 2-Benzyloxybenzaldehyde (202)¹⁷⁵ was prepared by treatment of salicylaldehyde with benzyl chloride in the presence of potassium carbonate in refluxing acetone, a modification of a literature procedure for alkylating phenols.¹⁷⁶

[†]See footnote in section 1.3.2.

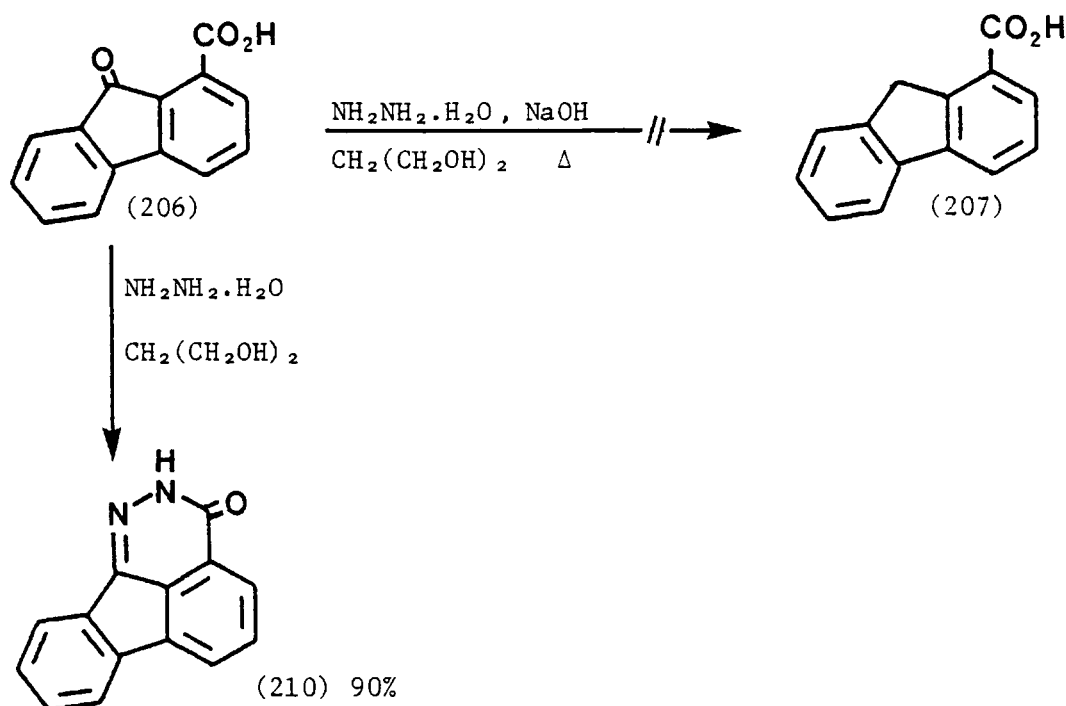
(c) 2-Benzylbenzaldehyde (204)¹⁷⁷ was prepared by the carbonylation of the Grignard reagent of 2-bromodiphenylmethane¹⁷⁷ with DMF, followed by acid work-up.¹⁷⁸

(d) Fluorene-1-carbaldehyde (205)¹⁷⁸ was prepared as outlined in Scheme 24.



The oxidation of fluoranthene to fluorenone-1-carboxylic acid (206)¹⁷⁹ proceeded smoothly. Some authors¹⁸⁰ have reported the failure of the Wolff-Kishner method for the reduction of the keto acid (206) but others¹⁸¹

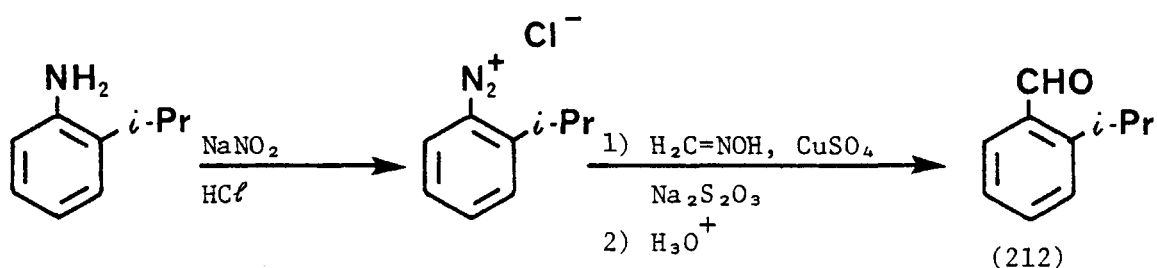
claim high yields of the acid (207) by this method. Several attempts to reduce the keto acid (206) by the Huang-Minlon modification of the Wolff-Kishner reaction¹⁸⁰ failed; intractable tars were formed. On treatment of the keto acid (206) with hydrazine hydrate in an attempt to form the hydrazone, the pyridazolone (210)¹⁷⁹ was formed in 90% yield.



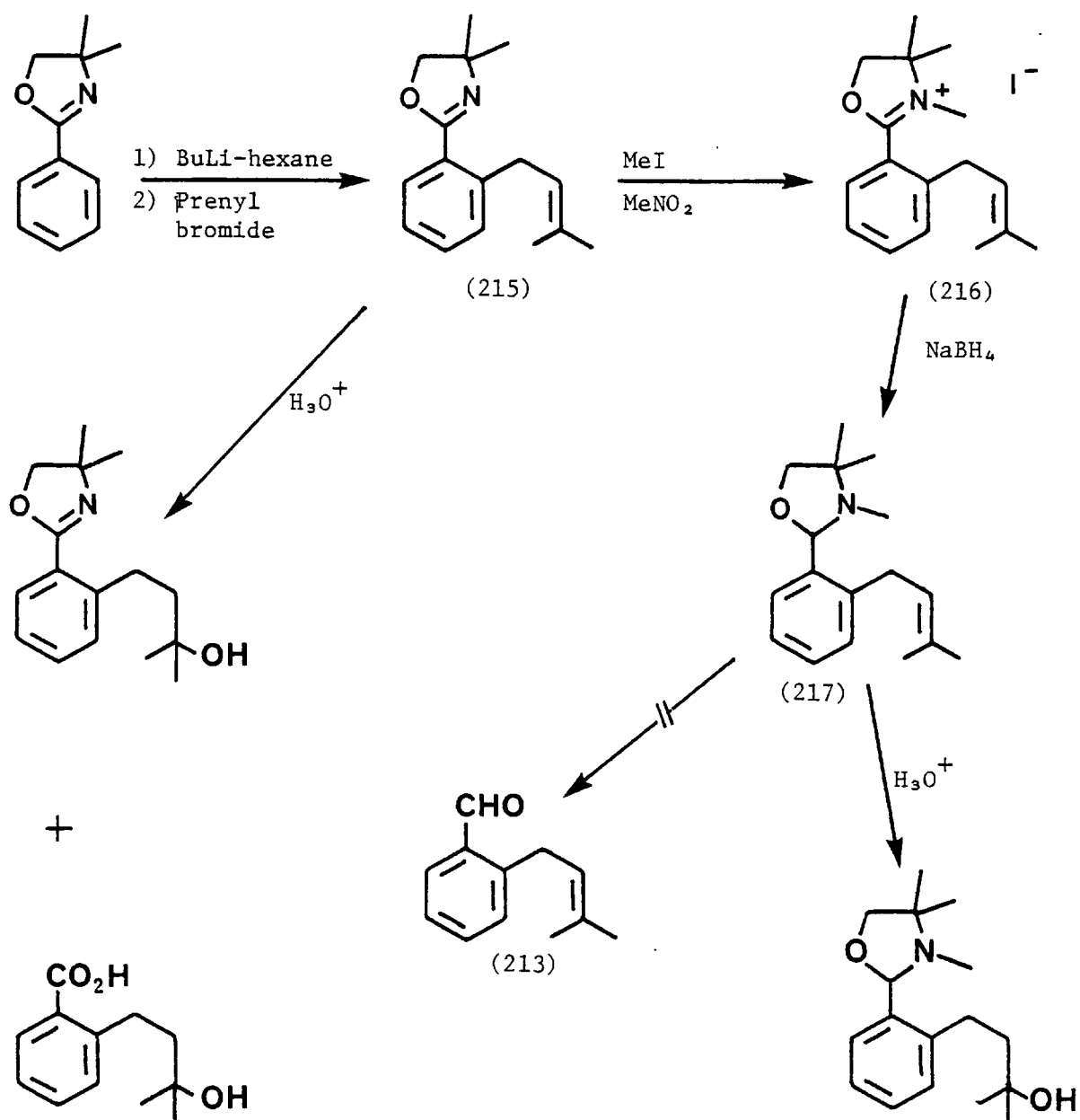
The keto acid (206) was reduced to fluorene-1-carboxylic acid (207) using sodium amalgam.¹⁷⁹

Attempts to reduce fluorene-1-carboxylic acid (207) with lithium aluminium hydride failed. A mixture of six to eight products was obtained. However, reduction of methyl fluorene-1-carboxylate (208)¹⁸² with lithium aluminium hydride in ether gave fluorene-1-methanol (209)¹⁸² (91%) which was then oxidised using the Jones reagent to fluorene-1-carbaldehyde (205) (88%).¹⁸¹

(d) 2-Isopropylbenzaldehyde (212)¹⁸³ was prepared from 2-isopropylaniline by a general procedure used for transforming anilines to benzaldehydes. This involves diazotisation of the aniline, followed by treatment with formaldoxime and acid hydrolysis (equation 25).¹⁸⁴



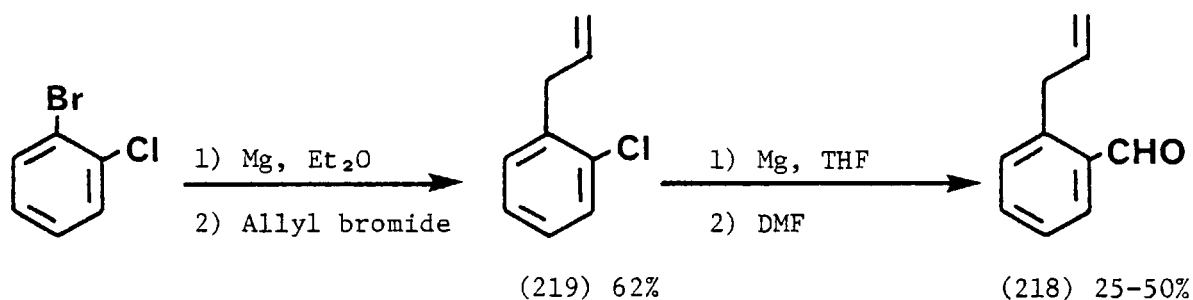
(e) 2-(3-Methylbut-2-enyl)benzaldehyde (213). An unsuccessful attempt was made to prepare the benzaldehyde (213) (Scheme 25). 1-Bromo-3-methylbut-2-ene ('prenyl bromide') (214) was prepared by reaction of isoprene with hydrogen bromide in glacial acetic acid. 4,4-Dimethyl-2-phenyl- Δ^2 -oxazoline¹⁸⁵ was treated with *n*-butyllithium³⁵ followed by the bromide (214) to give 4,4-dimethyl-2-[2-(3-methylbut-2-enyl)-phenyl]- Δ^2 -oxazoline (215) (55%). The oxazoline (215) was then *N*-methylated with methyl iodide in nitromethane¹⁸⁶ giving the 2-aryl-3,4,4-trimethyloxazolinium iodide (216) in 74% yield. Reduction with a large excess of sodium borohydride¹⁸⁶ produced the oxazolidine (217) (70-90%). Attempted hydrolysis of the oxazolidine to the required aldehyde (213) in 30% aq. oxalic acid^{35,187} and in 2N hydrochloric acid resulted in hydration of the double bond in the side chain, leaving the oxazolidine ring intact. Treatment of the oxazoline (215) with 3N hydrochloric acid at reflux temperature¹⁸⁵ gave



rise to partial hydrolysis of the oxazoline ring, but the side chain was completely hydrated.

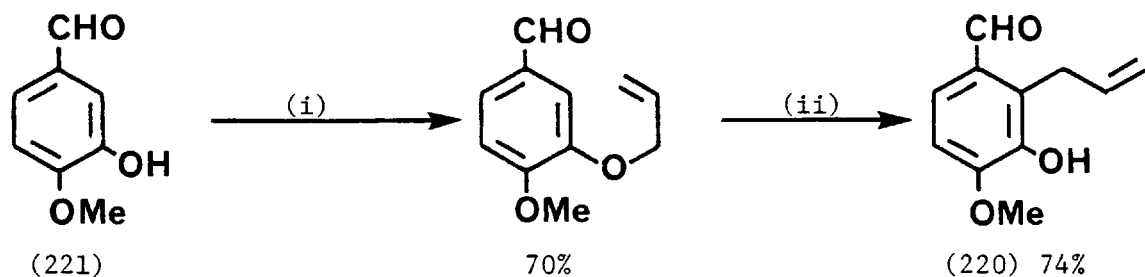
The attempted preparation of the aldehyde (213) was then abandoned.

(f) 2-Allylbenzaldehyde.¹⁸⁸ 2-Allylchlorobenzene (219) was prepared by treatment of 2-bromochlorobenzene with magnesium in ether, thus forming the mono-Grignard reagent, followed by addition of allyl bromide, giving (219) in 62% yield.¹⁸⁹ When this chlorobenzene (219) was added to active magnesium¹⁹⁰ the corresponding Grignard reagent was made which was treated *in situ* with DMF to give 2-allylbenzaldehyde (218) (25-50%) after work up.



The use of 2-bromochlorobenzene to give *o*-disubstituted benzenes appears to be a synthetically useful reaction. The only limitation is that the group first introduced must be stable to both Grignard reagents and mild hydrolysis. This reaction sequence was not applied to the synthesis of 2-(3-methylbut-2-enyl)benzaldehyde (213) as 2-allylbenzaldehyde (218) was used as a substitute, and it was also feared that even mild acid hydrolysis might cause the side chain double bond to hydrate as it had done in the previous attempted synthesis.

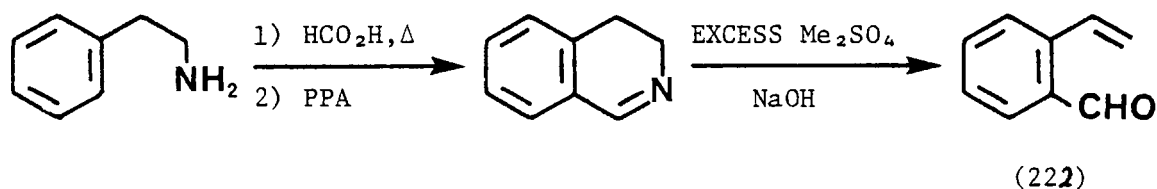
(g) 2-Allyl-3-hydroxy-4-methoxybenzaldehyde (220) was prepared from isovanillin (221) as outlined in Scheme 26.¹⁹¹



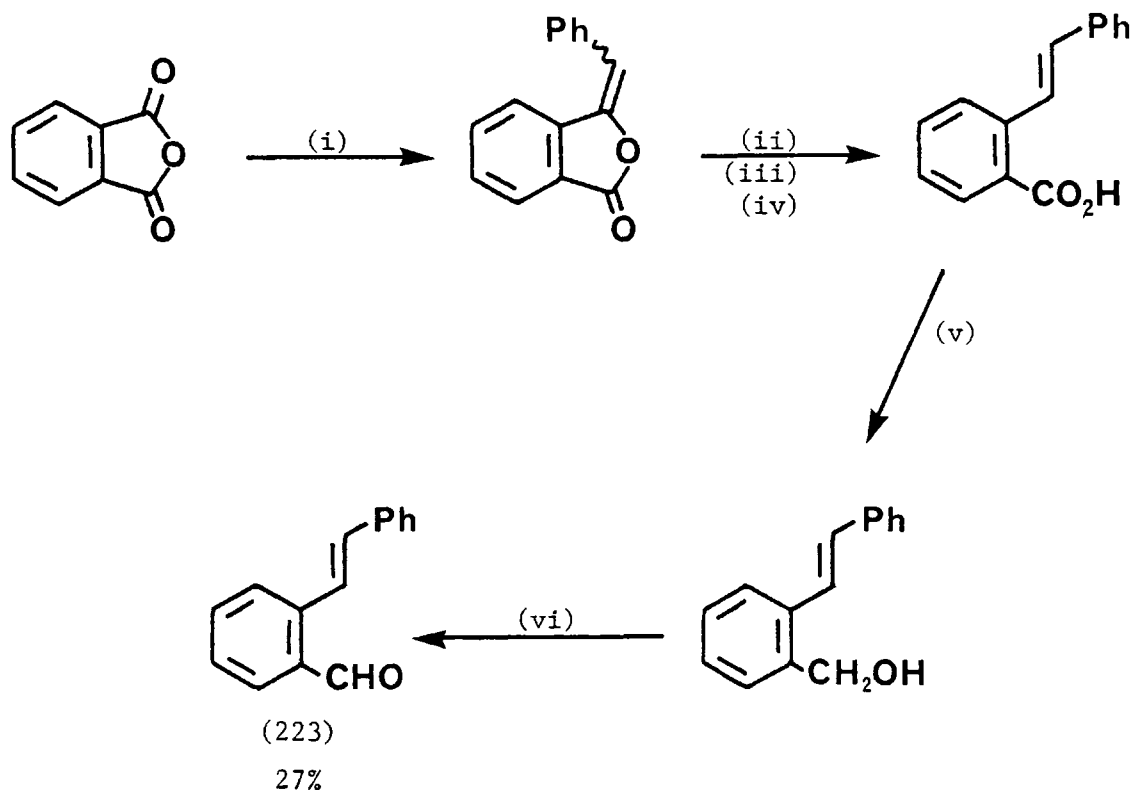
(i) K_2CO_3 , allyl bromide, MeOH, Δ
 (ii) $PhNMe_2$, Δ

SCHEME 26

(h) 2-Vinylbenzaldehyde (222) was prepared by treatment of 3,4-dihydro-isoquinoline with an excess of methyl sulphate in aqueous sodium hydroxide.¹⁹²



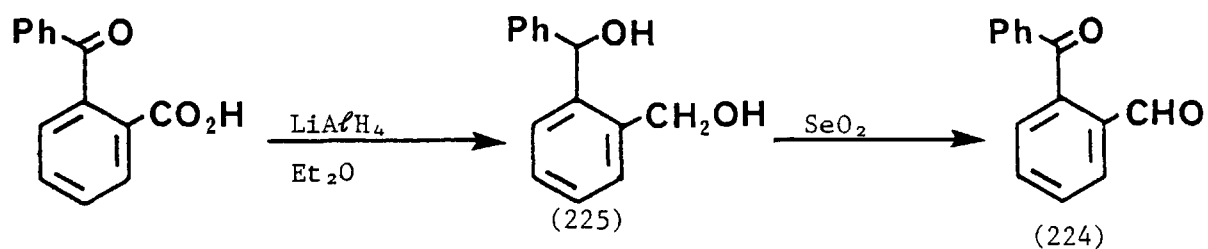
(i) E-Stilbene-2-carbaldehyde (223)¹⁹³ was prepared as shown in Scheme 27 by lithium aluminium hydride reduction of E-stilbene-2-carboxylic acid¹⁹⁴ giving E-stilbene-2-methanol,¹⁹⁵ followed by oxidation with the Jones reagent.



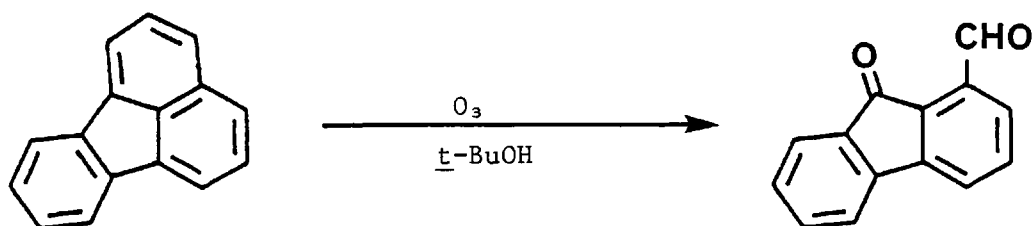
- (i) $\text{PhCH}_2\text{CO}_2\text{H}$, NaOAc , Δ ;
 (ii) Zn , KOH ;
 (iii) KOH , digol;
 (iv) H_3O^+ ;
 (v) LiAlH_4 , diethyl ether;
 (vi) CrO_3 , H_2SO_4 , H_2O .

SCHEME 27

(j) 2-Benzoylbenzaldehyde (224). Commercially available 2-benzoylbenzoic acid was reduced with lithium aluminium hydride to give the diol (225). Oxidation of the diol (225) with selenium dioxide in acetic acid and xylene gave the required aldehyde (224).¹⁹⁶



(k) Fluoren-9-one-1-carbaldehyde (226) was prepared by ozonolysis of fluoranthene.¹⁹⁷



(l) 2-Acetylbenzaldehyde (227) was similarly prepared by ozonolysis of 1-methylnaphthalene.¹⁹⁸

(m) Ethyl 2-formylbenzoate (229)¹⁹⁹ was prepared by esterification of 2-formylbenzoic acid with ethyl iodide in the presence of potassium carbonate.

2.3. PREPARATION OF VINYL AZIDES FROM ALDEHYDES.

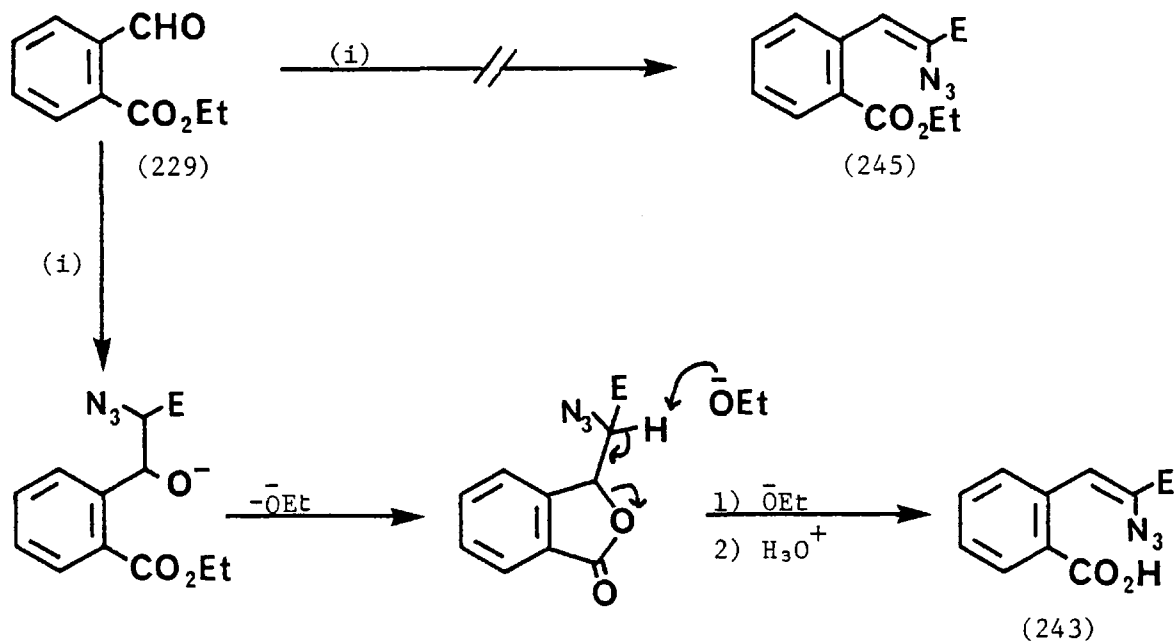
The vinyl azides $ArCH=C(N_3)CO_2Et$, (231)-(243), were prepared from the corresponding aldehydes by the method outlined in Scheme 23. The yields are given in Table 1.

An attempt to condense 2-acetylbenzaldehyde (227) with ethyl azidoacetate failed. The aldehyde was consumed but no recognisable products formed. When ethyl 2-formylbenzoate (229) was treated with ethyl azidoacetate in the presence of sodium ethoxide under the same

TABLE 1. Preparation of azides $\text{ArCH}=\text{C}(\text{N}_3)\text{CO}_2\text{Et}$ from ArCHO .

ALDEHYDE (ArCHO)		AZIDE	YIELD
(202)	$\text{Ar} = 2\text{-PhCH}_2\text{OC}_6\text{H}_4$	(231)	34%
(203)	$\text{Ar} = 2\text{-pyridyl}$	(232)	36%
(204)	$\text{Ar} = 2\text{-PhCH}_2\text{C}_6\text{H}_4$	(233)	56-64%
(205)	$\text{Ar} = 1\text{-fluorenyl}$	(234)	80%
(211)	$\text{Ar} = 2\text{-MeC}_6\text{H}_4$	(235)	54-74%
(212)	$\text{Ar} = 2\text{-}i\text{PrC}_6\text{H}_4$	(236)	63%
(218)	$\text{Ar} = 2\text{-allyl-C}_6\text{H}_4$	(237)	54%
(220)	$\text{Ar} = 2\text{-allyl-3-OH-4-OMe-C}_6\text{H}_2$	(238)	40%
(222)	$\text{Ar} = 2\text{-CH}_2=\text{CHC}_6\text{H}_4$	(239)	28%
(223)	$\text{Ar} = 2\text{-}E\text{-PhCH=CHC}_6\text{H}_4$	(240)	63%
(224)	$\text{Ar} = 2\text{-PhCOC}_6\text{H}_4$	(241)	35%
(226)	$\text{Ar} = 1\text{-fluoren-9-one}$	(242)	7.5%
(228)	$\text{Ar} = 2\text{-HO}_2\text{CC}_6\text{H}_4$	(243)	59%
(230)	$\text{Ar} = \text{Ph}$	(244)	50%

conditions the product isolated was the *o*-carboxyazidocinnamate (243) (41%), not the expected *o*-ethoxycarbonylazidocinnamate (245). It is possible that the hydrolysis occurred *via* an intermediate lactone (Scheme 28).



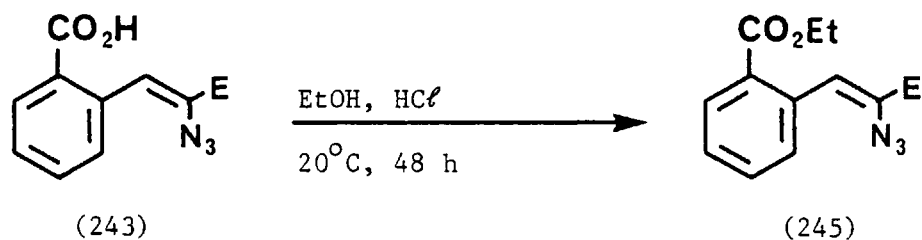
(i) $\text{N}_3\text{CH}_2\text{E}$, NaOEt , EtOH , -15°C

SCHEME 28

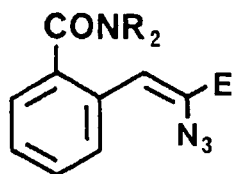
The low yield of the vinyl azide derivative (242) may have been due to the high dilution of the reactants in THF, necessitated by the insolubility of fluorenone-1-carbaldehyde (226). An attempt to condense pyridine-2-carbaldehyde with ethyl azidoacetate in 2% aqueous sodium hydroxide failed and the starting materials were recovered unchanged. An attempt to prepare the anion of ethyl azidoacetate with sodium ethoxide in ether at -78°C caused rapid decomposition of the azidoacetate.²⁰⁰ Thus, even though the method used to prepare the azides (231)-(243) was sometimes low yielding, it was the best of those tried.

2.4. MODIFICATION OF *o*-SUBSTITUENTS IN AZIDOCINNAMATES.

Azidocinnamate (243) has proved to be a useful precursor for other *o*-substituted azidocinnamates. Treatment of the acid (243) with hydrogen chloride gas in ethanol gave the corresponding ethyl ester (245) in 70% yield.



The amide derivatives (246) and (247) were prepared in the following way. The acid (243) was added to a suspension of the DMF/oxalyl chloride complex $[\text{Cl}^+(\text{H})\text{C}=\text{NMe}_2 \text{ Cl}^-]$ in DMF and acetonitrile at -20°C and then treated

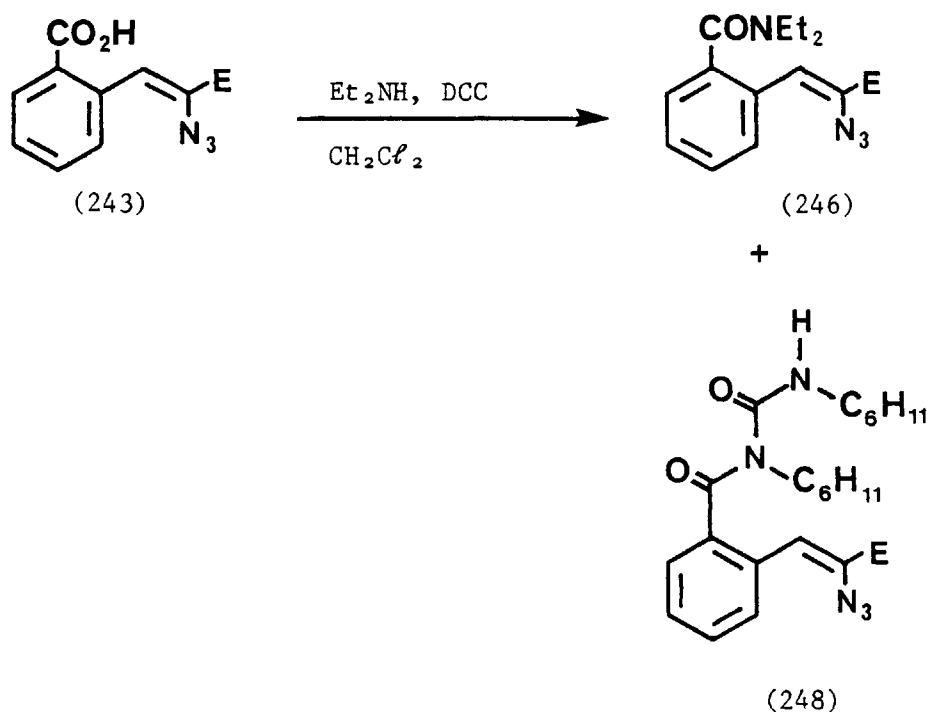


(246) R = Et

(247) R = H

with a solution of diethylamine in acetonitrile.²⁰¹ On warming to room temperature, followed by work-up the amide (246) was isolated in 50% yield. Treatment of the acid (243) and diethylamine with dicyclohexyl-

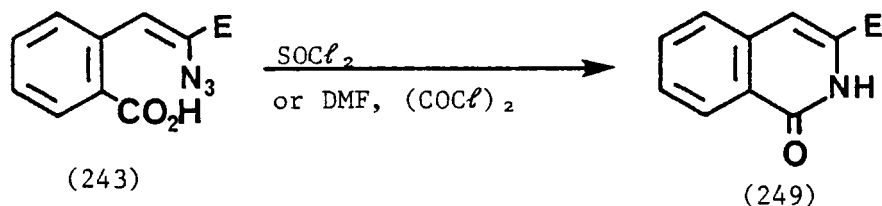
carbodiimide (DCC)²⁰² gave a 2:3 mixture of the amide (246) and the urea (248).



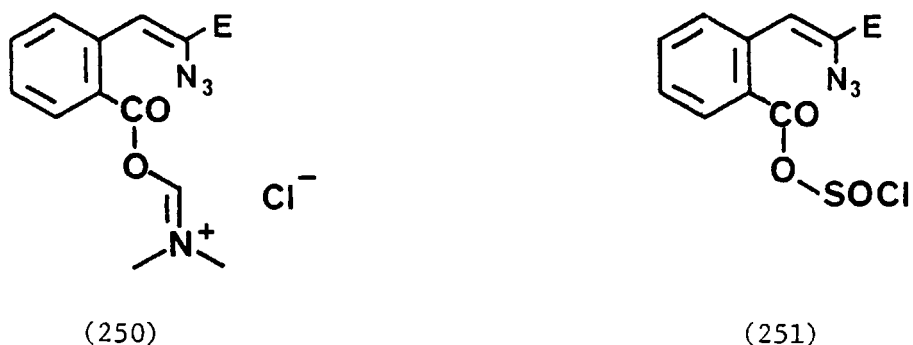
The amide (246) was also prepared by formation of the carboxylate anion of (243) with sodium hydride at room temperature and cooling to -20°C , followed by addition of an excess of thionyl chloride and then an excess of diethylamine. The amide was isolated in 69% yield after aqueous work-up.

Synthesis of the primary amide (247) was accomplished in a similar manner, although in general the yields were lower than those of the tertiary amide (246). Addition of the acid to DMF/oxalyl chloride at -20°C , followed by saturation of the solution with ammonia gas gave the required amide (247) (30%). The amide was also prepared in similar yield by treatment of the anion of the acid (243) with thionyl chloride followed by ammonia gas.

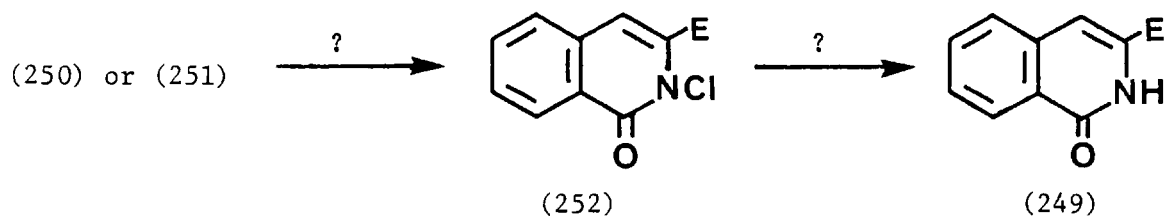
Attempts to prepare the acid chloride derivative of (243) were unsuccessful. When the acid (243) was added to a suspension of the DMF/oxalyl chloride complex at room temperature the compound isolated was the isoquinolone (249) (61%). Similarly, when thionyl chloride was added to a suspension of the sodium salt of the carboxylic acid (243) at -20°C and allowed to warm to room temperature the isolated product was again the isoquinolone (249) (73%).



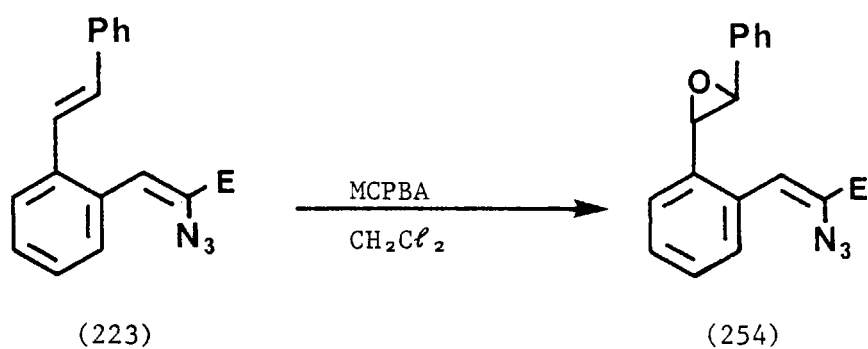
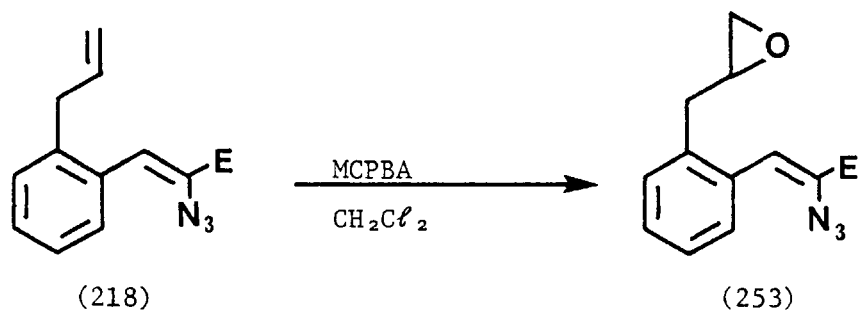
It seems likely that the intermediates (250) and (251) formed at -20°C can react with amines to form amides, but when they are warmed up



they decompose to give the isoquinolone (249) either directly or *via* the acid chloride. This is a formal reduction reaction and could occur *via* an intermediate *N*-chloroisoquinolone (252).



The vinyl azides (253) and (254) were produced by epoxidation of the azides (218) and (223) respectively with 3-chloroperbenzoic acid (MCPBA).



CHAPTER THREE

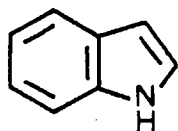
THERMAL DECOMPOSITION OF AZIDOCINNAMATES

BEARING *ORTHO*-ALKYL GROUPS

CHAPTER THREE: THERMAL DECOMPOSITION OF AZIDOCINNAMATES BEARING
ORTHO-ALKYL GROUPS.

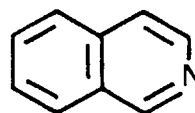
3.1. INTRODUCTION

Many natural products contain fused heterocyclic systems. One family is the alkaloids, some of which contain the indole (255), or isoquinoline (256) rings. Methods of making such systems are of considerable interest both to the pharmaceutical industry and to natural product chemists.



(255)

indole



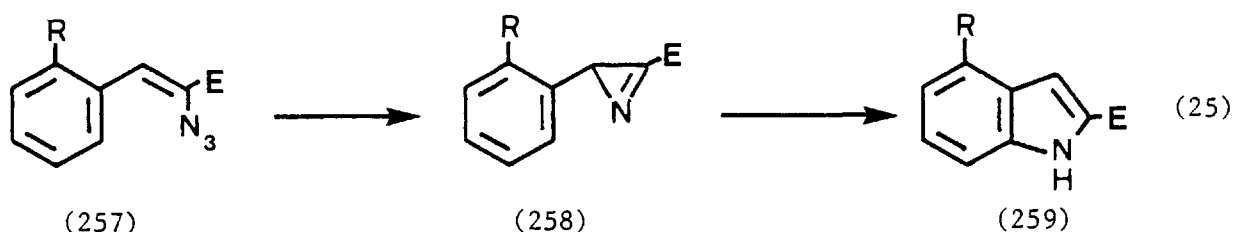
(256)

isoquinoline

There are numerous syntheses of indoles,²⁰⁴ including the Fischer, Madelung, Bischler and Reissert syntheses. Methods of making isoquinolines are not quite as numerous,²⁰⁵ and often require strongly acidic conditions or high temperatures. Examples include the Pictet-Spengler, the Bischler-Napieralski, and the Pommeranz-Fritsch syntheses, some of which require acidic conditions.

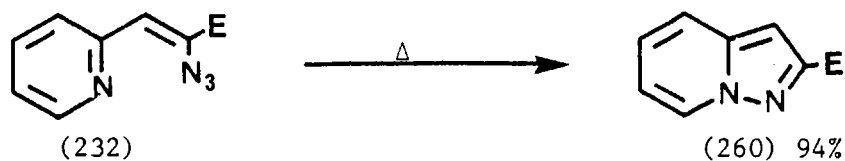
3.2. SYNTHESIS OF INDOLES AND THEIR ANALOGUES.

The thermal decomposition of *ortho*-substituted azidocinnamates (257) provides a convenient synthesis of 2,4-disubstituted indoles (259). This reaction has been shown to proceed *via* the isolable azirine intermediates (258) (equation 25).⁵⁹ On conversion to azirines the distinction between *E* and *Z* isomers of vinyl azides is lost. The stereochemistry about the vinyl bond is thus irrelevant in this Chapter.

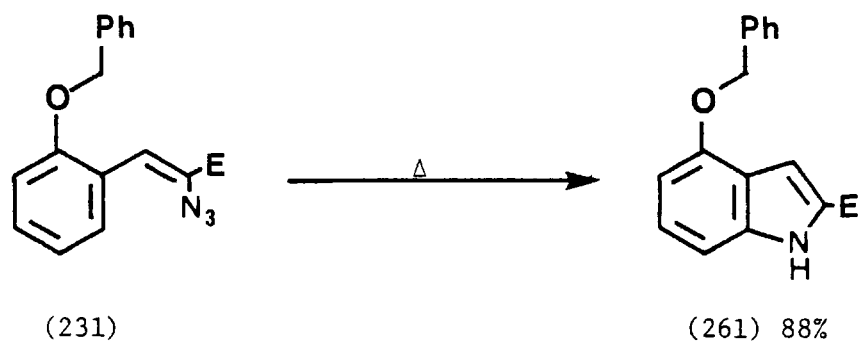


Indole-2-carboxylates have been hydrolysed and decarboxylated,^{60,206} thus increasing the usefulness of this 4-substituted indole synthesis. 4-Substituted indoles are often difficult to obtain.²⁰⁷

The thermal reactions of some simple β -arylvinyl azides were first investigated. Refluxing a solution of 2-azido-3-(2-pyridyl)propenoate (232) in toluene for 16 h gave the pyrazolo[1,5-a]pyridine (260) as the sole product (94% after chromatography). No cyclisation onto the 3-position of the pyridine ring was observed. This is entirely analogous to the formation of the 2-arylpyrazolopyridine (31) [section 1.3.3.(b)],⁶⁰ although the yield of (260) is higher. No nitrile was formed.



Vinyl azide (231) with an *o*-benzyloxy substituent was heated in refluxing toluene for 3.75 h and the corresponding indole (261) was isolated in 88% yield. No insertion into the benzyloxy side chain was observed.



3.3. SYNTHESIS OF FUSED PYRIDINES

3.3.1. Introduction.

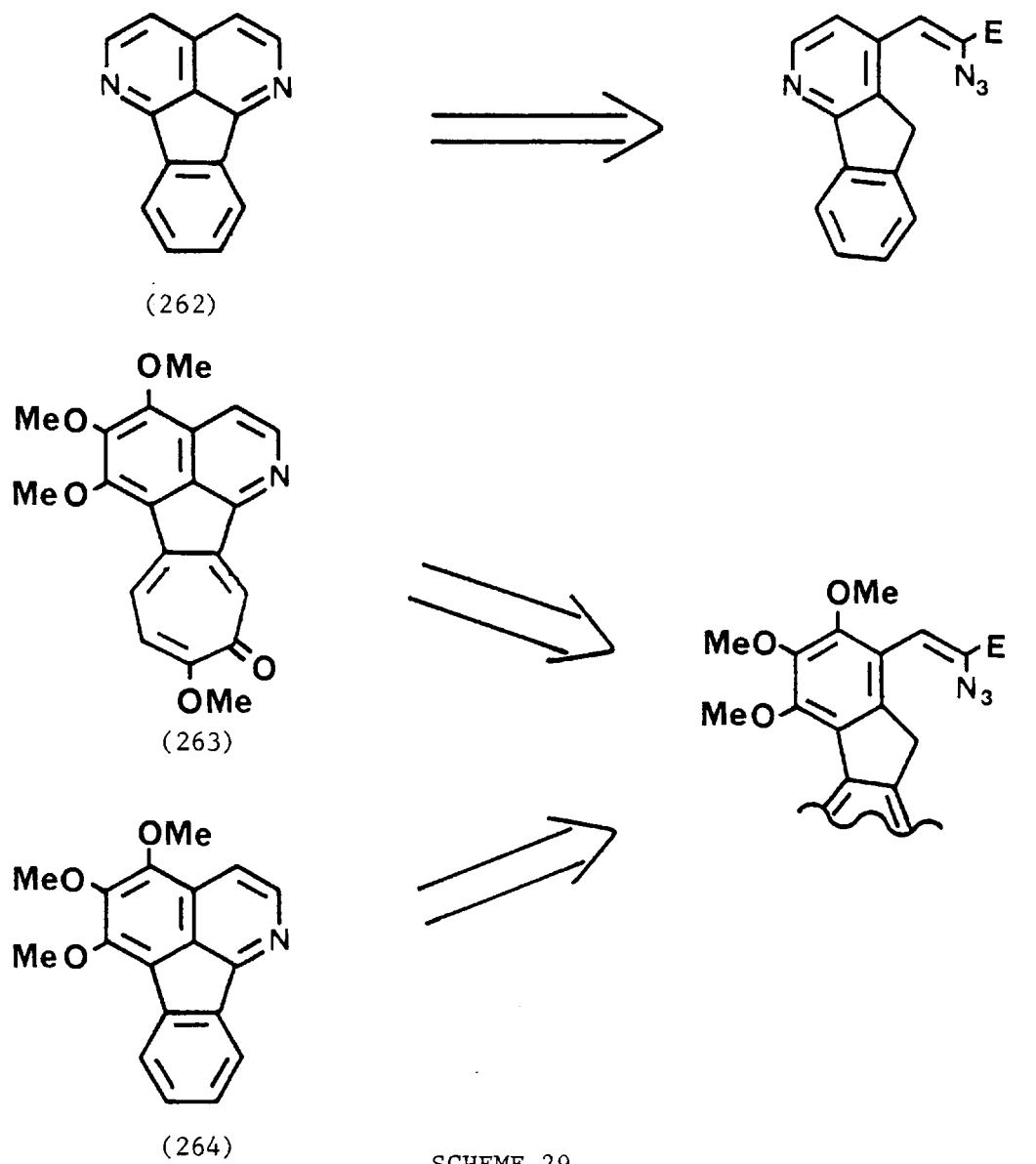
Recent work on the thermolysis of β -arylvinyl azides and the corresponding azirines has provided a new method of fused pyridine synthesis [Schemes 8 and 9, section 1.3.3.(b)].^{43,51,64} This is of particular interest when applied to the synthesis of isoquinolines.⁴³

The azidocinnamates were formed at -20 to 0°C and the thermolyses were conducted in neutral solution at relatively low temperatures (110 – 140°C). As the usual syntheses of fused pyridines require strongly acidic conditions or vigorous heating, the heterocyclic ring is formed early in the synthetic sequence, leaving much subsequent manipulation of substituents. By the above method involving vinyl azides the pyridine ring is formed under relatively mild conditions and thus it should be possible to incorporate substituents before formation of the heterocyclic ring.

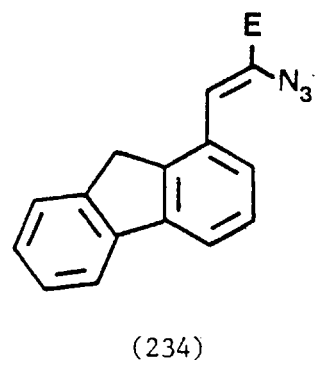
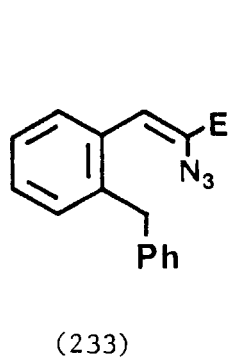
Formal insertion into an *o*-methyl group occurs only when cyclisation onto the aromatic ring is blocked (Scheme 9) or is disfavoured (Schemes 8 and 9). If an *o*-position is unsubstituted then cyclisation usually occurs to give 4-substituted indoles (equation 25), or analogues (Scheme 6).

This is a serious limitation on the use of this reaction in isoquinoline synthesis. An investigation of the thermal decomposition reactions of various azidocinnamates with only one *o*-substituent (258, R = alkyl) was undertaken to determine which, if any *o*-alkyl substituents would lead to isoquinoline production. The compounds first investigated were chosen as models for possible natural product precursors. Possible retrosyntheses for the alkaloids eupolauridine (262),²⁰⁹ imerubrine (263), and norrufescine (264)²¹⁰ are outlined in Scheme 29.

2-Azido-3-(2-benzylphenyl)propenoate (233) and 2-azido-3-(1-fluorenyl)propenoate (234) seemed the best models for such precursors.

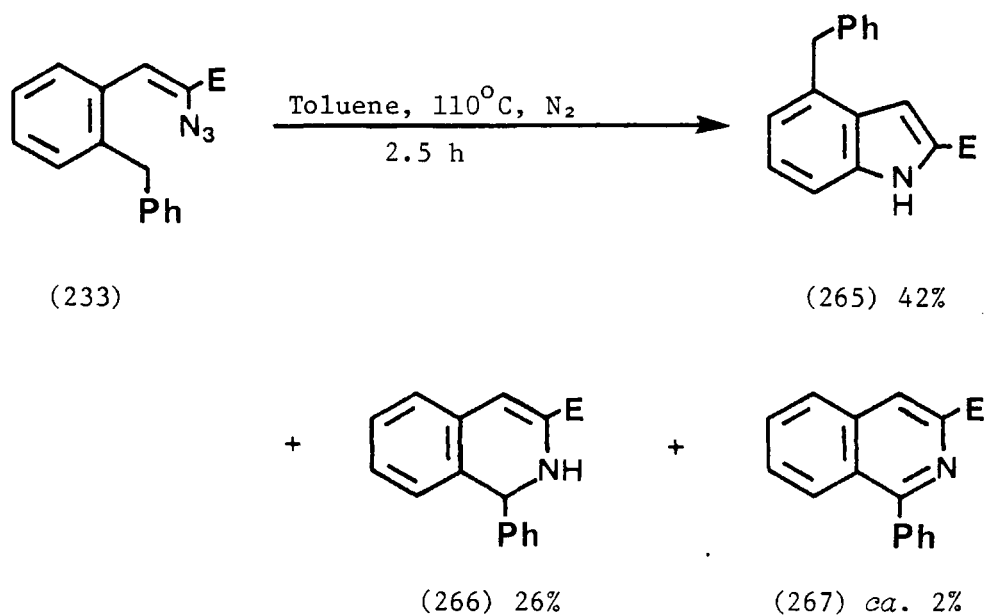


SCHEME 29



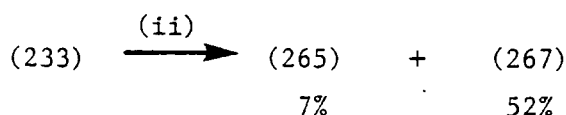
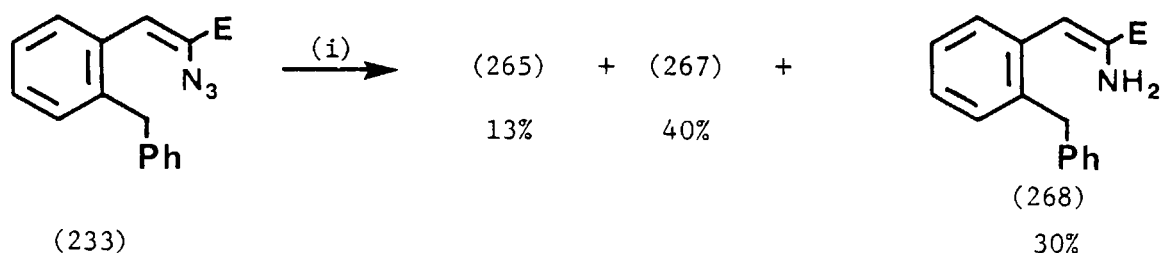
3.3.2. Thermolysis of ethyl 2-azido-3-(2-phenylmethylphenyl)propenoate
(233).

Decomposition of (233) in boiling toluene under nitrogen for 2.5 h gave the indole (265) (42%), the dihydroisoquinoline (266) (26%), and the isoquinoline (267) in trace amounts (0-2%). This appears to be the first example of formal insertion of a vinyl nitrene into an *ortho*-alkyl group when the nitrene can do an electrocyclic ring closure onto a free *ortho*-position.



As the yields of fused pyridines have been increased in at least one case by the use of the oxidising system iodine/potassium acetate it was decided to repeat the thermolysis in the presence of iodine. It was found that thermolysis under the same conditions in the presence of 0.1

molar equivalents of iodine gave the isoquinoline (267) (40%), indole (265) (13%) and the enamine (268) (20%), characterised as its *N*-acetyl²¹¹ derivative (269). The enamine (268) decomposed slightly on chromatography. An n.m.r. spectrum of the total crude reaction mixture indicated that the yield should have been 30%. No dihydroisoquinoline (266) was isolated under these conditions. It seemed likely that the enamine (268) was



(i) Toluene, 110°C, I₂ (0.1), 2.5 h; (ii) toluene, I₂ (1.0), K₂CO₃ (1.0) 2.5 h.

being formed from an intermediate nitrene by hydrogen-abstraction from the 1,2-dihydroisoquinoline. In an effort to suppress enamine formation and increase the yield of isoquinoline (267) the decomposition was performed in the presence of 1.0 molar equivalents of iodine and potassium acetate as oxidant. No enamine (268) was isolated but the yield of isoquinoline (267) was only increased to 52%, indole (265) being the other isolated product.

A sample of 1,2-dihydroisoquinoline (266) was recovered unchanged when heated in refluxing toluene for 2.75 h, but was converted rapidly into isoquinoline (267) when treated with one equivalent of iodine at 35°C in deuteriochloroform. The reaction was essentially complete after 0.3 h. The oxidation of dihydroisoquinoline (266) to isoquinoline (267) also occurs rapidly in the presence of a catalytic amount of iodine. This is probably due to reoxidation of hydrogen iodide produced to iodine by oxygen dissolved in the solvent. Such 1,2-dihydroisoquinolines are relatively rare,²¹² unlike the isomeric 3,4-dihydroisoquinolines. They usually oxidise rapidly to isoquinolines.

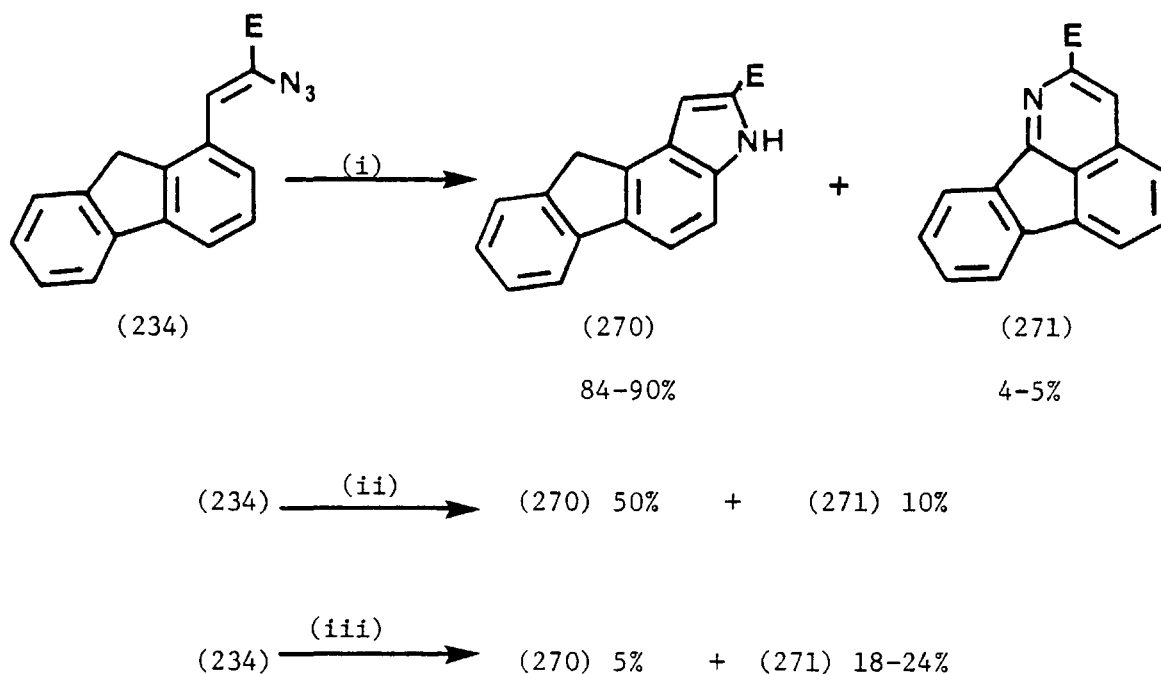
A sample of indole (265) was heated in refluxing toluene with 1.0 equivalents of iodine and was found to slowly convert into a moniodo-derivative which was observed on t.l.c. and by mass spectrometry.

The presence of iodine has a substantial and unexpected effect on the amount of isoquinolines [(266) and (267)] produced on decomposition of vinyl azide (233), increasing it from a total of 26-28% in the absence of iodine to 52% in the presence of 1.0 molar equivalents of iodine. Even 0.1 molar equivalents caused a substantial increase in the amount of isoquinoline produced. Possible reasons for and mechanisms for this effect will be discussed later.

3.3.3. Thermolysis of ethyl 2-azido-3-fluoren-1-ylpropenoate (234).

A similar effect was observed on thermolysis of the vinyl azide (234). Refluxing in xylene for 1 h gave the indole (270) (84-90%) and the azafluoranthene (271) (4-5%). When the azide was thermolysed in the presence of 0.1 molar equivalents of iodine then the yield of (271) increased to 10% and the yield of indole (270) dropped to 50%.

Increasing the amount of iodine to 1.0 molar equivalents increased the yield of isoquinoline (271) to 18-24%, but decreased the amount of isolated indole (270) to 5%. The total crude reaction mixture was very messy. No enamine corresponding to (268) was isolated.

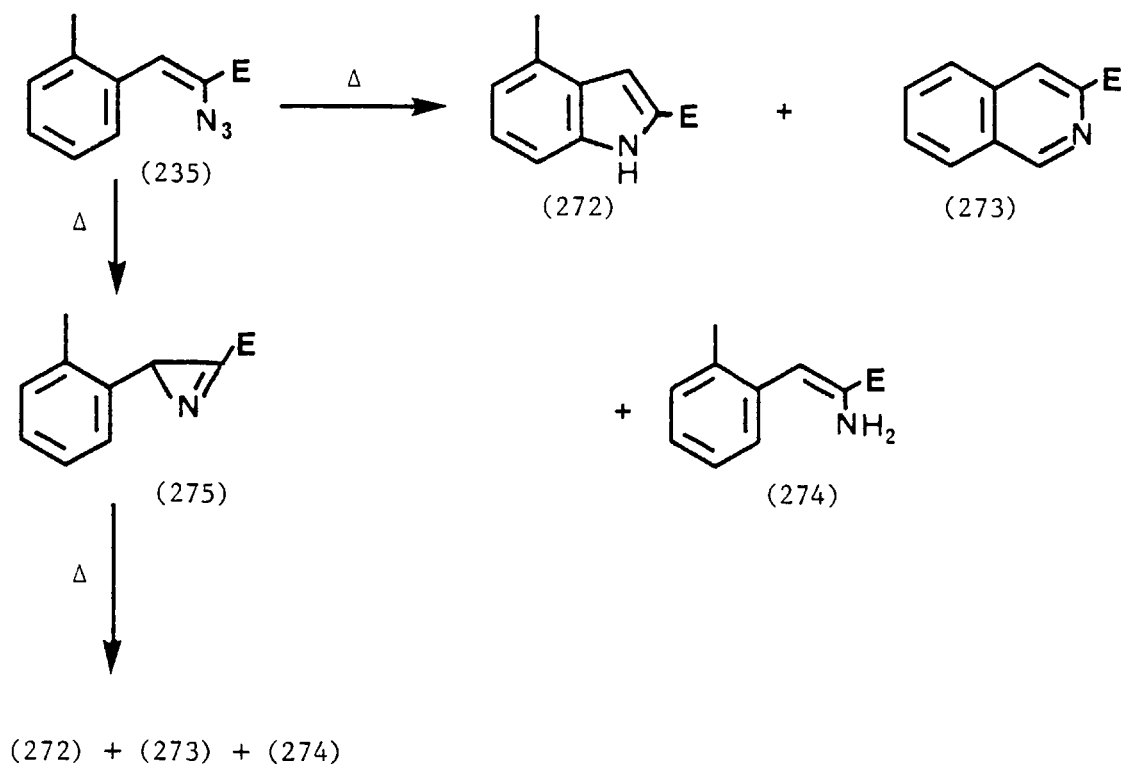


(i) xylene, 140°C; (ii) xylene, I₂ (0.1), 140°C; (iii) xylene, I₂ (1.0), 140°C.

The low yields of isoquinoline (271) from (234) did not bode well for the possibility of forming alkaloids such as imerubrine and eupolauridine by formal insertion reactions of vinylnitrenes. However, the effect of iodine which had been discovered seemed worth investigating, in the hope that other isoquinolines could be formed in good yields.

3.3.4. Thermolysis of ethyl 2-azido-3-(2-methylphenyl)propenoate (235).

To test the effect of iodine further the thermal decomposition of vinyl azide (235) was carried out, both in the presence and absence of iodine. Thermolysis of (235) in boiling toluene (2.75 h) gave exclusively the indole (272) as previously reported, whereas thermolysis with 0.1 molar equivalents of iodine reduced the yield of indole to 28% and gave the isoquinoline (273)²¹³ (20%) and the enamine (274) (13.5%) (Scheme 30). When the amount of iodine was increased to 1.0 molar equivalents then the yield of isoquinoline (273) was 32%. An n.m.r. spectrum of the total crude reaction mixture indicated that the yield of isoquinoline should have been higher (40-45%), but 32% was the highest isolated yield (Table 2).



SCHEME 30

TABLE 2. Thermolysis of vinyl azide (235) in refluxing toluene for 2.75 h.

Experiment Number	Added Reagents (molar equivalents)	Method of Analysis	Products (%)		
			(272)	(273)	(274)
1		A	100	-	-
2	I ₂ (0.1)	A	28	20	13.5
3	I ₂ (0.1), K ₂ CO ₃ (2.0)	B	55	15	5
4	I ₂ (1.0), KOAc (2.0)	A	-	32	-
5	I ₂ (1.0), K ₂ CO ₃ (2.0)	A	8	30	-
6	K ₂ CO ₃ (2.0)	B	100	-	-

A:- products isolated by chromatography; B:- Yields estimated on the basis of n.m.r. spectra of the total crude reaction mixture.

Even though the maximum yield of isoquinoline is low, the effect of iodine is dramatically shown in this example. In the absence of iodine only indole is formed.

During the thermolysis in the presence of only 0.1 molar equivalents of iodine, the iodine colour gradually disappeared, but some iodine was recovered on evaporation of the solvent. This was probably due to reoxidation of hydrogen iodide by air. When bases such as potassium carbonate or potassium acetate were used the hydrogen iodide was consumed and no iodine was produced on work-up. This could be the reason for the slightly reduced yields of isoquinoline (273) and enamine (274) in experiment 3. When the vinyl azide (235) was thermally decomposed in the presence of potassium carbonate only, the indole (272) was the sole product.

Decomposition of (235) in refluxing toluene for 1 h gave a 1:1 mixture of the indole (272) and azirine (275) (Scheme 30). The petrol-soluble azirine could be separated from the non petrol-soluble solid indole but dimerised on chromatography. The azirine was also produced on irradiation (300 nm, 25°C) of the azide (235). Thermolysis of the azirine (275) in refluxing toluene with and without iodine gave results, by n.m.r., very similar to those obtained when the vinyl azide was the starting material (Table 2), although the reactions involving iodine were not quite as clean. It thus appears that iodine has an effect on the vinylnitrene, not on the vinyl azide. Azirine (275) was recovered unchanged after treatment with iodine in toluene at 25°C.

3.3.5. Mechanism of the iodine effect.

A series of experiments (Tables 3,4) was undertaken to try to elucidate the mechanism of the reactions involving iodine. It seems likely that thermolysis of azidocinnamates in the absence of iodine gave singlet nitrenes *via* azirines, and that these nitrenes were responsible for the production of indoles and dihydroisoquinolines. This is in agreement with mechanisms proposed for similar reactions.^{38,51}

It was necessary therefore, to propose the existence, in the thermolyses carried out in the presence of iodine, of an intermediate (X) which behaved in a different manner and gave rise to isoquinolines and enamines. The formation of enamines seemed to suggest that this species had radical character, and therefore a triple nitrene (276) or a radical of the type (277) were likely possibilities.

TABLE 3. Thermolysis of 2-azido-3-(2-methylphenyl)propenoate (235)
in the presence of added reagents.

Experiment Number	Solvent* Tempera- ture, time	Added Reagents (Molar equivalents)	Method of Analysis	Products (%)		
				(272)	(273)	(274)
7	a	HI (0.1)	B	100	-	-
8	a	KI (1.0)	B	100	-	-
9	b		B	100	-	-
10	c		B	100	-	-
11	a	I ₂ (0.1), HI (0.1)	B	Similar to exp. 2 slightly more (273)		
12	a	Hydroquinone (2.0)	B	100	-	-
13	a	I ₂ (0.1), hydro- quinone (1.0)	A	51	-	26
			B	58	2	39
14	c	Hydroquinone (2.0)	B	100	-	-
15	a	Ph ₂ Se ₂ (0.1)	B	100	-	-
16	a	Ph ₂ S ₂ (1.0)	B	100	-	-
17	a	Bu ₂ O ₂ (0.2)	B	100	-	-
18	a	(PhCO ₂) ₂ (0.1)	B	100	-	-
19	a	I ₂ (0.1), α -methyl- styrene (1.0)	B	Similar to exp. 2, but less (274).		

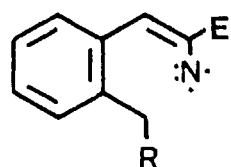
a: Toluene, 110°C, 3.25 h

b: Iodopropane, 102°C, 6 h

c: Bromobenzene, 110°C, 3 h

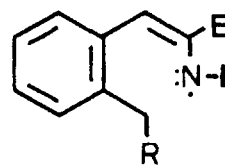
A: Products isolated by chromatography

B: Yields estimated on the basis of n.m.r. spectra of the total
crude reaction mixtures.



(276)

(X)



(277)

The radical character of this intermediate (X) was further demonstrated by the formation of enamines in larger quantities when the thermolyses were done in the presence of a hydrogen donor - hydroquinone (1.0 molar equivalents) - in addition to the iodine (0.1 molar equivalents) (experiment numbers 13 and 23). In experiment 13 very little isoquinoline was formed, whereas in experiment 23, the production of isoquinoline was only slightly reduced. When $R = H$ intermolecular hydrogen abstraction by (X) competed very effectively with the intramolecular reaction, whereas this is not the case when $R = Ph$ (experiment 23) where intramolecular hydrogen abstraction would be expected to be more favourable.

Hydrogen iodide and potassium iodide had little or no effect on the decomposition reactions of (235) (experiments 7, 8, and 11). The slightly increased yields (2-5%) of isoquinoline (273) in experiment 11 were probably due to aerial oxidation of hydrogen iodide to iodine.

When the decomposition of (235) was carried out in the presence of 'heavy atom' solvents such as iodopropane (experiment 9) or bromobenzene (experiment 10) no isoquinoline (273) was produced, indole (272) being the sole product. This indicates that I_2 was not acting simply as a

TABLE 4. Thermolysis of 2-azido-3-(2-phenylmethylphenyl)propenoate (233) in toluene for 2.75 h, under N₂ in the presence and absence of added reagents.

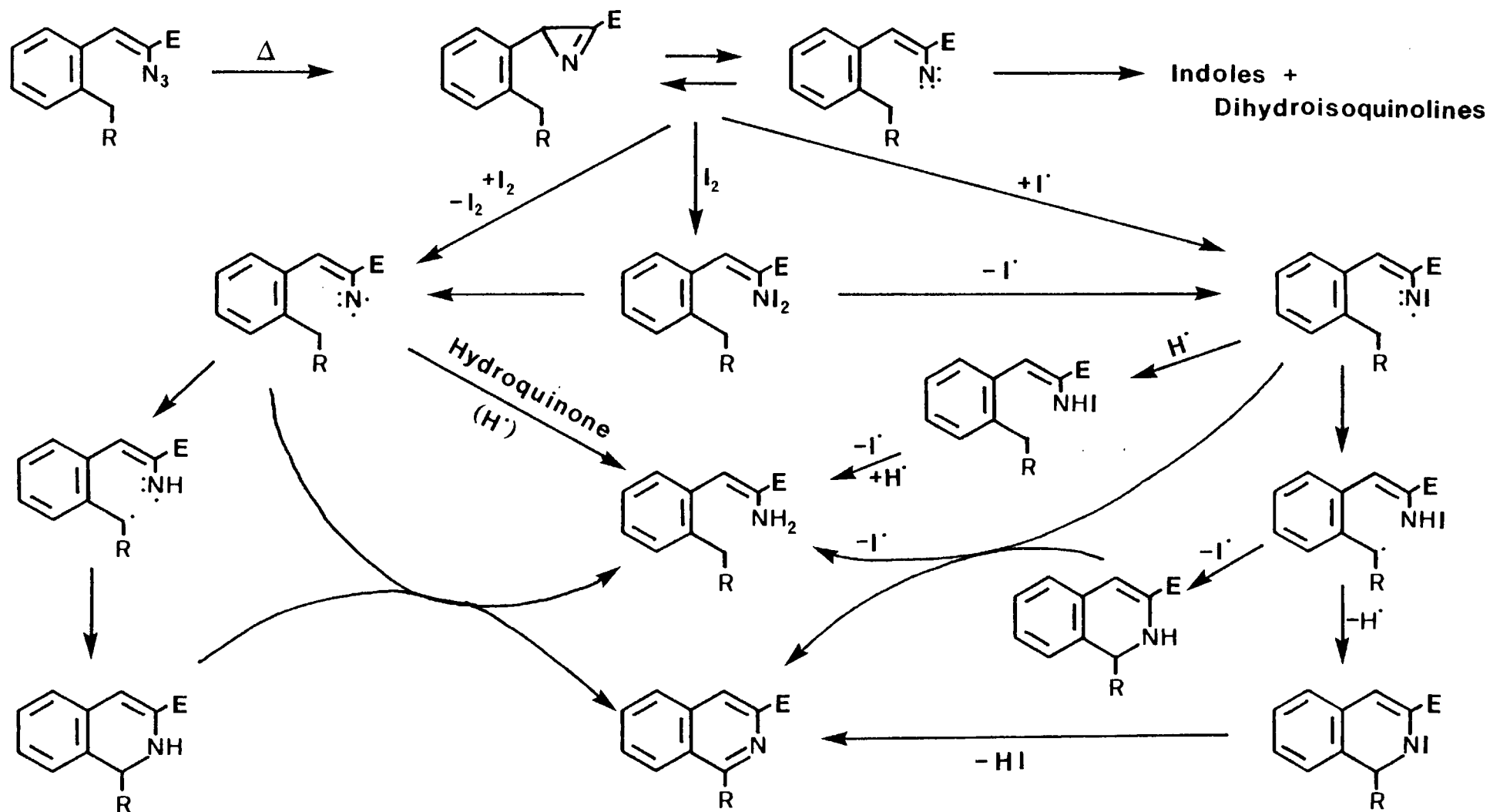
Experiment Number	Added Reagents (molar equivalents)	Method of Analysis	Products (%)			
			(265)	(266)	(267)	(268)
20	Hydroquinone (1.0)	A	41	26	0-2	0
21		B	Similar to exp. 20 enamine (268)			
22	I ₂ (0.1)	A	13	0	40	20
		B	~13	0	~40	~30
23	I ₂ (0.1), hydroquinone (1.0)	B	~10	0	~35	~50
24	I ₂ (1.0), KOAc (1.0)	A	7	0	52	0

A: Products isolated by chromatography.

B: Yields estimated on the basis of n.m.r. spectra of the total crude reaction mixture

heavy atom and facilitating singlet to triplet intersystem crossing. Some direct interaction of iodine with the nitrene or azirine must have been involved.

The presence of free radical initiators di-*t*-butyl peroxide and dibenzoyl peroxide in the thermolyses did not lead to isoquinoline (273) formation, nor did diphenyldiselenide or diphenyldisulphide. Whilst α -methylstyrene, a radical trap, caused a decrease in the amount of enamine (274) formed there was no substantial decrease in the amount of isoquinoline (273) formed. The above results are inconclusive.



SCHEME 31

A few of the most likely routes to isoquinolines are outlined in Scheme 31. The mechanism must involve iodine as a true catalyst as the increase in the amounts of isoquinolines plus enamines in the presence of 0.1 molar equivalents of iodine is greater than 20% which is the maximum expected if iodine were non-catalytic.

The experiments carried out did not distinguish between a mechanism involving triplet nitrenes (276) and one involving radicals (277), but indicate that the role of iodine is unique and cannot be mimicked by radical initiators, diaryl-disulphides or -diselenides, 'heavy atom' solvents or iodine-containing organic or inorganic compounds.

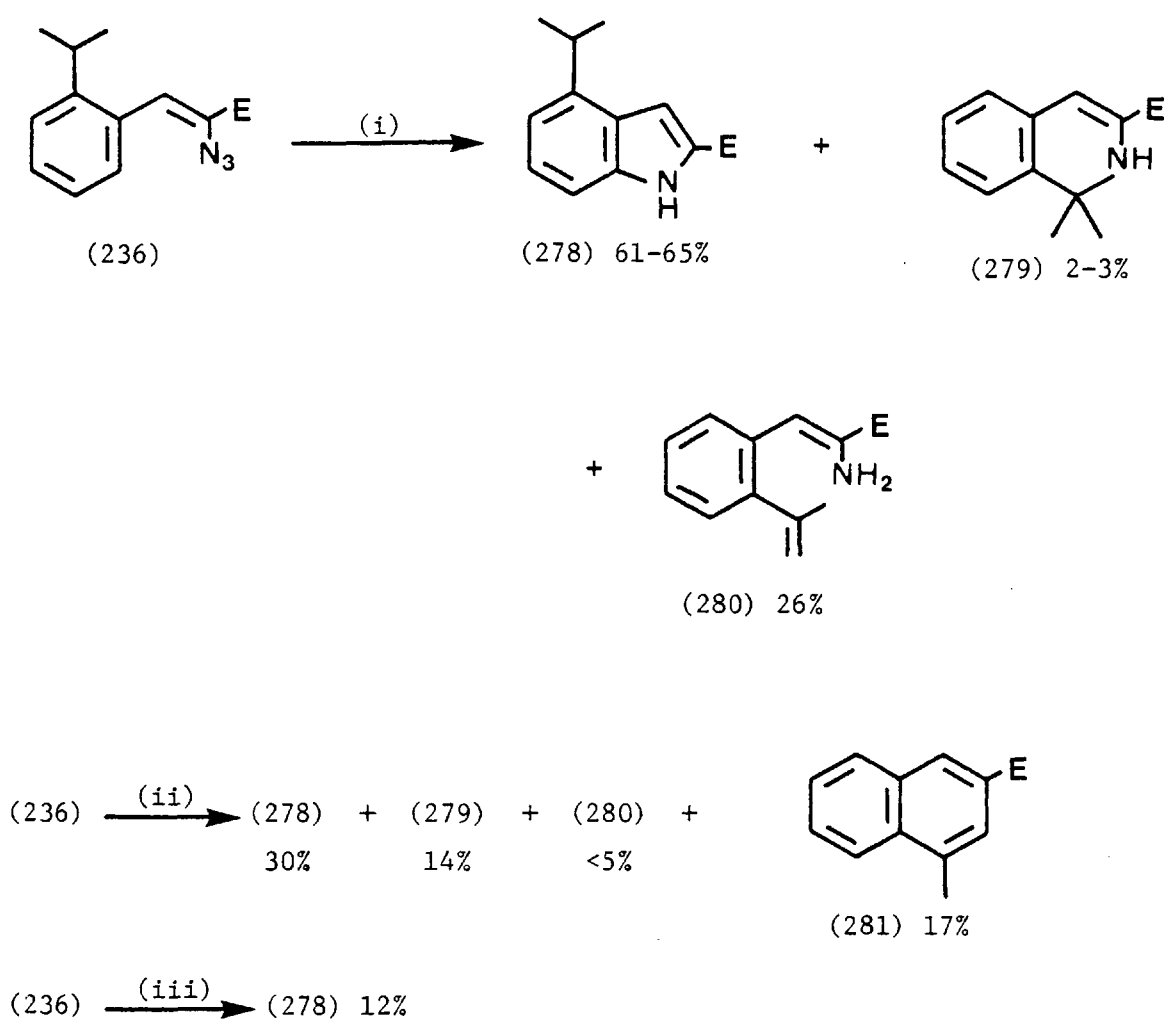
Attempts to increase the yield of isoquinolines by using co-oxidants with iodine were marginally successful. Thermolysis of azide (233) in refluxing toluene for 2.75 h in the presence of iodine (0.1 molar equivalents) and chloranil (2 molar equivalents) gave isoquinoline (267) and enamine (268) in roughly the same ratio as without chloranil. In a separate experiment chloranil was shown to dehydrogenate the 1,2-dihydroisoquinoline (266) rapidly. It appears that either the radical intermediate (X) is a better dehydrogenating agent than chloranil or that dihydroisoquinolines are not involved in the reaction. When two molar equivalents of manganese dioxide were used instead of chloranil a slight increase (~5%) in the amount of isoquinoline (267) produced was observed, and there was a substantial decrease in the amount of enamine (268). The mixture was not very clean, however. The use of iodine (0.1 molar equivalents) and barium manganate (2 molar equivalents) gave the best results. No enamine (268) was isolated, isoquinoline (267) was isolated in 49% yield and the indole (265) in 12.5% yield. The fact that very little or no enamine was formed may have been caused by the

oxidising reagent destroying any enamine formed, in which case the increased yield of isoquinoline could be due to reoxidation of hydrogen iodide to iodine. On the other hand, if no enamine were formed at all, due to manganese dioxide or barium manganate oxidising the dehydro-isoquinoline then the increased yield could be due to a greater percentage of the intermediate (X) reacting to form isoquinoline (267).

3.3.6. Decomposition of ethyl 2-azido-3-(isopropylphenyl)propenoate (236).

An attempt was then made to design a system where the formal insertion product of the vinylnitrene into an *o*-alkyl group is a 1,1-disubstituted -1,2-dihydroisoquinoline (i) in order to eliminate enamine formation and thus, hopefully, increase isoquinoline formation, and (ii) to act as a model for possible precursors for Erythrina alkaloids²¹⁴ in which the 1-position in the isoquinoline ring is spiro. The system chosen was the *o*-isopropylazidocinnamate (236). When the thermolysis was carried out in refluxing xylene the products isolated were the indole (278) (61-65%), the dihydroisoquinoline (279) (2-3%), and the enamine (280) (6-16%). The isolated yield of enamine (280) was low due to decomposition on chromatography. Analysis of the n.m.r. spectra of the total crude reaction mixtures shows that there is ca. 20% of (280) present before chromatography.

Heating a solution of the azide (236) in xylene in the presence of 0.1 molar equivalents of iodine reduced the yield of indole (278) to 30% and the yield of enamine (280) to trace amounts, but increased the yield of dihydroisoquinoline (279) to 14% and produced a new compound, the naphthalene (281) (17%). When 1.0 molar equivalents of iodine and potassium acetate were used the only isolated product was the indole (12%) and the reaction mixture was very messy.

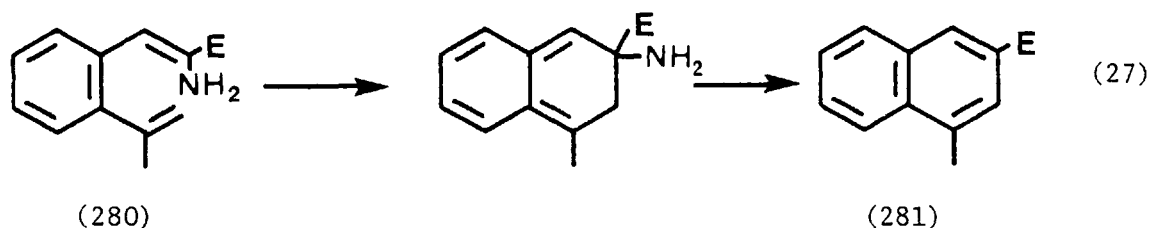


(i) xylene, 140°C , 0.75 h; (ii) xylene, I_2 (0.1), 140°C , 0.75 h;

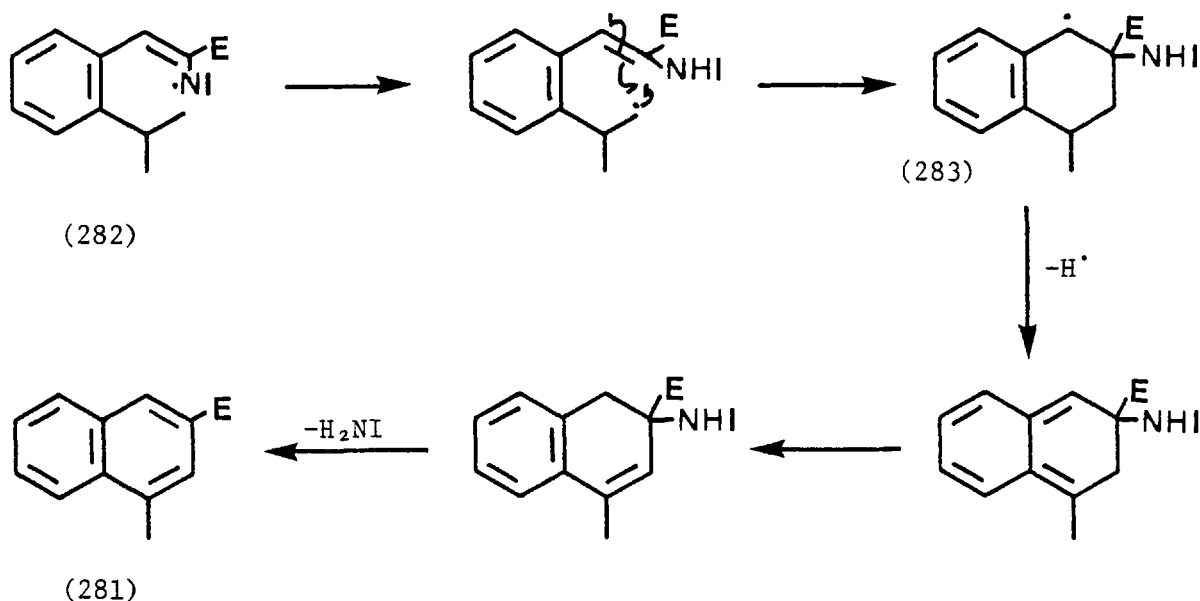
(iii) toluene, I_2 (1.0), KOAc (1.0), 110°C , 2.75 h.

Enamines such as (280) have been formed by interaction of vinyl-nitrenes with adjacent isopropyl and ethyl groups [section 1.3.3.(b)].⁵¹ It seems likely that the production of indole (278), dihydroisoquinoline (279), and enamine (280) (equation 26) involved a singlet nitrene, as has been postulated,⁵¹ but that the increased quantity of dihydroisoquinoline (279) produced in the presence of iodine was due to a radical intermediate of type (X).

The production of the naphthalene (281) is slightly puzzling. The simplest mechanism for its formation is an electrocyclic ring closure reaction of the enamine (280), followed by loss of ammonia (equation 27), but it is difficult to see why this thermal reaction should have occurred only in the presence of iodine.



One possible explanation is that a radical intermediate (282) abstracted a hydrogen radical from one of the methyl groups rather than the tertiary H to give a reactive primary radical which rearranged to the more stable benzylic radical (283). Loss of a hydrogen radical followed by loss of NH_2I would give the observed naphthalene (Scheme 32).



SCHEME 32

3.4. CONCLUSION

Only in the very simple *o*-alkyl-azidocinnamate (258) (alkyl-substituent R = Me) was indole formation the sole reaction on thermolysis. When R = *i*-propyl, or benzyl, or is part of the fluorenyl system, reaction of the intermediate nitrene with the *o*-group occurs to greater or lesser extents, depending on the particular *o*-group. The yields of indoles vary from 41 to 90%. The presence of iodine decreased the yields of indoles and increased the yields of products derived from reaction with the *o*-alkyl group. While the mechanism of this interaction is not clear, its effect is quite definite and reproducible.

CHAPTER FOUR
THERMAL DECOMPOSITION OF AZIDOCINNAMATES
WITH UNSATURATED *ORTHO*-SUBSTITUENTS

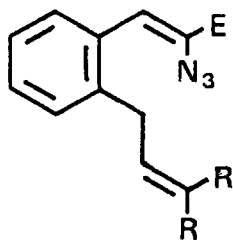
CHAPTER FOUR: THERMAL DECOMPOSITION OF AZIDOCINNAMATES WITH
UNSATURATED *ORTHO*-SUBSTITUENTS.

4.1. INTRODUCTION.

In the preceding Chapter it was shown that vinylnitrenes could interact with adjacent *o*-alkyl groups, iodine increasing the extent of this interaction. Azidocinnamates bearing *o*-alkenyl groups were then studied in order to find out if the unsaturated groups become involved in the reactions of the azides or the corresponding nitrenes. In each case only one *o*-position was substituted in order that the interactions with the unsaturated blocking groups would be in competition with the usual electrocyclic ring closure reaction.

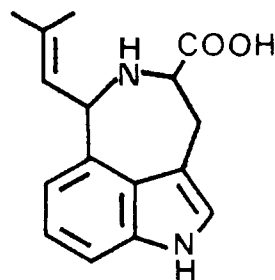
4.2. DECOMPOSITION OF ETHYL 2-AZIDO-3-(2-ALLYLPHENYL)PROPENOATE (237).

The system first studied was azidocinnamate (237).



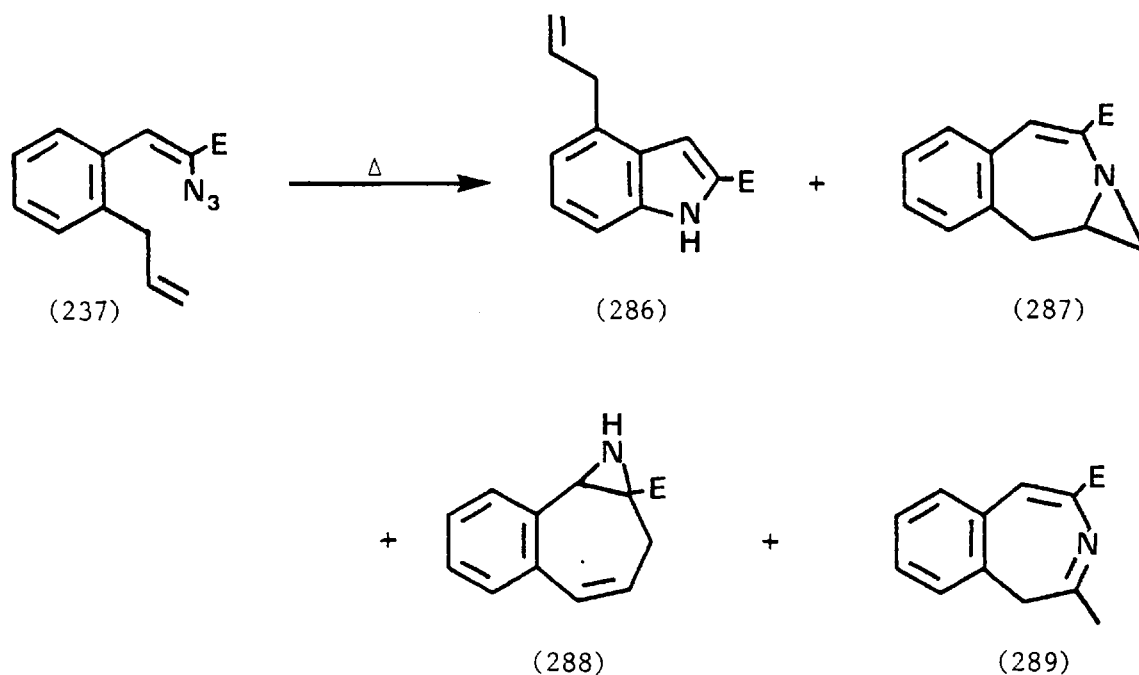
(237) R = H

(284) R = Me



(285)

It was originally hoped to study the system (284) since prenyl groups are common in natural products (*e.g.* terpenes and alkaloids such as clavicipitic acid (285)²¹⁵). However, when the synthesis of the required aldehyde was unsuccessful the simpler system (237) was studied. This compound was quite stable at room temperature but on heating was decomposed to give a mixture of four compounds, to which the structures (286)-(289) were assigned, based on the spectral data. No ethyl 1-vinylisoquinoline-3-carboxylate was observed.



The yields obtained at different temperatures are given in Table 5. The yields of indole (286) and aziridine (288) were found to increase with an increase in temperature, whereas the yields of aziridine (287) and benzazepine (289) decreased with an increase in temperature. Both

(287) and (288) decomposed slightly on chromatography and so both the isolated yields and the yields based on the n.m.r. spectra of the crude reaction mixtures are quoted.

TABLE 5. Thermolysis of ethyl 2-azido-3-(2-allylphenyl)propenoate (237).

SOLVENT AND TIME	TEMPER- ATURE (°C)	REACTION PRODUCTS			
		Estimated yields* (isolated yields) ^x			
		(286)	(287)	(288)	(289)
(i)	80	5 [†]	44 [†]	23 [†]	28 [†]
(ii)	110	9 (8)	35-39 (12)	34 (24-31)	22 (21-22)
(iii)	140	11 (11)	33 (20)	37 (29)	17 (16)
(iv)	190	20 (20)	13 (13)	44 (20)	7 (6)

* Yields estimated on the basis of n.m.r. spectra of the total crude reaction mixture

^x Yields of products isolated by chromatography

[†] Products not isolated

(i) Benzene, 4.5 h

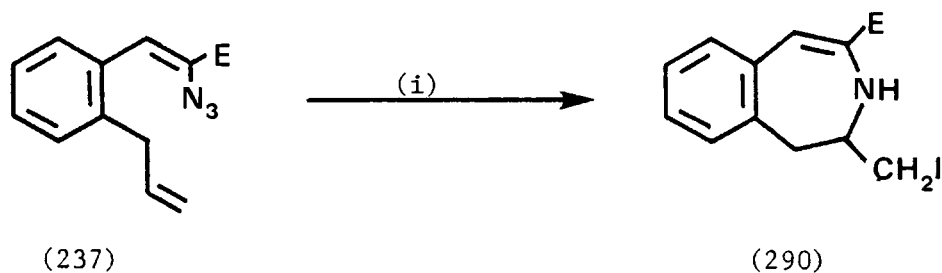
(ii) Toluene, 1.5-1.6 h

(iii) Xylene, 0.75 h

(iv) Decalin, 0.12 h

The *o*-allylazidocinnamate (237) was then heated in benzene at 60°C for 24 h in the presence of 1.0 molar equivalents of iodine. After work-up, involving washing with sodium thiosulphate solution, a yellow oil

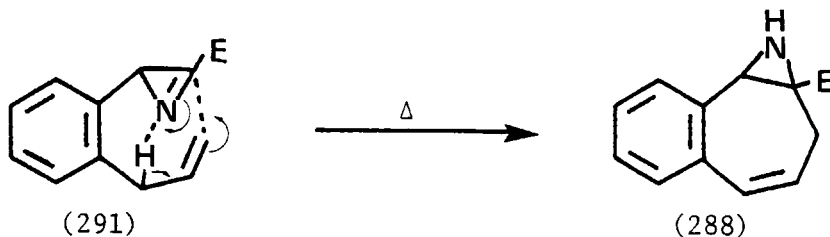
was obtained which was identified as the iodinated enamine (290) (30-40%). An n.m.r. spectrum of the total crude reaction mixture after work-up showed that (290) was the sole product.



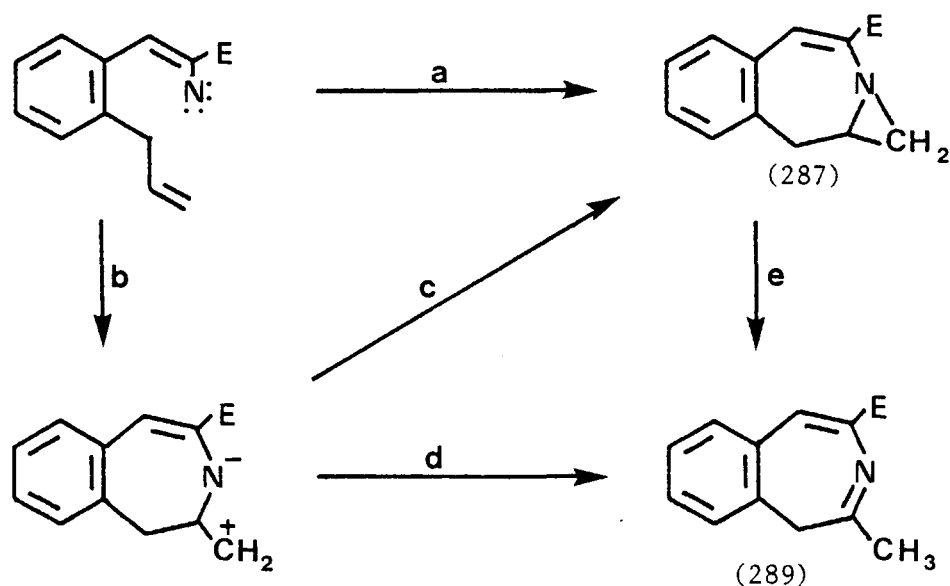
(i) benzene, I_2 (1.0), $60^\circ C$, 24 h

Thermolysis of (237) in refluxing toluene for 1.5 h in the presence of 0.1 molar equivalents of iodine gave the iodoenamine (290) in 13% yield, and compounds (286)-(289) were also present.

The indole (286) is probably produced by cyclisation of the corresponding vinylnitrene onto the unblocked *o*-position, followed by a [1,5]H shift. The formation of the aziridine (288) is rationalised by an intramolecular ene reaction of the intermediate azirine (291). Ene reactions involving C=N bonds are rare,²¹⁶ and although two examples involve azirines,²¹⁷ this appears to be the first intramolecular example.

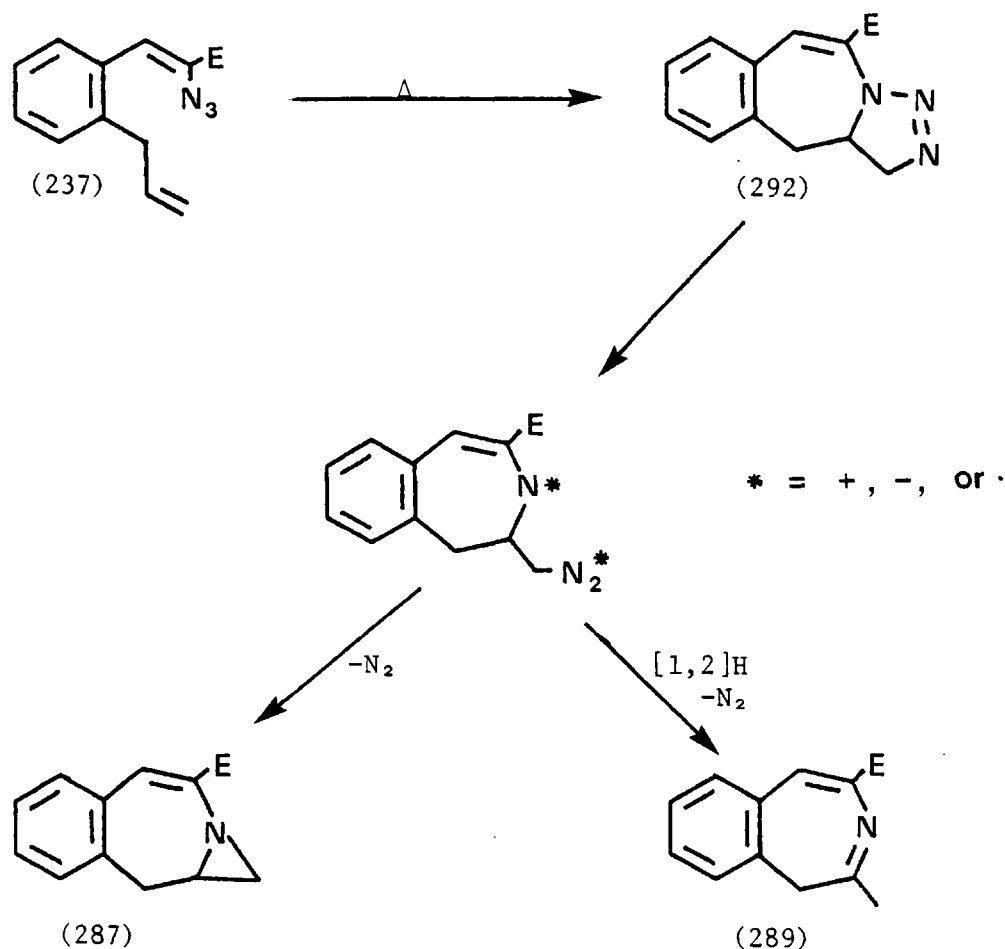


Several mechanisms of formation can be proposed for the two remaining compounds (287) and (289). The aziridine (287) can be visualised as being formed by simple addition of the singlet vinylnitrene to the allyl double bond, either in a concerted (pathway a) or stepwise manner (pathway c). The benzazepine (289) could arise *via* stepwise addition of the nitrene followed by rearrangement (pathway d) or by rearrangement of (287) (pathway e) (Scheme 33).



SCHEME 33

Alternatively, the azido group of (237) could have acted as a 1,3-dipole and added to the double bond giving an intermediate triazo-line (292), which could then have lost N_2 with, or without, rearrangement to give the benzazepine (289) and aziridine (287) respectively (Scheme 34).

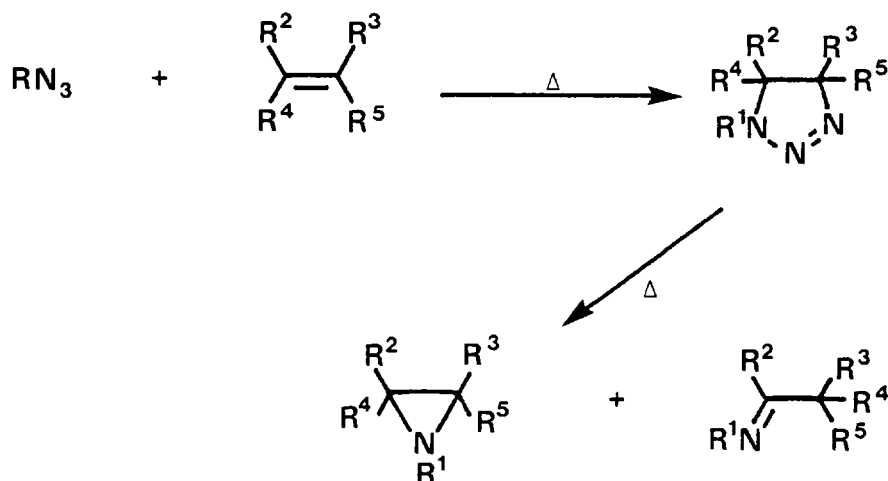


SCHEME 34

If the azepine (289) were formed *via* pathway (e) [*i.e.*, from (287)] then one would not expect to isolate any of (287) at higher temperatures. This is not the case however. Furthermore, a sample of (287) heated in toluene under the same conditions failed to give (289). Addition of nitrenes to double bonds is a well known reaction, although in the case of vinylnitrenes the intermediate vinyl aziridines have not been isolated.

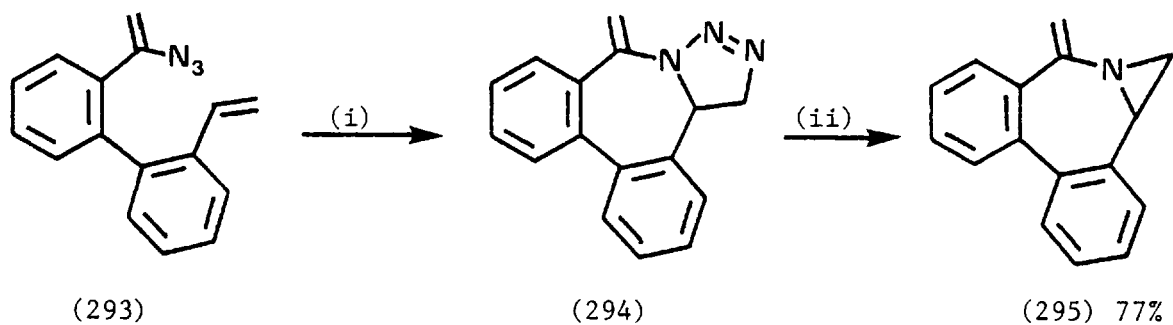
The addition of azides, including vinyl azides, to C=C bonds to give 1,2,3-triazolines is a well documented reaction. Such triazolines rearrange with loss of N₂ to imines and aziridines (Scheme 35). Both

inter- and intramolecular examples of triazoline formation are known, but the triazoline is not always isolated.²¹⁶⁻²¹⁸



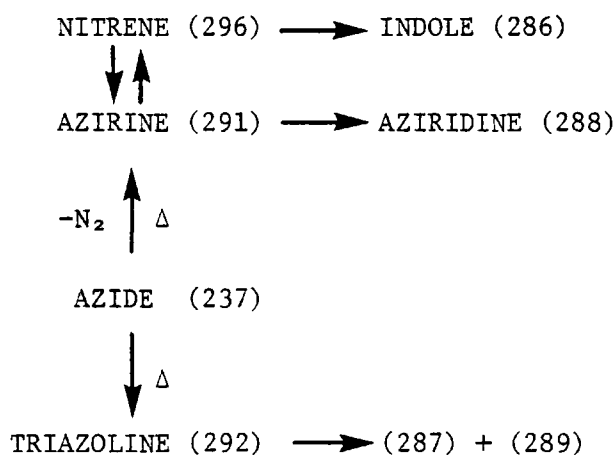
SCHEME 35

A related example of the above reaction is the transformation of the azide (293) to the aziridine (295) *via* the isolable triazoline (294).²¹⁸



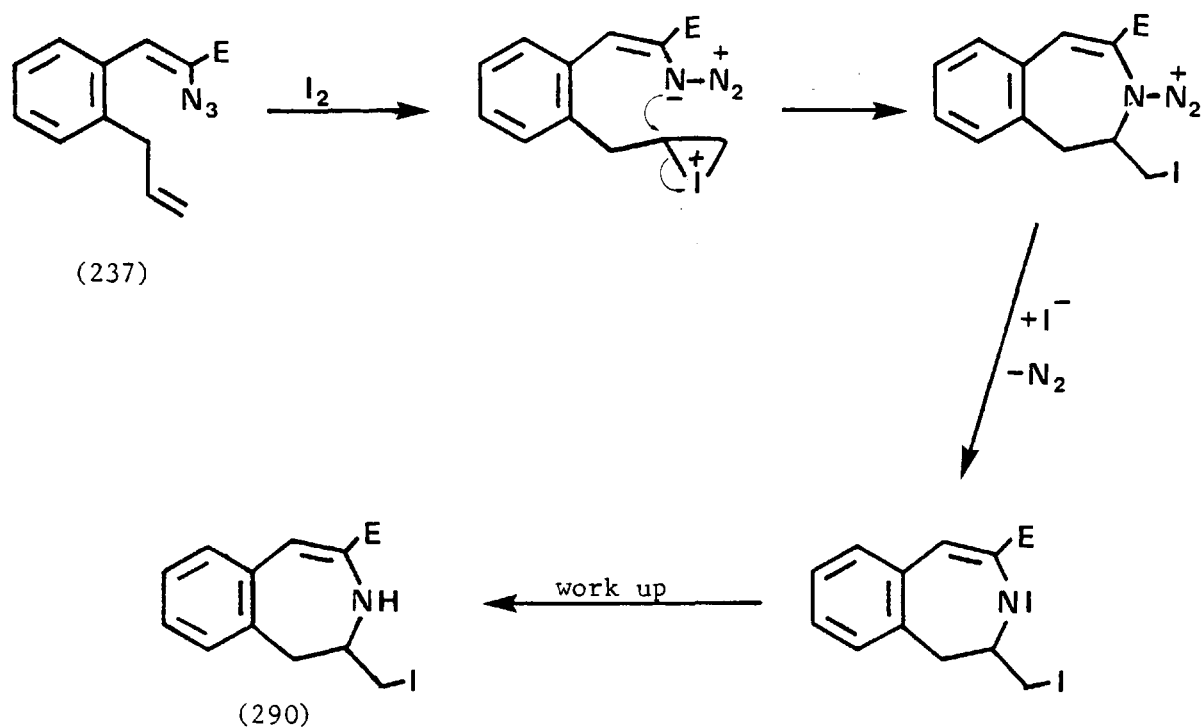
(i) 0°C, 3 days; (ii) 80°C, 14 h

The most reasonable mechanism for formation of (287) and (289) is *via* the triazoline (292). It explains why the yields of both (287) and (289) decrease with an increase in temperature, whereas the yields of indole (286) and aziridine (288) increase with an increase in temperature. This is due to a greater conversion of the vinyl azide (237) to the azirine (291) [in equilibrium with the corresponding nitrene (296)] at higher temperatures, thus reducing the production of triazoline (292) and hence the yields of (287) and (289) (Scheme 36).



SCHEME 36

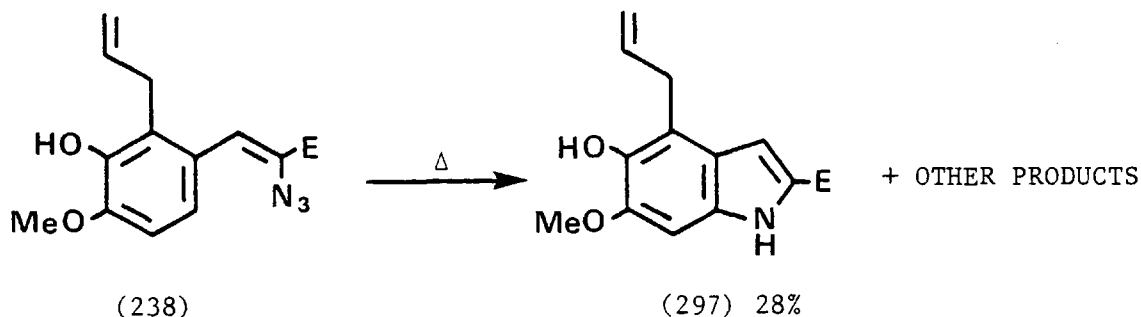
The isolation of the iodinated enamine (290) as the only product on treatment of (237) with iodine in benzene at 60°C suggests that the iodine diverted all of the vinyl azide (237) from azirine and triazoline formation, otherwise some of the products (286)-(289) might have been expected. A possible decomposition route is outlined in Scheme 37.



SCHEME 37

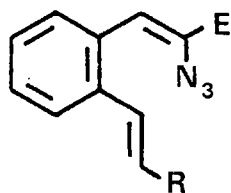
4.3. DECOMPOSITION OF ETHYL 2-AZIDO-3-(2-ALLYL-3-HYDROXY-4-METHOXYPHENYL)-
PROPENOATE (238).

On thermal decomposition the vinyl azide (238) gave products similar to those observed from the simpler system (237). However, only the indole (297) was isolated, in a yield considerably higher than that of the corresponding indole (286). Thermolysis of (238) in refluxing toluene for 0.75 h gave (297) in 28% yield. This is presumably due to the increased nucleophilicity of the ring causing it to interact more readily with the electron deficient nitrene.



4.4. DECOMPOSITION OF ETHYL 2-AZIDO-3-(2-VINYLPHENYL)PROPENOATE (239) AND ETHYL 2-AZIDO-3-(2-STYRYLPHENYL)PROPENOATE (240).

Having observed that the azidocinnamate (237) and the corresponding azirine interacted so readily with an *o*-allyl group, it was decided that the reactions of azidocinnamates with *o*-vinyl groups would be of considerable interest. Two such systems were prepared - (239) and (240).

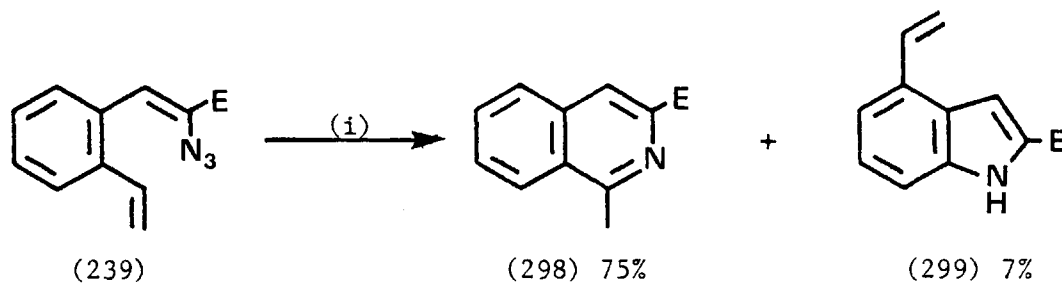


(239) R = H

(240) R = Ph

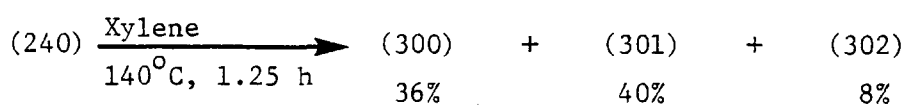
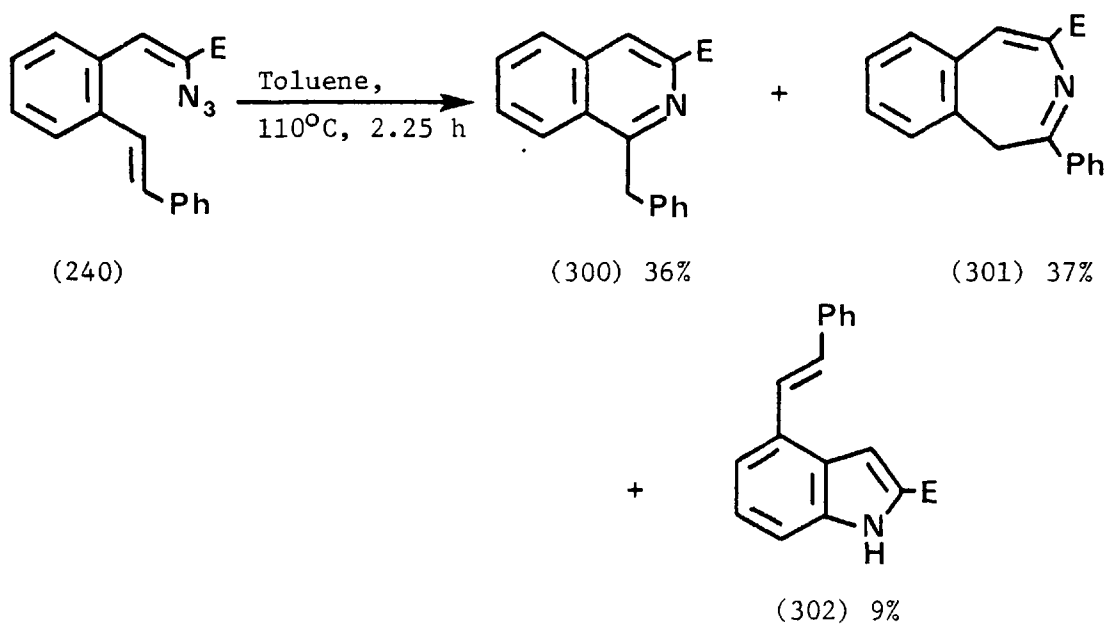
The vinyl azide (239) was found to be thermally unstable, decomposing slowly at 5°C over several weeks to ethyl 1-methylisoquinoline-3-carboxylate (298). Thermolysis in refluxing diethyl ether (19 h) or in deuteriochloroform at 35°C (21 h) showed a similar conversion into isoquinoline (298). The reaction was followed by n.m.r. but no intermediates could be observed. On heating a sample of the azide (239) in refluxing toluene

for 1.5 h the isoquinoline (298) was isolated in 75% yield, and the indole (299) in 7% yield.

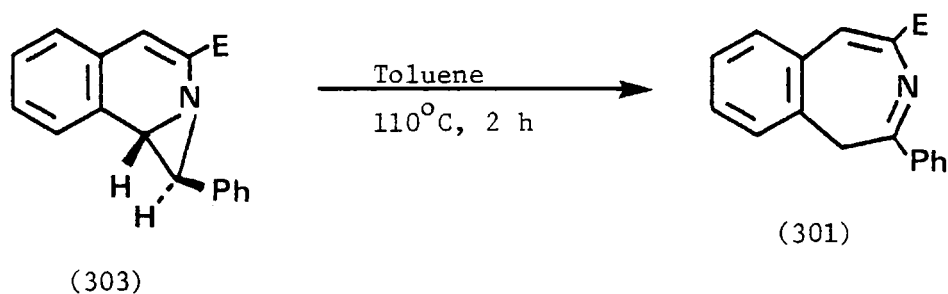


(i) toluene, 110°C, 1.5 h

The *o*-styryl derivative (240) was, however, thermally stable at room temperature but on heating decomposed to give a mixture of isoquinoline (300), benzazepine (301), and indole (302). The yields varied with temperature, the amount of benzazepine (301) increasing with an increase in temperature.

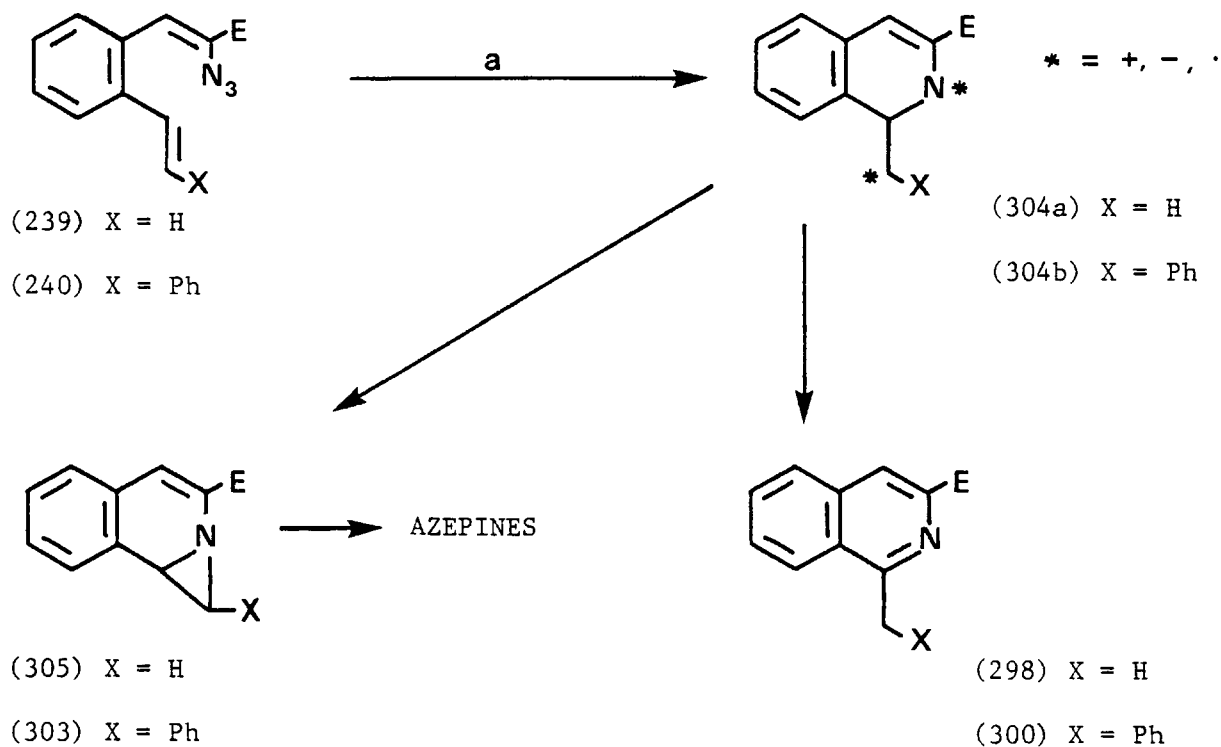


When the decomposition was carried out in refluxing benzene (4.5 h) the ratio of (301):(300) was lower than in toluene, whereas in refluxing decalin (190°C, 0.25 h) the ratio was higher than in xylene. No trace of the aziridine (303) was ever observed, but when this compound was isolated, (from a reaction which will be described in section 4.6), it was shown to be cleanly converted to the benzazepine (301) on refluxing in toluene for 2 h. This suggests that (301) is formed from (240) *via* (303) under the above reaction conditions.



Possible pathways for the formation of isoquinolines (298) and (300) and azepine (301) are outlined in Schemes 38 and 39. Vinyl azide (239) decomposed at temperatures lower than those required for thermal decomposition of vinyl azides to azirines. Anchimeric assistance from the adjacent vinyl group is thus inferred.

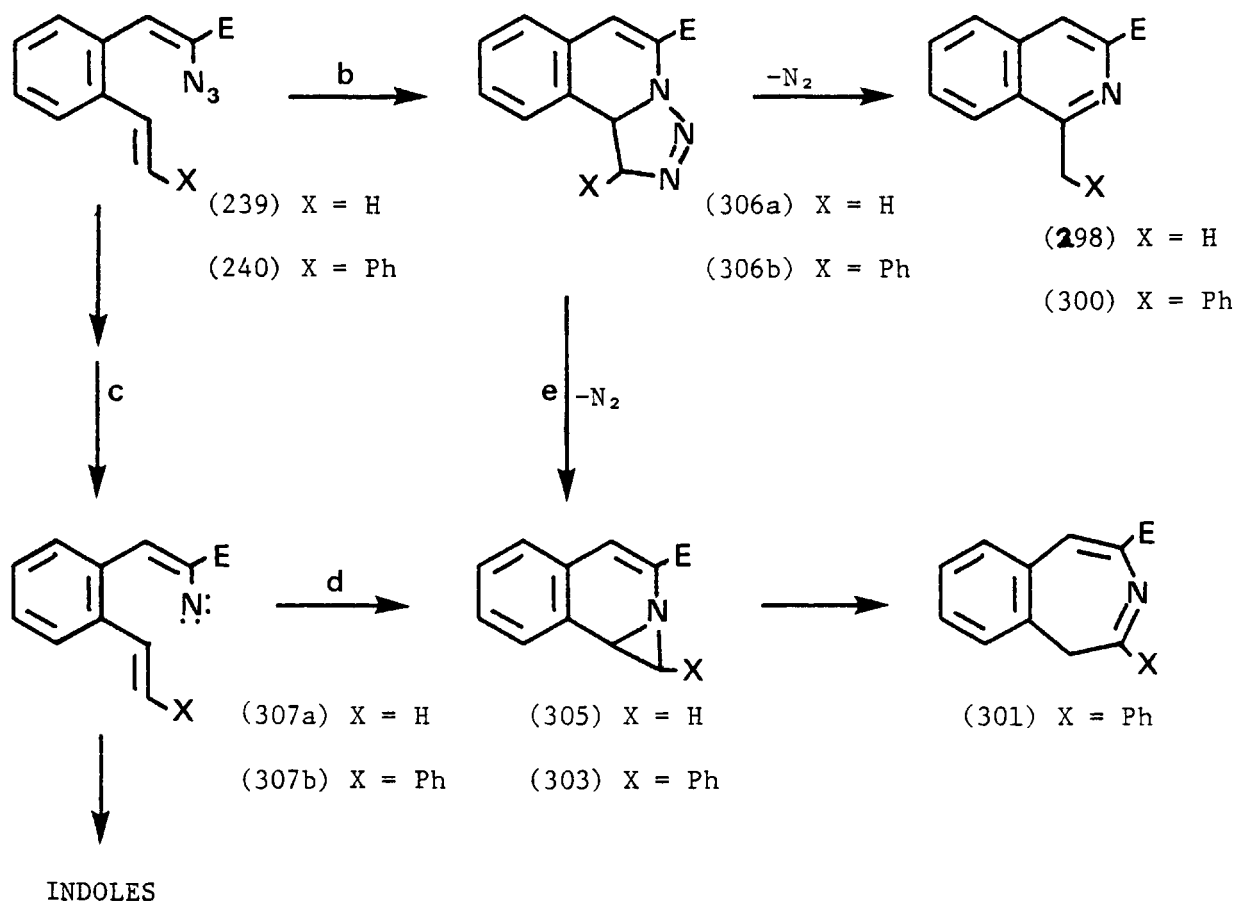
Pathway (a) is unlikely as it would predict that (240) (X = Ph) should be thermally less stable than (239) (X = H) due to the greater stability of the intermediate (304b). This is not the case, however. The intermediate (304) might also be expected to collapse to give aziridines (303) and (305), but products derived from (305) are not observed on thermolysis of (239).



SCHEME 38

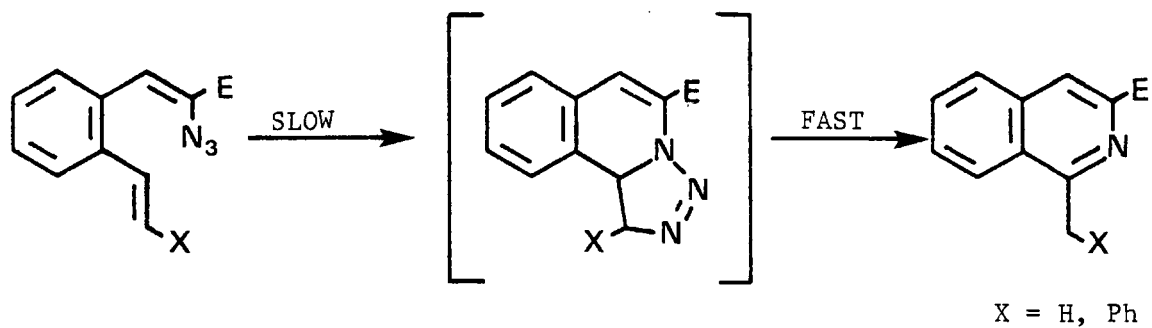
The triazoline (306) is a likely precursor of the isoquinolines (298) and (300), which can be formed by ring opening of the triazoline followed by rearrangement and loss of N_2 , in a manner similar to the formation of the azepine (289) from the azidocinnamate (237).

There are two possible routes to the aziridine (303), and hence to the azepine (301): addition of vinylnitrene (307b) to the double bond (pathway d) and decomposition of the triazoline (306) ($X = Ph$) (pathway e). The fact that the intermediate triazoline (306a) is not observed by n.m.r. on decomposition of the vinyl azide (239) in deuteriochloroform at $35^\circ C$ indicates that the slow step in the reaction is triazoline formation followed by fast triazoline decomposition (Scheme 40).



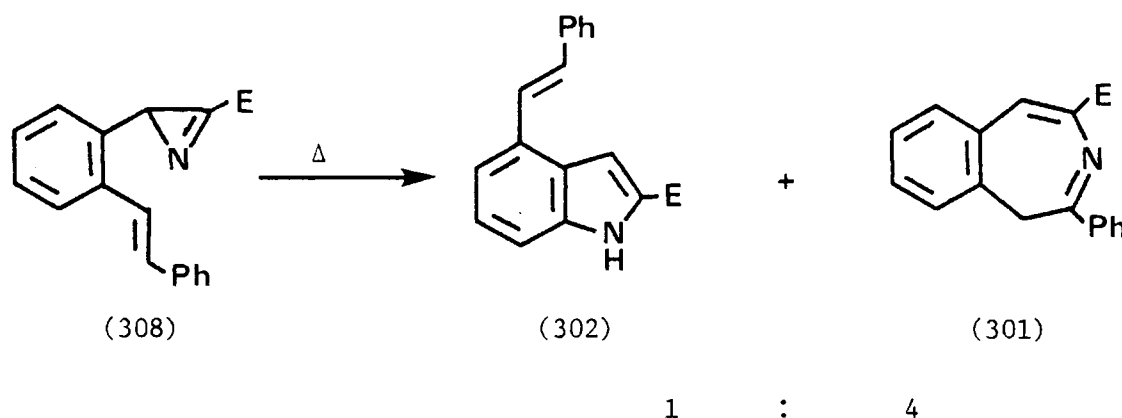
SCHEME 39

The triazoline decomposition reaction is often the slow step, but may have become the fast step in this example as a stable aromatic compound is being formed.



SCHEME 40

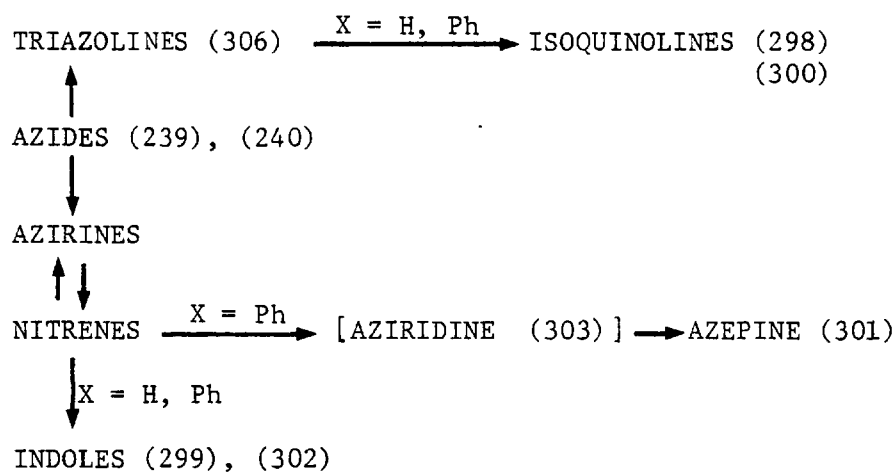
If this is so when $X = H$, then it should be equally true when $X = Ph$, hence no aziridine (303) should be formed. To attempt to determine whether or not the aziridine (303) was produced from nitrene addition to the $C=C$ bond (pathway d) the azirine (308) was prepared by photolysis of the azide with a low intensity lamp, at 350 nm in petrol for 1 h. This azirine was then heated in refluxing benzene for 4.5 h and the product mixture analysed by n.m.r. and isolation. No isoquinoline (300) had been produced, but a mixture of indole (302) and azepine (301) was produced in a ratio of 1 part indole to 4 parts azepine (quantities determined by separation by chromatography).



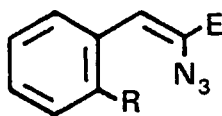
As this is roughly the ratio in which they are produced on thermolysis of the azide (240) it is almost certain that the azepine (301) was produced by pathway (d), not pathway (e) (Scheme 39). This also explains why the ratio of azepine (301) to isoquinoline (300) increases with temperature. The increase is due to increased nitrene production at higher temperatures as observed in decomposition of the *o*-allyl azido-cinnamate (237).

The observed decrease in the rate of triazoline formation in going from a vinyl-substituted azidocinnamate (238) to a styryl-substituted azidocinnamate finds precedent in the reactions of substituted styrenes with 1,3-dipoles where introduction of a second phenyl group into the α - or β -position of styrene is always accompanied by a decrease in reaction rate.²²⁰ The ease with which the vinyl azide (239) reacts intramolecularly to give the triazoline (306a) accounts for the very low yields of products which are nitrene derived, even at high temperatures (110°C).

A simple picture thus emerges; isoquinolines (298) and (300) are being formed from the azides (239) and (240) *via* triazolines (306) (pathway b) and the indoles (299) and (302) and the azepine (301) is being formed *via* a nitrene intermediate (307) (pathways c and d).



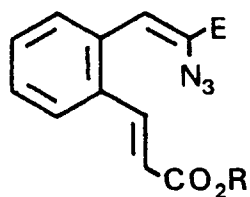
The reaction of the azidocinnamates (237), (239), and (240) to give intermediate triazolines, sometimes at relatively low temperatures suggests that the azidocinnamates exist in the *Z*-form as written (see section 2.1).



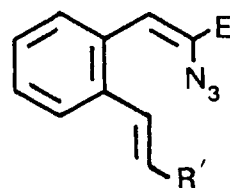
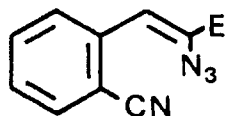
It is unlikely that *E/Z* isomerisation occurred prior to reaction. The low temperature decomposition of azidocinnamates (250) and (251) suggests that these compounds also exist in the *Z*-form.

4.5. EXTENSIONS

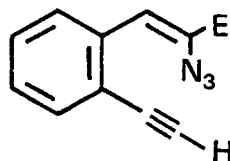
Possible extensions of this investigation include the azidocinnamates with unsaturated *o*-substituents (309)-(313).



(309)

(310) $R' = OR''$ (311) $R' = NR''_2$ 

(312)



(313)

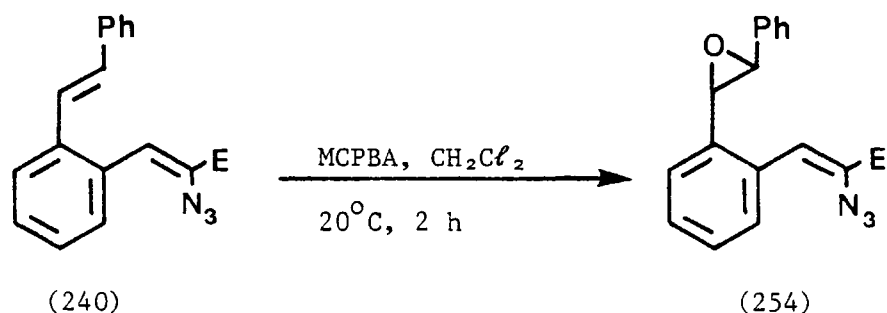
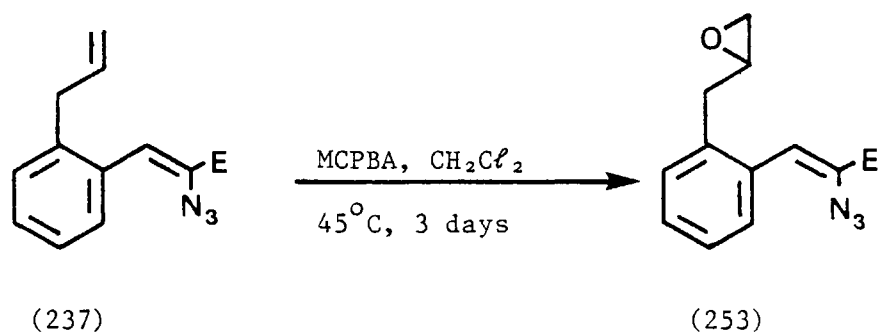
The reaction of (309) to give triazolines is expected to be very fast, by analogy with the reaction of phenyl azide with methyl acrylate.²¹⁶ High yields of isoquinolines are expected. On the other hand, triazoline formation from (310) and (311) should be very slow for electronic reasons, the addition of a nitrene onto the electron-rich double bond being the expected reaction, giving aziridines, and eventually azepines. The azidocinnamates (312) and (313) may not be stable to the temperatures required for cycloaddition of azides to nitriles or acetylenes. The 4-substituted indoles are the expected major products.

4.6. 'PROTECTION' OF THE SIDE CHAIN C=C BOND.

In an attempt to prevent interaction of the azido group or the nitrene with adjacent C=C bonds the vinyl azides (237) and (240) were treated with 3-chloroperbenzoic acid in methylene chloride to epoxidise the side chain double bonds. The epoxidation of (240) proceeded readily at room temperature, whereas (237) required refluxing in methylene chloride for several days. No epoxidation of the azido-substituted C=C bond was observed.

The azidocinnamate (254) was isolated as a white crystalline solid in 56% yield and appeared to be stable to chromatography. However, the epoxide (253), an oil, was very unstable to chromatography on both silica gel and basic alumina.

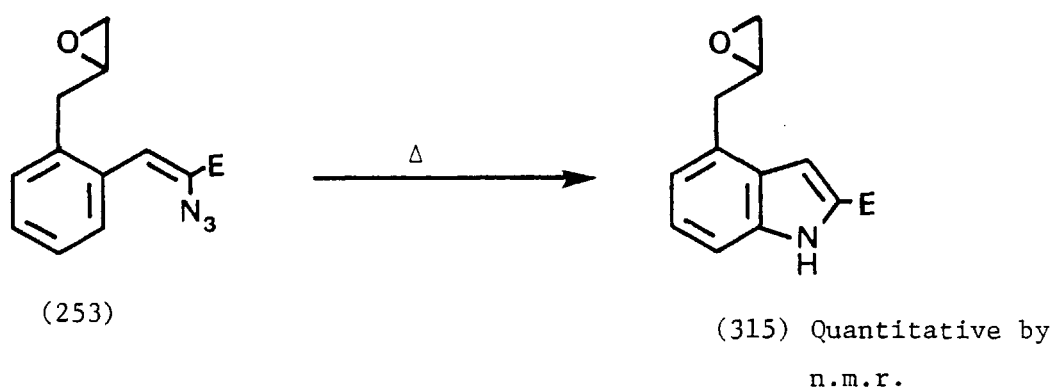
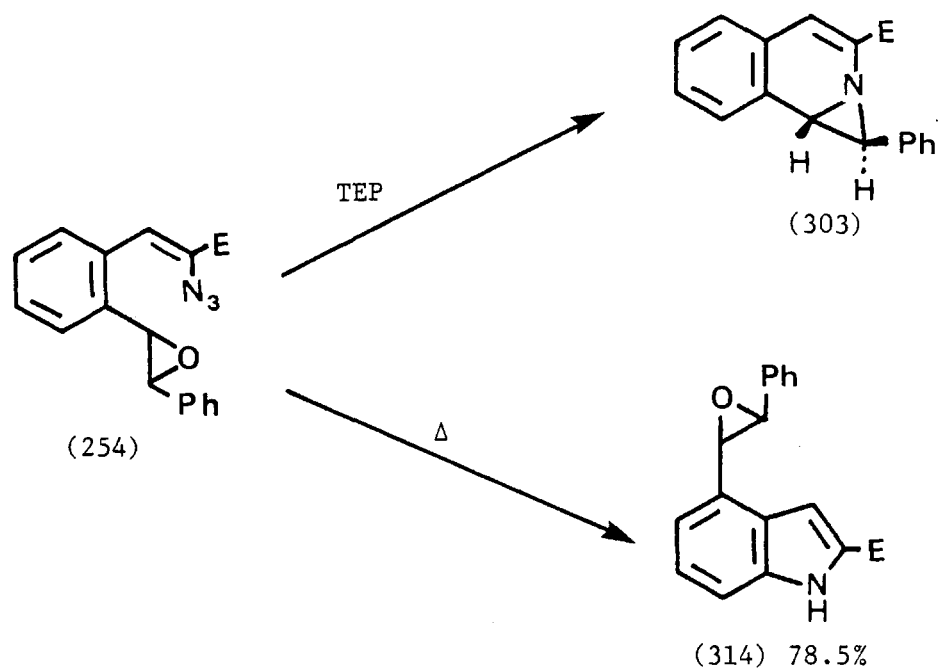
When a solution of (254) in toluene was heated at 110°C for 4.5 h the corresponding indole (314) was isolated in 78.5% yield. A sample of (253) when decomposed under the same conditions for 1.75 h was



cleanly converted to the indole (315), as shown by an n.m.r. spectrum of the total pyrolysate.

Treatment of the epoxide (254) with TEP (1.1 molar equivalents) in THF at room temperature for 12 h gave the aziridine (303) as the major product (40%), presumably *via* an iminophosphorane intermediate. Iminophosphanes are known to react intermolecularly with epoxides to give both aziridines and imines.²²¹ No trace of the corresponding imines (300) and (301) were observed however. As described previously, thermolysis of the aziridine (303) gave the azepine (301).

The indoles (314) and (315) should prove to be useful precursors for a variety of other 4-substituted indoles as epoxides can be modified by reaction with nucleophiles to give ring-opened species and deoxygenation to give alkenes.



A general picture thus emerges of interaction with an adjacent unsaturated substituent in preference to indole formation. However, when the unsaturation is removed by epoxidation interaction with the aromatic ring is preferred over reactions with the side chain, and indoles are the major products.

CHAPTER FIVE

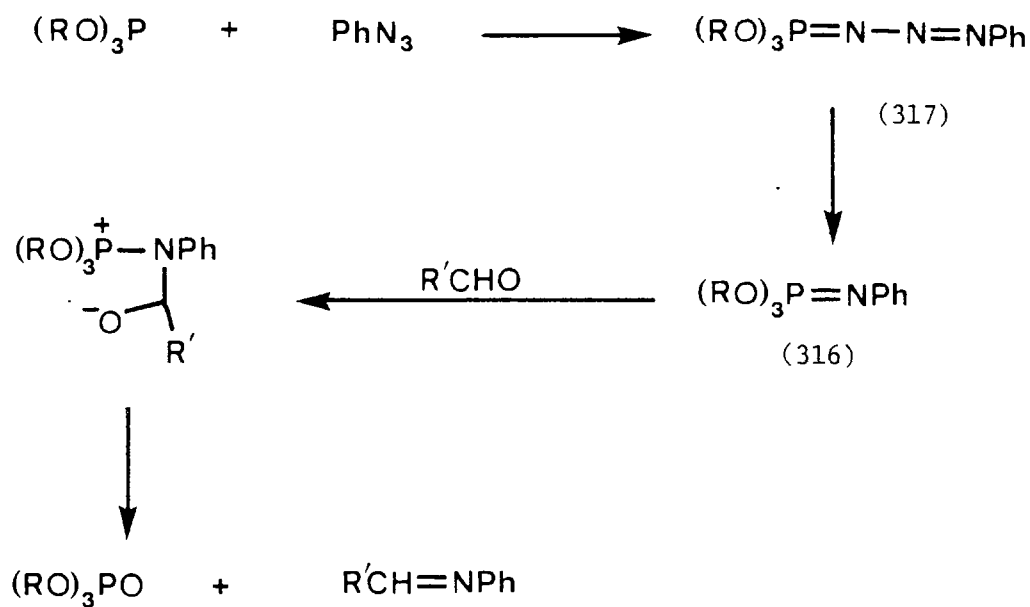
DECOMPOSITION OF AZIDOCINNAMATES CONTAINING

ORTHO-CARBONYL GROUPS

CHAPTER FIVE: DECOMPOSITION OF ALIDOCINNAMATES CONTAINING ORTHO-
CARBONYL GROUPS.

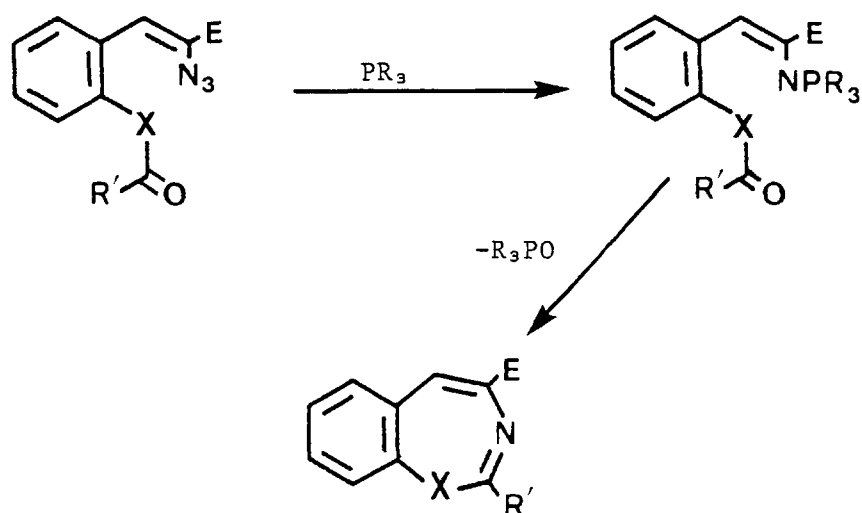
5.1. INTRODUCTION

Iminophosphoranes (316) have found wide use in the synthesis of a variety of nitrogen-containing compounds, including heterocyclics. They behave analogously to phosphoranes and react with carbonyl compounds to give C=N bonds, as shown in Scheme 41. The most common method of preparation of iminophosphoranes is by treatment of azides with phosphorus (III) reagents.²²¹ The initially formed triazenes (317) decompose to give the ylides (316).



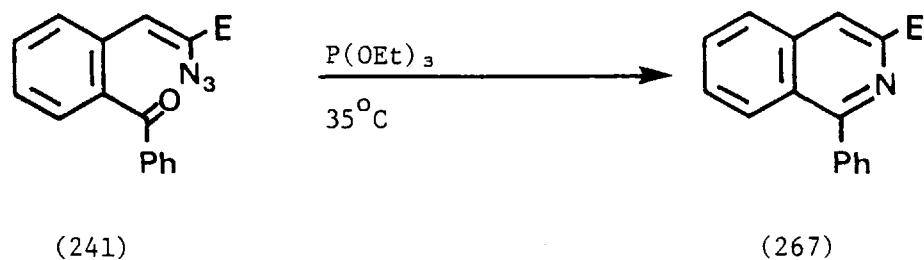
SCHEME 41

This ready conversion of the α -nitrogen of an azide into a good nucleophile suggested that a variety of heterocyclic compounds could be formed from azidocinnamates with *o*-side chains containing carbonyl groups (equation 28). In particular, the formation of isoquinolines [$X = (CH_2)_o$] would be a synthetically useful reaction.

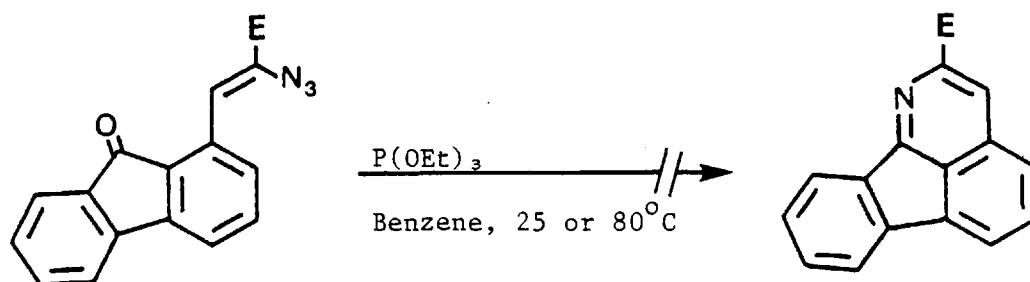


5.2. REACTION OF AZIDOCINNAMATES WITH *o*-CARBONYL GROUPS WITH TRIETHYLPHOSPHITE (TEP).

Several *o*-carbonylazidocinnamates were prepared to test this hypothesis. Treatment of vinyl azides (241) with triethylphosphite (TEP) (3 molar equivalents) in cyclohexane at 35°C for 1 h gave a quantitative yield of the isoquinoline (267).

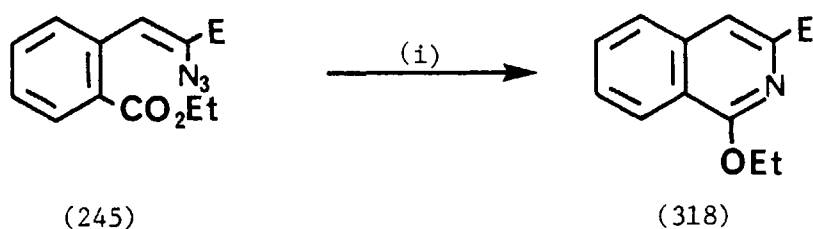


The structurally similar fluorenone derivative (242) did not, however, give any of the expected azafluoranthene (271) on treatment with TEP, even on heating. Decomposition of the azide did occur but no cyclisation to the 9-position on the fluorene ring was observed.



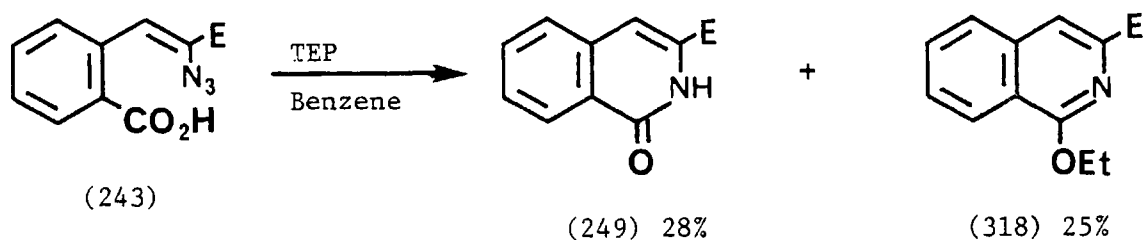
This parallels the low yields of (271) from the vinyl azide (234) on thermolysis. On examination of the models of the iminophosphoranes derived from (241) and (242) it can be seen that the rigidity of the fluorenone system renders attack of the iminophosphorane moiety on the C=O bond very much less favourable than attack in the non-constrained benzophenone system.

Ethyl 1-ethoxyisoquinoline-3-carboxylate (318) was obtained in 90% yield on treatment of vinyl azide (245) with TEP (2 molar equivalents) in benzene at 50-60°C for 0.5 h.



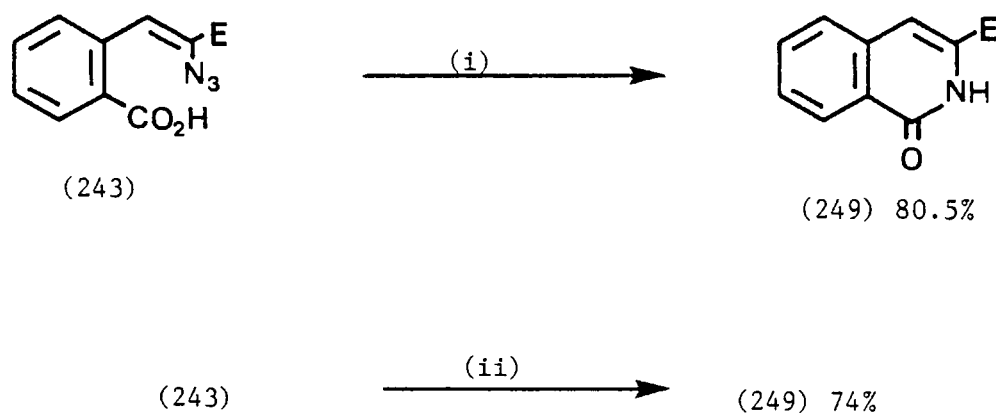
(i) TEP (2.0), benzene, 50-60°C, 0.5 h

However, when azide (243) was treated with TEP under similar conditions only 28% of the expected isoquinolone (249) was obtained. The only other identified product was the isoquinoline (318) (25%).



The isoquinoline (318) was not formed by alkylation of (249) by the triethylphosphate produced in the reaction mixture. Both the starting material (243) and the isoquinolone (249) were recovered unchanged after treatment with triethylphosphate under the same conditions.

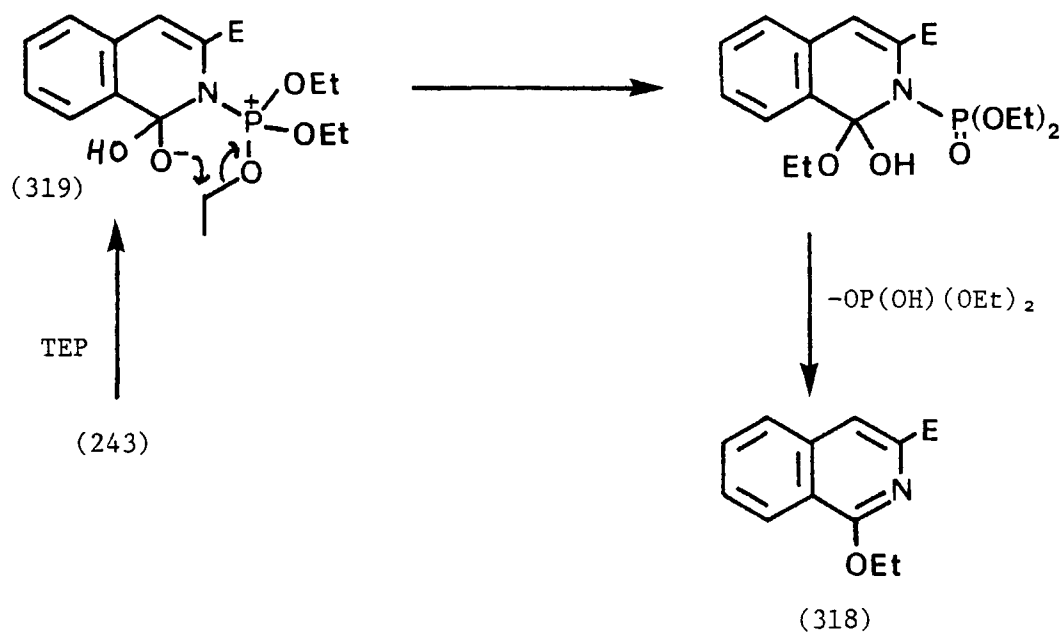
Surprisingly, no isoquinoline (318) was produced when 2 equivalents of triethylphosphate were added to the reaction mixture, and the yield of isoquinolone (249) was increased to 80.5%. A similar effect was observed when other solvating compounds were added to the benzene solution. When (243) was treated with TEP in benzene in the presence of small amounts of DMF or DMSO, the isoquinolone (249) was again the major product, with no isoquinoline (318) observed, and when the reaction was carried out using THF as solvent, instead of the less polar benzene, the isolated yield of (249) was 74%.



(i) TEP (1.1), Benzene, $\text{OP}(\text{OEt})_3$ (2.2), 20°C ;

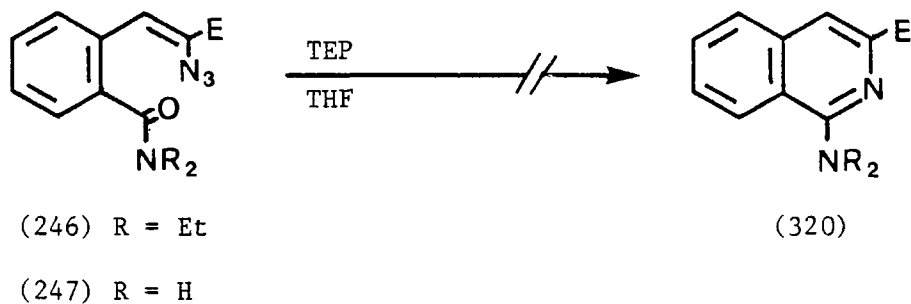
(ii) TEP (1.1), THF, 20°C .

It is likely that the ethoxyisoquinoline (318) is produced by an intramolecular alkylation in the intermediate (319) *via* a six-membered transition state (Scheme 42). This reaction is apparently disfavoured in good solvating media such as DMF, DMSO, triethylphosphate, and THF.

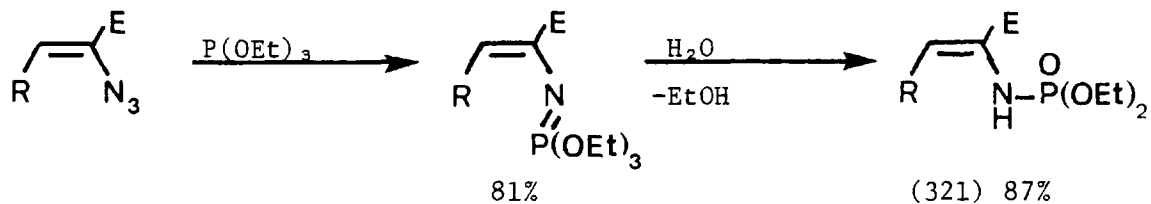


SCHEME 42

When the amides (246) and (247) were treated with TEP in THF, the corresponding isoquinolines (320) were not isolated. It may be possible, by varying conditions, or reagents to achieve this transformation.



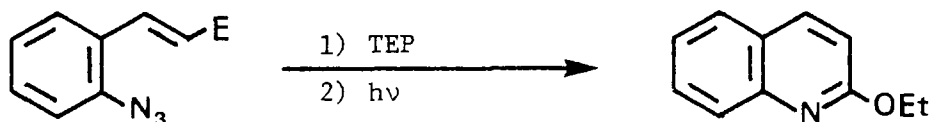
Iminophosphoranes derived from vinyl azides and TEP have previously been prepared,²²² and have been shown to be stable to heat. On chromatography they rearranged to give 2-diethoxyphosphinylamino-2-alkenoates (321).



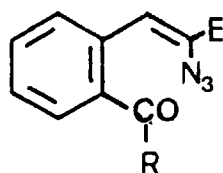
R = Me, Et, *n*-Pr, *i*-Pr, Ph.

While these ylides have not been reacted with electrophiles, there is one intramolecular example in the literature.²⁰⁰

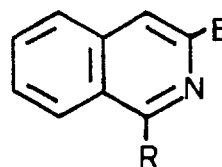
While a variety of heterocyclic compounds have been prepared by inter- and intramolecular reactions of iminophosphoranes, there are apparently no examples of isoquinoline formation by such reagents; quinolines, however, have been formed by treatment of *o*-azidocinnamates with TEP, followed by photolysis.²²³



The above results show that vinyl azide decomposition with TEP provides a mild and high yielding route to isoquinolines (323, R = Ph, OH, OEt). The generality of this route has yet to be fully demonstrated.



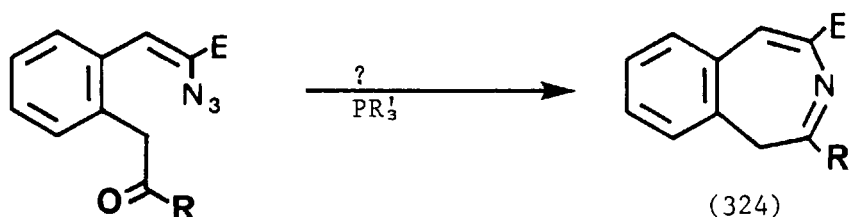
(322)



(323)

Attempts to prepare the systems (322, R = H, Me) were unsuccessful. These would give 1-unsubstituted- and 1-methylisoquinolines respectively. Attempts to condense 2-acetylbenzaldehyde (227) with ethyl azidoacetate, not surprisingly, failed probably due to self-condensation of the aldehyde. The condensation of *o*-phthalaldehyde also failed, although it may be possible to prepare (322, R = H) from the monoacetal of *o*-phthalaldehyde by condensation, followed by deprotection. Routes to *o*-ketoazidocinnamates (322) (R = Alk, Ar) *via* reactions of organometallic reagents with the intermediates (250) and (251) (section 2.4) may prove feasible.

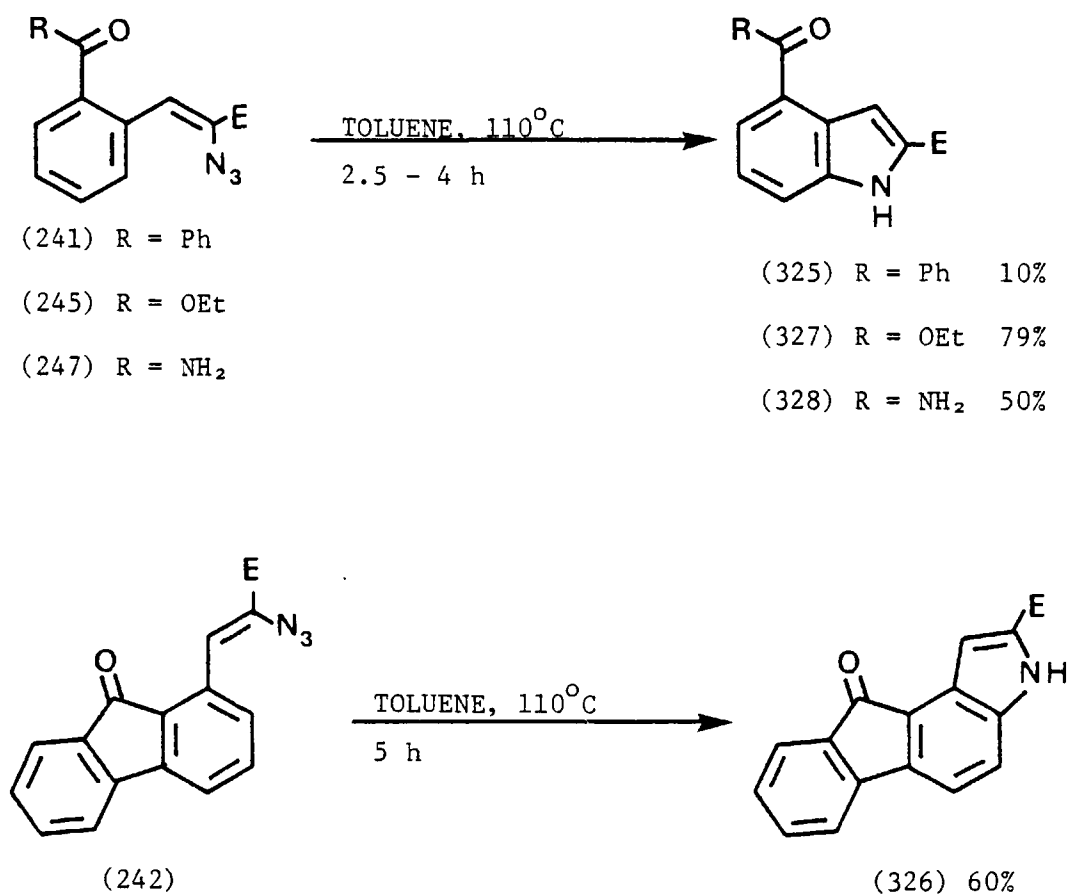
A further extension of this C=N bond forming reaction to the synthesis of rings of larger sizes, *i.e.*, X = CH₂ or C₂H₄ in equation 28, in particular benzazepines (324) when X = CH₂, may also be possible.



5.3. THERMAL DECOMPOSITION OF AZIDOCINNAMATES WITH *o*-CARBONYL GROUPS.

The vinyl azides described above (241)-(243), (245) and (247) were expected to give either 4-substituted indoles or products derived from interaction with the *o*-carbonyl groups on thermolysis. When the

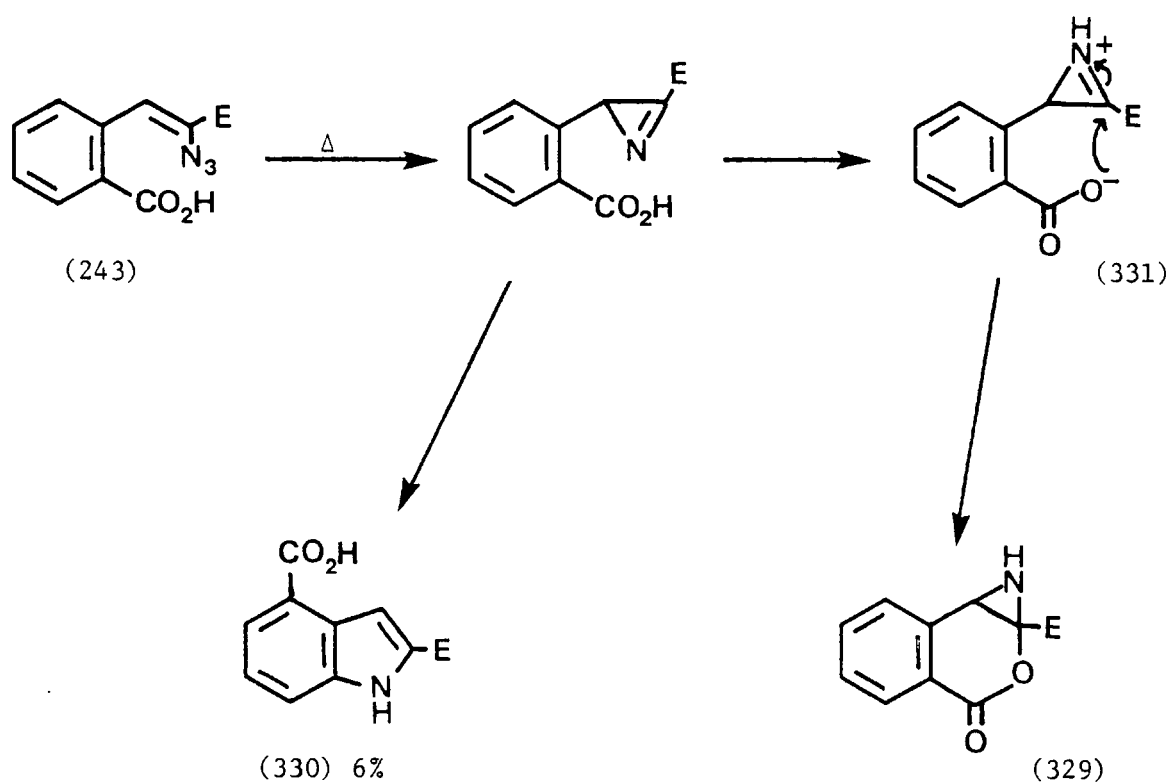
o-substituent was an alkene then 80-90% of the products obtained were derived from reaction with the unsaturated substituent (Chapter 4). However, heating solutions of the azides (241), (242), (245) and (247), in toluene (2.5-5 h) gave the corresponding indoles (325)-(328) in poor to good yields (Scheme 43).



SCHEME 43

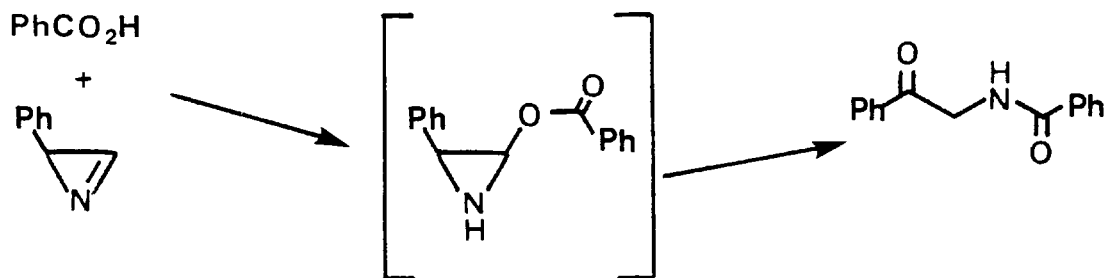
Vinyl azides (241) and (247) gave product mixtures on thermolysis that were difficult to separate and identify. No recognisable products other than the indoles could be isolated.

The *o*-carboxyazidocinnamate (243) behaved differently. On heating in toluene for 2.5–22 h (243) gave, after chromatography, 83–89% of a colourless crystalline compound to which the structure (329) was assigned based on spectral data. The corresponding indole (330) was also isolated (6%). The formation of the aziridine (329) is rationalised by intramolecular nucleophilic attack of the carboxylate ion on the protonated azirine in the intermediate (331) (Scheme 44).

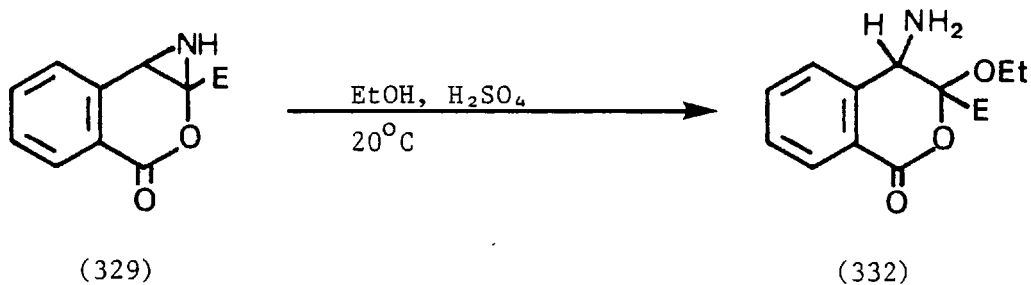


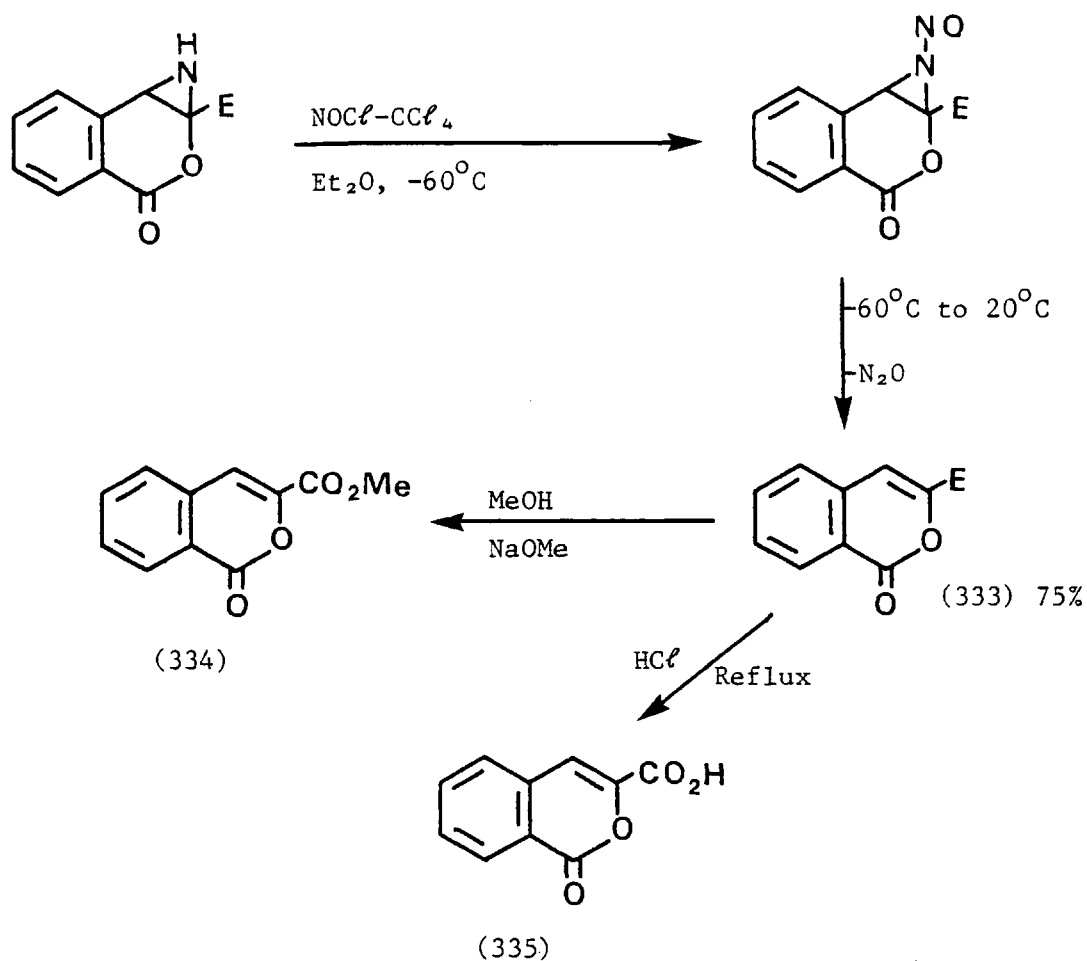
SCHEME 44

The intermolecular reaction between carboxylic acids and azirines is well documented, but the intermediate aziridines were not isolated as they rearranged to amides, *e.g.*, Scheme 45.⁷² The steric constraints on the cyclic system (329) prevents such a rearrangement occurring in this case.



On treatment with concentrated sulphuric acid in ethanol the aziridine (329) formed an addition product. The structure (332) fits the spectral data. Addition of ethanol to aziridines is known to give β -ethoxyamines.²²⁴ When a solution of (329) and triethylamine in ether at -60°C was treated with a solution of nitrosyl chloride in carbon tetrachloride and allowed to warm to room temperature the isocoumarin (333) was isolated in 75% yield. *N*-Nitrosoaziridines are known to extrude N_2O readily.²²⁵ The structure of (333) was confirmed by conversion to the corresponding methyl ester (334), m.p. $172\text{--}175^{\circ}\text{C}$ (lit.²²⁶ $173\text{--}174^{\circ}\text{C}$) and the acid (335) m.p. $250\text{--}253^{\circ}\text{C}$ (lit.²²⁷ $245\text{--}246^{\circ}\text{C}$).





5.4. CONCLUSIONS

The decomposition of *o*-carbonylazidocinnamates (322) provides routes to 1,3-disubstituted isoquinolines and 2,4-disubstituted indoles. The substituents, *e.g.*, CONH_2 , can be further modified to give synthetically useful heterocyclics. 4-Formylindoles are precursors for many natural products and are often difficult to obtain.²⁰⁷ The isoquinolone ring system is contained in alkaloids such as thalactamine and doryamine.²²⁸

Both the thermal decomposition of *o*-carbonylazidocinnamates to give indoles and decomposition with phosphorus reagents to give isoquinolines and isoquinolones should prove to be general and easily extended reactions.

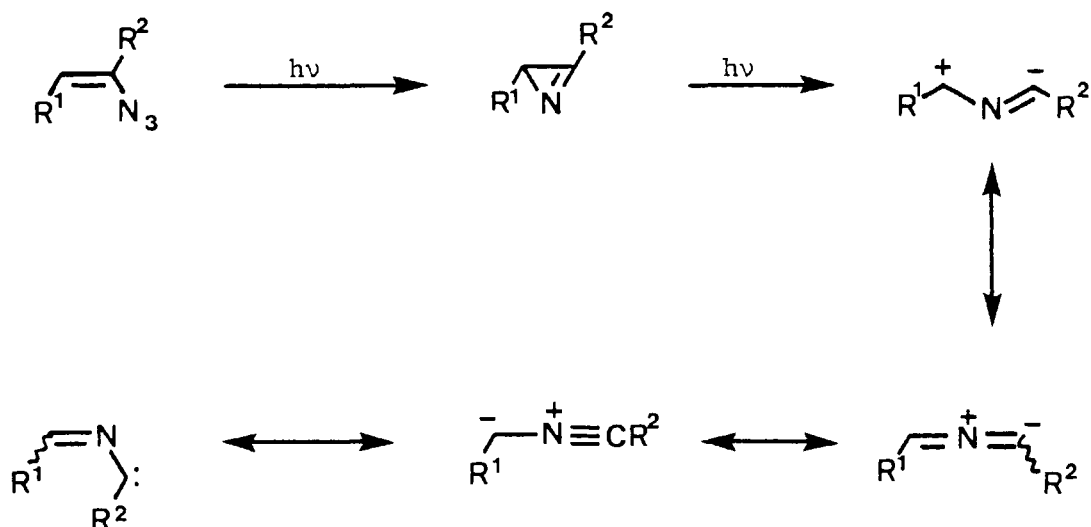
CHAPTER SIX

PHOTOCHEMICAL DECOMPOSITION OF VINYL AZIDES

CHAPTER SIX: PHOTOCHEMICAL DECOMPOSITION OF VINYL AZIDES.

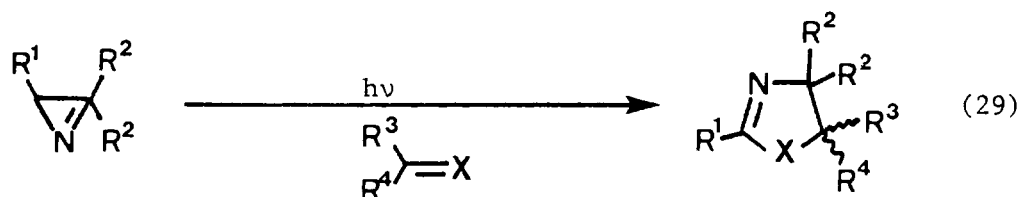
6.1. INTRODUCTION

Vinyl azides decompose on photolysis to azirines.³⁶⁻³⁸ Whereas the thermal reactions of azirines usually occur *via* reversible C-N bond cleavage to give vinylnitrenes, photochemical reactions occur *via* irreversible C-C bond cleavage to give nitrile ylides, which can react as 1,3-dipoles or as carbenes in both inter- and intramolecular reactions.



The photochemical reactions of azirines have been summarised in recent papers and reviews.^{33,35, 229,230.} Typical reactions are exemplified in equations 29 - 31.. Both inter- and intramolecular 1,3-dipolar cycloaddition occur (equation 29). Included in this type of reaction are the dimerisation and crossed-dimerisations of azirines (equation 30). These dimers were found to be photolabile rearranging to diazohexatrienes (337) (equation 31). The formation of (339)

by irradiation of the azirine (338) is an example of the 1,1-cycloaddition reactions of 2H-azirines.

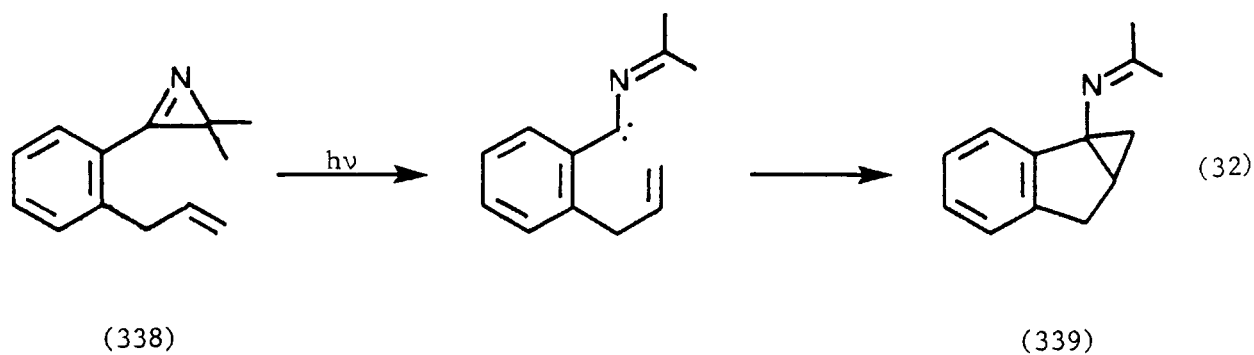
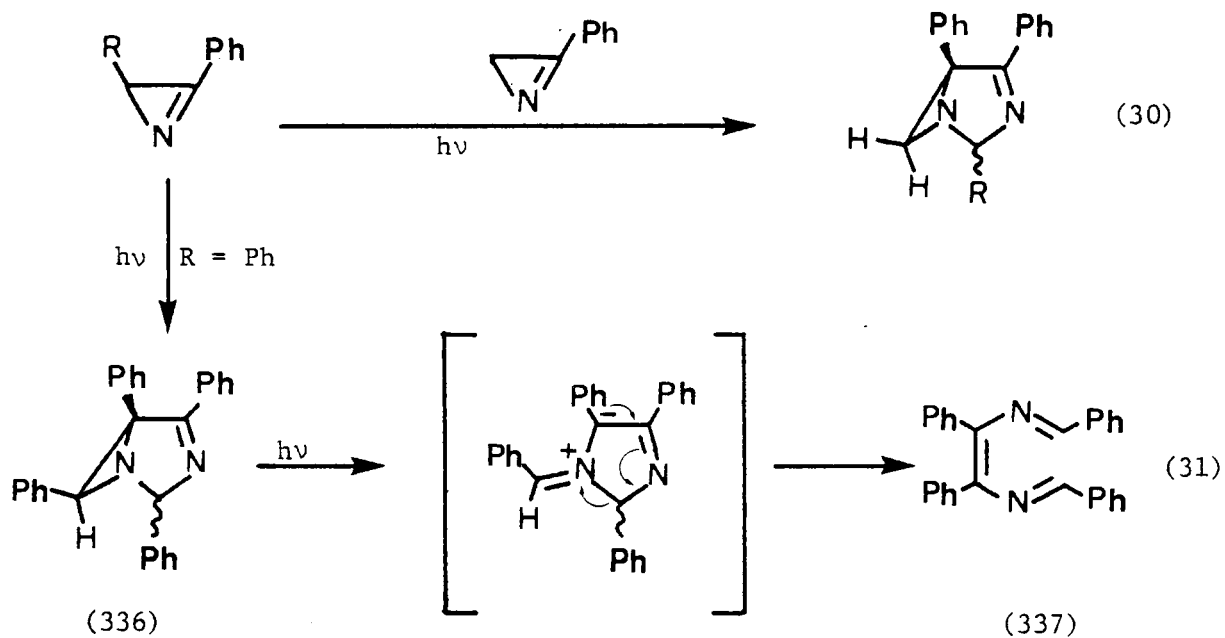


$\text{X} = \text{CH}_2$, $\text{R}^3 = \text{H}$, $\text{R}^4 = \text{CO}_2\text{Me}$, CN ;

$\text{X} = \text{O}$, $\text{R}^3 = \text{OEt}$, $\text{R}^4 = \text{CN}$;

$\text{X} = \text{S}$, $\text{R}^3 = \text{SMe}$, $\text{R}^4 = \text{Ph}$;

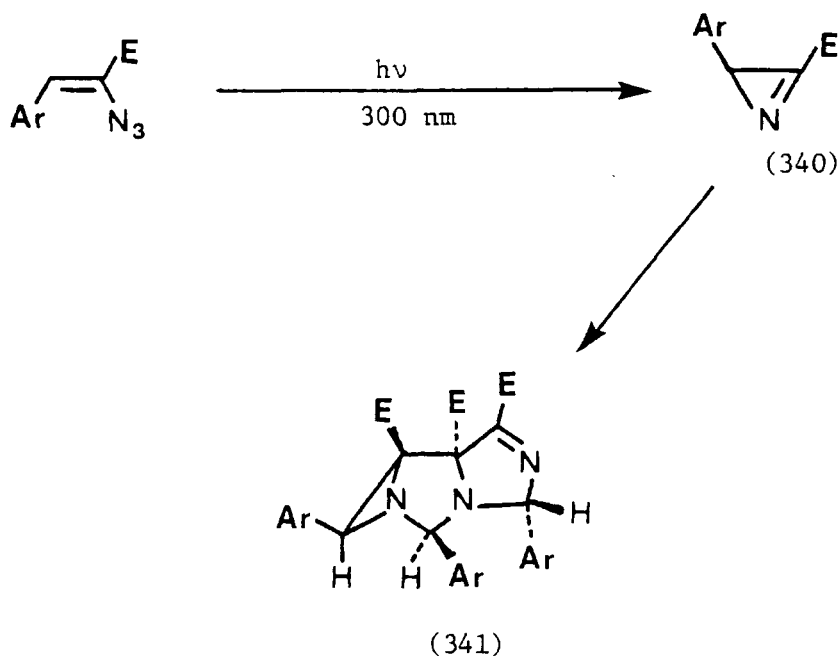
$\text{X} = \text{O}$, CH_2 , $\text{R}^3, \text{R}^4 = \text{NR}$, CHR .



6.2. PHOTOCHEMICAL DECOMPOSITION OF AZIDOCINNAMATES TO GIVE AZIRINE TRIMERS.

The photochemistry of azidocinnamates and the corresponding 2-arylazirine-3-carboxylates has not been previously studied.

Solutions of the azidocinnamates (233)-(236) and (244) in petrol were irradiated at 300 nm. The major products isolated were trimers of the azirines (340), the triazatricyclononenes (341, a-e) (Table 6). In a separate experiment, azirine (340, Ar = 2-tolyl) was isolated by photolysis of (235) at lower light intensity, and shown to be converted into the trimer (341c) on further irradiation.



The structure and relative stereochemistry of the trimer (341c) was determined by X-ray crystallography (Figure 1). Only one stereoisomer of the trimer was observed. N.O.e. difference spectra of (341c) allowed assignment of the various ^1H n.m.r. signals to particular groups in the

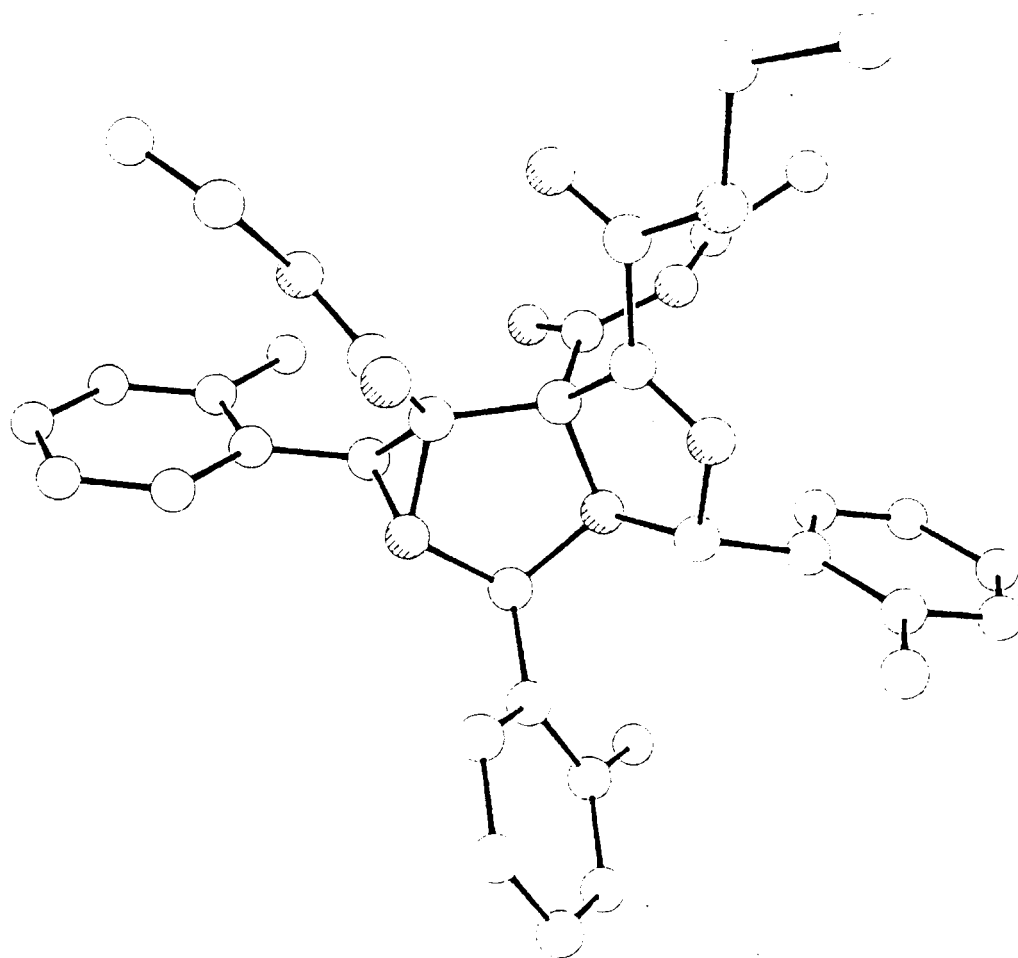


Figure 1. X-ray structure of triethyl 2,4,9-tri-(2-methylphenyl)-1,3,8-triaza-tricyclo[4.3.0.0^{3,5}]non-7-ene-5,6,7-tricarboxylate (341c).

TABLE 6. Photolysis of azidocinnamates (233)-(236) and (244).

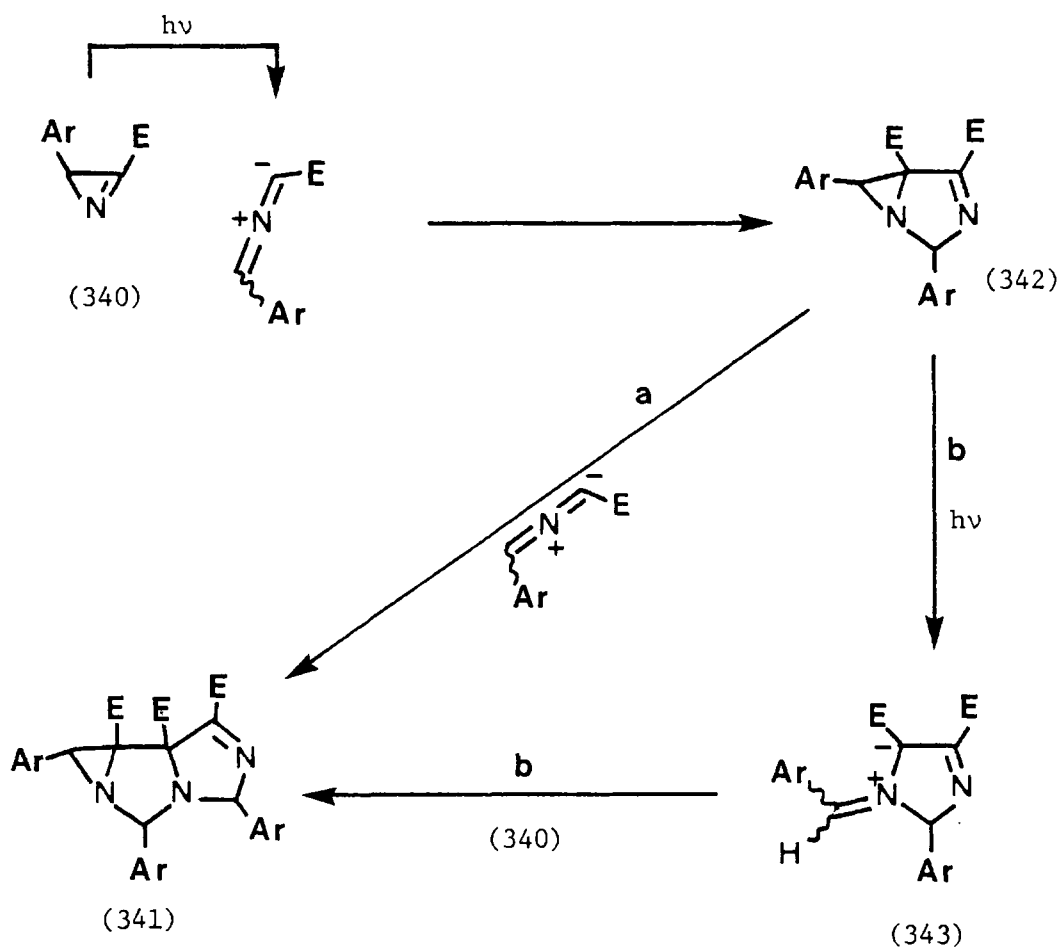
Starting Material $\text{ArCH}=\text{C}(\text{N}_3)\text{E}$		Reaction Time	Yields of (341, a-e) (%)
(233)	Ar = 2-PhCH ₂ -C ₆ H ₄	1 h	(a) 40
(234)	Ar = Fluoren-1-yl	0.13 h	(b) 60
(235)	Ar = 2-Me-C ₆ H ₄	1 h	(c) 56
(236)	Ar = Me ₂ CH-C ₆ H ₄	1 h	(d) 57
(244)	Ar = Ph	1 h	(e) 66

molecule and showed that the compound had the same average conformational structure in deuteriochloroform solution as in the solid state (see Appendix).

The trimer (341) is probably produced by initial formation of a dimer (342), followed by either addition of another azirine (pathway a) or a nitrile ylide (pathway b) (Scheme 45).

Evidence for the formation of dimer (342) as an intermediate in the photolysis reactions was sought. Although an intermediate could be detected by n.m.r., there was insufficient evidence to assign it the structure (342) unambiguously.

Only one diastereomer of the trimer (341) was isolated, in contrast to the previously reported dimers (equation 30) which were formed as diastereomeric mixtures. In order to account for the observed stereo-

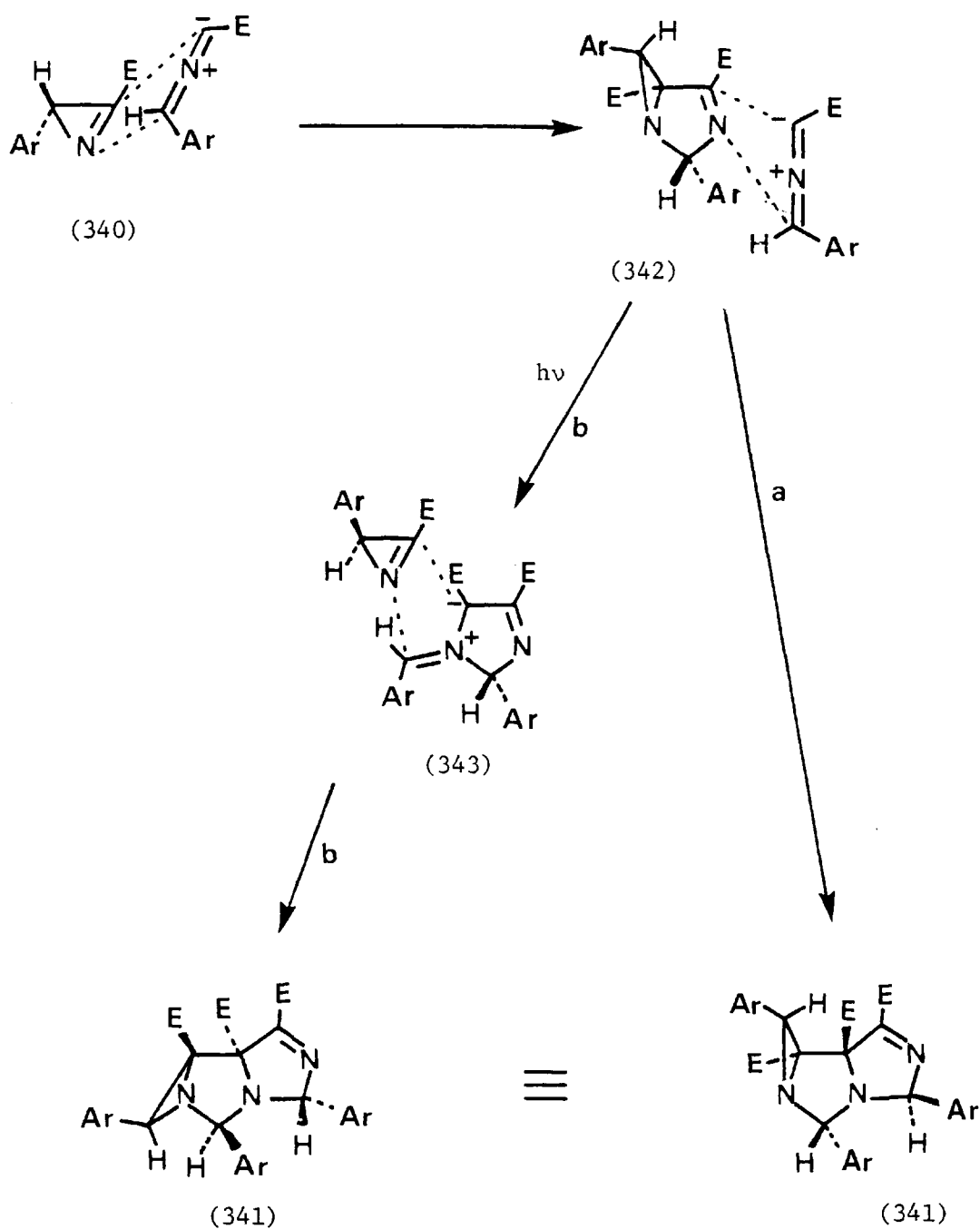


SCHEME 45

specificity by either pathway (a) or (b) the additions must occur as shown in Scheme 46.

In pathway (a) the addition of the nitrile imine to the azirine (340) to give the dimer (342) must be stereospecific, as shown, and this must be followed by a stereospecific addition of a nitrile ylide to the more hindered face of the dimer to give the observed trimer stereochemistry.

In pathway (b) the formation of (342) does not have to be stereospecific as the ring opening reaction to give the azomethine ylide (343) destroys the stereochemistry at two of the centres. The ylide



SCHEME 46

(343) must then add to the least hindered face of the azirine (340) to give the observed product (341).

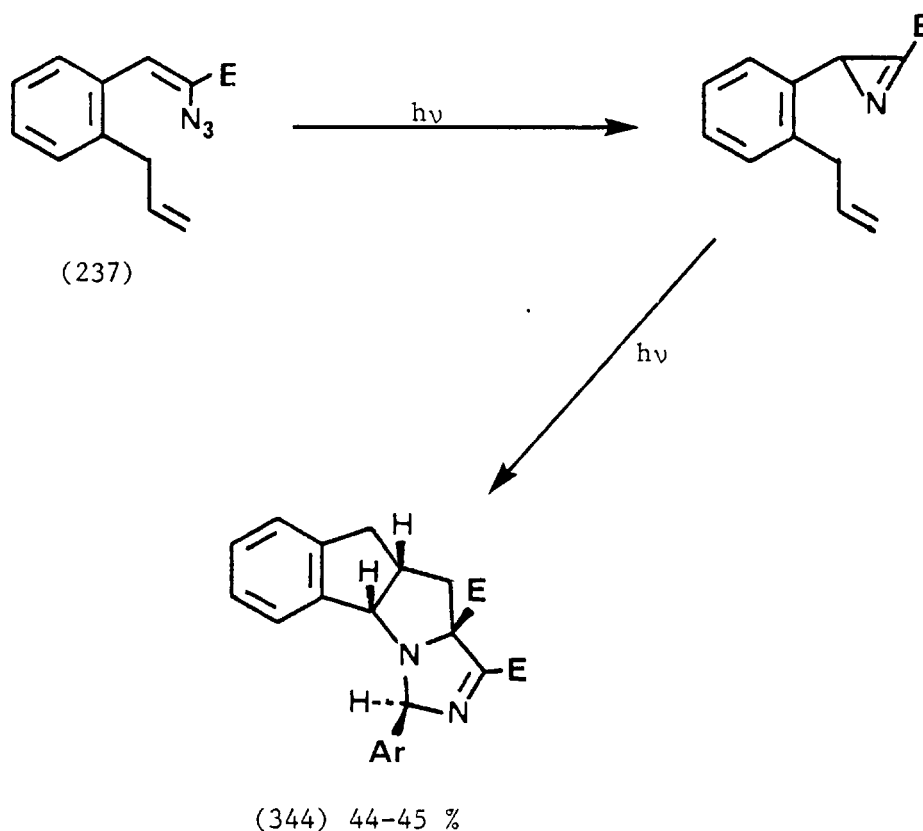
These steric factors therefore indicate that the most likely mechanism for formation of (341) is pathway (b) (Scheme 46).

6.3. PHOTOLYSIS OF VINYL AZIDES CONTAINING UNSATURATED OR NUCLEOPHILIC GROUPS.

Azirines containing unsaturated substituents would be expected to undergo intramolecular photochemical reactions. This is indeed the case.

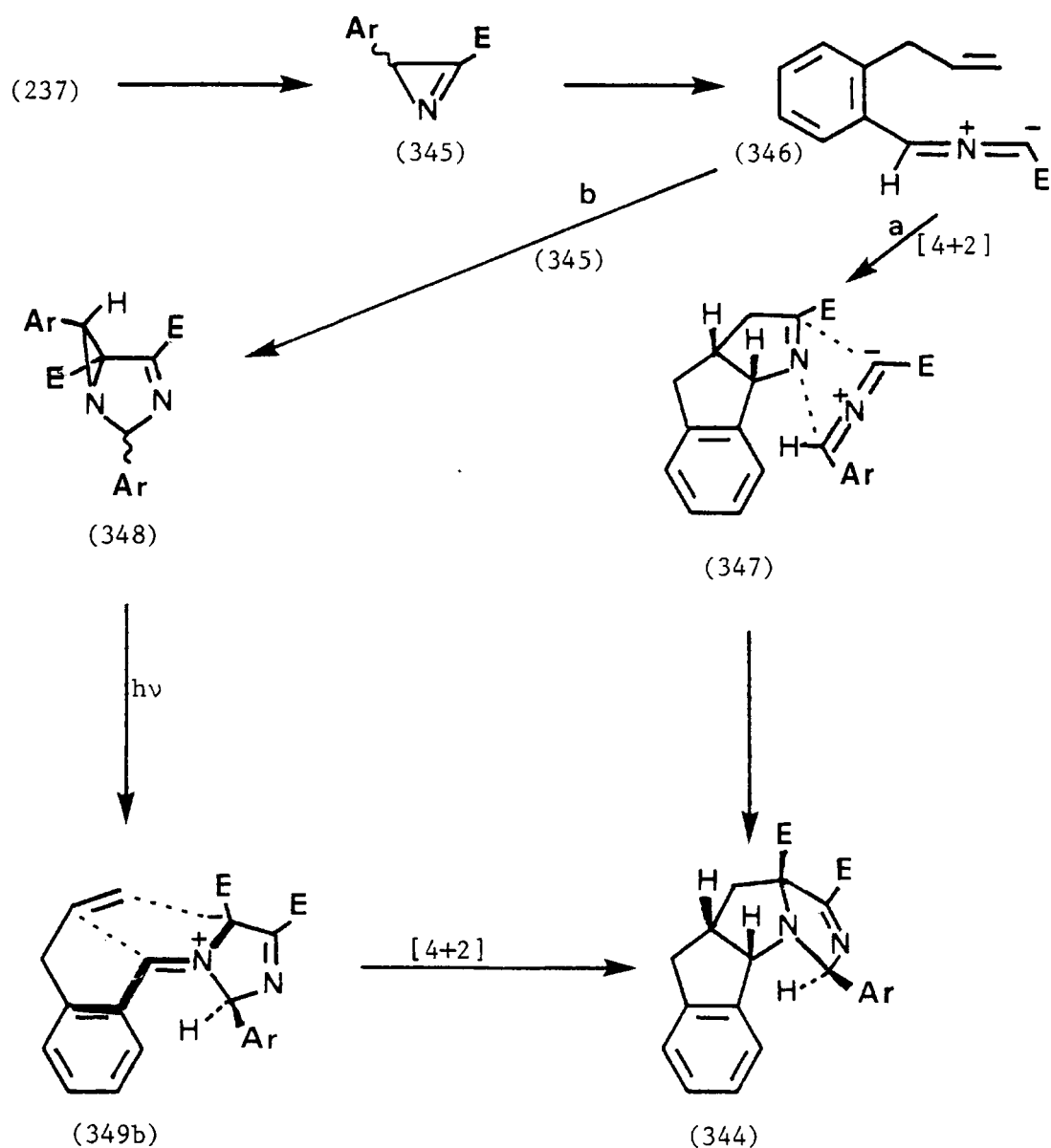
6.3.1. Photolysis of ethyl 2-azido-3-(2-allylphenyl)propenoate (237).

Photolysis of the *o*-allylazidocinnamate (237) in petrol at 300 nm for 1 h gave the azirine dimer (344) (44-54%). No trimeric products were observed. The stereochemistry was determined by n.o.e. experiments (see Appendix).



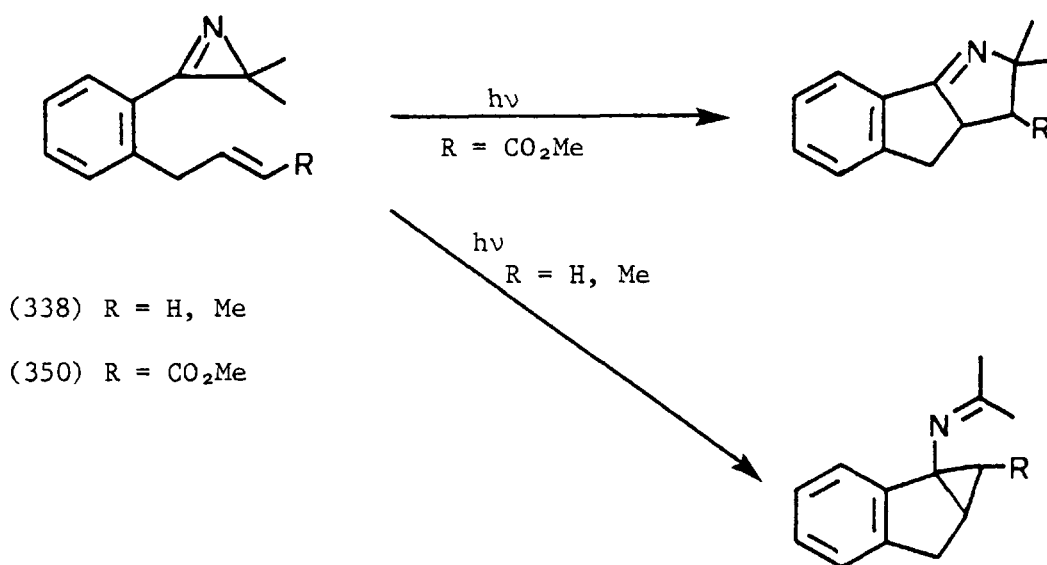
Ar = *o*-allylphenyl

Two mechanisms can again be proposed:- (i) intramolecular cycloaddition of the nitrile ylide (346) to give a 'monomer' (347), followed by intermolecular cycloaddition of another nitrile ylide to (347) (pathway a), or (ii) intermolecular addition of the nitrile ylide (346) to the azirine (345) to give a dimer (348), followed by ring opening to give the azomethine ylide (349b) which undergoes an intramolecular cycloaddition to give the isolated product (344) (pathway b) (Scheme 47).



SCHEME 47

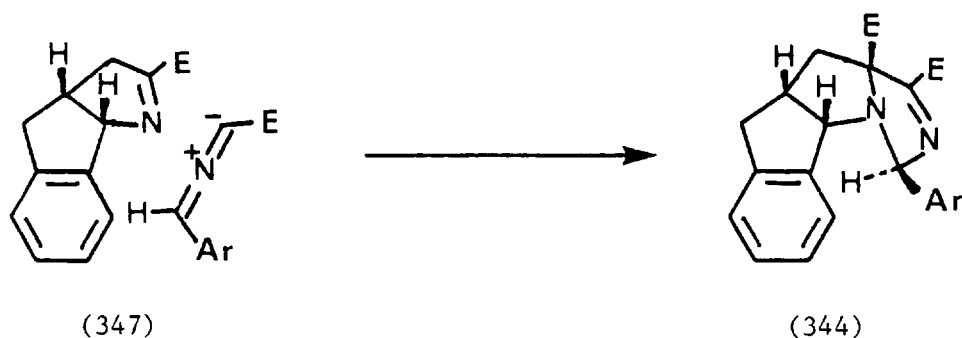
Pathway (a) requires the nitrile ylide (346) to undergo intramolecular 1,3-dipolar cycloaddition into the unactivated C=C bond. In the similar system (338) no 1,3-dipolar cycloaddition occurred and the nitrile ylide acted as an iminocarbene. Only when the C=C bond is electron deficient (350) does the [4+2] cycloaddition occur to give two fused five-membered rings.



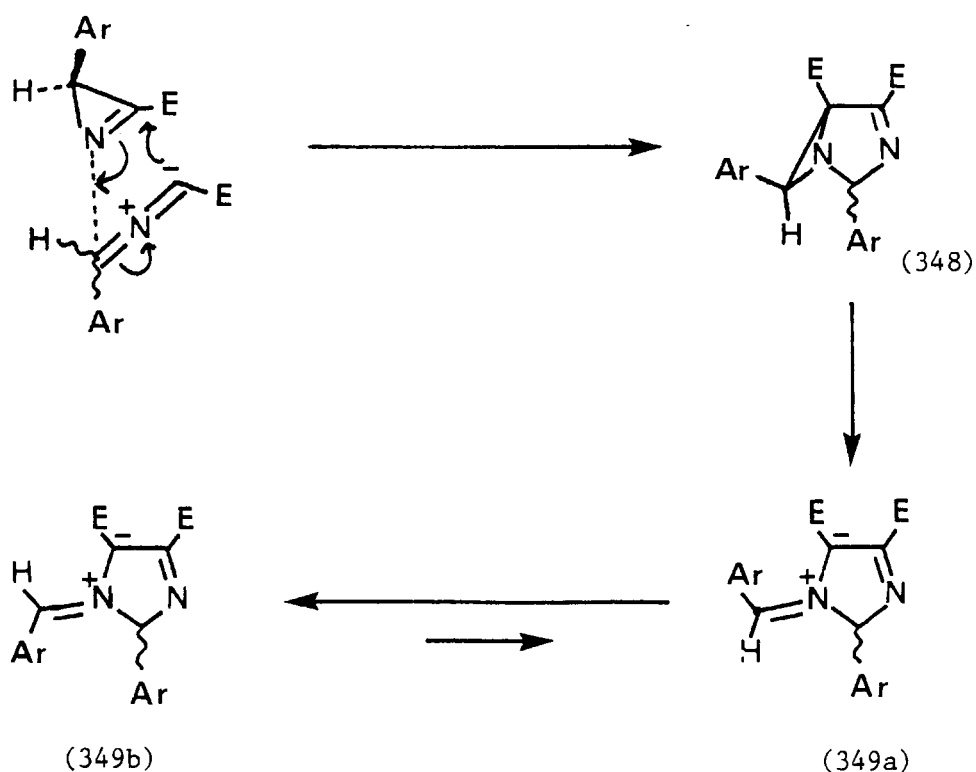
In the present work cycloaddition of nitrile ylide (346) to the unactivated C=C bond to give two fused five-membered rings is also unlikely on steric and electronic grounds. Therefore the 'monomer' (347) is unlikely to be involved.

However, if (347) were formed, then, in order to achieve the correct stereochemistry in the product (344), nitrile ylide addition to the C=N bond in (347) must occur from the more sterically hindered (*exo*) face.

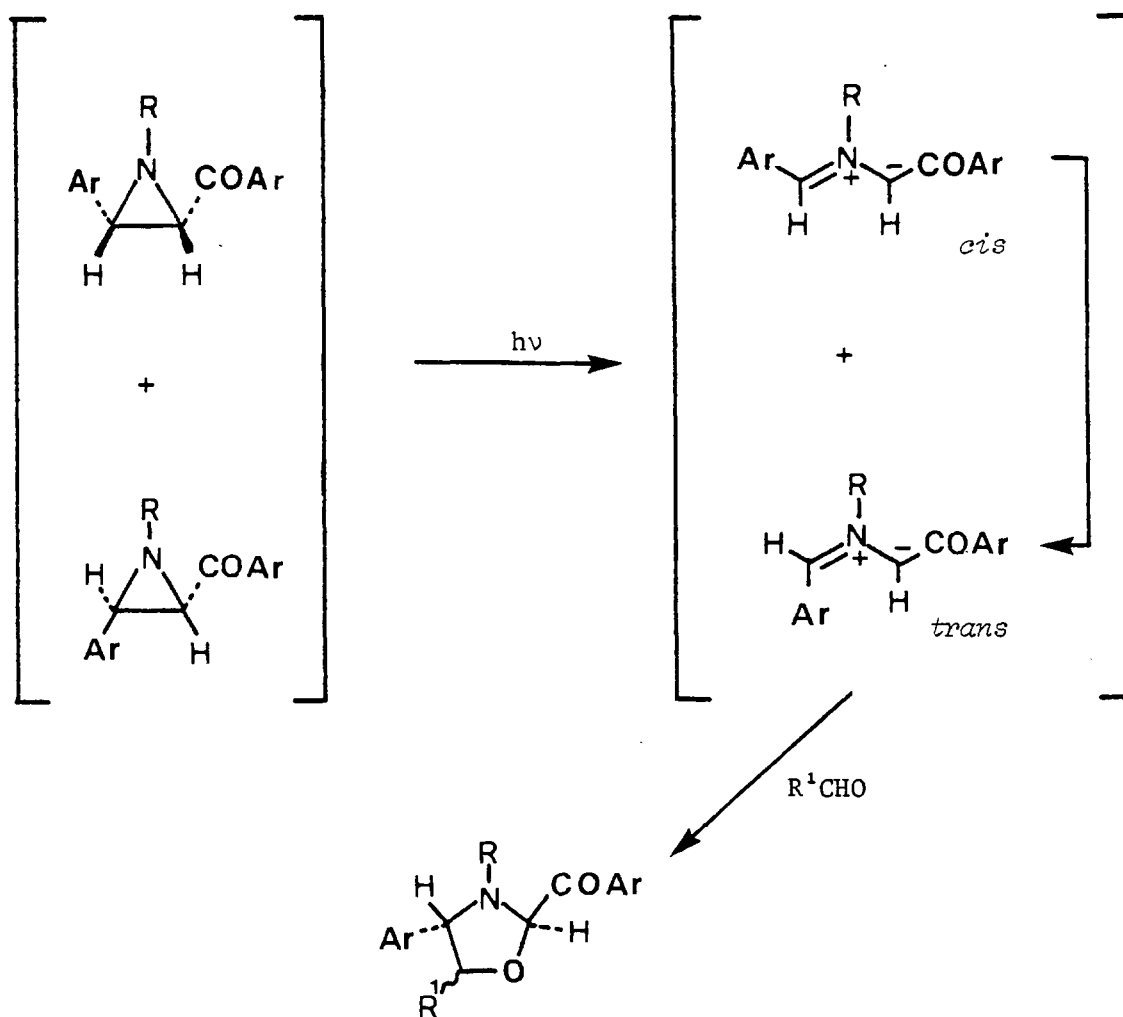
Both these facts argue strongly against pathway (a).



Therefore, the reaction involves the initial dimerisation of the azirine (345). Assuming this dimerisation parallels the dimerisation of 2,3-diphenylazirine (equation 31), then a mixture of diastereomers (348) should be formed resulting from addition of the nitrile ylide to the least hindered face of the azirine, *i.e.*, from the side opposite the aryl group. Photochemical disrotatory ring opening of the aziridine ring would give the *cis* azomethine ylide (349a) which would rapidly isomerise to the thermodynamically more stable *trans* ylide (349b).

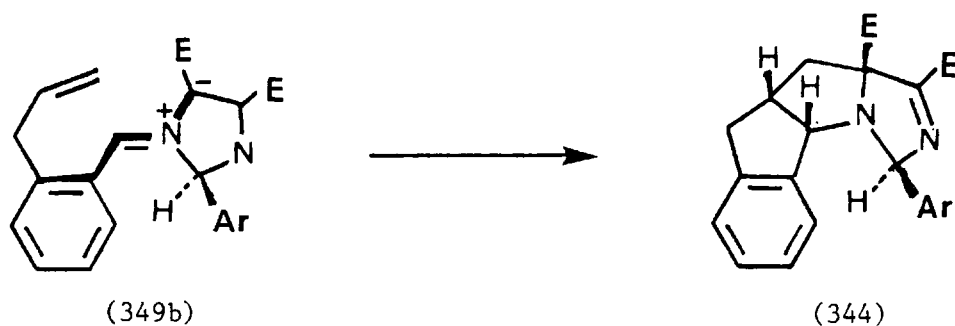


A similar *cis* to *trans* isomerisation has been observed for other azomethine ylides (e.g., Scheme 48).^{231,232}



SCHEME 48

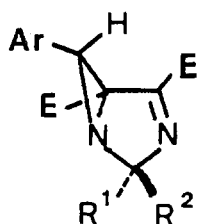
Addition of the azomethine ylide (349b) to the allyl C=C bond would then occur so that the allyl group approaches the nitrile ylide from the least hindered side, *i.e.*, opposite the aryl group, thus giving the observed stereoisomer of (344).



The azomethine ylide (349) is more likely to react with the allyl double bond than is the nitrile ylide (346), because (349) is inherently more reactive and its bent structure allows the two groups to approach one another more easily.

Therefore, the most likely mechanism for formation of (344) is pathway (b) (Scheme 47).

In the light of this conclusion the formation of the trimer (341) (Scheme 46) can be re-examined. The first step in both mechanisms is the formation of the azirine dimer (342). Pathway (a) requires that this is a stereospecific addition to give (342a), whereas for pathway (b) diastereomers (342a) and (342b) can be formed as in the dimerisation of 2,3-diphenylazirine.

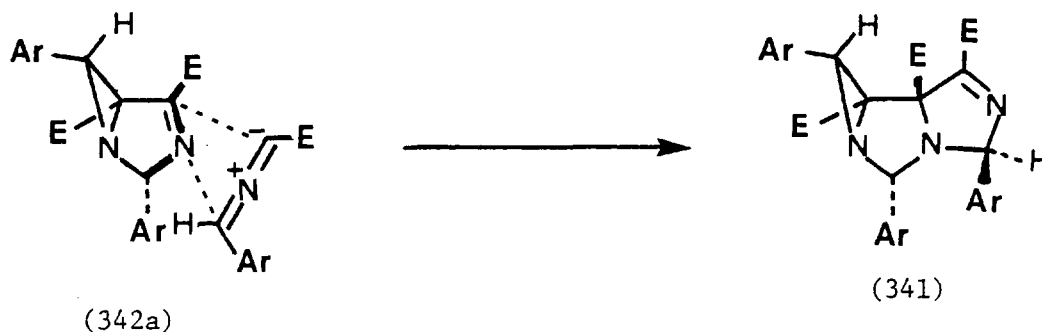


(342a) $R^1 = \text{Ar}, R^2 = \text{H}$

(342b) $R^1 = \text{H}, R^2 = \text{Ar}$

Ar as in Table 6.

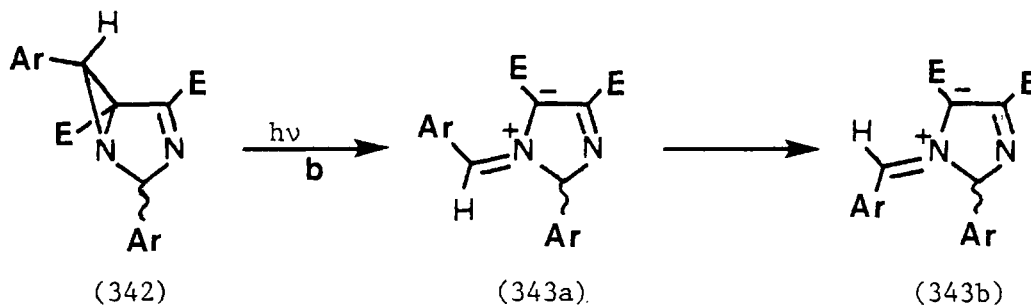
The second nitrile ylide addition (pathway a) must occur on the most highly hindered face, containing both bulky aryl and ester groups, and must be stereospecific with respect to the nitrile ylide, a feature not observed in the formation of the 3-phenylazirine dimers (equations 30 and 31).



Ar as in Table 6

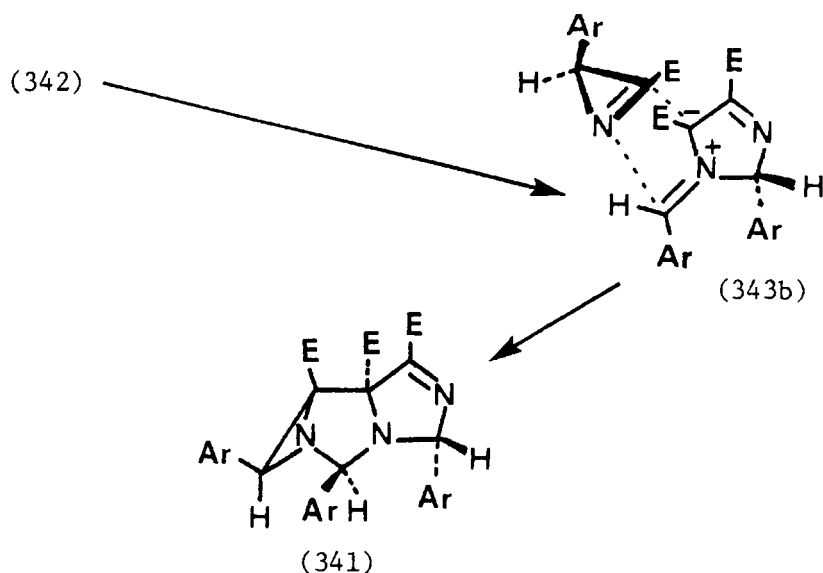
This mechanism does not give any explanation of why trimer formation should be faster than dimer formation and why tetramers are not formed by addition of another nitrile ylide to the trimer. Sterically, such a process is no more difficult than trimer formation by this mechanism.

Pathway (b), however, allows the formation of two diastereomers of the dimer (342) which ring open on photolysis to give the *cis*-azomethine ylide (343a) which then isomerises to the *trans*-ylide (343b) as in the case when Ar = *o*-allylphenyl.



Ar as in Table 6

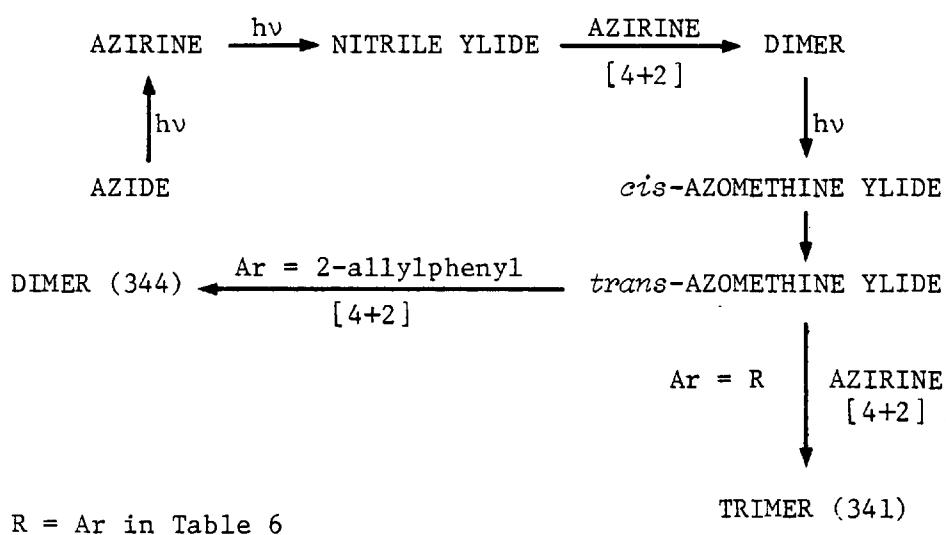
Addition of the more stable *trans*-azomethine ylide (343b) to the azirine (340) so that their bulky aryl groups cause least steric hindrance to the addition gives the observed trimer stereoisomer (341). It should be noted that the relative configuration at the five chiral centres in (341) is determined solely by the geometry of (343b), which contains only one chiral centre.



The ring opening of the aziridine ring in (341) is less likely than in (342) since the resulting azomethine ylides are of different stability. The azomethine ylide (343) from (342) is more stable due to delocalisation of the negative charge both into the ester group and into the C=N bond of the ring. Therefore, no tetramers are formed. Clearly, the stabilisation in (343) is such that ring opening of the dimer (342) is favourable and occurs readily whilst the azirine (340), a good dienophile, is still present.

Therefore, the mechanism involving azomethine ylides (343) (pathway b, Scheme 46) is preferred as it explains the isolation of the trimers (341) as the major products in preference to dimers or tetramers, and the observed stereochemistry of (341).

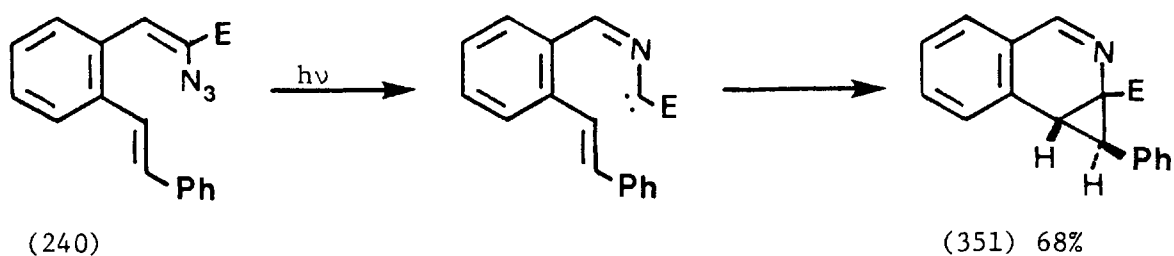
A common decomposition pathway is proposed for all the azidocinnamates so far described and is summarised in Scheme 49.



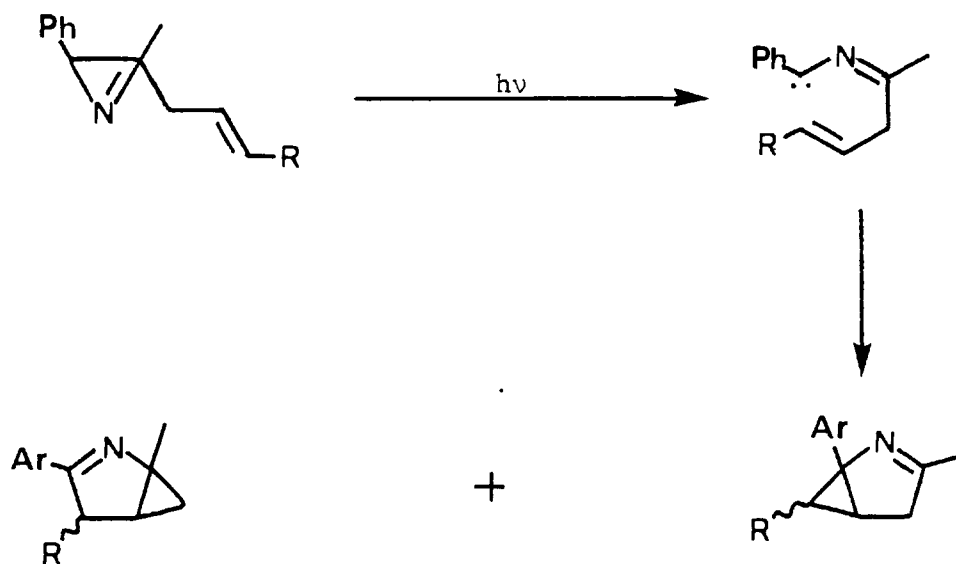
SCHEME 49

6.3.2. Photolysis of ethyl 2-azido-3-(2-styrylphenyl)propenoate (240).

Irradiation of the vinyl azide (240) at 300 nm for 1 h gave (351) as a colourless crystalline solid (68%). The intermediate nitrile ylide reacted *via* its iminocarbene form. The addition was stereospecific. No isomerisation to the *cis*-system was observed. No dimeric or trimeric products were isolated.



Similar photochemical 1,1-cycloadditions of iminocarbenes (Scheme 50) have been postulated to occur *via* a stepwise mechanism³³ but it has been proposed that the apparent non-stereospecificity was due to epimerisation of the products, rather than a stepwise reaction.²²⁹

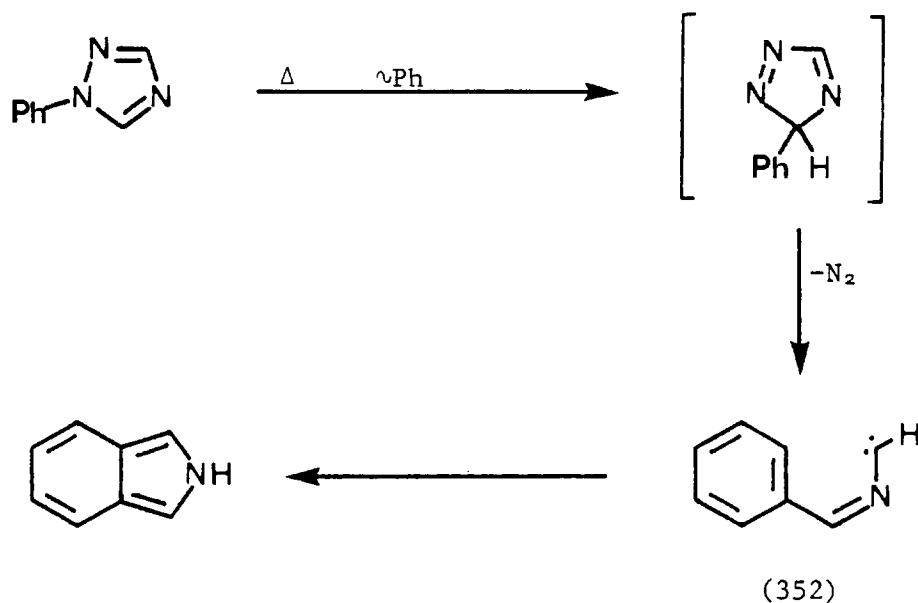


SCHEME 50

6.3.3. Photolysis of ethyl 2-azido-3-(2-pyridyl)propenoate (232).

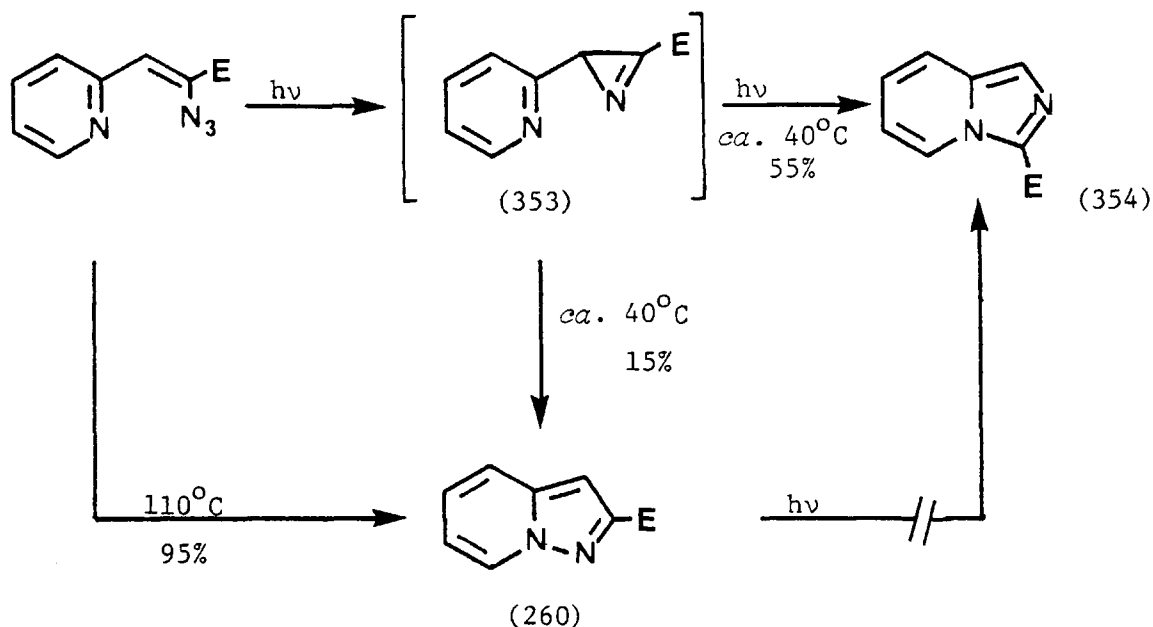
Whilst 2-vinylazirines isomerise to pyrroles on photolysis, no examples of cyclisation onto 2-phenyl substituents to give isoindoles have been reported.^{229,230} The only example of isoindole formation from

a nitrile ylide/iminocarbene intermediate is the formation of isoindole on pyrolysis of 1-phenyl-1,2,4-triazole where the carbene (352) was proposed as an intermediate.²³³



The conditions used in this reaction were quite different from those under which most photolytic decompositions of azides are carried out. 2-Pyridylazirines might, however, be expected to give imidazopyridines on photolysis, in a reaction analogous to the formation of imidazoles from 2-imidoylazirines.^{229,230}

This has been found to be the case in the photochemical decomposition of the azide (232) to give (354) (55%) which presumably occurs *via* the azirine (353). A small amount of the thermal product (260) was also produced, probably due to the heating of the solution, during the irradiation. No dimeric or trimeric products were observed.



The pyrazolopyridine (26D) was recovered unchanged after irradiation under the same conditions. The mechanism involves rapid trapping of the nitrile ylide by the nucleophilic pyridine nitrogen to give (354).



6.4. SUMMARY

In summary, photochemical decomposition of azidocinnamates gives azirine trimers except when there are unsaturated substituents present. In the latter case intramolecular cycloaddition onto the unsaturated group occurs, either by nitrile ylide/iminocarbene or by azomethine ylide intermediates to give monomeric or dimeric products. Nitrile ylides

can also be trapped by internal nucleophiles to give stable heterocyclic products.

PART THREE
EXPERIMENTAL, APPENDIX AND REFERENCES

CHAPTER SEVEN
EXPERIMENTAL

7.1. GENERAL PROCEDURES AND CONDITIONS

7.1. GENERAL PROCEDURES AND CONDITIONS.

Spectra

Infra-red spectra (i.r.) were recorded in the range $600\text{--}4000\text{ cm}^{-1}$ using Perkin-Elmer 257 and 298 spectrophotometers and calibrated against polystyrene. Spectra of solids were taken as Nujol mulls and liquids as thin films between sodium chloride plates or in solution cells with the appropriate solvents. All values quoted are medium to strong stretching bands in the spectra, and only structurally significant bands are quoted.

Ultra-violet and visible spectra (u.v.) were recorded in the range 200–700 nm or 200–450 nm using a Pye-Unicam SP 800 ultraviolet spectrophotometer using cells of 0.5 or 1.0 cm path length. Solvents used are indicated in the experimental data.

Proton nuclear magnetic resonance spectra (^1H n.m.r.) were recorded using Varian T60 (60 MHz), EM 360 A (60 MHz), Perkin-Elmer R32 (90 MHz), or Bruker WM 250 (250 MHz) instruments, with tetramethylsilane as internal standard. Unless otherwise stated the spectra were recorded on the Perkin-Elmer R32 (90 MHz). Signals are quoted as singlets (s), doublets (d), triplets (t), quartets (q), heptets (h), multiplets (m), or broad (br). A doublet of doublets is given by (dd), a doublet of triplets as (dt), *etc.* ^{13}C Nuclear magnetic resonance spectra (^{13}C n.m.r.) were recorded using the Bruker WM 250 (62.9 MHz) instrument with tetramethylsilane as internal standard. Signals are quoted as above for ^1H n.m.r.

Low and high resolution mass spectra were recorded on A.E.I. MS 12 and VG Micromass 7070 B instruments. Spectra were recorded at 70 or 12 eV using a direct insertion probe or septum inlet.

Melting Points.

Melting points were carried out on a Kofler Hot Stage apparatus and are uncorrected. The abbreviation for decomposed is dec.

Solvents.

Petroleum ether b.p., 40-60° and 60-80° C was distilled before use. Petrol in the experimental refers to 40-60°C b.p. range unless otherwise stated. Dichloromethane was distilled before use. Acetonitrile, dimethylformamide, and dimethylsulphoxide were dried over calcium hydride and distilled before use. Diethyl ether (ether) was dried over sodium wire, and when distilled was distilled from sodium and benzophenone and stored under nitrogen. The diethyl ether used for chromatography was not always distilled. Benzene, toluene, and xylene were dried over sodium wire and distilled before use. Tetrahydrofuran was dried over potassium and benzophenone and distilled and stored under dry nitrogen. Decalin and bromobenzene were distilled before use. Acetone, ethanol, and methanol were used as supplied commercially in AR grade. All water used was distilled.

Chromatography

Column chromatography was carried out using Silica gel H (type 60) (Merck or Rose Chemicals) at medium pressure using a hand bellows, or silica gel MFC under gravity, or aluminium oxide 60 H basic (type E) at

medium pressure. Approximately 20 g of silica gel or aluminium oxide per 1 g compound or mixture. Unless otherwise stated the use of silica gel and aluminium oxide (alumina) in the experimental will refer to silica gel H (type 60) and aluminium oxide 60 H basic (type E) respectively. When more than one eluant is quoted the column is started with the first mentioned solvent and then the percentage of the second solvent gradually increased until only the second solvent is used. When a third solvent is used the same procedure applies. Thin layer chromatography (t.l.c.) was used extensively to monitor reactions. Silica gel GF₂₅₄ (Merck) on glass plates, silica gel 60 F₂₅₄ precoated on aluminium sheets, and aluminium oxide PF₂₅₄ (Merck) on glass plates were used. Preparative layer chromatography (p.l.c.) was carried out on 20 x 20 cm and 20 x 40 cm plates using silica gel PF₂₅₄ and silica gel GF₂₅₄ (Merck).

Photolysis

Photochemical reactions were carried out using a Rayonet photochemical reactor of lamps 300 or 350 nm wavelength. The solvent used was degassed with dry nitrogen. Nitrogen was bubbled into the reaction mixture throughout photolysis. The Rayonet instrument has four lamps. When a lower intensity light was required only one of these lamps was used.

Drying Agents

Dried magnesium sulphate was used to dry organic solutions during work-up unless otherwise stated.

Removal of Solvents

In many of the work-up procedures the organic solutions were "dried and evaporated". In this context evaporation will be taken to mean distillation at reduced pressure on a rotary evaporator at the lowest temperature necessary to remove the solvent.

7.2. EXPERIMENTAL TO CHAPTER TWO

2-Benzyloxybenzaldehyde.¹⁷⁵

A mixture of salicylaldehyde (24.4 g, 0.2 mol), benzyl chloride (27.8 g, 0.22 mol) potassium carbonate (27 g, 0.2 mol), and acetone (150 ml) was refluxed for 48 h.¹⁷⁶ The acetone was then distilled from the reaction mixture and water (200 ml) added to the residue. The product was extracted with ether (2 x 100 ml) and then the combined organic extracts washed with aqueous sodium hydroxide (10%; 3 x 100 ml), dried and evaporated, to give the title compound (8 g, 40%) after distillation.

2-Bromodiphenylmethane.¹⁷⁷

A solution of 2-bromobenzoic acid (30 g, 0.149 mol) in excess thionyl chloride (165 g, 100 ml) was refluxed for 1.5 h, and then the excess thionyl chloride distilled under reduced pressure. The last traces of thionyl chloride were removed by azeotropic distillation with benzene to give the corresponding acid chloride as yellow oil (32.6 g, 98%), $\nu_{\max}$ (film) 1790 cm^{-1} .

To a stirred solution of the acid chloride (32.6 g, 0.148 mol) in benzene (200 ml) in a round bottomed flask, fitted with a reflux condenser and cooled to 0°C , powdered aluminium chloride (60 g) was added slowly. The contents of the flask were then stirred at room temperature for 1 h and poured onto ice. The two phases were separated, the aqueous phase extracted with ether (2 x 150 ml), the organic phases combined, washed with aqueous sodium bicarbonate solution (2 x 40 ml), and water (40 ml), dried and evaporated to give 2-bromobenzophenone as a pale green oil (35.4 g, 91.4%), $\nu_{\max}$ (film) 1670 cm^{-1} , δ (CDCl_3) 7.5–7.9 (m).

Zinc wool (60 g) was shaken for 0.25 h with mercuric chloride solution [mercuric chloride (3 g) in water (60 ml) and concentrated hydrochloric acid (3 ml)], and the amalgam so obtained was washed several

times with water by decantation. To this amalgam crude 2-bromobenzophenone (35 g) and concentrated hydrochloric acid (200 ml) were added, and the mixture refluxed for 48 h. The reaction was not complete after 24 h as had been reported.¹⁷⁷ The cooled reaction mixture was carefully diluted with water (200 ml), decanted from the remaining amalgam and extracted with dichloromethane (3 x 120 ml). The organic extracts were combined and washed with water (70 ml), dried and evaporated to give crude 2-bromodiphenylmethane as a yellow oil (26.9 g, 80%). Distillation of the crude material gave 2-bromodiphenylmethane as a colourless liquid (17.85 g, 53%), b.p., 84°C at 0.05 mmHg (lit.,¹⁷⁷ 175°C at 22 mmHg), ν_{max} (film) 3033-3065, 1609, 1571, 1498, 1456, 1024, 745, 685 cm^{-1} , $\delta(\text{CDCl}_3)$ 4.02 (2H, s), 6.87-7.27 (8H, m), 7.35-7.60 (1H, m).

2-Benzylbenzaldehyde (204).¹⁷⁷

2-Bromodiphenylmethane (14 g, 0.057 mol) in dry THF (200 ml) was added slowly to magnesium filings (1.5 g, 0.06 g atom) in THF (10 ml) over a period of 1 h. The Grignard reagent formation was initiated using a crystal of iodine and a drop of methyl iodide. The mixture was refluxed for 0.4 h and then cooled to ice-bath temperature. A solution of dry DMF (4.7 g, 0.064 mol) in THF (70 ml) was added dropwise to the cooled solution, which was then stirred at room temperature for 2.5 h. Water (50 ml) and 2N hydrochloric acid (50 ml) were then added and the aqueous solution extracted with ether (3 x 100 ml), and the organic extracts combined, dried and evaporated. Ether (25 ml) and alcohol (25 ml) were added to the crude aldehyde and the resulting solution allowed to stand at 5°C overnight, whereupon anthracene, a side product, precipitated. This was filtered off and the remaining aldehyde separated from residual

starting material by chromatography on silica gel MFC (petrol/ether).

2-Benzylbenzaldehyde¹⁷⁷ (204) was obtained as a colourless liquid (7.6 g, 69%), ν_{max} (film) 1700 cm^{-1} , δ (CDCl_3) 4.31 (2H, s, CH_2Ar), 7.00-7.30 (8H, m, ArH), 7.60-7.80 (1H, m, ArH), 10.13 (1H, s, CHO).

Fluoren-9-one-1-carboxylic acid (206).

Fluoranthene (50 g) was treated with chromium trioxide in glacial acetic acid and water and gave fluoren-9-one-1-carboxylic acid (206) (37 g, 69%) after work-up.¹⁷⁹ Recrystallisation from glacial acetic acid gave (206) as dark brown crystals, m.p., $190-191^\circ\text{C}$ (lit.,¹⁷⁹ $191-193^\circ\text{C}$).

Attempted reduction of fluoren-9-one-1-carboxylic acid (206) by the Huang-Minlon modification of the Wolff-Kishner reduction.¹⁸¹

A mixture of fluoren-9-one-1-carboxylic acid (9 g, 0.04 mol), sodium hydroxide (5.4 g, 0.135 mol), hydrazine hydrate (99%; 5.4 ml, 5.56 g, 0.11 mol) and 1,3-propanediol (70 ml) was heated at reflux temperature (150°C) for 3 h. The condenser was then removed and the contents heated more strongly. Fumes were evolved and the heating continued until the contents started to boil again. By this time the temperature of the contents of the flask had reached $195-200^\circ\text{C}$. The condenser was replaced and the refluxing resumed for a further 2.5 h. The reaction mixture was then cooled and poured into an ice cold solution of hydrochloric acid (2H). A black sticky oil precipitated. Attempts to purify portions of this oil by recrystallisation from glacial acetic acid or by dissolving it in dichloromethane, extracting it into saturated aqueous sodium bicarbonate solution and reprecipitating by addition of acid, failed, as did an attempted sublimation.

Attempted reduction of fluoren-9-one-1-carboxylic acid (206) using a further modification²³⁴ of the above method.

Fluoren-9-one-1-carboxylic acid (206) (1.1 g, 4.5 mmol) and hydrazine hydrate (1 ml, 20 mmol) were dissolved in propan-1-ol (80 ml) and the solution heated at reflux for 1 h. The solution was cooled in ice and the precipitated solid filtered off. The product was not the expected ~~hydrazine~~ but the pyridazolone (210) (0.87 g, 90%), m.p., 262-266°C (d) (lit.,¹⁸⁰ 262°C), ν_{max} (Nujol) 3120-3204, 1670, 1630, 1620 cm^{-1} , $\delta[(\text{CD}_3)_2\text{SO}]$ 12.2-13.3 (1H, br s), 7.1-8.4 (9H, m), m/e 220 (M^+), 164.

A solution of the pyridazolone (210) (375 mg, 1.57 mmol) and potassium *t*-butoxide (200 mg, 1.78 mmol) in dry toluene (10 ml) was refluxed for 4.5 h. Water (20 ml) and dichloromethane (10 ml) were added and a brown solid precipitated. This was filtered off and was found to be identical to the pyridazolone (210) by i.r. and t.l.c. The organic phase was separated from the aqueous phase and was dried and evaporated to give a further quantity of the pyridazolone. No reaction had occurred.

A solution of the pyridazolone (210) (0.177 g, 0.80 mmol) and potassium *t*-butoxide (0.1 g, 0.89 mmol) in freshly distilled DMSO (20 ml) was heated at reflux temperature for 12.5 h, added to hydrochloric acid (2N) and the resulting precipitate filtered off. This solid was found to be identical to the starting material (210) as was the solid which precipitated from the aqueous DMSO solution on concentrating and cooling.

Reduction of fluoren-9-one-1-carboxylic acid with 4% sodium amalgam.¹⁷⁹

The 4% sodium amalgam was prepared by a standard method.²³⁵ Fluoren-9-one-1-carboxylic acid (5 g, 0.022 mol) was added over a period of 1.5 h to 4% sodium amalgam (133 g) in distilled water (200 ml), heated on a steam bath. The mixture was well stirred by a mechanical stirrer. Care

was taken to maintain the pH of the solution near the neutral point by addition of hydrochloric acid (6N) at intervals. When all of the keto acid (206) had been added a further 55 g of amalgam was added and the mixture refluxed for a further 2 h, and stirred at 40°C for 3 h, after which it was shown by t.l.c. that only the product acid was present.

The alkaline solution was then decanted from the amalgam, filtered, and acidified whereupon fluorene-1-carboxylic acid (207) precipitated as an off-white solid. This was then filtered off, washed and dried (4.22 g, 90%), m.p., 237-240°C (lit.,¹⁷⁹ 245°C), $\nu_{\max}$ (Nujol) 2100-3000, 1685 cm^{-1} , δ [(CD₃)₂SO] 11.7-13.5 (1H, br s), 6.66-7.80 (7H, m), 3.70 (2H, s).

Attempted reduction of fluorene-1-carboxylic acid (207) with lithium aluminium hydride.

A solution of fluorene-1-carboxylic acid (207) (3.82 g, 18.2 mmol) in dry THF (100 ml) was added dropwise to a well stirred solution of lithium aluminium hydride (1.75 g, 46 mmol) in dry ether (40 ml) at a rate which maintained the solution refluxing gently. The mixture was then stirred at room temperature for 1.5 h and then the excess lithium aluminium hydride destroyed by addition of ethyl acetate (30 ml). The organic solution was then washed with hydrochloric acid (1N; 150 ml) and water (50 ml), dried and evaporated to give a brown oil (4 g) which was shown by t.l.c. and n.m.r. to be a mixture of six to eight compounds. Attempted separation of this mixture by silica gel chromatography failed.

Fluorene-1-carbaldehyde (205).

A solution of fluorene-1-carboxylic acid (14.5 g, 0.069 mol) and concentrated sulphuric acid (2 ml) in methanol (350 ml) was refluxed for 48 h. The solvent was then removed under reduced pressure and the residue dissolved in ether (150 ml), washed with sodium hydroxide solution (1N; 2 x 50 ml) and water (50 ml), dried and evaporated to give a dark brown solid (12 g). Chromatography on silica gel MFC (petrol/chloroform) gave methyl fluorene-1-carboxylate (208) as colourless prisms (8.5 g, 55%), m.p., 87°C (lit.,¹⁸² 84-85°C), $\nu_{\max}$ (Nujol) 1722 cm⁻¹.

Lithium aluminium hydride (0.8 g, 21 mmol) was added slowly to a stirred solution of methyl fluorene-1-carboxylate (208) (7.2 g, 32 mmol) in dry ether (120 ml). The reaction mixture was warmed for 2 h and then allowed to stand at room temperature for 14 h. Ethanol (10 ml), water (10 ml), and hydrochloric acid (2N; 70 ml) were then added, and the phases separated. The aqueous phase was washed with chloroform (50 ml), the organic extracts combined, washed with water (50 ml), dried and then evaporated to give fluorene-1-methanol (209) as a colourless crystalline solid (5.65 g, 91%), m.p., 144.5-146.5°C (lit.,¹⁸² 145.5-146.5°C), $\nu_{\max}$ (Nujol) 3100-3530 cm⁻¹.

The Jones reagent (1.18 M) was prepared by addition of concentrated sulphuric acid (18.3 ml) to a solution of chromium trioxide (21 g, 0.23 mol) in water (150 ml).

The Jones reagent (17.8 ml, 21.08 mmol) was added dropwise over a period of 0.3 h to a well stirred solution of fluorene-1-methanol (209) (6.2 g, 31.6 mmol) in acetone (200 ml). The mixture was stirred at room temperature for 0.3 h, then the solution was decanted from the precipitated green solid and this solid washed with chloroform (100 ml). The organic

solutions were combined, washed with sodium thiosulphate solution (10%; 50 ml), sodium hydroxide solution (2N; 50 ml) and saturated sodium chloride solution (50 ml), dried and evaporated to give fluorene-1-carbaldehyde (205) as a yellow solid (5.4 g, 88%), m.p., 89-90°C (from cyclohexane) (lit.,¹⁷⁸ 90°C), $\nu_{\max}$ (Nujol) 1693 cm⁻¹, δ (CDCl₃) 4.00 (2H, br,s, CH₂) 7.20-7.90 (7H, m, ArH), 10.06 (1H, s, CHO).

2-Isopropylbenzaldehyde (212).

The following is a modification of a general procedure for conversion of anilines to benzaldehydes.¹⁸⁴

A mixture of 2-isopropylaniline (33.75 g, 0.25 mol) and water (50 ml) was placed in a 1 litre three-necked round-bottomed flask fitted with a stirrer, a dropping funnel and a thermometer. The stirrer was started and concentrated hydrochloric acid (57 ml) was added slowly. The mixture was cooled to room temperature, ice (100 g) added and the temperature of the mixture maintained between -5°C and 5°C using an ice/salt bath. A solution of sodium nitrite (17.5 g, 0.25 mol) in water (25 ml) was then added. The mixture was stirred for 0.25 h and then made neutral to Congo red by addition of a solution of sodium acetate (22 g) in water (35 ml).

An aqueous formaldoxime solution (10%; 0.38 mol) was prepared by the literature method¹⁸⁴ and placed in a 2 litre three-necked round-bottomed flask. To this was added hydrated cupric sulphate (6.5 g, 0.026 mol), sodium sulphite (1.0 g, 7.9 mmol), and a solution of hydrated sodium acetate (160 g) in water (180 ml). The solution was stirred vigorously and maintained at 10°C by means of a cold water bath. The diazonium salt solution was then syphoned slowly into this flask and the mixture stirred

for 1 h, treated with concentrated hydrochloric acid (230 ml) and then refluxed for 2 h. The reaction product was steam distilled from the reaction mixture. The distillate was saturated with sodium chloride, extracted with ether (3 x 150 ml) and the organic extracts washed with saturated sodium chloride solution (3 x 20 ml), aqueous sodium bicarbonate (10%; 3 x 20 ml), and saturated sodium chloride solution (3 x 20 ml). The organic solution was then evaporated to give a red oil. To this oil was added aqueous sodium metabisulphite (40%; 90 ml), previously heated to 60°C. The mixture was shaken for 1 h and allowed to stir for 14 h. The solid addition product was filtered, washed well with ether then suspended in water (200 ml) in a round-bottomed flask. Concentrated sulphuric acid (40 ml) was added to this suspension and the mixture heated under reflux for 2 h. After cooling, the aqueous solution was extracted with ether (3 x 100 ml), the ether extracts combined and washed with saturated sodium chloride solution (3 x 15 ml), dried, and evaporated to give 2-isopropylbenzaldehyde¹⁸³ as a colourless oil (14 g, 38%), ν_{max} (film) 2980, 2860, 2730, 1680, 1594 cm^{-1} , δ (CCl_4), 1.24 (6H, d, J 6.5 Hz), 3.98 (1H, h, J 6.5 Hz) 7.15-7.54 (3H, m), 7.68-7.80 (1H, m), 10.25 (1H, s, CHO).

1-Bromo-3-methylbut-2-ene (prenyl bromide) (214).

To isoprene (68.6g, 1 mol), cooled to 0°C, a solution of hydrogen bromide in glacial acetic acid (45% w/v; 165 ml, 0.915 mol) was added dropwise over a period of 1.5 h. The mixture was then stirred at this temperature for 0.75 h after which it was diluted with dichloromethane (100 ml) and quickly washed with ice-cold aqueous sodium hydroxide (2N; 2 x 500 ml) and water (300 ml). The organic solution was dried and evaporated to give a colourless liquid (98.77 g). Distillation gave 1-bromo-3-methylbut-2-ene as a colourless liquid (55.7 g, 41%), b.p., 65-

70°C at 94-97 mmHg, δ (CCl₄) 1.65-1.85 (6H, m, 2 x CH₃), 3.96 (2H, d, J 11 Hz), 5.40-5.68 (1H, m). Some of the product was lost on distillation due to decomposition to isoprene and hydrogen bromide, both gases at this temperature.

4,4-Dimethyl-2-phenyl- Δ^2 -oxazoline was prepared by a literature method¹⁸⁵ and was obtained in 70% yield as a semisolid, m.p., *ca.*, 20°C (lit.,²³⁶ 23-24°C).

4,4-Dimethyl-2-[2-(3-methylbut-2-en-1-yl)phenyl]- Δ^2 -oxazoline (215).

A solution of 4,4-dimethyl-2-phenyl- Δ^2 -oxazoline (40.5 g, 0.23 mol) in THF (200 ml) cooled to -45°C and maintained under argon, was treated with a solution of *n*-butyl lithium in hexane (1.3M; 219 ml, 0.285 mol, 1.24 equivalents) and stirred at -45°C for 1.5 h. A solution of 1-bromo-3-methylbut-2-ene (42.6 g, 0.286 mol) was added dropwise and the solution allowed to warm to room temperature, and stirred for 2 h. This solution was then poured into water (300 ml) and extracted with ether (3 x 150 ml), the organic extracts combined, dried, and evaporated to give a colourless oil (60 g). The oil was dissolved in ether (200 ml), extracted with hydrochloric acid (2N; 2 x 150 ml), the aqueous layer separated and washed with petrol (100 ml), basified with aqueous sodium hydroxide and the liberated oil taken up in ether. The ethereal solution was dried and evaporated to give an oil (32 g) from which some of the contaminants had been removed. Chromatography on silica gel MFC (petrol/ether) yielded 4,4-dimethyl-2-phenyl- Δ^2 -oxazoline (11.2 g, 27%), and 4,4-dimethyl-2-[2-(3-methylbut-2-en-1-yl)phenyl]- Δ^2 -oxazoline (215) (15.2 g, 27%),

$\nu_{\max}$ (film) 1642 cm^{-1} , δ (CCl_4) 1.25 (6H, s, 2 x CH_3 on ring), 1.65 (6H, br s, 2 x CH_3 on side chain), 3.65-3.85 (2H, br d, CH_2 in side chain), 3.85 (2H, s, CH_2 in ring), 5.15-5.40 (1H, br t, side chain), 7.00-7.25 (3H, m, ArH), 7.75-7.80 (1H, m, ArH), m/e 243 (M^+ , 100%), 200.

The organic solution which had been washed with acid above was dried, evaporated and later chromatographed as before to give a further 28% of (215).

2-[2-(3-Methylbut-2-en-1-yl)phenyl]-3,4,4-trimethyloxazolidine (217).

A solution of oxazoline (215) (2.43 g, 0.01 mol) and methyl iodide (2.13 g, 0.015 mol) in nitromethane (6 ml) was heated at $70-75^\circ\text{C}$ for 19 h, then cooled and added to ether (6 ml). No solid precipitated as expected,¹⁸⁶ so an additional volume of ether (5 ml) was added. An oil was then liberated which solidified on cooling in ice. It was isolated by filtration and was washed well with petrol to give 2-[2-(3-methylbut-2-en-1-yl)phenyl]-3,4,4-trimethyl- Δ^2 -oxazolinium iodide (216) (2.85 g, 74%), $\nu_{\max}$ (Nujol) 1642 cm^{-1} , δ (CDCl_3) 1.55-1.81 (6H, m, 2 x CH_3 in side chain), 1.88 (6H, s, 2 x CH_3 on ring), 3.44 (3H, s, N-CH_3), 3.30-3.51 (2H, m, CH_2 in side chain), 5.23 (2H, s, CH_2 in ring), 5.05-5.28 (1H, m, side chain), 7.37-7.78 (3H, m, ArH), 8.12-8.25 (1H, m, ArH).

Sodium borohydride (0.55 g, 0.029 mol) was added over a period of 0.5 h to a solution of oxazolinium iodide (216) (5.6 g, 0.0145 mol) in absolute alcohol (20 ml) cooled in ice. The mixture was stirred at 5°C for 2 h, when a further portion (0.55 g) of sodium borohydride was added. After stirring at room temperature for 3 h sodium borohydride (0.25 g) was again added and the stirring continued. After 8 h t.l.c. showed that all the starting material had been consumed. The mixture was then poured into sodium hydroxide solution (5%; 30 ml) and extracted

with ether (3 x 50 ml). The ethereal extracts were combined, dried and evaporated to give a pale yellow oil (3.63 g, 90%) which was shown by n.m.r. spectroscopy to consist mostly of the required oxazolidine (217). Chromatography on silica gel (petrol/ether) followed by distillation gave clean 2-[2-(3-methylbut-2-en-1-yl)phenyl]-3,4,4-trimethyloxazolidine (217) (1.95 g, 52%), b.p., 133°C at 0.3 mmHg (Kugelrohr) (Found: M^+ + 2 261.2091. $C_{17}H_{27}NO$ requires 261.2093), $\nu_{\max}$ (film) 1455, 1055 cm^{-1} , δ (CDCl_3) 1.13 (6H, br s, 2 x CH_3 on ring), 1.73 (6H, s, 2 x CH_3 in side chain), 2.08 (3H, s, N- CH_3), 3.43 (1H, s, ring), 3.30-3.47 (2H, d, CH_2 in side chain), 3.61 (2H, s, CH_2 in ring), 5.10-5.37 (1H, m, side chain), 7.14-7.50 (4H, m, ArH), m/e 261 (M^+ + 2), 230 (100%). In carbon tetrachloride the hydrogen at the 2-position in the oxazolidine ring is shifted upfield to δ 3.34.

Attempted hydrolysis of 2-[2-(3-methylbut-2-en-1-yl)phenyl]-3,4,4-trimethyloxazolidine (217).

A solution of oxazolidine (217) (94.8 mg, 0.37 mmol) in hydrochloric acid (2N; 2 ml) and toluene (2 ml) was refluxed for 1 h. The organic layer was then separated and the aqueous layer extracted with ether (3 ml), the organic extract combined with the toluene solution, then dried and evaporated but a negligible quantity of material was obtained (4.1 mg). The aqueous solution was basified with aqueous sodium hydroxide (4N; 2 ml) and extracted with ether (2 x 4 ml). The ethereal extracts were combined, dried, and evaporated to give a colourless oil (51.6 mg), which was found to be 2-[2-(3-hydroxy-3-methylbut-1-yl)phenyl]-3,4,4-trimethyloxazolidine, $\nu_{\max}$ (film) 3100-3700 cm^{-1} , δ (CDCl_3) 1.14 (6H, s, 2 x CH_3 on side chain), 1.22 (6H, s, 2 x CH_3 on ring), 1.55-1.85 (2H,

m, CH₂ on side chain), 2.04 (3H, s, NCH₃), 2.67-3.20 (3H, m, ArCH₂ in side chain and OH), 3.45 (1H, s, ring), 3.64 (2H, s, CH₂ in ring) 7.08-7.35 (4H, m, ArH).

An attempted hydrolysis of oxazolidine (217) (75 mg, 0.25 mmol) in 30% aqueous oxalic acid solution^{35,187} (0.5 ml) at reflux temperature for 2 h gave the same alcohol. No aldehyde (213) was observed.

Attempted hydrolysis¹⁸⁵ of 4,4-dimethyl-2-[2-(3-methylbut-2-en-1-yl)-phenyl]- Δ^2 -oxazoline (215).

Oxazoline (215) (339 mg, 1.39 mmol) was dissolved in hydrochloric acid (3N; 3 ml) and the solution refluxed for 0.3 h. The solution was then quickly cooled, diluted with water (5 ml), extracted with chloroform (3 x 6 ml) and the organic extracts combined, dried, and evaporated to give an oil (125 mg). An n.m.r. spectrum of this oil shows that the signals corresponding to the 3-methylbut-2-en-1-yl side chain had disappeared, and that signals corresponding to the 3-hydroxy-3-methylbut-1-yl group were present; $\nu_{\max}$ (film) 3100-3700, 1715, 1635 cm⁻¹. Some hydrolysis of the oxazoline ring had occurred but the side chain had been hydrated completely. A solid precipitated from the aqueous phase on prolonged standing. This was shown to be the hydrolysed alcohol acid, $\nu_{\max}$ (Nujol) 2400-3600, 1725 cm⁻¹.

2-Allylbenzaldehyde (218).

2-Allylchlorobenzene (219) was prepared from 2-bromochlorobenzene¹⁸⁹ in 62% yield, b.p., 62-68°C at 5 mmHg (lit.,¹⁸⁹ 60-70°C at 5 mmHg).

Active magnesium (ca. 0.14 mol) in THF (250 ml) was prepared according to a literature procedure.¹⁹⁰ To this was added 2-allylchlorobenzene (219) (11.60 g, 0.08 mol) in THF (20 ml) and the mixture

stirred at room temperature under nitrogen for 3 h. An excess of DMF was then added and the mixture allowed to stir overnight. Hydrochloric acid (3N; 50 ml) and water (50 ml) were then added, and the two phases separated. The aqueous phase was washed with ether (2 x 50 ml), the ether extracts added to the organic phase, and the combined organic solutions washed with saturated aqueous sodium bicarbonate (2 x 50 ml) and saturated aqueous sodium chloride (2 x 50 ml), dried and evaporated to give a yellow oil (9.5 g). This oil was then chromatographed on silica gel (petrol/ether) to give 2-allylbenzaldehyde¹⁸⁸ (2.30 g, 21%), $\nu_{\max}$ 1790, 1600, 1210, 754 cm^{-1} , δ (CCl_4) 3.65-3.87 (2H, m, ArCH_2R), 4.78-5.17 (2H, m, $-\text{C}(\text{H})=\text{CH}_2$), 5.72-6.25 (1H, m, $-\text{C}(\text{H})=\text{CH}_2$), 7.10-7.60 (3H, m, ArH), 7.65-7.85 (1H, m, ArH), 10.14 (1H, s, CHO).

2-Allyl-3-hydroxy-4-methoxybenzaldehyde (220) was prepared from 3-hydroxy-4-methoxybenzaldehyde in 52% yield,¹⁹¹ b.p., 142-144°C at 0.8 mmHg, and recrystallised from ether, m.p., 57-58°C (lit.,¹⁹¹ 58-59°C).

2-Vinylbenzaldehyde (222) b.p., 88-92°C at 7 mmHg (lit.,¹⁹² 113-115°C at 18 mmHg).

E-Stilbene-2-carbaldehyde (223).

Treatment of *E*-stilbene-2-carboxylic acid¹⁹⁴ with lithium aluminium hydride in ether gave a quantitative yield of *E*-stilbene-2-methanol, m.p., 87-91°C (lit.,¹⁹⁵ 92°C). This alcohol was then oxidised with an excess of the Jones reagent to give *E*-stilbene-2-carbaldehyde (223) (85% after distillation), b.p., 164°C at 1 mmHg, $\nu_{\max}$ (film) 2740, 1685, 1595 cm^{-1} , δ (CDCl_3) 6.99 (1H, d, J 16 Hz), 7.20-7.83 (9H, m, ArH), 8.00 (1H, d, J 16 Hz), 10.21 (1H, s, CHO).

m/e 208 (M^+), 105 (100%). The literature¹⁹³ quotes this compound as having a m.p. of 83°C. The above sample did not, however, solidify.

2-Benzoylbenzaldehyde (224).

2-Benzoylbenzoic acid was treated with lithium aluminium hydride to give 2-(1-hydroxyphenylmethyl)benzyl alcohol, which was then treated with selenium dioxide in acetic acid and xylene giving 2-benzoylbenzaldehyde (224), m.p., 65-67°C (lit.,¹⁹⁶ 64-67°C).

Fluoren-9-one-1-carbaldehyde (226) was prepared by ozonolysis of fluorene in 60% yield,¹⁹⁷ m.p., 188-192°C (lit.,¹⁹⁷ 193-194°C).

2-Acetylbenzaldehyde (227).

A procedure similar to that used in the preparation of 9-fluorenone-1-carbaldehyde was used to prepare 2-acetylbenzaldehyde from 1-methylnaphthalene.¹⁹⁸

Ethyl-2-formylbenzoate (229) was prepared by esterification of 2-formylbenzoic acid with ethyl iodide in the presence of potassium carbonate, b.p., 108°C at 2 mmHg (lit.,¹⁹⁹ 240-3°C).

Ethyl azidoacetate.

The procedure is basically that used for the preparation of butyl azidoacetate.²³⁷

In a 1 litre round bottomed flask fitted with a reflux condenser were placed ethyl chloroacetate (73.5 g, 64 ml, 0.6 mol), sodium azide (72.15 g, 1.11 mol), acetone (162 ml) and water (108 ml), and the mixture refluxed for 18 h. After cooling, water (45 ml) was added and the two

phases separated. The aqueous phase was washed with ether (2 x 75 ml), the extracts added to the organic phase which was then dried and evaporated to give a colourless oil. Distillation gave ethyl azidoacetate as a colourless liquid, b.p., 102°C at 8.5 mmHg. (lit.,²³⁸ 44- 46°C , 2 mm Hg).

Preparation of the vinyl azides (231)-(244).

The vinyl azides (231)-(244) were prepared according to the procedure given below, a modification of literature procedures.^{46,174}

A sodium ethoxide solution was prepared by addition of sodium (1.84 g, 0.08 mol) to ethanol (55 ml). When all the sodium had reacted this solution was cooled to -20°C in a carbon tetrachloride/dry ice bath. A mixture of the aldehyde (0.02 mol) and ethyl azidoacetate (10.32 g, 0.08 mol) was added dropwise to the above stirred solution, the addition being regulated to maintain the temperature below -10°C . When the aldehyde contained an acidic group [*i.e.*, (220) and (228)] 0.10 mol of sodium was used. When the aldehyde was insoluble in ethyl azidoacetate ether or THF were used to dissolve the aldehyde before addition.

The reaction mixture was stirred at -15°C to -10°C for 1 to 5 h until t.l.c. showed the reaction to be complete. The solution was then allowed to warm slowly to room temperature, was poured into ice/water (200 ml), or hydrochloric acid (1N), and extracted with ether (3 x 100 ml). The combined organic extracts were washed with saturated sodium bicarbonate solution (50 ml) [except in the case of (243)] and water (50 ml), dried and evaporated to give the crude vinyl azide as an oil or solid. Chromatography on silica gel (petrol/ether) gave pure azides (231)-(244). Some of these azides were then recrystallised.

Ethyl 2-azido-3-(2-benzyloxyphenyl)propenoate (231) (34%) Colourless needles, m.p., 97.5-98.5°C from ether and petrol, $\nu_{\max}$ (Nujol) 2120, 1697 cm^{-1} , δ (CDCl_3) 1.30 (3H, t, J 7 Hz), 4.29 (2H, q, J 7 Hz), 5.05 (2H, s), 6.80-7.50 (8H, m, ArH), 7.56 (1H, s), 8.15-8.32 (1H, m, ArH), m/e 295 (M^+ -28).

Ethyl-2-azido-3-(2-pyridyl)propenoate (232) (32%), pale yellow prisms from ether, m.p., 36-38°C (Found: C, 54.75; H, 4.70; N, 25.41. $\text{C}_{10}\text{H}_{10}\text{N}_4\text{O}_2$ requires C, 55.04; H, 4.62; N, 25.41%), $\nu_{\max}$ (Nujol) 2120, 1710, 1617 cm^{-1} δ (CDCl_3) 1.36 (3H, t, J 7 Hz), 4.38 (2H, q, J 7 Hz), 7.00-7.30 (2H, m, 5'-H and vinyl H) 7.50-7.85 (1H, m, 4'-H), 8.10-8.30 (1H, m, 3'-H), 8.50-8.70 (1H, m, 6'-H), m/e 218 (M^+), 190, 162, 144, 118 (100%), 90, 78, $\lambda_{\max}$ (EtOH) 213, 310, 319 nm.

Ethyl 2-azido-3-(2-benzylphenyl)propenoate (233) (56-64%), pale yellow needles, m.p., 61-62°C (Found: C, 70.38; H, 5.63; N, 13.69. $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_2$ requires C, 70.34; H, 5.57; N, 13.67%), $\nu_{\max}$ (Nujol) 2130, 1725 cm^{-1} , δ (CDCl_3) 1.33 (3H, t, J 7 Hz), 4.03 (2H, br s), 4.30 (2H, q, J 7 Hz), 7.00-7.40 (9H, m), 7.90-8.05 (1H, m), m/e 307 (M^+), 279 (100%), 233, 202, 179, $\lambda_{\max}$ (EtOH) 206, 225, 306 nm.

Ethyl 2-azido-3-fluoren-1-ylpropenoate (234) (80%) pale yellow needles from dichloromethane and petrol, m.p., 110-112°C (Found: C, 71.04; H, 4.99; N, 13.44. $\text{C}_{18}\text{H}_{15}\text{N}_3\text{O}_2$ requires, C, 70.81; H, 4.95; N, 13.76%), $\nu_{\max}$ (Nujol) 2110, 1703 cm^{-1} , δ (CDCl_3) 1.35 (3H, t, J 7.2 Hz), 3.68 (2H, br s), 4.35 (2H, q, J 7.2 Hz), 6.95 (1H, s), 7.15-7.80 (4H, m), 7.98-8.12 (1H, m), m/e 305 (M^+), 277, 203, 194, 165 (100%).

Ethyl 2-azido-3-(2-methylphenyl)propenoate (235) (54-74%), m.p., 53-54°C from ethanol (lit.,¹⁷⁴ 55-56°C).

Ethyl 2-azido-3-(2-isopropylphenyl)propenoate (236) (63%), pale yellow oil (Found: C, 65.23; H, 6.77; N, 16.17. $C_{14}H_{17}N_3O_2$ requires C, 64.85; H, 6.61; N, 16.20%), $\nu_{\max}$ (film) 2130, 1715 cm^{-1} , δ (CCl_4) 1.25 (6H, d, J 7 Hz), 1.48 (3H, t, J 7 Hz), 3.19 (1H, h, J 7 Hz), 4.37 (2H, q, J 7 Hz), 7.05-7.35 (3H, m), 7.70-7.90 (2H, m, ArH and vinyl H), m/e 259 (M^+), 231, 216, 189, 172, 158, 144 (100%).

Ethyl 2-azido-3-(2-allylphenyl)propenoate (237) (54%), pale yellow oil, $\nu_{\max}$ (film) 2125, 1713 cm^{-1} , δ (CDCl_3) 1.39 (3H, t, J 7 Hz), 3.43 (2H, m, allyl CH_2), 4.37 (2H, q, J 7 Hz), 4.37-5.20 (2H, m, $\text{H}_2\text{C}=\text{CHR}$), 5.72-6.20 (1H, m, $\text{H}_2\text{C}=\text{CHR}$), 7.10-7.35 (4H, m, ArH and vinyl H), 7.88-8.09 (1H, m, ArH), m/e 257 (M^+), 229, 200, 156 (100%), $\lambda_{\max}$ (petrol) 307 nm.

Ethyl 2-azido-3-(2-allyl-3-hydroxy-4-methoxyphenyl)propenoate (238) (40%), pale yellow needles from ether and petrol, m.p., 97-99°C (Found: C, 59.14; H, 5.64; N, 13.67. $C_{15}H_{17}N_3O_4$ requires C, 59.40; H, 5.65; N, 13.85%), $\nu_{\max}$ (Nujol) 3510, 2120, 1710, 1610 cm^{-1} , δ (CDCl_3) 1.37 (3H, t, J 7 Hz), 3.40-3.60 (2H, m), 3.92 (3H, s, OCH_3), 4.36 (2H, q, J 7 Hz), 4.80-5.12 (2H, m), 5.65 (1H, s, OH), 5.62-6.10 (1H, m), 6.75 (1H, d, J 8 Hz, ArH), 7.13 (1H, s), 7.65 (1H, d, J 8 Hz, ArH), m/e 303 (M^+), 275 (100%), 248, 246, 229, 202, 186, 174, 144, $\lambda_{\max}$ (EtOH) 207, 250, 311 nm.

Ethyl 2-azido-3-(2-vinylphenyl)propenoate (239) (28%), pale yellow oil, $\nu_{\max}$ (film) 2120, 1710, 1617 cm^{-1} , δ (CDCl_3) 1.32 (3H, t, J 7 Hz), 4.33 (2H, q, J 7 Hz), 5.37 (1H, dd, J 1.5, 11 Hz), 5.60 (1H, dd, J 1.5, 17 Hz), 6.95 (1H, dd, J 11 17 Hz), 7.15-7.55 (4H, m), 7.77-7.95 (1H, m), m/e 215 ($M^+ - 28$, 100%), 186.

Ethyl 2-azido-3-(2-E-styrylphenyl)propenoate (240) (63%), pale yellow needles from ether and petrol, m.p., 69-70°C (Found: C, 71.37; H, 5.34; N, 12.99. $\text{C}_{19}\text{H}_{17}\text{N}_3\text{O}_2$ requires C, 71.46; H, 5.37; N, 13.16%), $\nu_{\max}$ (Nujol), 2120, 1705 cm^{-1} , δ (CDCl_3) 1.36 (3H, t, J 7.2 Hz), 4.40 (2H, q, J 7.2 Hz), 6.98 (1H, d, J 15 Hz), 7.30-8.05 (11H, m), m/e 291 ($M^+ - 28$), 100%), 262, 245, 219, 217.

Ethyl 2-azido-3-(2-benzoylphenyl)propenoate (241) (35%), pale yellow oil, $\nu_{\max}$ (film) 2120, 1710, 1660, cm^{-1} , δ (CDCl_3) 1.20 (3H, t, J 7 Hz), 4.15 (2H, q, J 7 Hz), 7.00 (1H, s), 7.20-8.20 (9H, m), m/e 293 ($M^+ - 28$), 254, 209 (100%), 194.

Ethyl 2-azido-3-(fluoren-9-on-1-yl)propenoate (242) (7.5%), bright yellow needles, m.p., 110-115°C (dec.), $\nu_{\max}$ (Nujol) 2120, 1750, 1710 cm^{-1} , δ (CDCl_3) 1.45 (3H, t, J 7.2 Hz), 4.43 (2H, q, J 7.2 Hz), 7.15-7.70 (6H, m) 8.00-8.22 (2H, m), m/e 319 (M^+), 291, 245 (100%).

Ethyl 2-azido-3-(2-carboxyphenyl)propenoate (243) (59%), colourless needles from chloroform and petrol, m.p., 118-120°C, $\nu_{\max}$ (CHCl_3) 3450-2450 (br), 2125, 1710 (br), 1620 cm^{-1} , δ (CDCl_3) 1.40 (3H, t, J 7.2 Hz), 4.43 (2H,

q, J 7.2 Hz), 7.30-8.25 (5H, m) (vinyl H at 7.87), 11.91 (1H, br),
 m/e 233 ($M^+ - 28$), 217, 189, 160, 143, 134, 132 (100%).

Ethyl 2-azido-3-phenylpropenoate (244) (50%), pale yellow prisms, m.p.,
 43°C (lit.,¹⁷⁴ 42-43°C).

Condensation of ethyl 2-formylbenzoate (229) with ethyl azidoacetate.

Ethyl 2-formylbenzoate (3.56 g, 0.02 mmol) and ethyl azidoacetate (10.32 g, 0.08 mol) were added dropwise to a stirred solution of sodium ethoxide (0.08 mol) in ethanol, cooled to -20°C as before. The solution was stirred for 3 h at -15°C and then allowed to warm to room temperature, was poured into water (200 ml) and acidified. The aqueous solution was then extracted with ether (3 x 100 ml) and the combined organic extracts dried and evaporated to give an orange solid (3.5 g). This mixture was then chromatographed on silica gel (petrol/ether) and the major fraction recrystallised from petrol and ether to give ethyl 2-azido-3-(2-carboxyphenyl)propenoate (243) (41%).

Attempted condensation of pyridine-2-carbaldehyde (203) with ethyl azidoacetate in 2% aqueous sodium hydroxide.

A mixture of pyridine-2-carbaldehyde (203) (2.14 g, 0.02 mol) and ethyl azidoacetate (10.32 g, 0.08 mol) was added dropwise to a well stirred solution of sodium hydroxide (0.75 g) in water (35 ml) at room temperature. The mixture was stirred for 24 h, but no reaction was apparent by t.l.c. The mixture was then extracted with ether (2 x 30 ml) and the extracts combined, dried and evaporated to give a yellow oil which was shown, by n.m.r. to consist of the aldehyde (203) and ethyl azidoacetate.

Ethyl 2-azido-3-(2-ethoxycarbonylphenyl)propenoate (245).

A solution of ethyl 2-azido-3-(2-carboxyphenyl)propenoate (243) (1.2 g, 4.6 mmol) in ethanol (50 ml) was cooled in an ice bath and saturated with hydrogen chloride gas. The flask was stoppered and allowed to stand at room temperature for 50 h. Solid sodium bicarbonate was then added to neutralise the solution which was then filtered and evaporated. The resulting oil was dissolved in ether (50 ml), washed with saturated sodium bicarbonate solution, dried, and evaporated, and the residue chromatographed on silica gel (petrol/ether) to give *ethyl 2-azido-3-(2-ethoxycarbonylphenyl)propenoate (245)* (0.93 g, 70%), as a colourless oil, $\nu_{\max}$ (film) 2125, 1715, 1685 cm^{-1} , δ (CDCl_3) 1.56 (6H, t, J 7 Hz), 4.48 (4H, q, J 7 Hz, can be seen to be splitting into two quartets), 7.26-7.65 (2H, m), 7.68 (1H, s), 7.85-8.05 (2H, m), m/e 279 (M^+), 261 (100%), 215.

Ethyl 2-azido-3-(2-*N,N*-diethylcarbamoylphenyl)propenoate (246).

(a) Preparation from ethyl 2-azido-3-(2-carboxylphenyl)propenoate (243) using oxalyl chloride and DMF.²⁰¹

DMF (1.0 ml) and acetonitrile (0.5 ml) were placed in a flask fitted with a nitrogen inlet and a septum, and cooled to -20°C . To this well stirred solution oxalyl chloride (90 μl , 1.05 mmol) was added whereupon a white precipitate of $\text{Cl}(\text{H})\text{C}=\text{NMe}_2$ Cl^- appeared. The mixture was stirred at -20°C for 0.12 h and then a solution of the acid (243) (261 mg, 1.0 mmol) in acetonitrile (0.5 ml) and DMF (1.0 ml) was added. The reaction mixture cleared and upon addition of diethylamine (219 mg, 3.0 mmol) became pale red and cloudy. The mixture was then allowed to warm to room temperature and saturated sodium bicarbonate solution (10 ml) added. This solution was then extracted with dichloromethane (2 x 10 ml), and

the organic extracts combined, dried, and evaporated to give an oil which was shown by n.m.r. to contain a quantity of DMF. This oil was then dissolved in petrol (20 ml) and ether (7 ml), washed well with water (4 x 10 ml), and was then dried and evaporated to give *ethyl-2-azido-3-(2-N,N-diethylcarbamoylphenyl)propenoate* (246) (159 mg, 50%) as a pale yellow oil, $\nu_{\max}$ (CCl_4) 2122, 1715, 1635 cm^{-1} , δ (CDCl_3) 1.20 (3H, t, J 7 Hz), 1.46 (3H, t, J 7 Hz), 1.52 (3H, t, J 7 Hz), 3.24 (2H, q, J 7 Hz), 3.75 (2H, br q, J 7 Hz), 4.48 (2H, q, J 7 Hz), 7.06 (1H, s), 7.30-7.60 (3H, m), 8.25-8.45 (1H, m), m/e 288 ($M^+ - 28$), 260, 216, 189 (100%), 160.

(b) Preparation from (243) using dicyclohexylcarbodiimide.²⁰²

Dicyclohexylcarbodiimide (DCC) (95.7 mg, 0.46 mmol) was added to a solution of the acid (243) (109 mg, 0.42 mmol) and diethylamine (31 mg, 0.42 mmol) in dichloromethane (10 ml) and the solution stirred at room temperature under nitrogen for 2.5 h. A solid appeared in the reaction mixture after 0.5 h. The reaction mixture was then filtered, washed with hydrochloric acid (1N; 10 ml) and saturated sodium bicarbonate solution (10 ml), then dried and evaporated to give an oil which was shown by n.m.r. to be a mixture of two compounds. This mixture was separated by chromatography on silica gel (petrol/ether) and was shown to be composed of *ethyl 2-azido-3-(2-N,N-diethylcarbamoylphenyl)propenoate* (246) (49 mg, 35%) and *ethyl 2-azido-3-[2-(N-(N-cyclohexylcarbamoyl)-N-cyclohexylcarbamoyl)phenyl]propenoate* (248) (106 mg, 50%), a pale yellow oil, δ (CDCl_3) 0.60-2.40 (29H, m), (23H expected), 3.20-3.70 (1H, m, NCH_2R_2), 3.80-4.25 (1H, m, NCH_2R_2), 4.39 (2H, q, J 7 Hz), 6.87 (1H, br d, NH), 7.07 (1H, s), 7.30-7.60 (3H, m), 7.86-8.04 (1H, m), m/e 469 (M^+ , 100%), 395, 354.

(c) Preparation from (243) using sodium hydride and thionyl chloride.

The sodium salt of (243) was prepared by treating the acid (243) (261 mg, 1 mmol) with sodium hydride (2 fold excess) in ether (5 ml). The suspension of the salt was then cooled to -20°C , thionyl chloride (1 ml) was added dropwise, whereupon the solution cleared. An excess of diethylamine was then added and the reaction mixture allowed to warm to room temperature. Water (10 ml) was then added slowly and the two phases separated. The aqueous phase was extracted with ether (10 ml) and the organic phases combined, washed with saturated sodium bicarbonate solution, dried and evaporated. The residue was chromatographed on silica gel to give the amide (246) (218 mg, 69%).

Ethyl-2-azido-3-(2-carbamoylphenyl)propenoate (247).

(a) Acetonitrile (5 ml) and DMF (5 ml) were placed in a round-bottomed flask fitted with a nitrogen inlet and a septum and cooled to -20°C . To this well stirred solution oxalyl chloride (0.68 ml, 8.0 mmol) was added whereupon a white precipitate of $\text{ClCH}=\text{NMe}_2^+ \text{Cl}^-$ appeared. This mixture was stirred at -20°C for 0.12 h and then a solution of the acid (243) (2 g, 7.6 mmol) in DMF (10 ml) was added. When the reaction mixture became clear ammonia gas was bubbled through. The solution went a pale red colour. The ammonia gas was continually bubbled through the reaction mixture while it was allowed to warm to room temperature. The work-up procedure was the same as that used for the preparation of (246). Chromatography on silica gel (petrol/ether/ethyl acetate) gave *ethyl 2-azido-3-(2-carbamoylphenyl)propenoate* (247) (601 mg, 30%) as pale yellow/green crystals which were recrystallised

from chloroform and petrol, m.p., 135°C (dec.) (Found: C, 55.8; H, 6.65; N, 21.4. $C_{12}H_{12}N_4O_3$ requires C, 55.4; H, 6.65; N, 21.5%), $\nu_{\max}$ (Nujol) 2875, 2700, 2125, 1714, 1643, 1620 cm^{-1} , δ (CDCl_3) 1.38 (3H, t, J 7 Hz), 4.40 (2H, q, J 7 Hz), 5.50-6.25 (2H, br s, NH_2), 7.30-7.70 (4H, m, ArH and vinyl H), 7.90-8.20 (1H, m, ArH), m/e 233 (M^+ -28), 186, 133 (100%).

(b) The amide (247) was prepared from the acid (243) by treatment of the acid with sodium hydride, thionyl chloride and ammonia gas. The procedure was similar to that used to prepare (246). The yield of (247) was 20-25%.

Attempted preparation of the acid chloride derivative of ethyl 2-azido-3-(2-carboxylphenyl)propenoate (243).

(a) To a well stirred solution of the acid (243) (261 mg, 1 mmol) and oxalyl chloride (87.2 μl , 1 mmol) in ether (10 ml), DMF (1 drop) was added and the mixture stirred at room temperature under nitrogen for 0.5 h. The mixture started to bubble immediately, and the bubbling ceased after 0.2 h. The solvent was evaporated and an i.r. spectrum of the residue taken. This showed no peaks corresponding to a vinyl azide or to an acid chloride. Chromatography on silica gel (petrol/ether) gave ethyl 1-isoquinolone-3-carboxylate (249) (133 mg, 61%) which was recrystallised from dichloromethane and petrol, m.p., 146.5-148.5°C (lit.,²³⁹ 147-148°C), ν (CCl_4) 3390, 1720, 1680 cm^{-1} , δ (CDCl_3) 1.44 (3H, t, J 7 Hz), 4.50 (2H, q, J 7 Hz), 7.41 (1H, s, vinyl H), 7.50-7.80 (3H, m, ArH), 8.40-8.60 (1H, m, ArH), 9.30-9.65 (1H, br s, exch. D_2O), m/e 217 (M^+ , 100%), 189, 155.

(b) Sodium hydride (5 fold excess) was added to a solution of the acid (243) (261 mg, 1 mmol) in ether (15 ml) and the mixture stirred at room temperature until it was shown by t.l.c. that all of the acid had been converted into its salt. The mixture was then cooled to -17°C and an excess of thionyl chloride (1.6 ml, 20 fold excess) added. The solution became clear, except for a suspension of unreacted sodium hydride. The mixture was allowed to warm to room temperature and heated at 35°C for 1 h, then cooled and water added dropwise until all of the unreacted sodium hydride and thionyl chloride had been destroyed. The ether solution was then washed with water (10 ml), dried and evaporated to give an oily solid which on chromatography on silica gel (petrol/ether) gave ethyl 1-isoquinolone-3-carboxylate (249) (159 mg, 73%).

Ethyl 2-azido-3-(2-oxiran-2-ylmethylphenyl)propenoate (253).

A solution of MCPBA (80%; 233.3 mg, 1.35 mmol) in dichloromethane (5 ml) was added dropwise to a solution of ethyl 2-azido-3-(2-allylphenyl)-propenoate (218) (285 mg, 1.11 mmol) in dichloromethane (5 ml) and the resulting solution refluxed for 10 h. By this time a precipitate had appeared in the solution, which dissolved when dichloromethane (10 ml) was added. The reaction mixture was then washed with aqueous sodium sulphite (10%, 10 ml) and saturated aqueous sodium bicarbonate (10 ml), and water (5 ml), dried and evaporated to give a red oil (190 mg). An n.m.r. spectrum of this oil indicated that the allyl group had been epoxidised. The material was then columned on alumina (petrol/ether) but the product decomposed on the column and only one fraction was obtained - ethyl 2-azido-3-[2-(oxiran-2-ylmethylphenyl)propenoate (253) (7 mg, 2%)

as a colourless oil, $\nu_{\max}$ (CCl_4), 2120, 1715, 1620, 1240 cm^{-1} , δ (CDCl_3) 1.39 (3H, t, J 6.9) 2.45–2.62 (1H, m), 2.70–2.85 (1H, m), 2.87–3.22 (3H, m), 4.41 (2H, q, J 6.9 Hz), 7.22 (1H, s, vinyl H), 7.20–7.45 (3H, m), 7.85–8.05 (1H, m), m/e 273 (M^+), 245 (100%), 199. A comparison of the n.m.r. spectrum of (253) with that of the total crude reaction mixture indicated that there was a large quantity of (253) (> 50%) present before chromatography.

Ethyl 2-azido-3-[2-(3-phenyloxiran-2-yl)phenyl]propenoate (254).

A solution of MCPBA (80%; 0.833 g, 3.8 mmol) in dichloromethane (10 ml) was added dropwise to a solution of ethyl 2-azido-3-(2-*E*-styrylphenyl)propenoate (223) (1.12 g, 3.5 mmol) in dichloromethane (5 ml) and stirred overnight at room temperature. A precipitate appeared in the solution which dissolved on addition of chloroform (10 ml). The reaction mixture was then washed with sodium sulphite solution (10%; 10 ml), saturated sodium bicarbonate solution (10 ml), and water (10 ml), then dried and evaporated. The solid residue was chromatographed on alumina (petrol/ether) to give *ethyl 2-azido-3[2-(3-phenyloxiran-2-yl)-phenyl]propenoate* (254); (662 mg, 56%) as colourless needles recrystallised from ether and petrol, m.p., 153.5–155°C (Found: C, 74.2; H, 5.55; N, 4.6. $\text{C}_{14}\text{H}_{17}\text{N}_3\text{O}_3$ requires C, 74.25; H, 5.6; N, 4.55%), $\nu_{\max}$ (Nujol) 2115, 1700 cm^{-1} , δ (CDCl_3) 1.12 (3H, t, J 7 Hz), 3.78 (1H, d, J 2 Hz), 4.02 (1H, d, J 2 Hz), 4.23 (2H, q, J 7 Hz), 7.14 (1H, s), 7.25–7.55 (8H, m), 7.90–8.05 (1H, m), m/e 307 (M^+), 278 (100%), 234, 204, 127, 105.

7.3. EXPERIMENTAL TO CHAPTER THREE

Thermolysis of ethyl 2-azido-3-(2-pyridyl)propenoate (232).

A solution of vinyl azide (232) (101 mg, 0.46 mmol) in toluene (25 ml) was refluxed under nitrogen for 16 h. The solvent was then evaporated and the residue chromatographed on silica gel (petrol/ether) to give *ethyl pyrazolo[1,5-a]pyridine-2-carboxylate (260)* (82.5 mg, 94%) which was recrystallised from dichloromethane and petrol, m.p., 47–48°C (Found: C, 63.0; H, 5.35; N, 14.6. $C_{10}H_{10}N_2O_2$ requires C, 63.15; H, 5.3; N, 14.7%), $\lambda_{\max}$ (MeOH) 220, 240, 247, 310 nm, $\nu_{\max}$ (Nujol), 1744, 1635 cm^{-1} , δ (CDCl₃) 1.46 (3H, t, J 7 Hz), 4.54 (2H, q, J 7 Hz), 6.85–7.05 (1H, m, 6-H), 7.15 (1H, s, 3-H), 7.18–7.35 (1H, m, 5-H), 7.58–7.75 (1H, m, 4-H), 8.50–8.68 (1H, m, 7-H), m/e 190 (M^+), 162, 145, 118 (100%), 90, 78.

Thermolysis of ethyl 2-azido-3-(2-benzyloxyphenyl)propenoate (231).

A solution of ethyl 2-azido-3-(2-benzyloxyphenyl)propenoate (231) in toluene (20 ml) was refluxed for 3.75 h. The solvent was then evaporated to give a solid residue which was recrystallised from dichloromethane and petrol to give ethyl 4-benzyloxyindole-2-carboxylate (261)²⁰⁸ (77 mg, 60%). The filtrate was chromatographed on silica gel (petrol/ether) to give a further quantity of (261) (36 mg, 28%). The combined yield of (261) (113 mg, 88%) was recrystallised from chloroform and petrol, m.p., 169–171°C (Found: C, 72.95; H, 5.8; N, 4.75. $C_{18}H_{17}NO_3$ requires C, 73.2; H, 5.8; N, 4.75), $\nu_{\max}$ (Nujol), 3325, 1685 cm^{-1} , δ (CDCl₃) 1.37 (3H, t, J 7 Hz), 4.41 (2H, q, J 7 Hz), 5.21 (2H, s), 6.45–6.70 (1H, m, ArH), 6.90–7.60 (8H, m), 9.05–9.45 (1H, br s, NH), m/e 295 (M^+), 222, 204, 99, 85, 83 (100%).

Thermolysis of ethyl 2-azido-3-(2-phenylmethylphenyl)propenoate (233).

(i) Without iodine. A solution of ethyl 2-azido-3-(2-phenylmethylphenyl)propenoate (233) (92 mg) in toluene (25 ml) was refluxed for 2.75 h, then the solvent evaporated. Chromatography on silica gel (petrol/ether) gave *ethyl 4-benzylindole-2-carboxylate* (265) (35 mg, 42%) m.p., 164-165°C (from chloroform and petrol) (Found: C, 77.5; H, 6.15; N, 5.0. $C_{18}H_{17}NO_2$ requires C, 77.4; H, 6.15, N, 5.0%), $\lambda_{\max}$ (EtOH) 207, 232, 296 nm, $\nu_{\max}$ (Nujol) 3315, 1682 cm^{-1} , δ (CDCl₃) 1.39 (3H, t, J 7Hz), 4.29 (2H, s, ArCH₂), 4.44 (2H, q, J 7 Hz) 6.85-7.05 (1H, m), 7.14-7.60 (8H, m), 9.05-9.50 (1H, br s, NH), m/e 279 (M^+ , 100%), 233, 204, 178; and *ethyl 1,2-dihydro-1-phenylisoquinoline-3-carboxylate* (266) (22 mg, 26%), m.p., 69-74°C (from petrol), $\nu_{\max}$ (Nujol) 3390, 1677 cm^{-1} , δ (CDCl₃) 1.35 (3H, t, J 7.3 Hz), 4.30 (2H, q, J 7.3 Hz), 4.73-4.92 (1H, br s, NH), 5.66 (1H, s, 1-H), 6.47 (1H, s, 4-H), 6.72-6.78 (1H, m), 7.05-7.20 (3H, m), 7.27-7.42 (5H, m), m/e 279 (M^+), 205, 202 (100%), 156, 128; and *ethyl 1-phenylisoquinoline-3-carboxylate* (267) (ca.2 mg, ca. 2%). A satisfactory analysis of (266) was not obtained. The spectra and analytical data for (267) will be given in the next experiment.

(ii) With iodine (0.1 molar equivalents). A solution of vinyl azide (233) (121 mg, 0.39 mmol) and iodine (11.3 mg, 0.04 mmol) in toluene (40 ml) was refluxed under nitrogen for 2.5 h. The iodine colour gradually disappeared but iodine sublimed from the reaction mixture when the solvent was evaporated. The residue was chromatographed to give *ethyl 4-benzylindole-3-carboxylate* (265) (14 mg, 13%); *ethyl 1-phenylisoquinoline-3-carboxylate*, m.p., 100-101°C (from ether and petrol) (Found: C, 77.7; H, 5.55; N, 4.9. $C_{18}H_{15}NO_2$ requires C, 77.95; H, 5.45; N, 5.05%), $\nu_{\max}$ (Nujol) 1740 cm^{-1} , δ (CDCl₃) 1.47 (3H, t, J 7 Hz), 4.52 (2H, q, J 7Hz),

7.45–8.30 (9H, m), 8.59 (1H, s, 4-H), m/e 277 (M^+), 233, 205 (100%), 176, 102; and *ethyl 2-amino-3-(2-benzylphenyl)propenoate* (268) (23 mg, 20%) as a colourless oil, $\nu_{\max}$ (film) 3485, 3390, 1701, 1633 cm^{-1} δ (CDCl_3) 1.33 (3H, t, J 6.9 Hz), 3.96 (4H, br s, ArCH_2Ph and NH_2), 4.25 (2H, q, J 6.9 Hz), 6.37 (1H, s, vinyl H), 6.97–7.30 (8H, m), 7.40–7.55 (1H, m), m/e 279 (M^+); *N-acetyl derivative*, m.p., 143–145°C (from dichloromethane and petrol) (Found: C, 73.9; H, 6.55; N, 4.3. $\text{C}_{20}\text{H}_{21}\text{NO}_3$ requires C, 74.3; H, 6.55; N, 4.3%), $\nu_{\max}$ (Nujol) 3260, 1725, 1655 cm^{-1} , δ (CDCl_3) 1.36, (3H, t, J 6.8 Hz), 1.85–2.05 (3H, br s, CH_3), 4.06 (2H, s, ArCH_2Ph), 4.31 (2H, q, J 6.8 Hz), 2.60–2.73 (1H, br s, exch. D_2O , NH) 7.05–7.50 (ca. 10H, m), m/e 323 (M^+), 264, 208 (100%), 191, 178.

(iii) With iodine (1.0 molar equivalents) and potassium acetate (1.0 molar equivalents). Potassium acetate (38 mg, 0.39 mmol) was added to a solution of (233) (119 mg, 0.39 mmol) and iodine (98.5 mg, 0.39 mmol) in toluene (20 ml) and the mixture refluxed under nitrogen for 2.75 h. The cooled reaction mixture was diluted with ether (20 ml) washed with saturated aqueous sodium thiosulphate (20 ml), saturated aqueous sodium chloride (10 ml), was dried and evaporated. The residue was chromatographed on alumina to give *ethyl 4-benzylindole-2-carboxylate* (265) (8 mg, 7%) and *ethyl 1-phenylisoquinoline-3-carboxylate* (267) (56 mg, 52%).

Preparation of ethyl 2-acetamido-3-(2-benzylphenyl)propenoate (269).²¹¹

A sample of the enamine (268) (ca. 20 mg) was dissolved in acetic anhydride, cooled to 0°C, and then pyridine (2 drops) added. The solution was then allowed to stir at room temperature for 0.75 h, and then water

(4 ml) added. After stirring for a further 1.5 h, water (19 ml) was again added. On standing for 8 h colourless crystals precipitated from this solution. These were collected by filtration. The aqueous filtrate was extracted with ether and the ether extracts combined, washed with dilute hydrochloric acid, dilute aqueous sodium hydroxide and water, dried and evaporated. The residue was combined with the crystals filtered off and the total product recrystallised from dichloromethane and petrol to give 2-acetamido-3-(2-benzylphenyl)propenoate (269) m.p., 143-145°C. The spectral and analytical data have already been given.

Reactions of ethyl 1,2-dihydro-1-phenylisoquinoline-3-carboxylate (266).

(i) A solution of ethyl 1,2-dihydro-1-phenylisoquinoline-3-carboxylate (266) (22 mg, 0.08 mmol) in toluene (5 ml) was refluxed in air for 2 h. The solvent was then evaporated and an n.m.r. spectrum of the residue taken. The spectrum was essentially that of the dihydroisoquinoline (266).

(ii) A sample of the dihydroisoquinoline (266) (8 mg, 0.03 mmol) in deuteriochloroform (0.5 ml) was placed in an n.m.r. tube and iodine (7.3 mg, 0.03 mmol) added. N.m.r. spectra were taken at regular intervals and showed a rapid and clean conversion of (266) to the isoquinoline (267). No products other than (267) were observed. The reaction was essentially complete after 0.3 h, though ca. 50% of the dihydroisoquinoline (266) had reacted after 30 s.

(iii) A solution of dihydroisoquinoline (266) (21 mg, 0.075 mmol) and iodine (2 mg, 0.0078 mmol) in toluene (4 ml) was refluxed under nitrogen for 0.5 h. After 0.3 h only the isoquinoline (267) was observed

in the reaction mixture, by t.l.c. The dihydroisoquinoline (266) had reacted completely. The heating was stopped after 0.5 h and the solvent evaporated. An n.m.r. spectrum of the residue indicated that only the isoquinoline (257) was present.

(iv) A sample of the dihydroisoquinoline (266) in toluene at room temperature was treated with an excess of chloranil. The dihydroisoquinoline (266) was immediately converted to the isoquinoline (267). This was shown by t.l.c.

Reaction of ethyl 4-benzylindole-2-carboxylate (265) with iodine.

A solution of the indole (265) (20 mg), iodine (70 mg) and potassium acetate (200 mg) in toluene (10 ml) was refluxed for 2 h. The reaction was followed by t.l.c. and the conversion of (265) into another compound of slightly lower r.f. was observed. The solvent was then evaporated and the mass spectrum of the residue indicated that an iodinated indole (M^+ 405) was present.

Thermal decomposition of ethyl 2-azido-3-(2-benzylphenyl)propenoate (233) in the presence of hydroquinone.

(i) Without iodine. A solution of hydroquinone (28.6 mg, 0.26 mmol) and vinyl azide (233) (40 mg, 0.13 mmol) in toluene (10 ml) was refluxed for 2.75 h. The solution was then cooled, diluted with ether (20 ml), then washed with aqueous sodium hydroxide (10%, 2 x 10 ml) and water (10 ml), dried, and evaporated. An n.m.r. spectrum of the residue showed that it was composed of indole (265) and dihydroisoquinoline (266) in roughly the same ratio as when the azide (233) was thermolysed without hydroquinone. No enamine (268) was produced.

(ii) With iodine. A solution of vinyl azide (233) (74 mg, 0.24 mmol), iodine (6 mg, 0.24 mmol) and hydroquinone (53 mg, 0.48 mmol) in toluene (15 ml) was refluxed for 2 h. The solution was then cooled and diluted with ether (10 ml), washed with aqueous sodium hydroxide (10%; 2 x 10 ml) and water (10 ml), dried and evaporated. An n.m.r. spectrum of the residue showed that it was composed of the following products: indole (265) (*ca.* 10%), isoquinoline (267) (*ca.* 35%), and enamine (268) (*ca.* 50%).

Thermal decomposition of ethyl 2-azido-3-(2-benzylphenyl)propenoate (233) in the presence of iodine and another oxidising agent.

(i) With iodine and chloranil. A solution of vinyl azide (233) (70 mg, 0.23 mmol), iodine (6 mg, 0.023 mmol) and chloranil (113 mg, 0.46 mmol) in toluene (12 ml) was refluxed for 2.75 h. The solvent was then evaporated and an n.m.r. spectrum of the residue indicated that it was a mixture of the isoquinoline (267) and enamine (268) in roughly the same ratio as had been observed for a similar reaction without chloranil.

(ii) With iodine and manganese dioxide. Manganese dioxide (35 mg, 0.50 mmol) was added to a solution of the vinyl azide (233) (61 mg, 0.20 mmol) and iodine (5 mg, 0.02 mmol) in toluene (10 ml) and the mixture refluxed for 2.75 h. The mixture was then allowed to cool, was filtered, and the solvent evaporated. An n.m.r. spectrum of the residue indicated that the mixture contained the isoquinoline (267) (*ca.* 45%), and the enamine (268) (*ca.* 5%), but the mixture was messy and no other products could be identified.

(iii) With iodine and barium manganate. Barium manganate (305 mg, 1.2 mmol) was added to a solution of the azide (233) (184.4 mg, 0.6 mmol) and iodine (30 mg, 0.12 mmol) in toluene (30 ml) and the mixture refluxed for 2.75 h. The mixture was then cooled, filtered, and evaporated. An

n.m.r. spectrum of the residue showed that the major product was the isoquinoline (267). No enamine (268) was present. Chromatography on silica gel (petrol/ether) gave the indole (265) (21 mg, 12.5%) and the isoquinoline (267) (81 mg, 49%).

Thermal decomposition of ethyl 2-azido-3-(fluoren-1-yl)propenoate (234).

A solution of the azide (234) (151 mg, 0.495 mmol) in toluene (30 ml) was refluxed under nitrogen for 24 h. The solvent was then evaporated and the residue chromatographed on silica gel (petrol/ether) to give *ethyl pyrrolo[3,2-a]fluorene-5-carboxylate* (270) (125 mg, 90%), m.p., 210-211.5°C (Found: C, 78.1; H, 5.45; N, 5.05. $C_{18}H_{15}NO_2$ requires C, 77.95; H, 5.45; N, 5.05%), $\nu_{\max}$ (Nujol), 3330, 1724, 1635 cm^{-1} , δ (CDCl_3) 8.90-9.30 (1H, br s, NH), 7.10-7.90 (7H, m), 4.46 (2H, q, J 7 Hz), 4.03 (2H, br s, CH_2), 1.40 (3H, t, J 7 Hz), m/e 277 (M^+), 204, 194, 165 (100%), and *ethyl 1-azafluoranthene-2-carboxylate* (271) (5 mg, 4%). The spectral and other data for (271) will be given in a later experiment. When the thermolysis was carried out in refluxing toluene for 1 h the yields of (270) and (271) were 84% and 4% respectively.

Thermal decomposition of ethyl 2-azido-3-(fluoren-1-yl)propenoate (234) in the presence of iodine.

(i) A solution of the azide (234) (100 mg, 0.33 mmol) and iodine (8.7 mg, 0.34 mmol) in xylene (20 ml) was refluxed under nitrogen for 1 h. The solvent was evaporated and the residue chromatographed on silica gel (petrol/ether) to give the indole (270) (45 mg, 49%) and the azafluoranthene (271) (10 mg, 10%).

(ii) A solution of the azide (234) (141 mg, 0.46 mmol) and iodine (117 mg, 0.46 mmol) in xylene (30 ml) was refluxed for 0.5 h. The solution was allowed to cool, then washed with sodium thiosulphate solution (10%, 2 x 15 ml) and water (10 ml), dried and evaporated. The residue was chromatographed on silica gel (petrol/ether) to give the pyrrolofluorene (270) (6 mg, 5%) and ethyl 1-azafluoranthene-2-carboxylate (271) (30 mg, 24%), m.p., 124.5-126.5°C (Found: M^+ 275.0942. $C_{18}H_{13}NO_2$ requires 275.0946), $\nu_{\max}$ 1744, 1635 cm^{-1} , δ (CDCl₃, 250 MHz), 1.53 (3H, t, J 7 Hz), 4.56 (2H, q, J 7 Hz), 7.35-7.95 (ca. 8H, m), 8.22-8.28 (ca. 1H, m), 8.52 (1H, s), m/e 275 (M^+), 203 (100%).

When this experiment was repeated in refluxing toluene in the presence of iodine (1 molar equivalent) and potassium acetate (2 molar equivalents) the yield of (271) was 18%.

Thermal decomposition of ethyl 2-azido-3-(2-methylphenyl)propenoate (235).

(i) No reagent added. A solution of vinyl azide (235) (131 mg, 0.57 mmol) in toluene was refluxed for 2.75 h. The solvent was then evaporated and the solid residue was shown by n.m.r. to be ethyl 4-methyl-indole-2-carboxylate (272) m.p., 139-140°C (from dichloromethane and petrol) (lit.,⁵⁹ 140.5°C).

(ii) With potassium carbonate. Anhydrous potassium carbonate was heated to 150°C under vacuum for 16 h, then a portion (158 mg, 1.2 mmol) added to a solution of the vinyl azide (235) (139 mg, 0.6 mmol) in toluene (30 ml). The mixture was then refluxed for 2.75 h, cooled, filtered, and evaporated. The residue was shown, by n.m.r. to be composed solely of the indole (272).

(iii) With hydrogen iodide. A solution of hydrogen iodide in toluene (0.06 M) was prepared²⁴⁰ and a portion (1.6 ml, 0.1 mmol) added to a solution of the azide (235) (231 mg, 1 mmol) in toluene (30 ml). This solution was then refluxed under nitrogen for 2.75 h, cooled and evaporated to give a solid residue which, by n.m.r., contained only the indole (272).

(iv) With potassium iodide. Potassium iodide (199 mg, 1.2 mmol) was added to a solution of (235) (138 mg, 0.6 mmol) in toluene (30 ml) and the mixture refluxed for 2.75 h, cooled, filtered, and evaporated to give a residue which, by n.m.r., contained only the indole (272).

(v) With hydroquinone. A solution of hydroquinone (33 mg, 0.35 mmol) and (235) (81 mg, 0.35 mmol) in toluene (18 ml) was refluxed for 2.75 h. The solution was then diluted with ether (20 ml) washed with aqueous sodium hydroxide (2 x 10 ml) to remove unreacted hydroquinone and then dried and evaporated. The residue was shown, by n.m.r., to consist solely of the indole (272).

(vi) With diphenyldiselenide. Diphenyldiselenide (10.3 mg, 0.033 mmol) was added to a solution of the azide (235) (76 mg, 0.33 mmol) in toluene (10 ml) and the resulting solution heated at reflux for 3 h. The solvent was then evaporated, and an n.m.r. spectrum of the residue showed that it was composed of the indole (272) and diphenyldiselenide only. No isoquinoline (273) was observed.

(vii) With diphenyldisulphide. Diphenyldisulphide (218 mg, 1 mmol) was added to a solution of vinyl azide (235) (231 mg, 1 mmol) in toluene (50 ml). The solution was refluxed for 2.75 h, then evaporated. The residue was shown by n.m.r. and t.l.c. to contain the indole (272) and diphenyldiselenide only.

(viii) With di-*t*-butylperoxide. A solution of vinyl azide (272) (120 mg, 0.52 mmol) and di-*t*-butylperoxide (15 mg, 0.10 mmol) in xylene (25 ml) was refluxed for 0.25 h, then evaporated. An n.m.r. spectrum of the residue showed that all of the azide (235) had been converted into indole (272).

(ix) With dibenzoylperoxide. Dibenzoylperoxide (6 mg, 0.026 mmol) was added to a solution of (235) (57 mg, 0.258 mmol) in toluene (16 ml) and the solution refluxed for 3 h. The solvent was then evaporated. An n.m.r. spectrum of the residue showed that the indole (272) was the only product.

(x) With iodine. A solution of vinyl azide (235) (241 mg, 1.04 mmol) and iodine (25 mg, 0.10 mmol) in toluene (40 ml) was refluxed for 3 h and then evaporated. As the solvent was evaporated some iodine distilled over also, even though there did not appear to be any in the pale yellow crude reaction mixture. The residue was chromatographed on silica gel to give ethyl 4-methylindole-2-carboxylate (272) (59 mg, 28%), ethyl isoquinoline-3-carboxylate (273) (42 mg, 20%), picrate, m.p., 156-158°C (lit.,²¹³ 154-5°C), and *ethyl 2-amino-3-(2-methylphenyl)-propenoate* (274) (28 mg, 13.5%). The spectral data for the enamine (274) is described in a later experiment. The spectral data for (273) was identical to that of an independently prepared sample²¹³ of ethyl isoquinoline-3-carboxylate.

(xi) With iodine (0.1 molar equivalents) and potassium carbonate. Potassium carbonate (158 mg, 1.2 mmol) was added to a solution of vinyl azide (235) (138 mg, 0.6 mmol) and iodine (15.3 mg, 0.06 mmol) in toluene (30 ml) and the mixture refluxed for 2 h. The colour of the iodine had disappeared completely after 0.75 h. The mixture was allowed to cool

and was filtered and the filtrate evaporated. No iodine distilled over with the solvent. An n.m.r. spectrum of the residue indicated that the following compounds were present: indole (272) (55%), isoquinoline (273) (15%), and enamine (274) (5%).

(xii) With iodine (1.0 molar equivalent) and potassium acetate. Potassium acetate (62 mg, 0.66 mmol) was added to a solution of vinyl azide (235) (154 mg, 0.66 mmol) and iodine (169 mg, 0.66 mmol) in toluene (33 ml) and the mixture refluxed for 2.75 h. Ether (10 ml) was then added and the solution washed with sodium thiosulphate solution (10%; 2 x 10 ml) and water (10 ml), dried and evaporated. An n.m.r. spectrum of the residue indicated that it was *ca.* 50% composed of ethyl isoquinoline-3-carboxylate (273). Chromatography on silica gel (petrol/ether) gave isoquinoline (273) (42.4 mg, 32%).

(xiii) With iodine (1.0 molar equivalents) and potassium carbonate. Potassium carbonate (1.65 g, 0.012 mmol) was added to a solution of vinyl azide (235) (1.38 g, 0.006 mol) and iodine (1.52 g, 0.006 mol) in toluene (300 ml) and the mixture refluxed for 2.75 h. The solution was then cooled and washed with sodium thiosulphate solution, (10%; 3 x 75 ml) and water (50 ml), dried, and evaporated and the residue chromatographed on silica gel to give indole (272) (98 mg, 8%) and isoquinoline (273) (359 mg, 30%).

(xiv) With iodine and hydroquinone. A solution of vinyl azide (235) (87.4 mg, 0.378 mmol), hydroquinone (41.6 mg, 0.378 mmol) and iodine (9.6 mg, 0.038 mmol) in toluene (20 ml) was refluxed for 3.25 h then cooled and diluted with ether (20 ml). This solution was then washed with saturated sodium thiosulphate solution (10 ml), sodium hydroxide solution (1M, 3 x 10 ml), saturated sodium chloride solution (10 ml) was dried and evaporated. An n.m.r. spectrum of the residue indicated that it was composed of indole (272) (*ca.* 58%), isoquinoline (273) (*ca.* 2%)

and enamine (274) (*ca.* 39%). Chromatography on silica gel gave indole (272) (39 mg, 51%) and a fraction which contained enamine (274) (20 mg, 26%). The isolated yield of ethyl 2-amino-3-(2-methylphenyl)propenoate (274) was *ca.* 20%. It was contaminated with two minor products but the following signals in the n.m.r. spectrum of the mixture could be assigned to (274), δ (CDCl_3), 1.37 (3H, t, J 7 Hz), 2.30 (3H, s, ArCH_3), 3.75-4.30 (2H, br s, *exch.* D_2O , NH_2), 4.32 (2H, q, J 7 Hz), 6.37 (1H, s, vinyl H), 7.05-7.55 (4H, m).

(xv) With iodine and α -methylstyrene. A solution of vinyl azide (235) (93 mg, 0.40 mmol), iodine (10 mg, 0.04 mmol) and freshly distilled α -methylstyrene (47.5 mg, 0.40 mmol) was refluxed for 3 h. The solvent was then evaporated and an n.m.r. spectrum of the residue taken. It was found to contain indole (272) and isoquinoline (273) in *ca.* 50% and 25% yield respectively, but the amount of enamine (274) was substantially decreased (*ca.* 2%).

(xvi) In bromobenzene. A solution of the azide (235) (60 mg, 0.26 mmol) in bromobenzene (17 ml) was heated at 110°C under nitrogen for 3 h. The solvent was then distilled under reduced pressure. An n.m.r. spectrum of the residue indicated that it was composed solely of the indole (272).

(xvii) In iodopropane. Iodopropane was doubly distilled to ensure that it was not contaminated with iodine. A solution of vinyl azide (235) (60 mg, 0.26 mmol) in iodopropane was refluxed for 6 h. The solvent was then evaporated and the residue was shown, by n.m.r. to be ethyl 4-methyl-indole-2-carboxylate (272).

Ethyl 2-(2-methylphenyl)-2H-azirine-3-carboxylate (275).

A solution of ethyl 2-azido-3-(2-methylphenyl)propenoate (235) (167 mg, 0.72 mmol) in toluene (30 ml) was refluxed for 1 h, then evaporated. An n.m.r. of the residue indicated that it was a 1:1 mixture of ethyl 4-methylindole-2-carboxylate (272) and *ethyl 2-(2-methylphenyl)-2H-azirine-3-carboxylate (275)*. The n.m.r. solvent was evaporated and petrol (5 ml) added to separate the mixture. The indole (272) was insoluble in the petrol whereas the azirine (275) was taken up into the petrol, which was then filtered and evaporated to give ethyl 2-(2-methylphenyl)-2H-azirine-3-carboxylate (275) as an oil, (ca. 50 mg), $\nu_{\max}$ (CCl₄) 1760, 1725 cm⁻¹, $\lambda_{\max}$ (EtOH), 212, 293 nm, δ (CDCl₃), 1.35 (3H, t, *J* 7.2 Hz), 2.49 (3H, s, ArCH₃), 3.52 (1H, s, 2-H), 4.45 (2H, q, *J* 7.2 Hz), 6.70-6.87 (1H, m), 7.00-7.30 (3H, m), *m/e* 203 (*M*⁺, 100%), 157, 131, 130, 104, 103, 77.

On silica gel chromatography (petrol/ether) a similar reaction mixture gave indole (272) (38%) and several dimers of the azirine (*M*⁺ 406), which were not identified. The azirine (275) was unstable to chromatography on silica gel.

Thermal decomposition of ethyl 2-(2-methylphenyl)-2H-azirine-3-carboxylate (275).

The azirine (275) was prepared by photolysis of ethyl 2-azido-3-(2-methylphenyl)propenoate (235) as described in section 7.6.

(i) A sample of the azirine (275) was dissolved in toluene and refluxed for 1.5 h. The solvent was evaporated and an n.m.r. spectrum of the residue indicated that it was composed of indole (272) only.

(ii) Potassium carbonate (298 mg, 2.26 mmol) was added to a solution of (275) (261 mg, 1.13 mmol) and iodine (28.7 mg, 0.11 mmol) in toluene (56 ml) and the mixture refluxed under nitrogen for 2.75 h. The solution was then filtered and evaporated. An n.m.r. spectrum of the residue showed

a similar ratio of products (272), (273) and (274) as in the thermal decomposition of ethyl 2-azido-3-(2-methylphenyl)propenoate (235) under the same conditions. The reaction mixture was not quite as clean however.

(iii) Potassium carbonate (219 mg, 1.66 mmol) was added to a solution of (275) (192 mg, 0.83 mmol) and iodine (211 mg, 0.83 mmol) in toluene (41 ml) and the mixture refluxed under nitrogen for 2.75 h. The mixture was then cooled, diluted with ether (20 ml), washed with sodium thiosulphate solution (10%; 2 x 20 ml), and saturated sodium chloride solution (10 ml), dried and evaporated, and an n.m.r. spectrum of the residue taken. The spectrum was similar but not as clean as that of the crude thermolysis mixture of vinyl azide (235) under the same conditions. Ethyl isoquinoline-3-carboxylate (273) was the major product.

(iv) A sample of azirine (275) (43 mg, 0.216 mmol) was dissolved in benzene (10 ml) and iodine (5.5 mg, 0.02 mmol) added. The solution was stirred at room temperature for 4 h, then the solvent evaporated. An n.m.r. spectrum of the residue indicated that the azirine had been unchanged by treatment with iodine at room temperature.

Treatment of ethyl 4-methylindole-2-carboxylate (272) with iodine.

A solution of indole (272) (95 mg, 0.41 mmol) in toluene (20 ml) was treated with iodine (104 mg, 0.41 mmol) and potassium carbonate (108 mg, 0.82 mmol) and the mixture refluxed for 2 h, then cooled, filtered, and evaporated. An n.m.r. spectrum of the residue indicated that the indole (272) had been unchanged by this treatment.

Treatment of ethyl isoquinoline-3-carboxylate (273) with iodine.

A solution of isoquinoline (273) (140 mg, 0.505 mmol) in toluene (25 ml) was treated with iodine (128 mg, 0.505 mmol) and potassium carbonate (139 mg, 1.01 mmol) and the mixture refluxed for 2.5 h. The mixture was then cooled, washed with sodium thiosulphate solution (10%; 2 x 20 ml) and water (10 ml), dried and evaporated to give isoquinoline (273) unchanged, as shown by n.m.r.

Ethyl isoquinoline-3-carboxylate (273).

This compound was prepared from phenylalanine by a literature method,²¹³ $\nu_{\max}$ (film) 1750, 1730, 1630 cm^{-1} , δ (CDCl_3 , 60 MHz), 1.47 (3H, t, J 7.4 Hz), 4.55 (2H, q, J 7.4 Hz), 7.50-8.30 (4H, m, ArH), 8.53 (1H, s, 4-H), 9.36 (1H, s, 1-H).

Thermal decomposition of ethyl 2-azido-3-(2-isopropylphenyl)propenoate (236).

(i) No added reagent. A solution of the azide (236) (0.212 g, 0.82 mmol) in xylene (40 ml) was refluxed for 0.75 h. The solvent was then evaporated and the residue chromatographed to give *ethyl 4-isopropylindole-2-carboxylate* (278) (122.5 mg, 65%), m.p., 105-108°C (from ether and petrol) (Found: C, 72.5; H, 7.45; N, 6.1. $\text{C}_{14}\text{H}_{17}\text{NO}_2$ requires C, 72.7; H, 7.4; N, 6.05%), $\nu_{\max}$ (Nujol) 3345, 1686 cm^{-1} , δ (CCl_4) 1.37 (6H, d, J 7 Hz), 1.41 (3H, t, J 7 Hz), 3.35 (1H, heptet, J 7 Hz), 4.44 (2H, q, J 7 Hz), 6.85-7.00 (1H, m, ArH), 7.13-7.35 (3H, m, ArH), 10.10 (1H, br s, NH), m/e 231 (M^+ , 100%), 216, 185, 170 and *ethyl 2-amino-3-(2-propen-2-ylphenyl)propenoate* (280), a colourless oil, $\nu_{\max}$ (film),

3460, 3370, 1705, 1630 cm^{-1} , δ (CCl_4) 1.36 (3H, t, J 7 Hz), 2.05 (3H, m, side chain CH_3), 3.75-4.35 (2H, br s, exch. D_2O , NH_2), 4.31 (2H, q, J 7 Hz), 4.95 (1H, m, side chain vinyl H), 5.23 (1H, m, side chain vinyl H), 6.41 (1H, s, vinyl H), 7.05-7.37 (3H, m, ArH), 7.50-7.66 (1H, m, ArH), m/e 231 (M^+), 216, 170, 140, 115, *N*-acetyl derivative m.p., 145-146°C, and ethyl 1,1-dimethyl-1,2-dihydroisoquinoline-3-carboxylate (279) (5.7 mg, 3%). The spectral data for (279) will be given in a later experiment.

When this experiment was repeated in refluxing xylene for 2.5 h the products isolated were: (278) (61%), (279) (3%), and (280) (6%).

The yields of (280) are lower than expected on examination of the n.m.r. spectra of the crude reaction mixture, which indicate that the yields of (280) should be ca. 20%.

(ii) With iodine (0.1 molar equivalents). A solution of vinyl azide (236) (184 mg, 0.71 mmol) and iodine (18 mg, 0.07 mmol) in xylene (35 ml) was refluxed under nitrogen for 0.75 h. The solvent was then removed and the residue chromatographed on silica gel (petrol/ether) and then on silica gel plates to give ethyl 4-isopropylindole-2-carboxylate (278) (49 mg, 30%), ethyl 1,1-dimethyl-1,2-dihydroisoquinoline-3-carboxylate (22 mg, 14%) which was recrystallised from dichloromethane and petrol to give pale yellow prisms, m.p., 89-91°C (Found: M^+ 231.1254. $\text{C}_{14}\text{H}_{17}\text{NO}_2$ requires 231.0848), ν_{max} (Nujol) 3365, 1690, 1620 cm^{-1} , δ (CCl_4), 1.30 (3H, t, J 7 Hz), 1.48 (6H, s, 2 x CH_3), 3.52 (1H, br s, exch. D_2O , NH), 4.29 (2H, q, J 7 Hz), 6.32 (1H, s, vinyl H), 6.97-7.20 (4H, m, ArH), m/e 231 (M^+) 216, 170, 142, 115, and ethyl 1-methylnaphthalene-3-carboxylate (281) (20 mg, 17%), a colourless oil, ν_{max} (film) 1713 cm^{-1} ,

δ (CCl_4) 1.45 (3H, t, J 7 Hz), 2.75 (3H, s, ArCH_3), 4.41 (2H, q, J 7 Hz), 7.45-7.70 (2H, m, 6-H and 7-H), 7.82-8.05 (3H, m, 2-H, 5-H and 8-H), 8.41 (1H, br s, 4-H), m/e 214 (M^+ , 100%), 199, 186, 169, 141, 115. Only a trace of the enamine (280) (< 5%) was observed.

(iii) With iodine (1.0 molar equivalents). Potassium acetate (98 mg, 1 mmol) was added to a solution of vinyl azide (236) (259 mg, 1 mmol) and iodine (254 mg, 1 mmol) in toluene (40 ml) and the mixture refluxed for 2.75 h. The mixture was then cooled, washed with aqueous sodium thiosulphate (10%, 2 x 40 ml) and water (20 ml), dried and evaporated, and an n.m.r. spectrum taken of the residue. This was very messy. Few recognisable products were present. Chromatography on alumina (petrol/ether) gave ethyl 4-isopropylindole-2-carboxylate (278) (28 mg, 12%) as the only characterisable product.

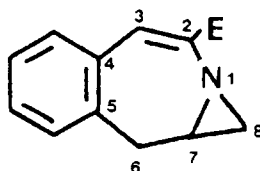
7.4. EXPERIMENTAL TO CHAPTER FOUR

Thermolysis of ethyl 2-azido-3-(2-allylphenyl)propenoate (237) without iodine.

A solution of ethyl 2-azido-3-(2-allylphenyl)propenoate (237) (107 mg, 0.42 mmol) in toluene (20 ml) was refluxed under nitrogen for 1.6 h. The solvent was removed by rotary evaporation and an n.m.r. spectrum taken of the residue. This mixture was then columned on silica gel (petrol/ether) to give (a) *ethyl 4-allylindole-2-carboxylate* (286) (8 mg, 8%); (b) *ethyl 1-azabenzobicyclo[5.1.0]oct-2-ene-2-carboxylate* (287) (11.5 mg, 12%); (c) *ethyl 8-azabenzobicyclo[5.1.0]oct-3-ene-1-carboxylate* (288) (29.5 mg, 31%); and (d) *ethyl 2-methyl-3H-benzodiazepine-7-carboxylate* (289) (20 mg, 21%). An n.m.r. spectrum of the crude reaction mixture indicated that the yields should have been *ca.* (286) (9%), (287) (35-39%), (288) (34%) and (289) (22%). The thermolysis of (237) was also conducted in refluxing benzene for 4.5 h. The products were not isolated by chromatography but the yields based on the n.m.r. spectrum of the total crude reaction mixture were (286) (5%), (287) (44%), (288) (23%), and (289) (28%). Heating a solution of (237) in xylene at 140°C for 0.75 h gave (286) (11%), (287) (20%), 288 (29%) and (289) (16%). The yields based on the n.m.r. spectrum of the total crude reaction mixture were 286 (11%), 287 (33%), 288 (37%), and (289) (17%). On thermolysis in refluxing decalin (190°C, 0.12 h) (237) gave (286) (20%), (287) (13%), (288) (20%), and (289) (6%). The yields based on the n.m.r. spectrum of the total crude reaction mixture were 286 (20%), (287) (13%), (288) (44%) and (289) (7%).

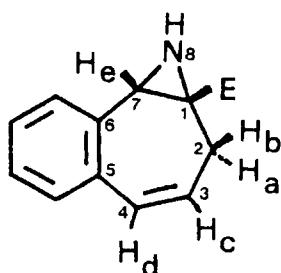
(a) Ethyl 4-allylindole-2-carboxylate (286), colourless prisms from ether and petrol, m.p., 89-91°C, ν_{max} (Nujol) 3310, 1692 cm^{-1} δ (CDCl₃, 250 MHz) 1.44 (3H, t, J 7 Hz), 3.68 (2H, br d, CH₂ of allyl group), 4.41 (2H, q, J 7 Hz), 5.06-5.22 (2H, m, -CH=CH₂), 6.00-6.17

(1H, m, $-\underline{\text{CH}}=\text{CH}_2$), 6.92–7.00 (1H, m, ArH), 7.20–7.40 (3H, m, ArH), 8.91 (1H, br s, NH), m/e 229 (M^+) 189, 183, 156, 143, 119 (100%), 116, 105.



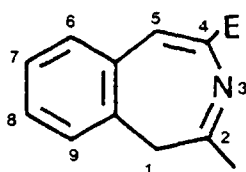
(287)

(b) Ethyl 1-azabenzob[b]bicyclo[5.1.0]oct-2-ene-2-carboxylate (287), a colourless oil, ν_{max} (CCl_4) 1715 cm^{-1} , δ (^1H , CDCl_3 , 250 MHz) 1.40 (3H, t, J 7 Hz), 1.57 (1H, br d, $^*J$ 5.5 Hz, 8-H), 2.23 (1H, br d, $^*J$ 7 Hz, 8-H), 2.35 (1H, dd, J 15, 21.5 Hz, 6-H), 3.00 (1H, dddd, J 5.5, 6.7, 15 Hz, 7-H), 3.30 (1H, dd, J 6, 21.5 Hz, 6-H), 4.34 (2H, q, J 7 Hz), 6.95 (1H, s, 3-H), 7.15–7.32 (4H, m, ArH), [* decoupling experiments also showed a small coupling (≤ 1 Hz) between the two protons at the 8-position], δ (^{13}C , CDCl_3 , 62.9 MHz), 14.6 (q, ester CH_3), 31.9 (t, 6-C or 8-C), 37.7 (t, 6-C or 8-C), 42.2 (d, 7-C), 61.2 (t, ester CH_2), 118.8, 127.1, 127.2, 128.6, 130.9 (five doublets, 3-C and the aryl CH's), 135.7, 138.9, 140.5 (three singlets, 2-C, 4-C and 5-C), 165.7 (s, $\text{C}=\text{O}$), m/e 229 (M^+), 200, 155, 115, 85, 83 (100%).



(288)

(c) Ethyl 8-azabenzo[*e*]bicyclo[5.1.0]oct-3-ene-1-carboxylate (288), a colourless oil, $\nu_{\max}$ (CCl_4), 3300, 1720 cm^{-1} , δ (^1H , CDCl_3 , 250 MHz) 1.34 (3H, t, J 7 Hz), 2.11 (1H, br s, exch. D_2O , NH), 2.50 [1H, dd, J 8, 15 Hz, 2-H (H_a)], 2.91 [1H, dd, J 5.7, 15 Hz, 2-H (H_b)], 3.23 [1H, br.s, 7-H (H_e)], 4.31 (2H, AB quartet of quartets, J 2.5, 7 Hz, ester CH_2), 6.05 [1H, ddd, J 5.7, 8, 11.5 Hz, 3-H (H_c)], 6.59 [1H, d, J 11.5 Hz, 4-H (H_d)], 7.05-7.65 (4H, m, ArH), decoupling experiments determined the couplings shown above and also indicated that small couplings (< 1 Hz) exist between H_b and H_d , H_a and H_d , H_b and H_e (w coupling) and possible between H_a and H_e , δ (^{13}C , CDCl_3 , 62.9 MHz), 14.2 (q, ester, CH_3), 27.7 (t, 2-C), 44.2 (d, 7-C), 61.9 (t, ester CH_2), 62.0 (s, 1-C), 126.9, 127.4, 128.2, 130.4, 131.3, 131.8 (six doublets, 3-C, 4-C and aryl CH's), 135.1, 135.2 (two singlets, 5-C and 6-C), 172.4 (s, C=O), m/e 229 (M^+), 200, 183, 156, 119 (100%), 117.



(289)

(d) Ethyl 2-methyl-1H-3-benzazepine-4-carboxylate (289), a colourless oil, $\nu_{\max}$ (CCl_4) 1710, 1635 cm^{-1} , δ (^1H , CDCl_3) 1.41 (3H, t, J 7 Hz), 2.28 (3H, s, CH_3), 3.15 (2H, br s, CH_2), 4.39 (2H, q, J 7 Hz), 7.25-7.50 (4H, m, ArH), 7.82 (1H, s, vinyl H), δ (^{13}C , CDCl_3 , 62.9 MHz), 14.4 (q, ester, CH_3), 26.6 (q, ring CH_3), 42.6 (t, ring CH_2), 61.4 (t, ester CH_2), 124.6, 126.7, 127.4, 129.3, 130.8 (5 doublets, 5-C to 9-C), 131.3, 133.2, 138.6 (3 singlets, 4-C, 5a-C, and 9a-C), 160.5, 166.1 (2 singlets, C=O and C=N), m/e 229 (M^+), 200 (100%), 143, 129, 115.

Thermolysis of ethyl 2-azido-3-(2-allylphenyl)propenoate (237) with iodine.

A solution of ethyl 2-azido-3-(2-allylphenyl)propenoate (237) (53 mg, 0.206 mmol) and iodine (52.4 mg, 0.206 mmol) in benzene (15 ml) was heated at 60°C under nitrogen for 24 h. The solution was then washed with aqueous sodium thiosulphate (10%; 10 ml) and water (10 ml), was dried and evaporated and an n.m.r. spectrum of the residue taken. Chromatography in silica gel (p.l.c.) (petrol/ether 2:1) gave *ethyl 2,3-dihydro-2-iodomethyl-1H-3-benzazepine-4-carboxylate* (290) as a colourless oil (30 mg, 40%), $\nu_{\max}$ (CCl₄) 3390, 1697, 1625 cm⁻¹, δ (CDCl₃ or CCl₄) 1.40 (3H, t, J 7 Hz), 2.94 (1H, dd, J 7.4, 10.1 Hz, -CH₂I), 3.02 (1H, dd, J 7.3, 10.1 Hz, -CH₂I), 3.03 (1H, d, J 14.7 Hz, 1-H¹), 3.30 (1H, dd, J 6.2, 14.7 Hz, 1-H²), 3.95 (1H, m, approximately quintet in CCl₄, coupled to 1-H², -CH₂I, and NH, quartet in D₂O or in CDCl₃), 4.33 (2H, q, J 7 Hz), 5.55 (1H, br d in CCl₄, J 5.3 Hz, exch. D₂O, NH, very broad in CDCl₃), 6.49 (1H, d, J 2 Hz in CCl₄, 5-H coupled to NH in CCl₄ but not in CDCl₃), 7.05-7.37 (4H, m, ArH), the coupling constants were confirmed and accurately determined by decoupling experiments, m/e 357 (M^+ , 100%), 230, 216, 200.

The n.m.r. spectrum of the total crude reaction mixture indicated that (290) was the sole product. In a separate experiment under the same conditions the yield of (290) was 30%.

When a solution of the azidocinnamate (237) was heated in toluene at 110°C for 1.5 h in the presence of iodine (0.1 molar equivalents) the isolated products were: (isolated yield, n.m.r. yields) (286) (*ca.* 3%, *ca.* 3%), (287) (12%, 17%), (288) (15%, 24%), (289) (12%, 26%) and (290) (13%, 15%).

Decomposition of ethyl 2-azido-3-(2-allyl-3-hydroxy-4-methoxyphenyl)-propenoate (238).

A solution of the azidocinnamate (238) (207 mg, 0.68 mmol) in toluene (30 ml) was heated at 110°C for 0.75 h and the solvent then evaporated. An n.m.r. spectrum of the residue showed that the products were analogous to those obtained from ethyl 2-azido-3-(2-allylphenyl)propenoate (237). Chromatography on silica gel (petrol/ether/dichloromethane) gave ethyl 4-allyl-5-hydroxy-6-methoxyindole-2-carboxylate (297) (53 mg, 28%), as well as other products which were not characterised. The indole (297) was recrystallised from chloroform and petrol to give colourless prisms, m.p., 179-180.5°C (Found: C, 65.3; H, 6.3; N, 5.1. $C_{15}H_{17}NO_4$ requires C, 65.45; H, 6.2; N, 5.1%), $\nu_{\max}$ (nujol) 3548, 3465, 1687, 1637 cm^{-1} , δ (CDCl₃) 1.40 (3H, t, J 6.8 Hz, ester CH₃), 3.69 (2H, m, ArCH₂R), 3.95 (3H, s, OCH₃), 4.43 (2H, q, J 6.8 Hz, ester CH₂), 4.96-5.30 (2H, m, -C(H)=CH₂), 5.63 (1H, s, OH), 5.85-6.30 (1H, m, -C(H)=CH₂), 6.77 (1H, s, ArH), 7.22 (1H, s, ArH), 8.74-9.05 (1H, br s, NH), m/e 275 (M^+ , 100%), 229, 202, 186.

Decomposition of ethyl 2-azido-3-(2-vinylphenyl)propenoate (239).

A solution of ethyl 2-azido-3-(2-vinylphenyl)propenoate (239) (168 mg, 0.689 mmol) in toluene (38 ml) was refluxed under nitrogen for 1.5 h and the solvent then evaporated. An n.m.r. spectrum of the crude reaction mixture indicated that one major product had been formed. Chromatography on silica gel (petrol/ether) gave ethyl 4-vinylindole-2-carboxylate (299) (ca. 10 mg, 7%), δ (CDCl₃) 1.40 (3H, t, J 7 Hz), 4.44 (2H, q, J 7 Hz), 5.46 (1H, dd, J 1.5, 11 Hz), 5.95 (1H, dd, J 1.5, 17 Hz), 7.14 (1H, dd, J 11, 17 Hz), 7.20-7.52 (4H, m, ArH), 8.70-9.10 (1H, br s, NH), and ethyl 1-methylisoquinoline-3-carboxylate (298) (112 mg, 75%), m.p., 104°C (from chloroform and petrol) (Found: C, 72.85; H, 6.1; N, 6.55. $C_{13}H_{13}NO_2$

requires C, 72.55; H, 6.1; N, 6.5%), $\nu_{\max}$ (Nujol) 1727 cm^{-1} , δ (CDCl_3) 1.46 (3H, t, J 7 Hz), 3.00 (3H, s, ArCH_3), 4.53 (2H, q, J 7 Hz), 7.55-8.20 (4H, m, ArH), 8.37 (1H, s, 4-H), m/e 215 (M^+), 171, 170, 143 (100%).

When a solution of (239) in deuteriochloroform or diethyl ether was heated at 35°C for 19-21 h the azide (239) was shown by n.m.r. to be converted to the isoquinoline (298) in *ca.* 75-80% yield. The reaction in CDCl_3 was followed by n.m.r. No intermediates were observed in the decomposition of (239) to (298).

When (239) was allowed to stand at 5°C for 21 days *ca.* 50% of the sample had been converted into the isoquinoline (298) which precipitated from the liquid azide (239).

Decomposition of ethyl 2-azido-3-(2-*E*-styrylphenyl)propenoate (240).

A solution of ethyl 2-azido-3-(2-*E*-styrylphenyl)propenoate (240) (254 mg, 0.8 mmol) in toluene (40 ml) was refluxed under nitrogen for 2.25 h. The solvent was then evaporated and an n.m.r. spectrum of the residue taken which indicated that two major products had been formed. This mixture was then chromatographed on silica gel (petrol/ether) to give (a) *ethyl 1-benzylisoquinoline-3-carboxylate* (300) (84 mg, 36%), which was recrystallised from chloroform and petrol, m.p., 94°C (Found: C, 78.2; H, 5.9; N, 4.75. $\text{C}_{19}\text{H}_{17}\text{NO}_2$ requires C, 78.3; H, 5.9; N, 4.8%), $\nu_{\max}$ (Nujol) $1725, 1240, 1210\text{ cm}^{-1}$, δ (CDCl_3) 1.45 (3H, t, J 7.1 Hz) 4.54 (2H, q, J 7.1 Hz), 4.79 (2H, s, ArCH_2Ph), 7.10-7.38 (5H, m, ArH), 7.45-7.75 (2H, m, ArH), 7.80-8.00 (1H, m, ArH), 8.07-8.25 (1H, m, ArH), 8.47 (1H, s, 4-H), m/e 291 (M^+), 262, 245, 217, 216 (100%), and (b) *ethyl 2-phenyl-1H-3-benzazepine-4-carboxylate* (or its isomer: *ethyl 4-phenyl-1H-3-benzazepine-2-carboxylate*, see Appendix) (301) (86 mg,

37%) a yellow/orange oil, b.p., 160°C at 0.3 mmHg (Kugelrohr) (Found: C, 77.95; H, 5.9; N, 4.85. $C_{19}H_{17}NO_2$ requires C, 78.3; H, 5.9; N, 4.8%), $\nu_{\max}$ (CCl_4) 1722, 1634 cm^{-1} , δ (^1H , $CDCl_3$) 1.32 (3H, t, J 7 Hz), 3.30–3.90 (2H, br s, ring CH_2), 4.34 (2H, q, J 7 Hz), 7.28 (1H, s, vinyl H), 7.30–7.65 (8H, m, ArH), and 7.85–8.03 (2H, m, ArH), δ (^{13}C , $CDCl_3$, 250 MHz), 14.2 (q, ester CH_3), 36.8 (t, ring CH_2), 62.1 (t, ester CH_2), 117.3 (d), 126.3 (d, phenyl group 2-C or 3-C), 126.9 (d), 128.0 (d), 128.4 (d), 128.6 (d, phenyl group, 2-C or 3-C), 128.9 (d), 128.9 (s), 130.1 (d), 135.0 (s), 139.0 (s), 144.9 (s), 147.2 (s), 163.2 (s), m/e 291 (M^+) 219, 102 (100%), and (c) *ethyl 4-E-styrylindole-2-carboxylate* (302) (ca. 20 mg, ca. 9%) recrystallised from ether, m.p., 173–174°C, (Found: C, 78.55; H, 5.9; N, 4.8; $C_{19}H_{17}NO_2$ requires C, 78.3; H, 5.9; N, 4.8%), $\nu_{\max}$ 3350, 3315, 1690, 1672 cm^{-1} , δ ($CDCl_3$) 1.43 (3H, t, J 7 Hz), 4.48 (2H, q, J 7 Hz), 6.97–7.80 (ca. 11–14H, m), 8.90–9.20 (1H, br s, NH), m/e 291 (M^+ , 100%), 245, 217, 216.

When the thermolysis was carried out in refluxing xylene the yields of the isolated products were (300) (30%), (301) (40%), and (302) (ca. 8%). When the thermolysis of (240) was carried out in refluxing benzene (4.5 h) the ratio of (301):(300) was lower (by n.m.r.) than in toluene, and when the thermolysis was carried out in refluxing decalin (0.25 h) the ratio of (301):(300) was higher than in xylene.

Thermal decomposition of ethyl 7-phenyl-1-azabenzod[bicyclo[4.1.0]non-2-ene-2-carboxylate (303).

A sample of the aziridine (303) was heated in toluene for 2 h and the solvent then evaporated. An n.m.r. spectrum of the residue indicated that (303) had been cleanly converted into the benzazepine (301). No trace of the isoquinoline (300) was observed.

Preparation of ethyl 2-*E*-styrylphenyl-2H-azirine-3-carboxylate (308) and its thermal decomposition.

A solution of ethyl 2-azido-3-(2-*E*-styrylphenyl)propenoate (240) in petrol (b.p., 60-80°C) (0.5 mg/ml) was irradiated with a low intensity 350 nm lamp for 1 h, when it could be seen, by t.l.c., that all of the azide (240) had reacted. The solvent was then evaporated at room temperature and an n.m.r. spectrum taken of the residue. This indicated that it was a mixture of the *azirine* (308) and the photo-product (351) of (240). An attempted separation of this mixture failed.

The mixture which contained (308) and (351) in a ratio of 2 parts (308) to 1 part (351) was then dissolved in benzene and heated at reflux for 4.5 h. The solvent was then removed and an n.m.r. spectrum of the residue indicated that it contained both the indole (302) and the benzazepine (301), but not the isoquinoline (300), as well as the photo-product (351). A portion of this mixture was chromatographed on a silica gel plate and the indole (302) (10 mg) and the benzazepine (301) (42 mg) isolated.

In a separate experiment the photo-product (351) was shown to be relatively stable to these conditions, decomposing slowly in refluxing toluene. No benzazepine (301) or indole (302) was produced in this reaction.

Thermal decomposition of ethyl 2-azido-3-[2-(3-phenyloxiran-2-yl)phenyl]-propenoate (254).

A solution of (254) (59.4 mg, 0.177 mmol) in toluene (5 ml) was refluxed for 5.5 h and the solvent then evaporated. An n.m.r. spectrum of the residue indicated that there was one major product. The mixture was chromatographed on alumina to give *ethyl 4-(3-phenyloxiran-2-yl)-*

indole-2-carboxylate (314) (42.7 mg, 78.5%), which was recrystallised from chloroform and petrol to give colourless needles, m.p., 153.5–155°C (Found: C, 74.2; H, 5.55; N, 4.6. $C_{19}H_{17}NO_3$ requires C, 74.25; H, 5.6; N, 4.55%), $\nu_{\max}$ (Nujol) 3300, 1700 cm^{-1} , δ (CDCl_3) 1.38 (3H, t, J 7 Hz), 4.10 (1H, d, J 2 Hz), 4.23 (1H, d, J 2 Hz), 4.43 (2H, q, J 7 Hz), 7.05–7.60 (9H, m), 9.35–9.60 (1H, br s, NH), m/e 307 (M^+), 278 (100%), 234, 204, 127, 105.

Decomposition of ethyl 2-azido-3-[2-(3-phenyloxiran-2-yl)phenyl]-propenoate (254) with triethyl phosphite.

A solution of the azidocinnamate (254) (95 mg, 0.28 mmol) and triethyl phosphite (51.8 mg, 0.31 mmol) in THF (5 ml) was allowed to stir at room temperature for 12 h. The solvent was then removed and the residue chromatographed on alumina (petrol/ether). *Ethyl 7-phenyl-1-azabenzod]-bicyclo[4.1.0]hept-2-ene-2-carboxylate* (303) (33 mg, 40%), was isolated as a colourless oil, $\nu_{\max}$ (CCl_4) 1710, 1625 cm^{-1} , δ (CDCl_3) 1.30 (3H, t, J 6.9 Hz), 2.84 (1H, d, J 3 Hz), 3.46 (1H, d, J 3 Hz), 4.30 (2H, q, J 6.9 Hz), 7.10 (1H, s, vinyl H), 7.15–7.55 (9H, m, ArH), m/e 291 (M^+ , 100%), 262, 219. The stereochemistry was assigned as *trans* by analogy with similar systems.²⁴²

Thermal decomposition of ethyl 2-azido-3-[2-(oxiran-2-ylmethyl)phenyl]-propenoate (253).

A solution of the azide (253) (ca. 6 mg) in toluene (5 ml) was refluxed for 1.75 h and then the solvent was removed. An n.m.r. spectrum of the residue indicated that it contained only the corresponding indole-ethyl 4-(oxiran-2-ylmethyl)indole-2-carboxylate (315), $\nu_{\max}$ (CCl_4) 3475, 1715 cm^{-1} , (Found: M^+ 254.1052. $C_{14}H_{15}NO_3$ requires 254.1052), δ (CDCl_3 , 250 MHz), 1.44 (3H, t, J 7 Hz), 2.55–2.60 (1H, m), 2.77–2.83 (1H, m), 3.05–3.30 (3H, m), 4.42 (2H, q, J 7 Hz), 7.00–7.40 (ca. 7H, m),

9.85-10.0 (1H, br s, NH), m/e 245 (M^+ , 100%), 199, 156. It was not possible to purify this sample, which was found to decompose slowly on standing.

7.5. EXPERIMENTAL TO CHAPTER FIVE

Reaction of ethyl 2-azido-3-(2-benzoylphenyl)propenoate (241) with TEP.

A solution of TEP (53 mg, 0.32 mmol) in cyclohexane (1 ml) was added to a well stirred solution of ethyl 2-azido-3-(2-benzoylphenyl)propenoate (241) (103 mg, 0.32 mmol) in cyclohexane (2 ml). A gas was formed immediately, and bubbled off slowly. After 0.15 h, a further molar equivalent of TEP was added and after 0.6 h yet another molar equivalent was added. The solution was then warmed to 35°C and stirred at this temperature for 1.3 h, when it was shown by t.l.c. that the vinyl azide (241) had been converted to a single product. The solvent was then removed by rotary evaporation and petrol (4 ml) added to precipitate the product. The product precipitated was ethyl 1-phenylisoquinoline-3-carboxylate (267) (59 mg, 64%), which was shown by n.m.r. to be identical with that obtained from other reactions (Chapter 3). Upon standing a further quantity of isoquinoline (267) (28 mg, 30%) precipitated. By t.l.c. no other products were observed.

Reaction of ethyl 2-azido-3-(fluoren-1-yl)propenoate (242) with TEP.

A solution of ethyl 2-azido-3-(fluoren-1-yl)propenoate (242) (70 mg, 0.22 mmol) and TEP (73 mg, 0.44 mmol) in ether (10 ml) was heated at 35°C for 1 h. Samples of the reaction mixture were analysed by t.l.c. at intervals and the conversion of the azide (242) to one major product could be seen. This product was bright orange and non-polar on the t.l.c. plate. There was no trace of the azafluoranthene (271). The solvent was removed by evaporation and an n.m.r. spectrum of the residue taken. The sample was then dissolved in benzene (10 ml) and refluxed for 2 h. No change was observed by t.l.c. or n.m.r. No azafluoranthene

(271) was observed. The sample was chromatographed rapidly on silica gel (ether) and an orange compound obtained, which, though not characterised, appeared, by n.m.r., to contain both the fluorenone system and a phosphate/phosphite portion.

The difficulties encountered in obtaining large quantities of the vinyl azide (242) prevented further investigation of this reaction.

Reaction of ethyl 2-azido-3-(2-ethoxycarbonylphenyl)propenoate (245) with TEP.

TEP (290 mg, 1.75 mmol) was added dropwise to a solution of ethyl 2-azido-3-(2-ethoxycarbonylphenyl)propenoate (245) (253 mg, 0.875 mmol) in benzene (20 ml) and the solution heated in a water bath at 50-60°C for 0.5 h. The solvent was then removed by rotary evaporation and an n.m.r. spectrum of the residue taken. This indicated that the azide (245) had been converted to one major product. After chromatography on silica gel (petrol/ether) *ethyl 1-ethoxyisoquinoline-3-carboxylate* (318) (192 mg, 90%) was obtained as colourless needles which were recrystallised from chloroform and petrol, m.p., 93-94°C (Found: C, 68.4; H, 6.15; N, 5.7. $C_{14}H_{15}NO_3$ requires C, 68.55; H, 6.15; N, 5.7%), $\nu_{\max}$ (CCl_4), 1735, 1715, 1617, 1570 cm^{-1} , δ (CCl_4) 1.43 (3H, t, J 7 Hz), 1.53 (3H, t, J 7 Hz), 4.42 (2H, q, J 7 Hz), 4.72 (2H, q, J 7 Hz), 7.55-7.95 (3H, m, ArH), 8.04 (1H, s), 8.20-8.37 (1H, m, ArH), m/e 245 (M^+), 230, 217 (100%).

Reaction of ethyl 2-azido-3-(2-carboxyphenyl)propenoate (243) with TEP.

(i) A solution of ethyl 2-azido-3-(2-carboxyphenyl)propenoate (243) (213 mg, 0.82 mmol) and TEP (145 mg, 0.88 mmol) in benzene (30 ml) was stirred at 30-50°C for 2 h. Upon addition of the TEP to the benzene

solution of the acid the solution became cloudy. When it could be seen by t.l.c. that all of the azide (243) had reacted the solvent was evaporated and the residue chromatographed on silica gel (petrol/ether) to give (a) ethyl 1-ethoxyisoquinoline-3-carboxylate (318) (51 mg, 25%), (b) ethyl isoquinol-1-one-3-carboxylate (249) (50 mg, 28%), m.p., 146.5-148.5°C (lit., ²³⁹ 147-148°C), $\nu_{\max}$ (CCl₄) 3390, 1720, 1680, cm⁻¹, δ (CDCl₃) 1.44 (3H, t, *J* 7 Hz), 4.50 (2H, q, *J* 7 Hz), 7.41 (1H, s, 4-H), 7.50-7.80 (3H, m, ArH), 8.40-8.60 (1H, m, ArH), 9.30-9.65 (1H, br s, exch. D₂O, NH), *m/e* 217 (*M*⁺, 100%), 189, 155 and (c) a colourless oil (46 mg, ca. 26%), $\nu_{\max}$ (film) 2115, 17785, 1710 cm⁻¹, δ (CDCl₃) 1.30 (3H, t, *J* 7 Hz), 4.33 (2H, q, *J* 7 Hz), 6.57 (1H, s), 7.48-8.05 (4H, m), *m/e* (140°C) 217, 189, 145, 143. This last compound has not yet been identified.

(ii) A solution of ethyl 2-azido-3-(2-carboxyphenyl)propenoate (243) (104 mg, 0.4 mmol), TEP (73 mg, 0.44 mmol) and triethyl phosphate (160 mg, 0.88 mmol) in benzene (5 ml) was stirred at room temperature for 16 h. The reaction mixture did not become cloudy, and after 16 h, was shown, by n.m.r., to be comprised mainly of the isoquinolone (249), the ethoxyisoquinoline (318) being completely absent. The solvent was removed by evaporation and an n.m.r. spectrum of the residue taken. The reaction mixture was then chromatographed on silica gel (petrol/ether) to give ethyl isoquinol-1-one-3-carboxylate (249) (70 mg, 80.5%). No trace of the isoquinoline (318) was observed, but a small amount (ca. 10%) if the oil, above, was present in the crude reaction mixture.

(iii) A solution of the vinyl azide (243) (49 mg, 0.19 mmol) and TEP (34 mg, 0.21 mmol) in THF (2.5 ml) was allowed to stir at room temperature for 16 h, and then the solvent removed by evaporation. An n.m.r. spectrum was taken of the residue which was then chromatographed on silica gel (petrol/ether) to give ethyl isoquinol-1-one-3-carboxylate (249) (30.5 mg, 74%). No trace of the isoquinoline (318) was observed.

(iv) A solution of the azide (243) (52 mg, 0.20 mmol), TEP (36 mg, 0.22 mmol), and DMF (160 mg) in benzene (2.5 ml) was allowed to stir at room temperature for 16 h, and the solvent was then evaporated. The residue was shown, by n.m.r. and t.l.c., to comprise mostly (*ca.* 80%) of the isoquinolone (249) as well as DMF and phosphate compounds. No isoquinoline (318) was observed, and the solution had remained clear throughout the reaction.

(v) A solution of the azide (243) (52 mg, 0.20 mmol), TEP (36 mg, 0.22 mmol) and DMSO (160 mg) in benzene (2.5 ml) was stirred at room temperature for 16 h. The solution did not go cloudy at any stage during the reaction. The solvent was then removed and an n.m.r. spectrum of the residue taken. This indicated that the major product was the isoquinolone (249) (*ca.* 80%). No trace of the isoquinoline (318) was observed by n.m.r. or t.l.c.

(vi) Blank Experiments. A solution of ethyl 2-azido-3-(2-carboxyphenyl)propenoate (243) (126 mg, 0.48 mmol) and triethyl phosphate (99 mg, 0.53 mmol) in benzene (5 ml) was stirred at room temperature for 1 h, then heated at 60°C for 1 h. No reaction occurred under these conditions, by t.l.c., and when TEP (85 mg, 0.53 mmol) and triethyl phosphate (99 mg, 0.53 mmol) were then added, the azide (243) decomposed to give a similar mixture of products as observed in experiment (ii). No ethyl 1-ethoxyisoquinoline-3-carboxylate was formed.

A solution of ethyl isoquinol-1-one-3-carboxylate (249) (26 mg, 0.12 mmol) and triethyl phosphate (21.8 mg, 0.12 mmol) in benzene (2 ml) was stirred at 45°C for 2.25 h, and then at room temperature for 14 h. No reaction of the isoquinolone (249) was observed by t.l.c. and no isoquinoline (318) was formed.

Reaction of ethyl 2-azido-3-(2-*N,N*-diethylcarbamoylphenyl)propenoate (246) with TEP.

A solution of the azide (246) (188 mg, 0.59 mmol) and TEP (197 mg, 1.19 mmol) in benzene (6 ml) was stirred at room temperature for 16 h. The solvent was then evaporated and an n.m.r. spectrum of the residue taken. This indicated that the major product was either dimeric in nature or that there was an approximate 1:1 mixture of two products. The mixture was chromatographed on silica gel (petrol/ether) and an n.m.r. spectrum of the major fraction taken. The spectrum was essentially that of the crude reaction mixture with some of the triethyl phosphite and triethyl phosphate removed. The sample was again chromatographed as before but this procedure failed to separate the mixture, if it were a mixture. Only one spot is apparent by t.l.c. This compound also contains ethoxy groups which are bound to phosphorus, as can be seen in the n.m.r. spectrum. The n.m.r. spectrum has the following peaks:

δ (CDCl₃) 1.00 (ca. 6H, t, *J* 7 Hz), 1.15-1.53 (ca. 66H, m), 3.15 (ca. 4H, q, *J* 7 Hz), 3.97-4.40 (ca. 44H, m), 6.64 (1H, s), 6.73 (1H, s), 7.27-7.50 (7H, m), 8.87-9.01 [2H, m (ca. d)], 10.68 (1H, s). Whilst it appears that this is not the required isoquinoline (320, R = Et), a structure has not yet been assigned to this compound (or mixture of compounds).

Reaction of ethyl 2-azido-3-(2-carbamoylphenyl)propenoate (247) with TEP.

A solution of the azide (247) (40 mg, 0.15 mmol) in THF (5 ml) was treated with TEP (30 mg, 0.18 mmol) and allowed to stir at room temperature for 14 h. The solvent was then removed under reduced pressure. An n.m.r. spectrum of the residue indicated that the azide (247) had been consumed and that there was one major product present. Chromatography on silica gel (petrol/ether) failed to give any major product. Only the minor products were observed. It is possible that the product decomposed on chromatography. The n.m.r. spectrum of the crude reaction mixture cannot be unambiguously assigned to the required isoquinolone (320, R = H)

Thermal decomposition of ethyl 2-azido-3-(2-benzoylphenyl)propenoate (241).

A solution of vinyl azide (241) (253 mg, 0.85 mmol) in toluene (42 ml) was refluxed under nitrogen for 2.5 h. The solvent was then evaporated and an n.m.r. spectrum of the residue taken. This indicated that the reaction mixture was a mixture of many products. Chromatography on silica gel (petrol/ether) failed to separate many of these products, but one fraction (32 mg) was composed of *ca.* 70% of *ethyl 4-benzoyl-indole-3-carboxylate*. This indicates that the indole was present in the crude reaction mixture in *ca.* 8-10% yield. The n.m.r. spectrum of the mixture (32 mg) was: δ (CDCl₃) 1.15-1.55 (3H, *ca.* t), 4.40 (2H, *ca.* q), 7.00-8.20 (*ca.* 12H, m), 9.35-9.85 (0.7H, br s).

Thermal decomposition of ethyl 2-azido-3-(fluoren-9-on-1-yl)propenoate (242).

A solution of the vinyl azide (242) (32 mg, 0.10 mmol) in toluene (10 ml) was heated at reflux under nitrogen for 2 h. The solvent was then removed and the residue chromatographed to give *ethyl pyrrolo[3,2-a]-fluorenone-5-carboxylate (326)* (17.7 mg, 60%), m.p., 267-269°C (from

chloroform) (Found: M^+ 291.0895. $C_{18}H_{13}NO_3$ requires 291.0895), $\nu_{\max}$ (Nujol) 3322, 1692 (with shoulders at 1710 and 1685), 1610 cm^{-1} , δ $[(CD_3)_2SO]$ 1.45 (3H, t, J 6.5 Hz), 4.44 (2H, q, J 6.5 Hz), 7.13–7.80 (7H, m), 12.20–12.55 (1H, br s, NH); m/e 291 (M^+), 245 (100%), 217, 189.

Thermal decomposition of ethyl 2-azido-3-(2-ethoxycarbonylphenyl)-propenoate (245).

A solution of the azide (245) (231 mg, 0.80 mmol) in toluene (30 ml) was refluxed under nitrogen for 4 h. The solvent was removed under reduced pressure at the lowest possible temperature in order to prevent the product from subliming. The residue was chromatographed on silica gel (petrol/ether) to give diethyl indole-2,4-dicarboxylate (327) (165 mg, 79%) which was recrystallised from dichloromethane and petrol to give colourless needles, m.p., $142\text{--}143^\circ\text{C}$ (lit.,²⁴¹ $131\text{--}132^\circ\text{C}$) (Found: C, 64.25; H, 5.75; N, 5.3. $C_{14}H_{11}NO_4$ requires C, 64.35; H, 5.80; N, 5.35%), $\nu_{\max}$ (Nujol) 3330, 1702, 1685 cm^{-1} , δ (CDCl₃) 1.42 (3H, t, J 7 Hz), 1.46 (3H, t, J 7 Hz), 4.49 (2H, q, J 7 Hz), 4.52 (2H, q, J 7 Hz), 7.27–8.08 (4H, m), 9.75–10.10 (1H, br s, NH), m/e 261 (M^+ , 100%), 215, 188, 187, 170.

Thermal decomposition of ethyl 2-azido-3-(2-carbamoylphenyl)propenoate (247).

A solution of the vinyl azide (247) (100 mg, 0.38 mmol) in toluene (20 ml) was refluxed for 5 h. The solvent was then evaporated and the residue chromatographed to give a compound (51 mg, 58%), which was recrystallised from ethyl acetate to give yellow/brown prisms (44 mg, 50%), m.p., $232\text{--}234^\circ\text{C}$ (Found: M^+ 232.0851. $C_{12}H_{12}N_2O_3$ requires 232.0848) $\nu_{\max}$ (Nujol) 3495, 3280, 3220, 1680, 1646, 1620, 1608 cm^{-1} , δ $[(CD_3)_2SO]$

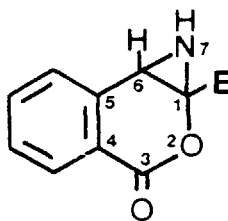
1.35 (3H, t, J ca. 7Hz), 4.35 (2H, q, J ca. 7Hz) 6.60–7.00 (1–2H, br s), 7.20–7.90 (4–5H, m), 8.05–8.30 (ca. 2H, m), 9.75–10.20 (ca. 0.7 H, br s), m/e 234 ($M^+ + 2$) 233 ($M^+ + 1$), 174, 130, 117 (100%), to which the structure *ethyl 4-carbamoylindole-2-carboxylate* (328) is tentatively assigned.

The reaction mixture was very messy; no other products were isolated.

Thermal decomposition of ethyl 2-azido-3-(2-carboxyphenyl)propenoate (243).

A solution of the vinyl azide (243) (330 mg, 1.26 mmol) in toluene (50 ml) was refluxed under nitrogen for 22 h. The solvent was then evaporated and the residue chromatographed on silica gel (petrol/ether) to give *ethyl 3-oxo-7-aza-2-oxabenzod[bicyclo[4.1.0]heptane-1-carboxylate* (329) (262 mg, 89%), which was recrystallised from ether and petrol to give colourless prisms, m.p., 100–101°C (Found: C, 61.85; H, 4.75; N, 6.0. $C_{12}H_{14}NO_4$ requires C, 61.8; H, 4.75; N, 6.0%), $\nu_{\max}$ (Nujol) 3300, 1733, 1717 cm^{-1} , δ (CDCl_3) 1.36 (3H, t, J 7 Hz), 3.07 (1H, br d, J 10 Hz, exch. D_2O , NH), 3.78 (1H, d, J 10 Hz, s in D_2O , 6-H), 4.44 (2H, q, J 7 Hz), 7.40–7.83 (3H, m, ArH), 8.15–8.35 (1H, m, ca. d, ArH), δ (^{13}C , CDCl_3 , 250 MHz), 14.05 (q, ester CH_3), 37.2 (d, 6-C), 63.5 (t, ester CH_2), 69.9 (s, 1-C) 122.1 (s, 5-C), 128.8, 129.1, 131.2, 134.1, (4 doublets, aromatic C-H), 138.4 (s, 4-C), 160.8, 166.7 (2 singlets, 2 x C=O), m/e 233 (M^+), 159, 132 (100%).

When the azide (243) (253 mg, 0.97 mmol) was heated in refluxing toluene (30 ml) for 2.5 h the yield of (329) after chromatography was 83% (187 mg). Another product was also produced in ca. 5% yield, but sufficient quantities were not obtained to determine whether or not this was the indole (330).



(329)

Reaction of ethyl 3-oxo-7-aza-2-oxabenzod[bicyclo[4.1.0]heptane-1-carboxylate (329) with sulphuric acid in ethanol.

A solution of (329) (*ca.* 50 mg) in ethanol (20 ml) was stirred at room temperature and concentrated sulphuric acid (3 drops) added. After 0.15 h solid sodium bicarbonate was added to neutralise the solution which was then diluted with ether (20 ml), filtered, and evaporated. The residue was shown, by n.m.r., to consist mainly (> 90%) of one product. The *compound* was isolated as a colourless oil after chromatography on silica gel (petrol/ether), ν_{max} (film) 3400, 3320, 1740 (br), 1665 cm^{-1} , δ (CDCl_3) 1.05-1.35 (6H, 2 x t, J *ca.* 7 Hz), 1.60-2.00 (2H, br s, NH_2), 3.40-4.20 (2H, AB quartet of quartets, 3.56, 3.96, J 7, 9 Hz), 4.29 (2H, q, J 7 Hz), 4.40 (1H, s), 7.30-7.78 (3H, m), 8.05-8.18 (1H, m), m/e 280 ($M^+ + 1$), 261 ($M^+ - 18$), 234 ($M^+ - 45$), 233 ($M^+ - 46$), 206 ($M^+ - 73$, 100%), 187. The structure ethyl 4-amino-3,4-dihydro-3-ethoxy-1-oxo-2-benzopyran-3-carboxylate (332) was assigned to this compound.

Reaction of ethyl 3-oxo-7-aza-2-oxabenzod[bicyclo[4.1.0]heptane-1-carboxylate (329) with nitrosyl chloride and triethylamine.²²⁵

A solution of nitrosyl chloride in carbon tetrachloride (0.417 M; 0.44 ml, 0.185 mmol) was added dropwise to a solution of (329) (43 mg, 0.185 mmol) and triethylamine (18.7 mg, 0.185 mmol) in THF (5 ml), cooled to -60°C . A precipitate appeared and the supernatant liquid turned yellow. The mixture was allowed to warm slowly to room temperature, by which time the yellow colour had disappeared. The mixture was allowed to stand at room temperature for 14 h, then diluted with ether (10 ml), filtered, and evaporated. The residue was chromatographed to give *ethyl 1-oxo-1H-2-benzopyran-3-carboxylate (333)* (30.3 mg, 75%), which was recrystallised from dichloromethane and petrol, to give colourless needles, m.p., $124\text{--}125^{\circ}\text{C}$ (Found: M^{+} 218.0576. $\text{C}_{12}\text{H}_{10}\text{O}_4$ requires 218.0579), ν_{max} (CCl_4) 1754, 1727 cm^{-1} , δ (CDCl_3 , 250 MHz), 1.42 (3H, t, J 7 Hz), 4.45 (2H, q, J 7 Hz), 7.50 (1H, s, vinyl H), 7.55–7.72 (2H, m, ArH), 7.76–7.86 (1H, m, ArH), 8.34–8.40 (1H, m, ArH), m/e 218 (M^{+}), 145, 89 (100%).

A sample of this ester (333) was dissolved in methanol and solid sodium methoxide (0.1 molar equivalents) added. The mixture was heated to reflux for 1 h, then cooled and diluted with ether, washed with water, dried and evaporated. The residue was chromatographed to give *methyl 1-oxo-1H-2-benzopyran-3-carboxylate (334)* (ca. 60–70%), m.p., $172\text{--}175^{\circ}\text{C}$ (lit.,²²⁶ $173\text{--}174^{\circ}\text{C}$) ν_{max} (CHCl_3) 1730, 1720 cm^{-1} .

A sample of the ester (333) was added to concentrated hydrochloric acid and the mixture heated at reflux for 1 h. The mixture was then cooled, diluted with water and extracted with ether, the ether extracts combined, dried and evaporated to give the crude 1-oxo-1H-2-benzopyran-3-carboxylic acid (335). A sample of this compound was sublimed to give colourless prisms m.p., $250\text{--}253^{\circ}\text{C}$ (lit.,²⁶⁷ $245\text{--}246^{\circ}\text{C}$).

7.6. EXPERIMENTAL TO CHAPTER SIX

Photochemical decomposition of ethyl 2-azido-3-(2-benzylphenyl)propenoate (233).

A solution of ethyl 2-azido-3-(2-benzylphenyl)propenoate (233) (185 mg, 0.60 mmol) in petrol (b.p., 60-80°C; 150 ml) was degassed with nitrogen and irradiated at 300 nm for 1 h. Nitrogen gas was bubbled through the solution during irradiation. The solvent was then evaporated and an n.m.r. spectrum of the residue taken. This mixture was then chromatographed on silica gel (petrol/ether) to give *triethyl 2,4,9-tri-(2-benzylphenyl)-1-3,8-triazatricyclo[4.3.0.0^{3,5}]non-7-ene-5,6,7-tricarboxylate (341a)* (66 mg, 40%) as colourless prisms which were recrystallised from ether and petrol, m.p., 135-136.5°C (Found: C, 77.65; H, 6.2; N, 5.05. $C_{54}H_{51}N_3O_6$ requires C, 77.4; H, 6.15; N, 5.0%), $\nu_{\max}$ (Nujol) 1758, 1740, 1719, 1646 cm^{-1} , δ (CDCl₃, 250 MHz) 0.80 (3H, t, J 7 Hz), 1.32 (3H, t, J 7 Hz), 1.35 (3H, t, J 7 Hz), 3.15 (1H, d, J 15 Hz, ArCH₂Ph), 3.18 (1H, d, J 15 Hz, ArCH₂Ph), 3.66 (1H, d, J 15 Hz, ArCH₂Ph, coupled to proton at 3.18), 3.69 (1H, d, J 15 Hz, ArCH₂Ph, coupled to proton at 3.15), 3.81 (1H, dq, J 12, 7 Hz, ester methylene proton coupled to protons at 0.80 and 3.94), 3.94 (1H, dq, J 12, 7 Hz, ester methylene proton coupled to protons at 0.80 and 3.81) (3.81 and 3.94 make an AB quartet of quartets), 4.06 (1H, s), 4.22-4.52 (5H, m, 2 x ester CH₂ and 1 x benzyl CH₂), 5.10 (1H, s), 6.59 (1H, s), 6.60-6.75 (4H, m, ArH), 6.90-7.05 (3H, m, ArH), 7.05-7.33 (16H, m, ArH), 7.35-7.45 (1H, m, ArH), 7.45-7.54 (1H, m, ArH), 7.57-7.68 (1H, m, ArH), 8.52 (1H, d, ArH), m/e 837 (M^+), 748, 644.

Photochemical decomposition of ethyl 2-azido-3-fluoren-1-ylpropenoate (234).

A solution of ethyl 2-azido-3-fluoren-1-ylpropenoate (234) (93 mg, 0.30 mmol) in petrol (b.p., 40-60°C; 100 ml) was deaerated by a slow stream of nitrogen gas and then irradiated at 300 nm for 0.13 h. The solvent was evaporated and an n.m.r. spectrum of the residue taken. There was no evidence of the azide (234) or the corresponding azirine in the sample so it was chromatographed on silica gel (petrol/ether) to give *triethyl-2,4,9-trifluoren-1-yl-1,3,8-triazatricyclo[4.3.0.0^{3,5}]non-7-ene-5,6,7-tricarboxylate (341b)* (52 mg, 61%) which was recrystallised from chloroform and petrol to give colourless needles, m.p., 159-160°C.

$\nu_{\max}$ 1742, 1725 cm⁻¹, δ (CDCl₃, 250 MHz), 0.66 (3H, t, J 7 Hz), 1.33 (3H, t, J 7 Hz), 1.35 (3H, t, J 7 Hz), 2.95 (1H, d, J 23 Hz), 3.22 (1H, d, J 23 Hz), 3.63 (1H, d, J 23 Hz), 3.72 (1H, d, J 23 Hz), 3.70-4.00 (2H, m, ester CH₂, approximate AB quartet of quartets), 4.19 (2H, s, ArCH₂Ar), 4.25-4.50 (5H, m, 2 x ester CH₂, and 1 H, s at 4.42), 5.51 (1H, s), 6.35 (1H, s), 7.06-7.83 (ca. 20 H, ArH), 8.13 (1H, m, ArH), m/e 831(M^+).

Photochemical decomposition of ethyl 2-azido-3-(2-methylphenyl)propenoate (235).

(i) A solution of ethyl 2-azido-3-(2-methylphenyl)propenoate (235) (312 mg, 1.35 mmol) in petrol (60-80°C, 200 ml) was deaerated with nitrogen gas and irradiated at 300 nm for 1 h. The solvent was then removed and the residue chromatographed on silica gel (petrol/ether) to give a colourless solid which was recrystallised from chloroform and petrol to give *triethyl 2,4,9-tri-(2-methylphenyl)-1,3,8-triazatricyclo[4.3.0.0^{3,5}]non-2-ene-5,6,7-tricarboxylate (341c)* (138 mg, 50%) as colourless prisms, m.p., 135-136°C (Found: C, 70.75; H, 6.45; N, 6.9. C₃₆H₃₉N₃O₆ requires C, 70.9; H, 6.45; N, 6.9%), $\nu_{\max}$ (Nujol) 1755, 1733, 1652 cm⁻¹, $\lambda_{\max}$ (EtOH)

218 (ϵ , 10 800), 264 (ϵ , 1,460), δ (CDCl_3 , 250 MHz) 0.77 (3H, t, J 7 Hz), 1.34 (3H, t, J 7 Hz), 1.38 (3H, t, J 7 Hz), 1.77 (3H, s), 1.79 (3H, s), 2.58 (3H, s), 3.71-3.97 (2H, AB quartet of quartets, ester CH_2), 4.18 (1H, s), 4.23-4.50 (4H, m, 2 x ester CH_2), 5.20 (1H, s), 6.39 (1H, s), 6.80-6.90 (2H, m, ArH), 7.00-7.38 (7H, m, ArH), 7.44-7.50 (2H, m, ArH), 8.44 (1H, d, ArH), (see Appendix for an assignment of these peaks), δ (^{13}C , CDCl_3 , 62.9 MHz), 13.33, 13.99, 14.08 (3 x ester CH_3), 18.38, 18.44, 19.64 (3 x aryl CH_3), 56.55 (2-C, 4-C, or 9-C), 61.11, 62.26, 62.42 (3 x ester CH_2), 63.49 (5-C), 87-19 (6-C), 87.54 (2-C, 4-C or 9-C), 88.96 (2-C, 4-C or 9-C), 125.27, 125.45, 126.07, 127.40, 127.44, 127.80 (2 x aryl C's), 128.64, 128.70 (2 x C), 129.48, 129.75, 130.12, 134.26, 134.82, 136.36, 136.58, 137.13, 159.09, 161.09, 167.30, 168.44, m/e 609 (M^+), 536, 417, 315, 311, 239, 222 (100%), 168.

(ii) A solution of the azide (235) (246 mg) in petrol (b.p. 60-80°C; 50 ml) was deaerated as before and irradiated at low intensity at 300 nm for 3.5 h. The solvent was removed at room temperature by rotary evaporation. An n.m.r. spectrum of the residue showed that it was composed of the azirine (340, Ar = *o*-tolyl) $\rightleftharpoons$ (275), whose spectral data have already been described. This azirine was redissolved in petrol (b.p. 60-80°C; 50 ml) and irradiated at the normal intensity at 300 nm for 1 h. The solvent was again removed and an n.m.r. spectrum of the residue taken. The residue was shown, by n.m.r. to contain the trimer (341c) in *ca.* 60% yield.

Photochemical decomposition of ethyl 2-azido-3-(2-isopropylphenyl)-propenoate (236).

A solution of ethyl 2-azido-3-(2-isopropylphenyl)propenoate (236) (393 mg, 1.5 mmol) in petrol (b.p., 40-60°C; 200 ml) was irradiated at 300 nm for 1 h. During the irradiation a slow stream of nitrogen gas was passed through the solution. The solvent was then evaporated and

residue chromatographed on silica gel (petrol/ether) to give *triethyl 2,4,9-tri-(2-isopropylphenyl)-1,3,8-triazatricyclo[4.3.0.0^{3,5}]non-7-ene-5,6,7-tricarboxylate (341d)* (200 mg, 57%) as colourless prisms, which were recrystallised from chloroform and petrol, m.p., 128-130°C (Found: C, 72.95; H, 7.45; N, 6.05. $C_{42}H_{51}N_3O_6$ requires C, 72.7; H, 7.4; N, 6.05%), $\nu_{\max}$ (Nujol) 1750, 1740 cm^{-1} , δ (CDCl_3 , 250 MHz), 0.37 (3H, d, J 6 Hz), 0.66-0.83 (6H, m, ester CH_3 (t) and side chain CH_3 (d)), 1.00 (3H, d, J 6 Hz), 1.10 (3H, d, J 6 Hz), 1.25-1.40 (9H, m, 2 x ester CH_3 and 1 x side chain CH_3), 2.60 (1H, heptet), 1.88 (1H, heptet), 2.65-2.97 (3H, m, ester CH_2 and side chain CH), 3.20-3.45 (5H, m, 2 x ester CH_2 and ring CH), 5.42 (1H, s), 6.51 (1H, s), 6.95-7.37 (9H, m, ArH), 7.48 (1H, d, J 5 Hz, ArH), 7.56 (1H, d, J 5 Hz, ArH), 8.36 (1H, d, J 5 Hz, ArH), m/e 693 (M^+), 647, 620, 503, 472 (100%).

Photochemical decomposition of ethyl 2-azido-3-phenylpropenoate (244).

A solution of ethyl 2-azido-3-phenylpropenoate (244) (411 mg, 1.89 mmol) in petrol (b.p., 60-80°C; 250 ml) was irradiated at 300 nm for 1 h. A slow stream of nitrogen gas was passed through the solution during the irradiation. The solvent was then evaporated and the residue chromatographed on silica gel (petrol/ether) to give *triethyl 2,4,9-triphenyl-1,3,8-triazatricyclo[4.3.0.0^{3,5}]non-7-ene-5,6,7-tricarboxylate (341e)* (236 mg, 66%), as colourless prisms which were recrystallised from chloroform and petrol, m.p., 105-106°C (Found: C, 69.7; H, 5.85; N, 7.4. $C_{33}H_{33}N_3O_6$ requires C, 69.85; H, 5.85; N, 7.4%), $\nu_{\max}$ (Nujol) ca. 1745 (broad), 1640 cm^{-1} , δ (CDCl_3 , 250 MHz), 0.84 (3H, t, J 7 Hz), 0.90 (3H, t, J 7 Hz), 1.36 (3H, t, J 7 Hz), 3.79-4.17 (4H, m, 2 x ester CH_2 , 2 AB quartets of quartets), 4.28 (1H, s), 4.22-4.46 (2H, m, ester CH_2 , AB quartet of quartets), 5.47 (1H, s), 6.01 (1H, s), 7.15-7.37 (11H, m, ArH), 7.42-7.55 (4H, m, ArH), m/e 567 (M^+), 521, 494, 301, 299 (100%).

Photochemical decomposition of ethyl 2-azido-3-(2-allylphenyl)propenoate (237).

A solution of ethyl 2-azido-3-(2-allylphenyl)propenoate (237) (100 mg, 0.39 mmol) in petrol (b.p., 60-80°C; 100 ml) was irradiated at 300 nm for 1 h. A slow stream of nitrogen gas was passed through the solution during irradiation. The solvent was then removed and the residue chromatographed twice on silica gel (petrol/ether) to give ethyl 1-azabenzobicyclo[5.1.0]oct-2-ene-2-carboxylate (287) (26 mg, 29%) and diethyl 11-(2-allylphenyl)-1,10-diazabenzotricyclo[6.3.0.^{2,6}]undec-9-ene-1,10-dicarboxylate (344) (39 mg, 44%), as a colourless oil, $\nu_{\max}$ (CCl₄) 1742, 1725, 1638 cm⁻¹, δ (CDCl₃, 250 MHz) 1.28 (3H, t, J ca. 7 Hz), 1.32 (3H, t, J ca. 7 Hz), 1.98 (1H, dd, J 5, 13 Hz), 2.71 (1H, dd, J 6, 17 Hz), 3.03-3.27 (4H, m), 3.47-3.65 (1H, m), 4.26 (2H, dq, J 2, 7 Hz), 4.31 (2H, q, J 7 Hz), 4.82-4.95 (2H, m, allyl-C(H)=CH₂), 5.00 (1H, d, J 7 Hz), 5.60-5.77 (1H, m, allyl -CH=CH₂), 6.13 (1H, s), 6.77 (1H, d, ArH), 6.92-7.30 (6H, m, ArH), 7.70-7.75 (1H, m, ArH), (For a more detailed analysis of the spectrum and n.o.e. experiment, see Appendix), δ (¹³C, CDCl₃, 62.9 MHz), 14.0 (ester CH₃), 14.1 (ester CH₃), 36.4, 39.0, 39.1, 46.5 (5-C, 6-C, 7-C and CH₂ of allyl group), 61.5 (ester CH₂), 62.0 (ester CH₂), 73.0 (2-C or 11-C), 87.7 (8-C), 89.0 (2-C or 11-C), 115.8 (allyl -C(H)=CH₂), 125.3, 126.2, 126.7, 126.9, 128.0 (2 x C), 128.7, 129.1, 136.8 (9 x C-H, 8 x aromatic C-H and allyl group -C(H)=CH₂), 138.1, 138.2, 139.0, 145.3 (4 aromatic quaternary carbons), 161.4, 162.2 (C=N, and C=O on 8-C), 171.3 (C=O on 9-C), m/e 458 (M^+), 385 (100%), 339, 311, 269.

Photochemical decomposition of ethyl 2-azido-3-(2-*E*-styrylphenyl)-propenoate (240).

A solution of the 2-azido-3-(2-*E*-styrylphenyl)propenoate (240) (410 mg, 1.28 mmol) in petrol (b.p., 60–80°C, 200 ml) was irradiated at 300 nm for 1 h. A slow stream of nitrogen gas was passed through the solution during the irradiation. The solvent was then evaporated and the residue chromatographed on silica gel (petrol/ether) to give *ethyl 7-phenyl-2-azabenzod[bicyclo[4.1.0]hept-2-ene-1-carboxylate* (351) (254 mg, 68%), which was then recrystallised from ether and petrol to give colourless plates, m.p., 92–93°C (Found: C, 78.45; H, 5.9; N, 4.8. $C_{19}H_{17}NO_2$ requires C, 78.35; H, 5.9; N, 4.8%), $\nu_{\max}$ (Nujol) 1743, 1617, 1140 cm^{-1} , δ (CDCl_3) 1.04 (3H, t, J 7 Hz), 1.90 (1H, d, J 7 Hz), 3.82 (1H, d, J 7 Hz), 4.06 (2H, AB quartet of quartets, J 3, 7 Hz), 7.20–7.66 (9H, m), 8.24 (1H, s), m/e 219 (M^+), 262, 245, 218 (100%). The structure was assigned the *trans* (*exo*) isomer by comparison with similar systems.²⁴³

Photochemical decomposition of ethyl 2-azido-3-(2-pyridyl)propenoate (232).

A solution of ethyl 2-azido-3-(2-pyridyl)propenoate (232) (158 mg, 0.72 mmol) in petrol (b.p., 60–80°C, 150 ml) was irradiated at 300 nm for 1 h. A slow stream of nitrogen gas was passed through the solution during irradiation. The solvent was then evaporated and the residue chromatographed on silica gel (petrol/ether) to give *ethyl pyrazolo[1,5-*a*]-pyridine-2-carboxylate* (261) (21 mg, 15%) and *ethyl imidazo[1,5-*a*]pyridine-3-carboxylate* (354) (74 mg, 54%), m.p., 80°C (from dichloromethane and petrol) (Found: C, 63.15; H, 5.3; N, 14.7. $C_{10}H_{10}N_2O_3$ requires C, 64.15; H, 5.3; N, 14.75%), $\nu_{\max}$ 1687, 1633 cm^{-1} , δ (CDCl_3) 1.49 (3H, t, J 7 Hz),

4.57 (2H, q, J 7 Hz), 6.86-7.23 (2H, m, 6-H and 7-H), 7.60-7.77 (2H, m, 1-H, and 8-H), 9.27-9.46 (1H, m, 5-H), m/e 190 (M^+ , 100%), 145, 131, 118.

A solution of the pyrazolopyridine (261) was recovered unchanged after irradiation under the same conditions.

APPENDIX

CHAPTER EIGHT

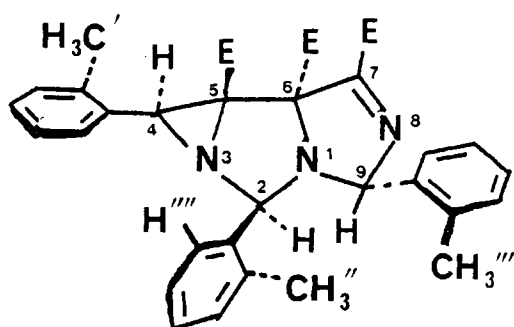
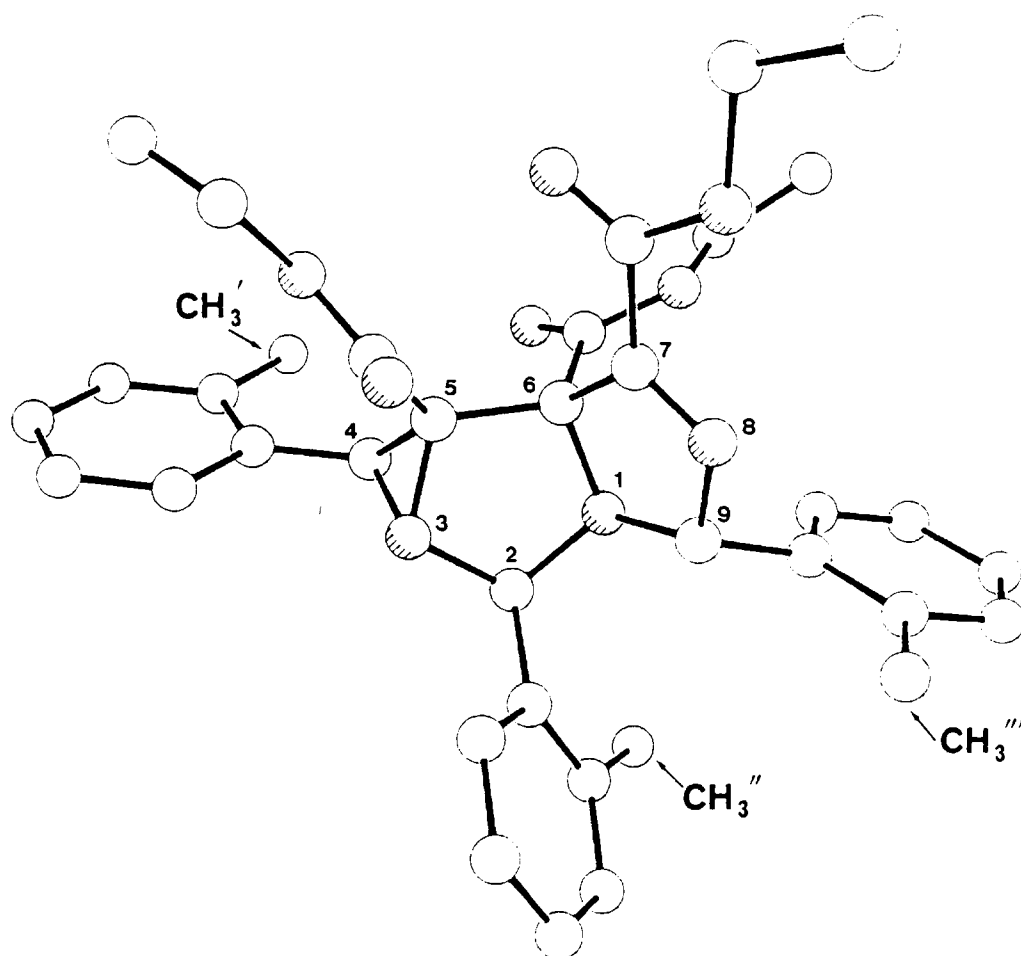
8.1. NUCLEAR OVERHAUSER EFFECT SPECTRA OF TRIETHYL 2,4,9-TRI-(2-METHYLPHENYL)-1,3,8-TRIAZATRICYCLO[4.3.0.0^{3,5}]NON-2-ENE-5,6,7-TRICARBOXYLATE (34lc).

The ^1H n.m.r. spectrum (CDCl_3 , 250 MHz) of (34lc) is given in Figure 3, showing the signals $\text{H}^a\text{-H}^i$ which were irradiated. The n.O.e. difference spectra are given in Figures 4 and 5. Reference will be made to the three dimensional drawing of (34lc) in Figure 2. A molecular model was also used to provide the following interpretation of the n.O.e. spectra.

Irradiation of CH_3^a shows an effect on CH_2^e which is a combination of the n.O.e. and indor effects. CH_3^a is therefore coupled to CH_2^e , but this signal cannot be assigned to a particular ester group in the molecule.

H^f and H^g have a large effect on one another, but not on H^h . From this one can conclude that H^f and H^g are 2-H and 4-H, implying that H^h is 9-H. This then assigns CH_3'' to CH_3^b as being the closest methyl group to 9-H, and thus having the largest effect on it. H^i is tentatively assigned as H''' as it has an effect on H^h (9-H) and *vice versa*. CH_3^e has a large effect on H^g , and *vice versa* and CH_3^d has a large effect on H^f and *vice versa*.

H^g has a weak effect on H^h and H^i , whereas H^f has none. H^g is therefore assigned to 2-H, and thus H^f to 4-H. It therefore follows that CH_3^c is CH_3'' and CH_3^d is CH_3''' . The observed shifts of 2-H, 4-H and 9-H are similar to those which would be predicted on the basis of calculations alone. From a study of the n.O.e. spectra and a molecular model of (34lc) it was apparent that the average configuration of (34lc) in deuteriochloroform solution was similar to that in the solid state.



(341c)

FIGURE 2

Figure 3. ^1H n.m.r. spectrum of (341c)

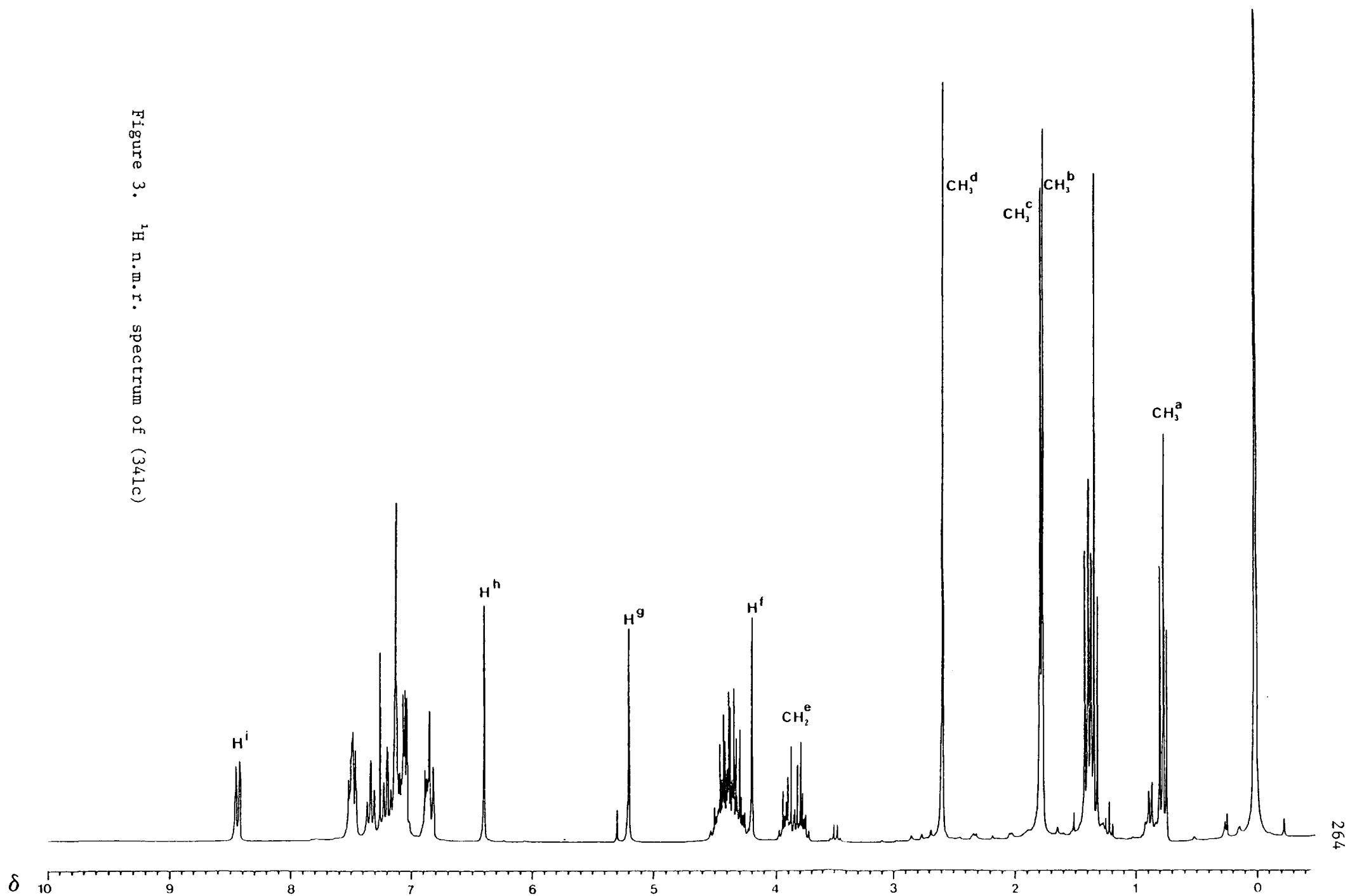


Figure 4. n.O.e. difference spectra of (341c)

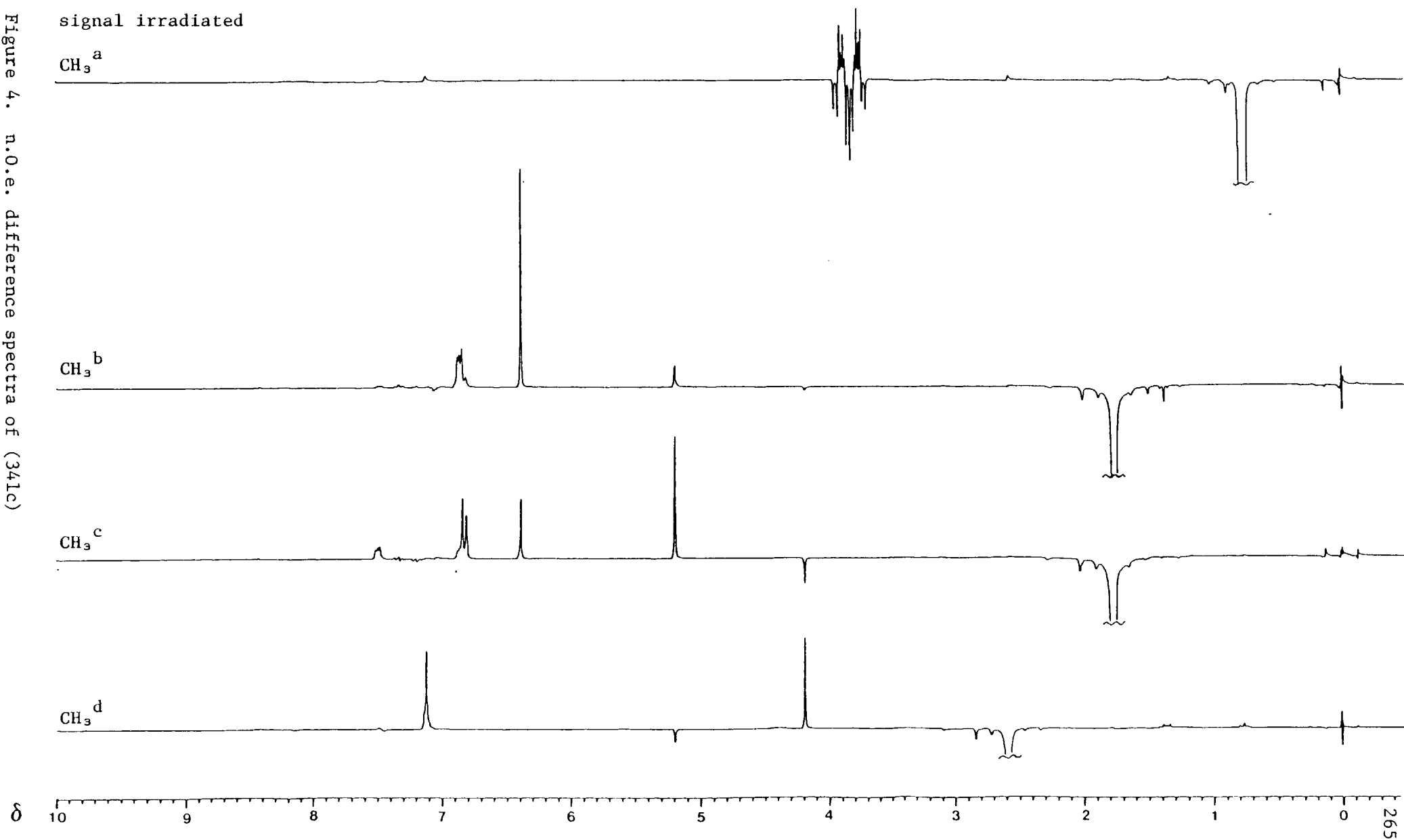
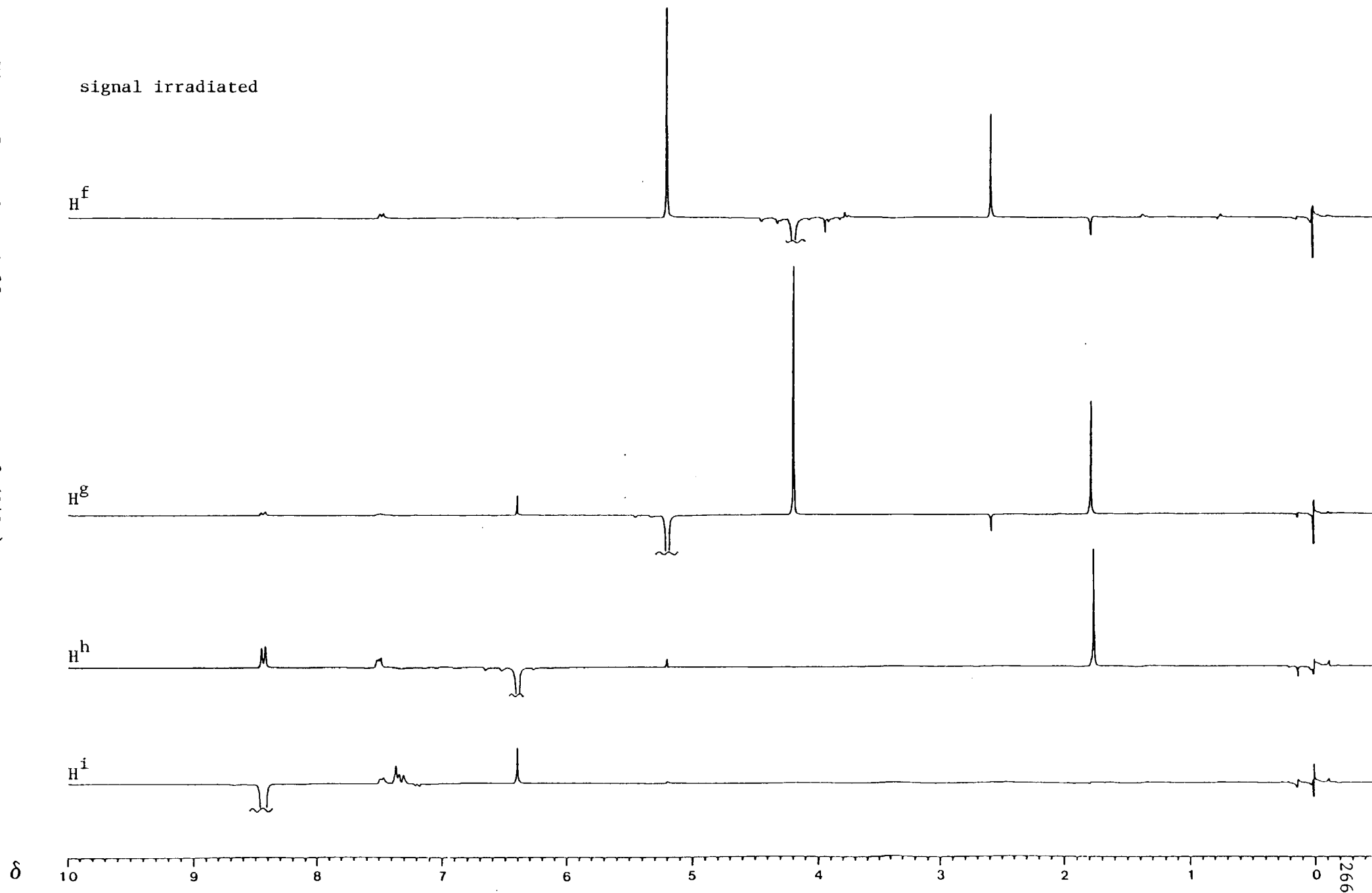


Figure 5. n.O.e. difference spectra of (341c)



8.2. NUCLEAR OVERHAUSER EFFECT SPECTRA OF DIETHYL 11-(2-ALLYLPHENYL)-1,10-DIAZABENZO[c]TRICYCLO[6.3.0.0^{2,6}]UNDEC-9-ENE-8,9-DICARBOXY-LATE (344).

The ¹H n.m.r. spectrum (CDCl₃, 250 MHz) of (344) is shown in Figure 6. The signals of interest are shown, *i.e.*, H^a - Hⁱ. The signals from the allyl group have not been marked.

The n.O.e. spectra are summarised in Table 7. The effects are given as strong (s), medium (m), weak (w), or non-existent (-).

TABLE 6. Summary of n.O.e. spectra of (344).

Effect on H ^x	Proton Irradiated				
	H ^a	H ^b	H ^e	H ^f	H ^g
H ^a		w	-	-	w
H ^b	w		-	-	w
H ^c	s	-	m	-	-
H ^d	-	s	m	-	-
H ^e	-	-		s	-
H ^f	-	-	s		m
H ^g	w	w	-	m	
H ^h	-	-	-	m	s
H ⁱ	-	-	-	m	s

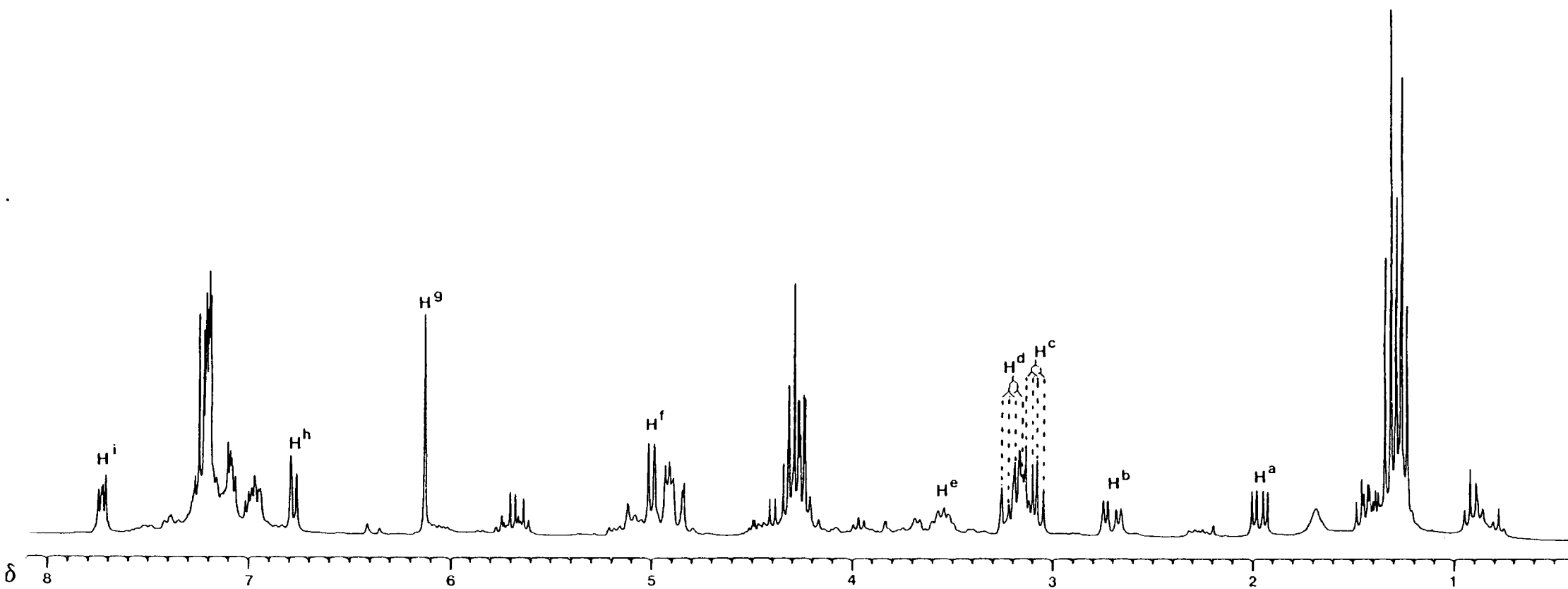
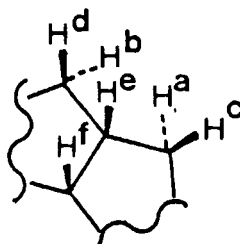


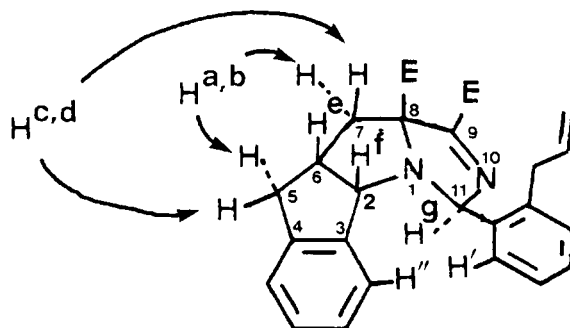
Figure 6. ^1H n.m.r. spectrum of (344)

Both the n.O.e. and decoupling experiments indicate that H^a-H^f exist as shown in Figure 7.



While H^a, H^b, H^c and H^d are attached to 5-C and 7-C it was not possible to unambiguously assign each pair.

The existence of an n.o.e. between H^g (11-H) and H^a and H^b, and the absence of an effect between H^g and H^c, H^d and H^e suggested that the stereochemistry shown in Figure 8 was correct.

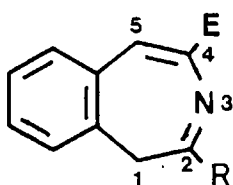


Molecular models of the various diastereoisomers were studied and the diastereomer shown best fits the data. It also explains the existence of an n.O.e. between the aryl protons H^h and H^i and both H^f and H^g . H^h and H^i are probably the *ortho*-protons, H' and H'' , and thus close to both H^f (2-H) and H^g (11-H).

The relatively weak n.O.e. between H^a and H^b which are close to one another in space is due to large amounts of relaxation that these protons obtain from H^c and H^d respectively.

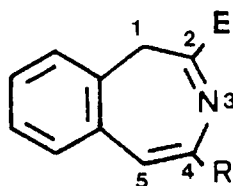
8.3. ISOMERISM IN THE BENZAZEPINES (289) AND (301).

The 1*H*-3-benzazepines (289) and (301) can exist in two forms, (a) and (b).



(289a) R = CH₃

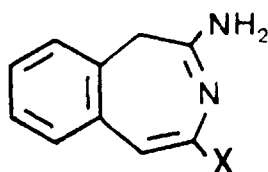
(301a) R = Ph



(289b) R = CH₃

(301b) R = Ph

A survey of the literature provides only two examples of 1*H*-3-benzazepines, the aminobenzazepines (355)²⁴⁴ which are not helpful in distinguishing between the (a) and (b) isomers above.



(355) X = Br, I

The observed and calculated n.m.r. chemical shifts for the 1- and 5-position protons are given in Table 7.

This data indicates that (289) is almost certainly in the (a) form. Whilst the observed chemical shifts of (301) are closer to those of (301b) than (301a), it is not possible, due to the approximations used

in the calculations, to distinguish between the two isomers on the basis of the data given . The i.r. spectra of (289) ($\nu_{\max}$ 1710, 1635 cm^{-1}) and (301) (1715, 1625 cm^{-1}) do not provide a means of distinguishing the isomers. It may be possible to do so by obtaining a fully coupled ^{13}C n.m.r. spectrum.

TABLE 7. Chemical shifts of the 1- and 5-protons in (289) and (301).

Structure	Vinyl H (5-H)		Methylene H's (1-H)	
Number	Calculated	Observed	Calculated	Observed
(289a)	7.4-7.8	7.80	3.2-3.4	3.15
(289b)	6.3-6.6	7.80	3.4-3.7	3.15
(301a)	7.5-7.8	7.28	3.7-3.9	3.52
(301b)	6.9-7.1	7.28	3.4-3.7	3.52

REFERENCES

REFERENCES

1. F. Tiemann, Ber., 1891, 24, 4162.
2. T. Stieglitz, Amer. Chem. J., 1896, 18, 751; T. Curtius and F. Schmidt, Ber., 1922, 55, 1571.
3. W. Lwowski, Angew. Chem., Int. Ed. Engl., 1967, 6, 897; S. Linke, G.T. Tissue, and W. Lwowski, J. Am. Chem. Soc., 1967, 89, 6308; G.T. Tissue, S. Linke and W. Lwowski, J. Am. Chem. Soc., 1967, 89, 6303.
4. J.M. Elder, Monatsh. Chem., 1892, 12, 86; H.H. Frank and H. Reichardt, Naturwissenschaften, 1936, 24, 171; L.F. Keyser, J. Am. Chem. Soc., 1960, 82, 5245.
5. R.S. Berry in "Nitrenes" (W. Lwowski, ed), Chapter 2. Wiley (Interscience), New York, 1970.
6. G. Smolinsky, E. Wasserman, and W.A. Yager, J. Am. Chem. Soc., 1962, 84, 3220.
7. M. Sumitani, S. Nakara, and K. Yoshihara, Bull. Chem. Soc. Jpn., 1976, 49, 2995.
8. W. Lwowski, ed., "Nitrenes" . Wiley (Interscience), New York, 1970.
9. W. Lwowski, React. Intermed., 1978, 1, 197.
10. C. Wentrup, Adv. Heterocycl. Chem., 1981, 28, 231, and references therein.
11. Organic Reaction Mechanisms, 1965-1967, Chapter 10 (B. Capon, M.J. Perkins, and C.W. Rees, ed.); ibid., 1967-1972, Chapter 10 (B. Capon and C.W. Rees, ed.); ibid., 1973-1976, Chapter 5 (A.R. Butler and M.J. Perkins, ed.); ibid., 1977-1982, Chapter 5 (A.C. Knipe and W.E. Watters, ed).

12. V.P. Semenov, A.N. Studenikov, and A.A. Potekhim, Khim. Geterotsikl. Soedin., 1978, 233.
13. V.P. Semanov, A.N. Studenikov, and A.A. Potekhim, Khim. Geterotskil. Soedin., 1979, 467.
14. F.D. Lewis and W.H. Saunders, Jr., in "Nitrenes" (W. Lwowski, ed.), Chapter 3. Wiley (Interscience), New York, 1970.
15. R.A. Abramovitch and E.P. Kyba in "The Chemistry of the Azido Group" (S. Patai, ed.), Chapter 5. Wiley (Interscience), New York, 1971; F.C. Montgomery and W.H. Saunders, J. Org. Chem., 1976, 41, 2368.
16. G. Szeimes, U. Siefken, and R. Rinck, Angew. Chem., Int. Ed. Engl., 1973, 12, 161; A. Hassner, A.B. Levy, E.E. McEntire and J.E. Galle, J. Org. Chem., 1974, 39, 585.
17. J.S. Millership and H. Suschitzky, J. Chem. Soc., Chem. Commun., 1971, 1496.
18. Y. Tamura, M.W. Chun, H. Nishida, S. Kwon, and M. Ikida, Chem. Pharm. Bull., 1978, 26, 2866.
19. L.A. Plink and G.E. Hilbert, J. Am. Chem. Soc., 1937, 59, 8.
20. J-P. LeRouse, P-L. Desbene, and M. Seguin, Tetrahedron Lett., 1976, 3141.
21. R.H.B. Galt, J.D. Loudon, and A.B.D. Sloan, J. Chem. Soc., 1958, 1598.
22. J.J. Looker, J. Org. Chem., 1971, 36, 2681.
23. R.A. Abramovitch and E.P. Kyba, J. Chem. Soc., Chem. Commun., 1969, 265.
24. D.H.R. Barton and L.M. Morgan, Jr., Proc. Chem. Soc., 1961, 206; J. Chem. Soc., 1962, 622; D.H.R. Barton and A.N. Starrat, J. Chem. Soc., 1965, 2444.
25. R.M. Moriarity and M. Rahman, Tetrahedron, 1965, 21, 2877.
26. J.W. Timberlake, J. Alender, A.W. Garner, M.L. Hodges, C. Ozmeral, S. Szilagyi, and J.O. Jacobus, J. Org. Chem., 1981, 46, 2082.
27. W. Pritzkow and D. Timm, J. Prakt. Chem., 1966, 32, 178.

28. T. Nishiwaki, A. Nakano, and H. Matsuko, J. Chem. Soc., C, 1970, 1825; T. Nishiwaki and F. Fuliya, J. Chem. Soc., Perkin Trans. I, 1972, 1456.
29. T. Nishiwaki, Tetrahedron Lett., 1969, 2049.
30. A. Padwa, J. Smolanoff and A. Tremper, J. Org. Chem., 1976, 41, 534.
31. T. Nishiwaki, J. Chem. Soc., Chem. Commun., 1972, 565.
32. K. Isomura, G-I. Ayabe, S. Hatano, and H. Taniguchi, J. Chem. Soc., Chem. Commun., 1980, 252.
33. A. Padwa, Acc. Chem. Res., 1976, 9, 371.
34. P. Gilgen, H. Heimgartner, H. Schmid, and H-J. Hansen, Heterocycles, 1977, 6, 143.
35. A. Padwa and A. Ku, J. Am. Chem. Soc., 1978, 100, 2181, and references cited therein.
36. V. Nair and K.H. Kim, Heterocycles, 1977, 7, 353.
37. F.W. Fowler, Adv. Heterocycl. Chem., 1971, 13, 45; G. Smolinsky and C.A. Pryde, in "The Chemistry of the Azido Group" (S. Patai, ed.), Chapter 10, Wiley (Interscience), New York, 1971; G. L'abbe and A. Hassner, Angew. Chem. Int. Ed. Engl., 1971, 10, 98.
38. G. L'abbe, Angew. Chem., Int. Ed. Engl., 1975, 14, 775.
39. J.H. Boyer, W.E. Krueger, and G.J. Mikol, J. Am. Chem. Soc., 1969, 89, 5504.
40. G. L'abbe and G. Mathys, J. Org. Chem., 1974, 39, 1778.
41. L.A. Burke, G. Leroy, M.T. Nguyen, and M. Sana, J. Am. Chem. Soc., 1962, 27, 3557.
42. G. Smolinsky, J. Am. Chem. Soc., 1961, 83, 4483; J. Org. Chem., 1962, 27, 3557.
43. T.L. Gilchrist, C.W. Rees, and J.A.R. Rodrigues, J. Chem. Soc., Chem. Commun., 1979, 627.

44. K. Friedrich, G. Bock, and H. Fritz, Tetrahedron Lett., 1978, 3327.
45. H. Hemetsberger, I. Spira, and W. Schonfelder, J. Chem. Res. (S), 1977, 247.
46. J.P. Boukou-Poba, M. Farnier, and R. Guillard, Tetrahedron Lett., 1979, 1717.
47. A. Padwa, J. Smolanoff and A.I. Tremper, J. Am. Chem. Soc., 1974, 96, 3486.
48. K. Isomura, M. Okada, and H. Taniguchi, Chem. Lett., 1972, 629.
49. P. Germeraad and H.W. Moore, J. Chem. Soc., Chem. Commun., 1973, 358; J. Org. Chem., 1974, 39, 774.
50. G. Buhr, Chem. Ber., 1973, 106, 3544.
51. K. Isomura, S. Naguchi, M. Saruwatari, S. Hatano, and H. Taniguchi, Tetrahedron Lett., 1980, 3879.
52. K. Isomura, T. Tanaka, and H. Taniguchi, Chem. Lett., 1977, 397.
53. A. Padwa, J. Smolanoff, and A. Tremper, J. Am. Chem. Soc., 1975, 97, 4682.
54. H. Alper, J.E. Prickett and S. Wollowitz, J. Am. Chem. Soc., 1977, 99, 4330.
55. K. Isomura, S. Kobayashi, and H. Taniguchi, Tetrahedron Lett., 1968, 3499; K. Isomura, M. Okade, and H. Taniguchi, ibid., 1969, 4073.
56. K. Isomura, K. Uto, and H. Taniguchi, J. Chem. Soc., Chem. Commun., 1977, 664.
57. D.J. Anderson, T. Gilchrist, G.E. Gymer, and C.W. Rees, J. Chem. Soc., Perkin Trans. I, 1973, 550.
58. T.L. Gilchrist, C.W. Rees and E. Stanton, J. Chem. Soc., C, 1971, 3036.
59. H. Hemetsberger, D. Knittel, and H. Wiedmann, Monatsh. Chem., 1970, 101, 161.
60. H. Hemetsberger and D. Knittel, Monatsh. Chem., 1972, 103, 194.

61. A. Krutosikova, J. Kovak, and J. Kristofcak, Collect. Czech. Chem. Commun., 1979, 44, 1799.
62. S. Soth, M. Farnier and C. Paulmier, Can. J. Chem., 1978, 56, 1429;
M. Farnier, S. Soth, and P. Fournari, Can. J. Chem., 1976, 54, 1074.
63. J.I.G. Cadogan, M. Cameron-Wood, R.K. Mackie, and R.J.G. Searle, J. Chem. Soc., 1965, 4831.
64. H. Taniguchi, K. Isomura, and T. Tanaka, Heterocycles, 1977, 6, 721.
65. K. Isomura, H. Taguchi, T. Tanaka, and H. Taniguchi, Chem. Lett., 1977, 401.
66. D. Knittel, H. Hemetsberger, R. Leipert, and W. Weidmann, Tetrahedron Lett., 1970, 1459.
67. K. Yakushijin, S. Yoshima, and A. Tanaka, Heterocycles, 1977, 6, 721.
68. M. Farnier, S. Soth, and P. Fournari, Can. J. Chem., 1976, 54, 1066.
69. R.D. Grant, C.J. Moody, C.W. Rees, and S.C. Tsoi, J. Chem. Soc., Chem. Commun., 1982, 884.
70. A. Padwa and P.H.J. Carlsen, J. Org. Chem., 1978, 43, 2029.
71. A. Padwa and N. Kamigata, J. Am. Chem. Soc., 1977, 99, 1871.
72. A. Hassner, and V. Alexian, New Trends in Heterocyclic Chemistry, 1979, 3, 178.
73. A. Hassner, Heterocycles, 1980, 14, 1517.
74. W. Lwowski, in "Nitrenes" (W. Lwowski, ed.), Chapter 6, Wiley (Interscience), New York, 1970.
75. O.E. Edwards, in "Nitrenes" (W. Lwowski, ed.), Chapter 7, Wiley (Interscience), New York, 1970.
76. G.R. Felt, S. Linke and W. Lwowski, Tetrahedron Lett., 1972, 2037.
77. G. Just, and W. Zehetner, Tetrahedron Lett., 1968, 319.
78. J. Sauer and K.K. Mayer, Tetrahedron Lett., 1967, 3389.

79. N. Furukawa, T. Nishio, M. Fukumura, and S. Oae, Chem. Lett., 1978, 209; N. Furukawa, M. Fukumura, T. Nishio, and S. Oae, Phosphorus Sulfur, 1978, 5, 231.
80. R. Kreher and G.H. Blockhorn, Angew. Chem. Int. Ed. Engl., 1964, 3, 589.
81. P. Puttner and K. Hafner, Tetrahedron Lett., 1964, 3119.
82. P.F. Alewood, M. Benn, and R. Reinfried, Can. J. Chem., 1974, 52, 4083.
83. T. Kato, Y. Suzuki, and M. Sato, Chem. Lett., 1978, 697.
84. K. Hafner and W. Kaiser, Tetrahedron Lett., 1967, 891.
85. M.S. Chauhan and D.M. McKinnon, Can. J. Chem., 1976, 54, 3879.
86. R.F. Bleiholder and H. Shechter, J. Am. Chem. Soc., 1968, 90, 2131.
87. E.M. Bingham and J.C. Gilbert, J. Org. Chem., 1975, 40, 224.
88. W.J. Kauffman, J. Org. Chem., 1970, 35, 4244.
89. T. Kametani, K. Sota, and M. Shio, J. Heterocycl. Chem., 1970, 7, 807.
90. S.M.A. Hai and W. Lwowski, J. Org. Chem., 1973, 38, 2442.
91. W. Lwowski, A. Hartenstein, C. de Vita, and R.L. Smick, Tetrahedron Lett., 1964, 2497.
92. R. Huisgen and J-P. Anselme, Chem. Ber., 1965, 98, 2998; R. Huisgen and L. Blasihka, Justus Liebigs Ann. Chem., 1965, 686, 145.
93. N. Koga, G. Koga and J-P. Anselme, Tetrahedron, 1972, 28, 4515.
94. T. Kametani and M. Shio, J. Heterocycl. Chem., 1970, 7, 831; *ibid.*, 1971, 8, 545.
95. L.E. Chapman and R.F. Robbins, Chem. Ind., 1966, 1266.
96. W. Lwowski and O. Subba Rao, Tetrahedron Lett., 1980, 727.
97. O. Meth-Cohn and S. Rhonati, J. Chem. Soc., Chem. Commun., 1980, 1161.
98. R.C. Kerber and P.J. Heffron, J. Org. Chem., 1972, 39, 1592.
99. J. Sauer and K.K. Mayer, Tetrahedron Lett., 1968, 319.

100. J.A. Chapman, J. Crosby, C.A. Cummings, R.A.C. Rennie, and R.M. Paton, J. Chem. Soc., Chem. Commun., 1976, 240; C. Grundmann, and S.K. Datta, J. Org. Chem., 1969, 34, 2016; C. Grundmann, P. Kochs, and J.R. Boal, Justus Liebigs Ann. Chem., 1972, 761, 162.
101. A. Holm, N. Harrit, and I. Trabjerg, J. Chem. Soc., Perkin Trans. I, 1978, 748; A. Holm, L. Carlsen, and E. Larsen, J. Org. Chem., 1978, 43, 4816.
102. A. Holm, J.J. Christiansen, and C. Lohse, J. Chem. Soc., Perkin Trans. I, 1976, 960; A. Holm, and N. Toubro, ibid., 1978, 1445; A. Holm, Adv. Heterocycl. Chem., 1976, 20, 145.
103. P.A.S. Smith and E. Leon, J. Am. Chem. Soc., 1958, 80, 4647; J. Vaughan and P.A.S. Smith, J. Org. Chem., 1958, 23, 1909.
104. P.A.S. Smith, in "Nitrenes" (W. Lwowski, ed.), Chapter 4, Wiley (Interscience), New York, 1970.
105. R.M. Moriarity and J.M. Kliegman, J. Am. Chem. Soc., 1967, 89, 5959.
106. T.L. Gilchrist, C.J. Moody, and C.W. Rees, J. Chem. Soc., Perkin Trans. I, 1975, 1964; T.L. Gilchrist, C.J. Moody, and C.W. Rees, J. Chem. Soc., Perkin Trans. I, 1979, 1871.
107. C.W. Rees, Pure Appl. Chem., 1979, 51, 1243; T. Gilchrist, P.F. Gordon, D.F. Pipe, and C.W. Rees, J. Chem. Soc., Perkin Trans. I, 1979, 2303.
108. M. Casey, C.J. Moody and C.W. Rees, J. Chem. Soc., Chem. Commun., 1982, 714; M. Casey, unpublished work.
109. D. Pocar, R. Stradi and B. Gioia, Tetrahedron Lett., 1976, 1839.
110. L. Garanti and G. Zecchi, Tetrahedron Lett., 1980, 21, 559.
111. C. Wentrup, Helv. Chim. Acta, 1978, 61, 1755.
112. R.M. Moriarity, J.M. Kliegman, and C. Shovlin, J. Am. Chem. Soc., 1967, 89, 5958.

113. R.M. Moriarity and P. Serridge, J. Am. Chem. Soc., 1971, 93, 1534.
114. T. Fuchigani and K. Odo, Bull. Chem. Soc., Jpn., 1977, 93, 1534.
115. R. Huisgen, Angew. Chem., 1960, 72, 359.
116. C. Wentrup, Tetrahedron, 1971, 27, 1281.
117. J.H. Boyer in "Nitrenes" (W. Lwowski, ed.), Chapter 5, Wiley (Interscience), New York, 1970.
118. W.D. Crow and C. Wentrup, Tetrahedron Lett., 1968, 6149.
119. C. Wentrup, J. Chem. Soc., Chem. Commun., 1965, 1386.
120. R.J. Sundberg, S.R. Suter, and M. Brenner, J. Am. Chem. Soc., 1972, 94, 513.
121. B. Iddon, M.W. Pickering, and H. Suschitzky, J. Chem. Soc., Chem. Commun., 1974, 759.
122. B. Nay, E.F.V. Scriven, H. Suschitzky, and Z.U. Khan, Synthesis, 1977, 757.
123. M. Ogata, H. Matsumo, and H. Kano, Tetrahedron, 1969, 25, 5205.
124. M.A. Berwick, J. Am. Chem. Soc., 1971, 93, 5780.
125. R. Purvis, R.K. Smalley, W.A. Strachen, and H. Suschitzky, J. Chem. Soc., Perkin Trans. I, 1978, 191.
126. T. de Boer, J.I.G. Cadogan, H.M. McWilliam, and A.G. Rowley, J. Chem. Soc., Perkin Trans. II, 1975, 554.
127. S.S. Mochalov, A.N. Fedotov, A.I. Sizov, and Yu. S. Shavarov, Zh. Org. Khim., 1979, 15, 1425.
128. C. Wentrup, and H-W. Winder, J. Am. Chem. Soc., 1980, 102, 6159.
129. D.S. Pearce, M-S. Lee and H.W. Moore, J. Org. Chem., 1974, 39, 1362.
130. R.J. Sundberg and S.R. Suter, J. Org. Chem., 1970, 35, 827.
131. K. Nishyama and J-P. Anselme, J. Org. Chem., 1977, 42, 2636.
132. T. Kametani, F.F. Ebetino, T. Yamanaka, and K.K. Nyu, Heterocycles, 1974, 2, 209.

133. J.M. Lindley, I.M. McRobbie, O. Meth-Cohn, and H. Suschitzky, J. Chem. Soc., Perkin Trans. I, 1977, 2194.
134. D.E. Ames, K.J. Hansen and N.D. Griffiths, J. Chem. Soc., Perkin Trans. I, 1973, 2818; R. Kreher and W. Gerhardt, Tetrahedron Lett., 1977, 3465.
135. B. Iddon, O. Meth-Cohn, E.F.V. Scriven, H. Suschitzky, and T. Gallagher, Agnew. Chem. Int. Ed. Engl., 1979, 18, 900.
136. L. Krbecek and H. Takimoto, J. Org. Chem., 1968, 33, 4286; G.R. Cliff, E.W. Collington, and G. Jones, J. Chem. Soc., C, 1970, 1490.
137. R.N. Carde, P.C. Hayes, G. Jones, C.J. Cliff, J. Chem. Soc., Perkin Trans. I, 1981, 1132.
138. J.I.G. Cadogan, Acc. Chem. Res., 1972, 5, 303.
139. O. Meth-Cohn, Heterocycles, 1980, 14, 1492.
140. R.Y. Ning, J.F. Blount, P.B. Madan, and R.I. Fryer, J. Org. Chem., 1977, 42, 1791.
141. A. Yabe and K. Honda, Tetrahedron Lett., 1975, 1079.
142. A. Yabe, K. Honda, S. Oikawa and M. Tsuda, Chem. Lett., 1976, 823.
143. S. Bradbury and C.W. Rees, J. Chem. Soc., Perkin Trans. I, 1972, 72.
144. C.J. Moody, C.W. Rees, S.C. Tsoi and D.J. Williams, J. Chem. Soc., Chem. Commun., 1981, 927.
145. R.A. Abramovitch, S.R. Chelland, and Y. Yamada, J. Org. Chem., 1975, 40, 1541.
146. P.F. Tsui, Y.H. Chang, T.M. Vogel and G. Zon, J. Org. Chem., 1976, 41, 3381.
147. H. Yamada, H. Shizuka and K. Matsui, J. Org. Chem., 1975, 40, 1351.
148. E.B. Mullock and H. Suschitzky, J. Chem. Soc., C, 1968, 1937; R. Garner, E.B. Mullock, and H. Suschitzky, J. Chem. Soc., C, 1966, 1980.

149. R.J. Sundberg, R.H. Smith and J.E. Floor, J. Am. Chem. Soc., 1969, 91, 3392.
150. C.J. Moody, C.W. Rees, and S.C. Tsoi, J. Chem. Soc., Chem. Commun., 1981, 550.
151. T. Gilchrist and C.W. Rees "Carbenes, Nitrenes, and Arynes" Nelson, London, 1965.
152. D.M. Lemal, in "Nitrenes" (W. Lwowski, ed.), Chapter 10, Wiley (Interscience), New York, 1970.
153. B.V. Ioffe and M.A. Kugnetsov, Russ. Chem. Rev., (Engl. Trans.), 1972, 41, 131.
154. R.S. Atkinson and C.W. Rees, J. Chem. Soc., Chem. Commun., 1967, 1230.
155. R.S. Atkinson and C.W. Rees, J. Chem. Soc., (C), 1969, 722.
156. L. Hoesch, N. Egger, and A.S. Drieding, Helv. Chim. Acta, 1978, 61, 795.
157. R.S. Atkinson, J.R. Malpass, K.L. Skinner, and K.L. Woodthorpe, J. Chem. Soc., Chem. Commun., 1981, 549, and references cited therein.
158. D.J. Anderson, T.L. Gilchrist, and C.W. Rees, J. Chem. Soc., Chem. Commun., 1969, 149.
159. D.W. Jones, J. Chem. Soc., Chem. Commun., 1973, 67.
160. R.S. Atkinson, J.R. Malpass, and K.L. Woodthorpe, J. Chem. Soc., Chem. Commun., 1981, 160.
161. B.M. Adger, S. Bradbury, M. Keeting, C.W. Rees, and R.C. Storr, J. Chem. Soc., Perkin Trans. I, 1975, 31.
162. C.W. Rees, R.C. Storr, and P.J. Whittle, J. Chem. Soc., Chem. Commun., 1976, 411; B.M. Adger, C.W. Rees and R.C. Storr, J. Chem. Soc., Perkin Trans. I, 1975, 45.

163. A.G. Anastassiou, J. Am. Chem. Soc., 1965, 87, 5512; ibid., 1968, 90, 1527.
164. F.D. March and H.E. Simmons, J. Am. Chem. Soc., 1965, 87, 3529.
165. D.S. Breslow in "Nitrenes" (W. Lwowski, ed.), Chapter 8, Wiley (Interscience), New York, 1970.
166. R.A. Abramovitch, T. Chellathurai, W.D. Holcomb, I.T. McMaster, and D.P. Vanderpool, J. Org. Chem., 1977, 42, 2920.
167. R.A. Abramovitch, T. Chellathurai, I.T. McMaster, T. Takaya, C.I. Azogu, and D.P. Vanderpool, J. Org. Chem., 1977, 42, 2914.
168. R.A. Abramovitch, C.I. Azogu, I.T. McMaster, and D.P. Vanderpool, J. Org. Chem., 1978, 43, 1218; R.A. Abramovitch and D.P. Vanderpool, J. Chem. Soc., Chem. Commun., 1977, 18.
169. R.A. Abramovitch, C.I. Azogu, and I.T. McMaster, J. Am. Chem. Soc., 1969, 91, 1219.
170. R.A. Abramovitch, W.D. Holcomb, and S. Wake, J. Am. Chem. Soc., 1981, 103, 1525.
171. R.A. Abramovitch, S.B. Hendi and A.O. Kress, J. Chem. Soc., Chem. Commun., 1981, 1087.
172. J. Martin, O. Meth-Cohn, and H. Suschitzky, J. Chem. Soc., Perkin Trans. I, 1974, 2451.
173. A.G. Anastassiou, J.N. Shepelavy, H.E. Simmons, and F.D. Marsh in "Nitrenes" (W. Lwowski, ed.), Chapter 9, Wiley (Interscience), New York, 1970.
174. H. Hemetsberger, D. Knittel, and H. Weidmann, Monatsh. Chem., 1969, 100, 1559.
175. "Hefbron Dictionary of Organic Compounds", 1965, 5, 2881.

176. C.F.H. Allen and J.W. Gates, Jr., Org. Synth., Col. Vol. 3, 140.
177. E. Bergmann, J. Org. Chem., 1939, 4, 1; B.J. Arnold, Ph.D. Thesis, University of London, 1973, 179.
178. T.P.C. Mulholland and G. Ward, J. Chem. Soc., 1954, 4676.
179. L. Fieser and A.M. Seligman, J. Am. Chem. Soc., 1935, 57, 2174.
180. E.D. Bergmann and R. Ikan, J. Am. Chem. Soc., 1956, 78, 2821.
181. E. Bergmann and M. Orchin, J. Am. Chem. Soc., 1947, 71, 1111.
182. A.W. Johnson and R.B. LaCount, J. Am. Chem. Soc., 1961, 83, 417.
183. M.H. Klouwen and H. Boelens, Rec. Trav. Chim., 1960, 79, 1022.
184. S.D. Jolad and S. Rajagopal, Org. Synth., Coll. Vol. 5, 139.
185. A.I. Meyers, D.L. Temple, D. Haidukewych, and E.D. Mihelich, J. Org. Chem., 1974, 39, 2787.
186. I.C. Nordin, J. Heterocycl. Chem., 1966, 3, 531.
187. A.I. Meyers, A. Nabeya, H.W. Adickes, I.R. Politzer, G.R. Malone, A.C. Kovclesky, R.L. Nolen, and R.C. Portnoy, J. Org. Chem., 1973 38, 36.
188. L-F. Tietze, G. Kinast, and H.C. Uzer, Angew. Chem., 1979, 91, 576.
189. L.V. Interrante, M.A. Bennett, and R.S. Nyholm, Inorg. Chem., 1966, 5, 2122.
190. R.D. Reike, S.E. Bales, P.M. Hudnall, and G.S. Poindexter, Org. Synth., 59, 85.
191. F. Caesar and A. Mondon, Chem. Ber., 1968, 101, 990.
192. W.J. Dale, L. Starr and C.W. Strobel, J. Org. Chem., 1961, 26, 2225.
193. S. Natelson and S.P. Gottfried, J. Am. Chem. Soc., 1956, 78, 475.
194. E.F. De Tar and L.A. Carpino, J. Am. Chem. Soc., 1956, 78, 475.
195. V.I. Bendall and S.S. Dharamshi, J. Chem. Soc., Perkin Trans., I, 1972, 2732.

196. W. Metlesics, T. Anton, M. Chaykovsky, V. Toome, and L.H. Sternback, J. Org. Chem., 1968, 33, 2874.
197. R.H. Callighan, M.F. Tarker, and M.H. Wilt, J. Org. Chem., 1960, 25, 820.
198. S.F. Schaeren and A.Furlenmeir, Chem. Abs., 1969, 71, P 124817g.
199. H. Meyer, Monatsh. Chem., 1904, 25, 497.
200. W. Flitsch and E. Mukidjam, Chem. Ber., 1979, 112, 3577.
201. P.A. Stadler, Helv. Chim. Acta, 1978, 61, 1675.
202. W.A. Bonner and P.I. McNamee, J. Org. Chem., 1961, 26, 2554.
203. L.F. Fieser and M. Fieser, "Reagents for Organic Chemistry", 1965, 1, 135.
204. O.P. Norman, "Principles of Organic Synthesis, pp. 595-599.
205. O.P. Norman, "Principles of Organic Synthesis, pp. 613-614.
206. J.A. Anderson and R.D. Kohler, Synthesis, 1974, 277.
207. A.P. Kozikowski, Heterocycles, 1981, 16, 267.
208. F. Troxler, Chem. Abs., 1974, 80, P 36995u.
209. B.F. Blowden, K. Pickler, E. Ritchie, and W.C. Taylor, Austral. J. Chem., 1972, 25, 2659, and references cited therein.
210. J.V. Silverton, C. Kabuto, K.T. Buck, and M.P. Cava, J. Am. Chem. Soc., 1977, 99, 6708, and references cited therein.
211. U. Hengartner, D. Valentine, Jr., K.K. Johnson, M.E. Larsheid, F. Pigott, F. Scheidl, J.W. Scott, R.C. Sun, J.M. Townsend, and T.H. Williams, J. Org. Chem., 1979, 44, 3741.
212. T.R. Kasturi and L. Krishnan, Tetrahedron Lett., 1980, 21, 856 and references cited therein.
213. G.R. Clemo and S.P. Popli, J. Chem. Soc., 1951, 1406; G.R. Clemo, and M. Hogarth, J. Chem. Soc., 1954, 95.
214. T. Kametani, "The Chemistry of the Isoquinoline Alkaloids", Chapter 18, (Elsevier Publishing Co., 1969).

215. G.S. King, E.S. Waight, P.G. Mantle, and C.A. Szczybrak, J. Chem. Soc., Perkin Trans. I, 1977, 2099.
216. T. Sheradsky in "The Chemistry of the Azido Group" (S. Patai, ed.), Chapter 6, Wiley (Interscience), New York, 1970.
217. G. Bianci, C. De Micheli, and R. Gandolfi, in "The Chemistry of Functional Groups, Supplement A: The Chemistry of Double-Bonded Functional Groups", (S. Patai, ed.), Chapter 6, Wiley (Interscience), New York, 1977.
218. A. Padwa, A. Ku, H. Ku, and A. Mazzu, J. Org. Chem., 1978, 43, 66, and references cited therein.
219. R.A. Abramovitch and E.P. Kyba in "The Chemistry of the Azido Group" (S. Patai, ed.), Chapter 5, Wiley (Interscience), New York, 1971.
220. R. Huisgen, Angew. Chem. Int. Ed. Engl., 1963, 2, 633.
221. "Organophosphorus Reagents in Organic Synthesis" (J.I.G. Cadogan, ed.), Chapters 3 and 4, Academic Press, 1979.
222. C.-g. Shin, Y. Yonezawa, K. Watanabe, and J. Yoshimura, Bull. Chem. Soc., Jpn., 1981, 54, 3811.
223. S.A. Foster, L.J. Leyshon, and D.G. Saunders, J. Chem. Soc., Chem. Commun., 1973, 29.
224. O.C. Dermer and G.E. Ham, "Ethylenimine and other Aziridines", pp. 224-227, 256-257, Academic Press, Inc., New York, 1969.
225. W. Rundel and E. Muller, Chem. Ber., 1963, 96, 2528; R.D. Clark, and G.K. Helmkamp, J. Org. Chem., 1964, 29, 1316.
226. A. Padwa and A. Au, J. Am. Chem. Soc., 1976, 98, 5581.
227. H.W. Johnston, C.E. Kaslow, A. Langsjoen, and R.L. Shriner, J. Org. Chem., 1948, 13, 477.

228. R. Beugelmans, H. Ginsberg, and M. Bois-Choussy, J. Chem. Soc., 1982, 1149.
229. D.J. Anderson and A. Hassner, Synthesis, 1975, 8, 483, and references cited therein.
230. A. Padwa, Chem. Rev., 1977, 77, 37.
231. C. Dallas, J.W. Lown, and J.P. Moser, J. Chem. Soc., (D), 1970, 278.
232. G. Bianchi, C. De. Micheli and R. Gandolfi in "The Chemistry of Double-Bonded Functional Groups (Supplement A, Part 1)", (S. Patai, ed.), Chapter 6, 1977.
233. T.L. Gilchrist, C.W. Rees, and C. Thomas, J. Chem. Soc., Perkin Trans. I, 1975, 12.
234. M.F. Grundon, H.B. Henbest, and M.D. Scott, J. Chem. Soc., 1963, 1855.
235. L.F. Fieser and M. Fieser, "Reagents for Organic Synthesis", 1, 1030.
236. R.N. Boyd, and R.C. Rittner, J. Am. Chem. Soc., 1960, 82, 2032.
237. A.T. Moore and H.N. Rydon, Org. Synth., 1965, 45, 47.
238. M.O. Forster and H.E. Firg, J. Chem. Soc., 1908, 93, 72.
239. E.T. Stiller, J. Chem. Soc., 1937, 473.
240. "Vogel's Textbook of Practical Organic Chemistry", 4th Edition, p. 298.
241. J. Bonnstein, S.A. Seone, W.F. Sullivan, and O.F. Bennett, J. Am. Chem. Soc., 1957, 79, 1745.
242. V.D. Orlov, F.G. Yaremenko, N.N. Kolos, N.S. Pivnenko, and V.F. Lavrushin, Khim. Geterosikl. Soedin., 1980, 544.
243. P. Murray-Rust, H.B. Burgi, and P.J. Dunitz, J. Am. Chem. Soc., 1975, 97, 923 and references cited therein.
244. F. Johnson and W.A. Nasutavicus, J. Heterocycl. Chem., 1965, 2, 26.