INTRAMOLECULAR REACTIONS OF 1,3-DIPOLES WITH EXTENDED CONJUGATION

by

IAN R. ROBERTSON, B.Sc.

Thesis presented for the degree of

DOCTOR OF PHILOSOPHY

UNIVERSITY OF EDINBURGH

April 1984

FOR THE HELL OF IT

ACKNOWLEDGEMENTS

I would like to express sincere gratitude to Dr.J.T. Sharp for his excellent supervision of this work, and for his invaluable advice, encouragement and tolerance throughout the course of this work. I am also indebted to the staff of the Department of Chemistry, University of Edinburgh, in particular Messrs. J.Broom, L.Bell, D.Thomas and especially Mr.J.R.A.Millar for his enthusiasm and patience in running numerous n.m.r. spectra. I would like to thank Mrs C.G. Ranken for her efficient and rapid typing of this thesis. Finally I thank all my colleagues in Lab.29 for providing an interesting and enjoyable three years.

A part-time demonstratorship from the University of Edinburgh (1980-1981) and an S.E.R.C. studentship (1981-1983) are gratefully acknowledged.

Declaration

I declare that this thesis is my own composition, that the work of which it is a record has been carried out by myself, and that it has not been submitted in any previous application for a Higher Degree.

The thesis describes the results of research carried out in the Department of Chemistry, University of Edinburgh, under the supervision of Dr.J.T. Sharp since 1st October 1980, the date of my admission as a research student.

Post-graduate Lecture Courses

The following is a statement of the courses attended during the period of research.

Organic Research Seminars (3 years attendance).
Bio-organic Chemistry, various lecturers (5 lectures).
Synthesis and Mechanism of Action of the β-Lactam Antibiotics, Glaxo Group Research (5 lectures).
1,3-Dipoles in Organic Synthesis, Dr.J.T. Sharp and Dr. R.M. Paton (5 lectures).
Current Topics in Organic Chemistry, various lecturers (15 lectures).
Pulse Sequences and their Applications to N.M.R. Spectroscopy Dr. G.A. Morris, (5 lectures).

Abstract

The major part of this thesis was the investigation of the electrocyclisation of diazo-compounds having α,β:γ,δ-olefinic unsaturation.

Compounds having acyclic and cycloalkenyl α,β-unsaturation were investigated. In both cases it was found that substrates having a Z hydrogen atom on the δ carbon cyclised exclusively *via* 1,7 - ring closure to give a range of 3*H*-1,2-diazepines. The reaction proceeds in two steps, the seven membered ring being formed by an 8π electron 1,7-electrocyclisation followed by a rapid [1,5] hydrogen shift. Reactants having a Z substituent other than hydrogen cyclised *via* 1,5 - ring closure to give 3*H*-pyrazoles which in most cases underwent further rearrangement to give aromatic products. However, it was shown that photochemical 1,7-cyclisation carried out at -60°C was not subject to blockage by Z groups larger than hydrogen.

Some of the 3*H*-1,2-diazepines which were obtained in the course of these studies were subjected to mild oxidation. The structure and properties of the resulting *N*-oxides were investigated.

The reactions of α,β:γ,δ-unsaturated nitrile ylides having α,β aromatic type unsaturation were also investigated. In these cases 1,1-cycloaddition occurred to give trihydrocyclopropa[c]isoquinolines. This mode of cyclisation was unaffected by the presence of a Zδ substituent. These products were thermally unstable and rearranged at 80°C to give benzazepines *via* ring expansion and/or a walk rearrangement depending on the nature of the substituents.

CONTENTS

Page No

INTRODUCTION

Introduction

1) 1,3-DIPOLES

1.1) Structure

A 1,3-dipole may be defined[1] as a system a-b-c in which a has an electron sextet, i.e. an incomplete valence shell, and carries a formal positive charge; and c is a negatively charged centre having an unshared electron pair. Dipoles in which the positive centre a is an electron deficient carbon, nitrogen or oxygen are generally not stable enough for long-lived existence. However stabilisation is possible if an unshared pair of electrons at atom b can relieve the electron deficiency at a as shown below.

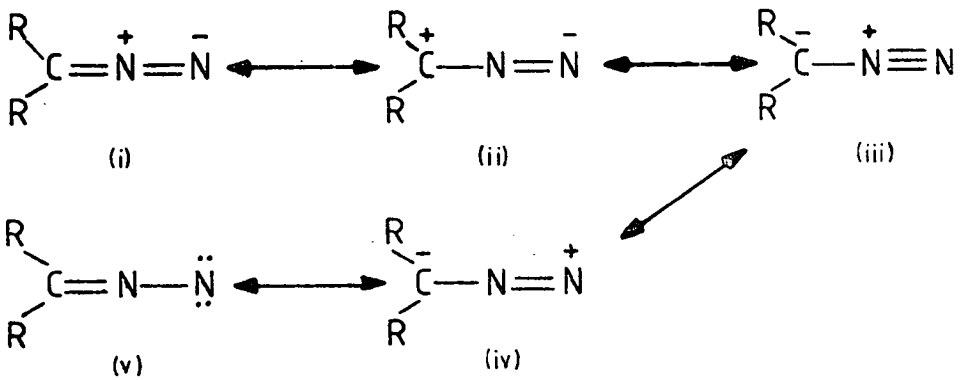
An all octet structure is thus attained in which b becomes the site of formal positive charge. By varying atoms a, b and c it is possible to build up a series of 1,3-dipoles as shown in Table 1. This type of dipole is described as having octet stabilisation and can be divided into two classes.

The first class is octet stabilised 1,3-dipoles with an orthogonal double bond. These have nitrogen as the central atom b, since this is the only element which can supply an unshared electron pair while in a neutral trivalent state.

The second class is the octet stabilised 1,3-dipole without an orthogonal double bond in which the central b atom can be nitrogen or oxygen. The geometry of the two types of

dipole described is different, since the orthogonal π bond tends to cause the 1,3-dipoles of the first type to be linear, whereas dipoles of the other class are bent. In addition there are also a number of systems with no octet stabilisation which will not be discussed as they are not relevant to this thesis.

1,3-Dipoles are best described as resonance structures, for example (i)-(v) are the canonical forms for a diazoalkane.



The all octet structures (i) and (iii) are the main contributors to the stability of these compounds. The term 1,3-dipole which best describes the mode of reaction, derives from the sextet structures (ii) and (iv) but these, and the nitrenic structure (v), give much less significant contributions.

1,3-Dipoles react readily with most multiple bond systems d=e, the dipolarophile, forming two σ bonds at the a and c termini to form a five-membered cyclic product. The product which is formed in this type of addition (i.e.[3+2→5]) has zero net charge.

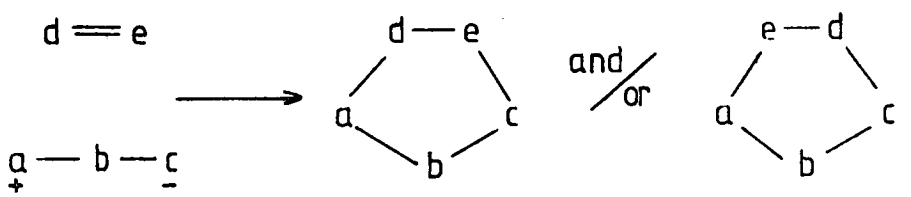
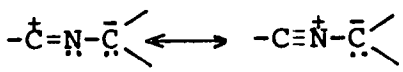


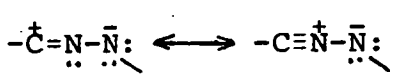
Table 1 1,3-Dipoles with octet stabilisation

(Only two of the contributing resonance structures are shown for each dipole).

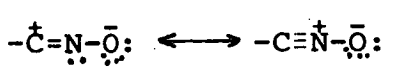
(a) 1,3-Dipoles with an orthogonal double bond



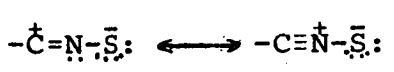
Nitrile ylides



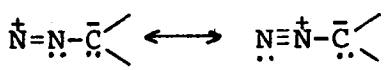
Nitrile imines



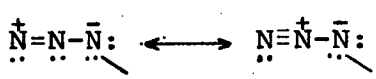
Nitrile oxides



Nitrile sulphides



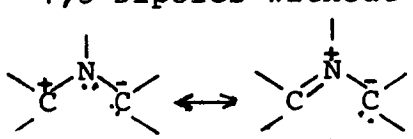
Diazo compounds



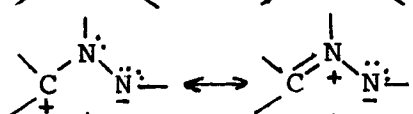
Azides

Nitrous oxide

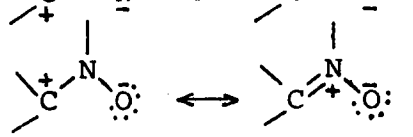
(b) 1,3-Dipoles without an orthogonal double bond



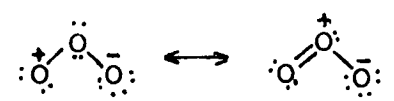
Azomethine ylides



Azomethine imines



Nitrones (azomethine oxides)



Ozone

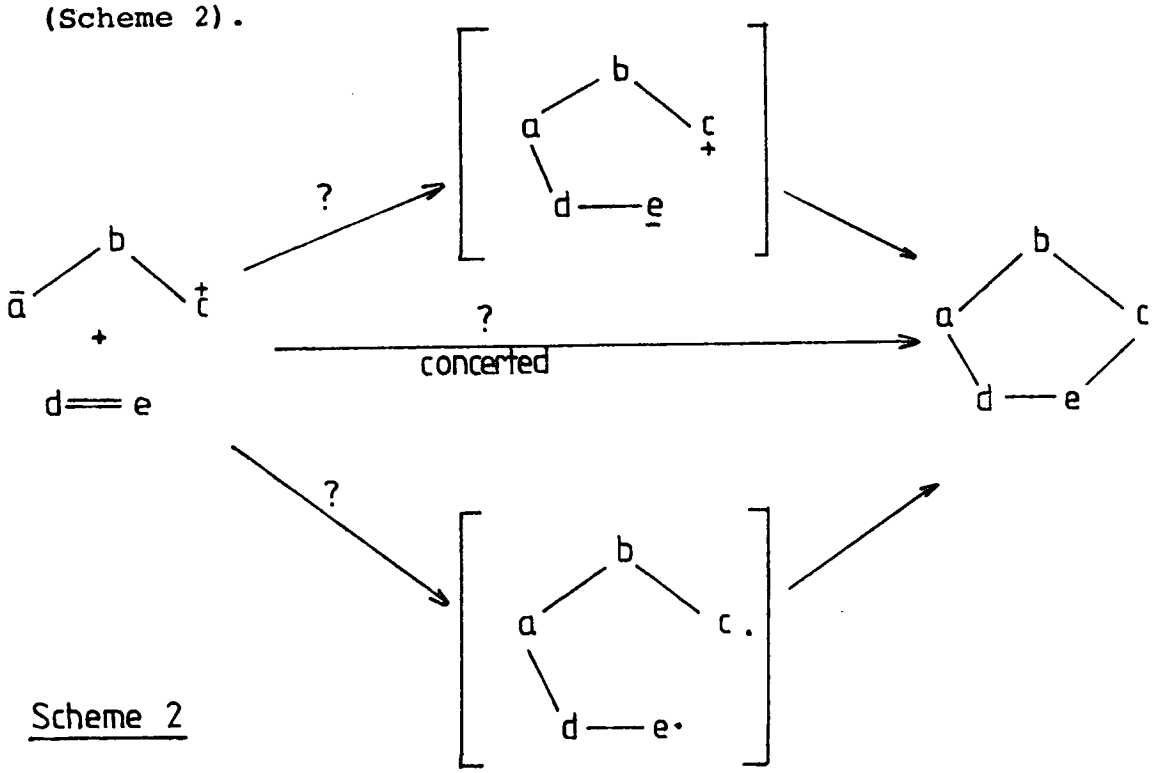
Carbonyl oxides

This 1,3-dipolar cycloaddition can be of two types, either "inter-" or "intra-"molecular and will now be discussed under these headings.

1.2) Intermolecular 1,3-Dipolar Cycloadditions

The mechanism of 1,3-dipolar cycloadditions has been extensively studied by Huisgen *et al.*[1-3] Common mechanistic features are exhibited by all reactions of this type i) they are not markedly influenced as to rate or stereochemistry by solvent polarity, ii) they show low enthalpies of activation, iii) they show large negative entropies of activation, iv) they produce five membered rings in which the olefin stereochemistry is retained, and v) reaction rates are markedly increased by conjugation of the dipolarophile, but reduced by the steric effects of all types of substituent.

The mechanism of 1,3-dipolar cycloaddition has been the subject of much controversy, the basic problem being the alternative propositions of a concerted and a two step mechanism (Scheme 2).

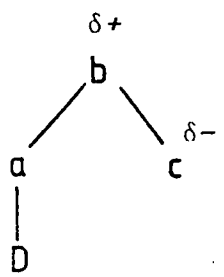


Scheme 2

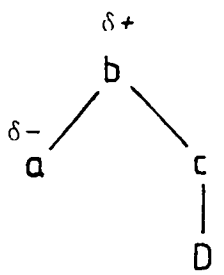
Originally Huisgen[1,2] proposed a concerted [3+2] mechanism, involving a cyclic transition state, but no discrete intermediate, basing his argument on the *cis* stereospecificity of the cycloaddition. The subsequent publication of the Woodward-Hoffmann rules[4], showing that Huisgen's mechanism was allowed by orbital symmetry, provided a theoretical basis for this mechanism. However, an alternative mechanism has been proposed by Firestone[5] as a two step process involving the formation of a discrete spin paired diradical intermediate as the rate determining step. The fact that the stereochemistry of the addition was *cis* was explained by the assertion that ring-closure was a more favoured pathway energetically than bond rotation. Conjugation and solvent effects were also shown to favour the diradical intermediate although Huisgen explained these as being due to synchronous, but not simultaneous, two bond formation. Firestone also claimed that the orientation could be predicted by considering "the best looking" of the four possible diradical intermediates, taking into account steric, kinetic and σ bond energy factors, a problem which the concerted mechanism could not explain. Firestone did however admit that the factors governing radical formation and stability were so poorly understood that few accurate predictions could be made. The reply by Huisgen[6] strongly defended the concerted mechanism on stereochemical, energetic and electronic grounds, while acknowledging that orientation remained an unsolved problem.

In 1972, the diradical mechanism was presented by Firestone[7], his arguments based on two main considerations. Firstly, the predominant unidirectionality of orientation exhibited by most

1,3-dipoles toward both electron-rich and electron-poor dipolarophiles conflicted with the concerted mechanism but was in accord with the diradical mechanism. This was based on the consideration of the possible diradical intermediates (1) and (2) in the reaction as Linnett structures.[8]

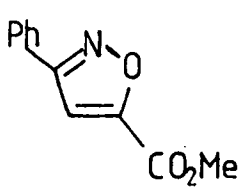


(1)

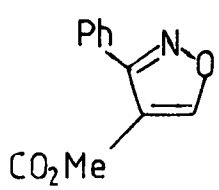


(2)

These have partial formal charge, with the more stable diradical being that in which the more electronegative atom bears the most electronegative charge. This will then be the favoured diradical irrespective of whether the dipolarophile (D) is electron withdrawing or donating, and hence the unidirectionality of the orientation regardless of the nature of dipolarophile. The second factor favouring the diradical mechanism was steric, although earlier this had been one of the cornerstones in the interpretation of orientation according to the concerted mechanism.[1,2] Thus, the regioselectivity of (3) over (4) of 72% was actually rationalised as being due to steric interaction.



(3)



(4)

However, when the phenyl ring was replaced by hydrogen, the regioselectivity of (3) over (4) increased to 84% instead of decreasing, which cannot be accommodated by the concerted mechanism on steric grounds. Firestone therefore concluded that, apart from the stereospecificity, the weight of evidence favoured the diradical mechanism.

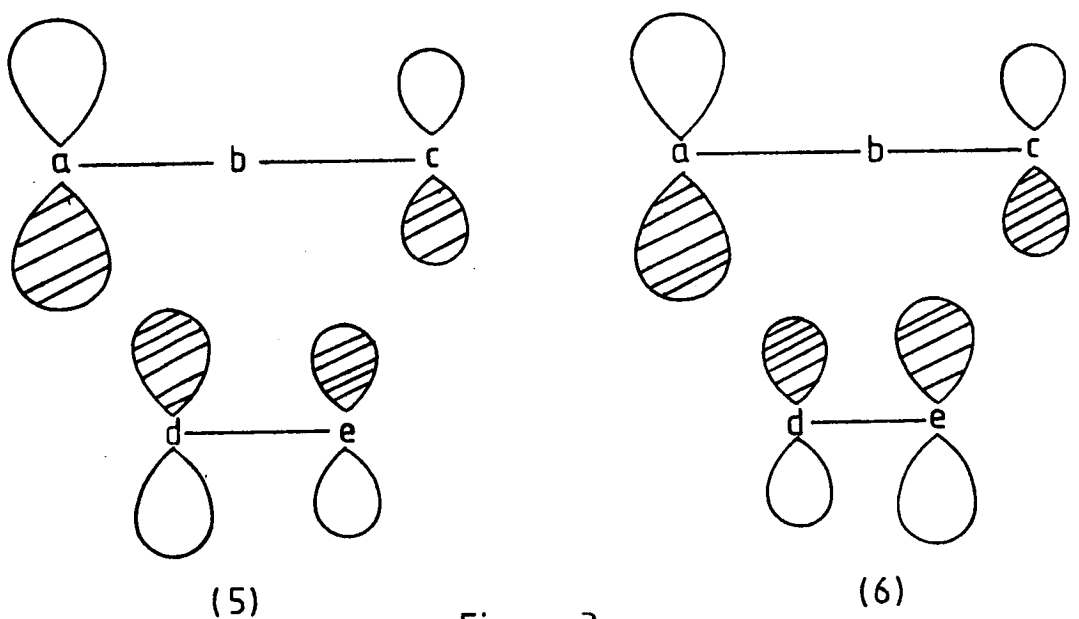
In 1973 however, Houk and co-workers[9,10] developed a new and powerful method which rationalised substituent effects on rates, regioselectively and periselectivity of concerted 1,3-dipolar cycloadditions.

This was based on perturbation theory and utilised the relative energies and coefficients of the frontier orbitals of the interacting 1,3-dipoles and dipolarophiles which were calculated by CNDO/2. The calculated orbital energies were then adjusted with the help of known ionisation potentials and $\pi \rightarrow \pi^*$ transitions. Fukui[11] had earlier postulated that reactions take place in the direction of maximum frontier orbital overlap i.e. between the HO (highest occupied) and LU (lowest unoccupied) orbitals. Therefore, in the concerted cycloadditions the favoured orientation will be that in which the centres whose frontier orbitals have the largest coefficients interact.

For diazomethane, the squares of the products of the CNDO/2 calculated frontier orbital coefficients, interacting with a dipolarophile at 175 pm separation, were as follows:-

	HO			LU		
$N\equiv\overset{+}{N}-\overset{-}{C}H_2$	N	N	CH_2	N	N	CH_2
	0·85	0·04	1·57	0·56	1·12	0·66

It can be seen from this calculation that the two termini have different orbital coefficients (as do the termini of unsymmetrical dipolarophiles d-e). The sizes of these coefficients can be represented pictorially as lobes. Thus, when 1,3-dipolar cycloaddition occurs, two possible transition states (5) and (6) may be visualised (Fig.3) depending on the relative orientation of dipole and dipolarophile. The preferred transition state will always be that in which the larger orbital coefficients interact, in this case (5).



(5) (6)

Figure 3

Since the relative energies of the HO and LU orbitals are determined by the substituents, and are the chief factors in determining the mode of regioselectivity and rates of reaction. Houk was able to achieve a complete rationalisation of the observed results in terms of substituent effects. Huisgen[12] used this molecular orbital perturbation treatment as additional support for the concerted mechanism besides refuting the earlier diradical arguments of Firestone, who, however retains his convictions. He has argued[13] that perturbational molecular

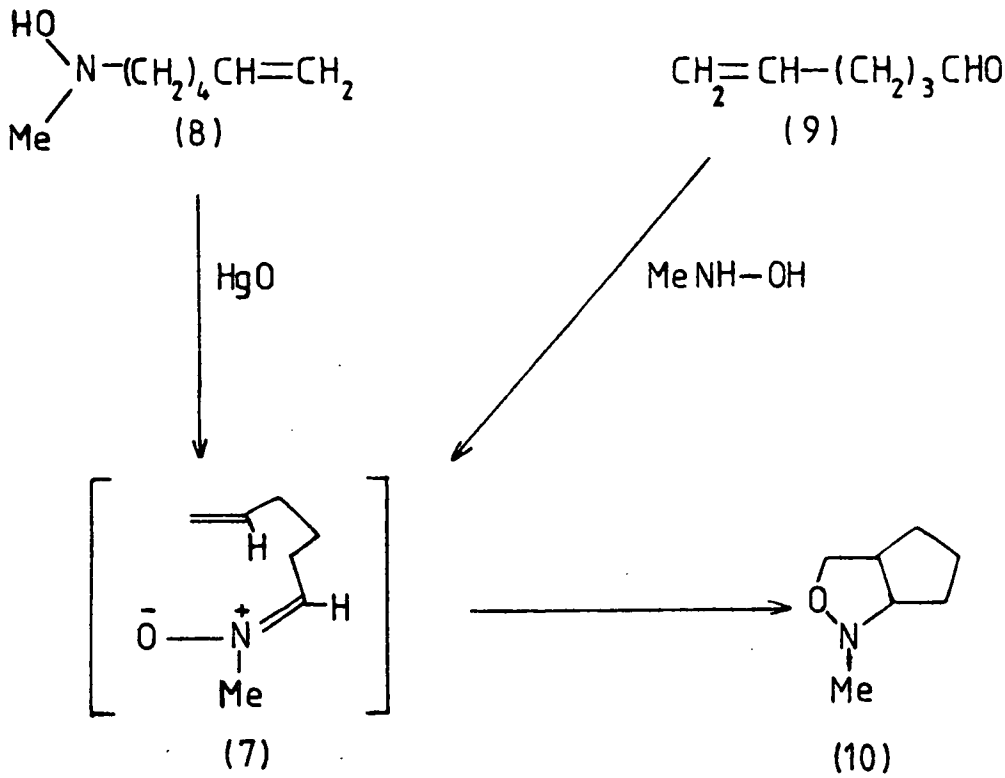
orbital theory bases its predictions on ground state interactions between reactants, and maintains that calculations of ground state orbitals are meaningless when the transition state lies more than 30-70 kJ/mole above the ground state in energy. It seems at the present time, that the concerted mechanism is the more likely for 1,3-dipolar cycloaddition.

However, despite the continuing controversy, the usefulness of the intermolecular cycloadditions of 1,3-dipoles to form five member heterocycles remains unquestioned. Numerous papers and reviews have dealt with 1,3-dipolar cycloaddition with alkenes[1] and alkynes[14] as well as other double bond functions,[15] but since these are not directly relevant to this thesis it is not intended to include a detailed discussion of them here.

1.3) Intramolecular 1,3-Dipolar Cycloadditions

In an intramolecular cycloaddition reaction, both the dipole and the dipolarophile are incorporated in the same molecule. The cyclisation occurs as in the intermolecular case by a [3+2→5] mechanism to form a product containing a five membered ring. Two reviews[16,17] on intramolecular cycloaddition have been recently published and many papers have reported the use of this reaction in the synthesis of natural products.[18,19] Nitrones, diazoalkanes, azides, azomethine imines, nitrile imines, nitrile ylides, carbonyl oxides and nitrile oxides have been shown to undergo such intramolecular cycloadditions.[16]

For example the nitrone (7),[20] prepared from either oxidation of a *N*-alkenylhydroxylamine (8) by mercuric oxide or condensation of an unsaturated aldehyde (9) with *N*-methyl hydroxylamine gave a fused bicyclic isoxazolidine (10).



1.4) Electrocyclic Reactions

When a 1,3-dipole and the dipolarophile are present in the same molecule and are in conjugation then another type of 1,3-dipolar intramolecular cycloaddition[67] can occur, which is known as an electrocyclic reaction. An electrocyclic reaction is defined[21] as one in which an unsaturated system undergoes a ring closure in a process that can be regarded as a cyclic electron shift, its net result being the conversion of a π bond into a σ bond. It is in principle a reversible process and cyclic systems can open by electrocyclic ring opening to give polyenes. (Figure 4)

Electrocyclisation reactions can occur in both neutral and charged species of various ring sizes.[21,31] 1,3-Dipolar electrocyclic reactions fall into three main classes; 1,3-retro-electrocyclisation (4π), 1,5-electrocyclisations (6π)

Figure 4

and 1,7-electrocyclisations (8π).

1,3-Retro-electrocyclisations are of great use in the generation of 1,3-dipoles especially nitrile ylides, azomethine ylides by the thermolysis of aziridines,[22,23] azomethine imines by the thermolysis of diaziridines[24,25] and carbonyl ylides by the thermolysis or photolysis of oxiranes.[26-28] (Figure 5)

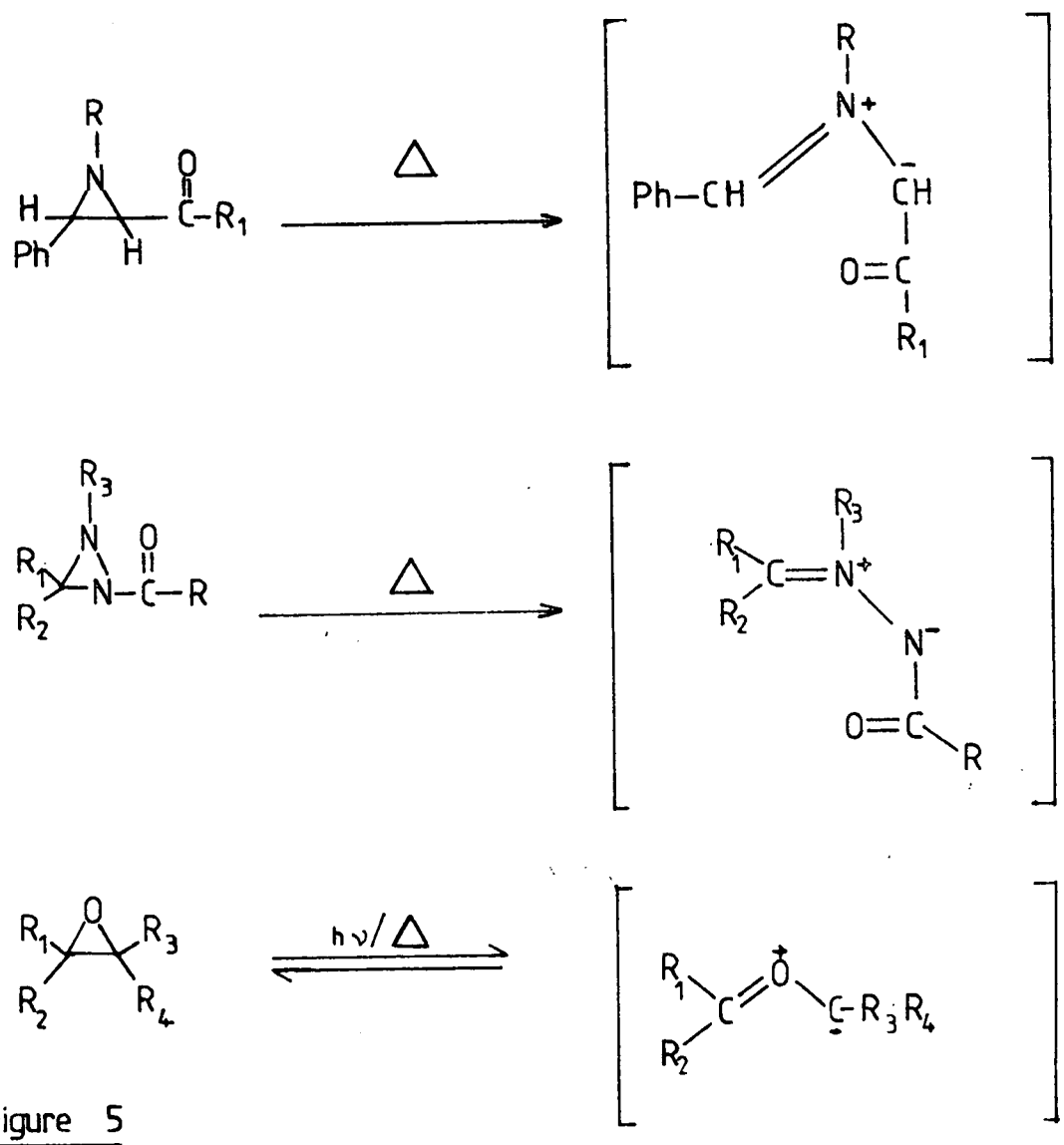
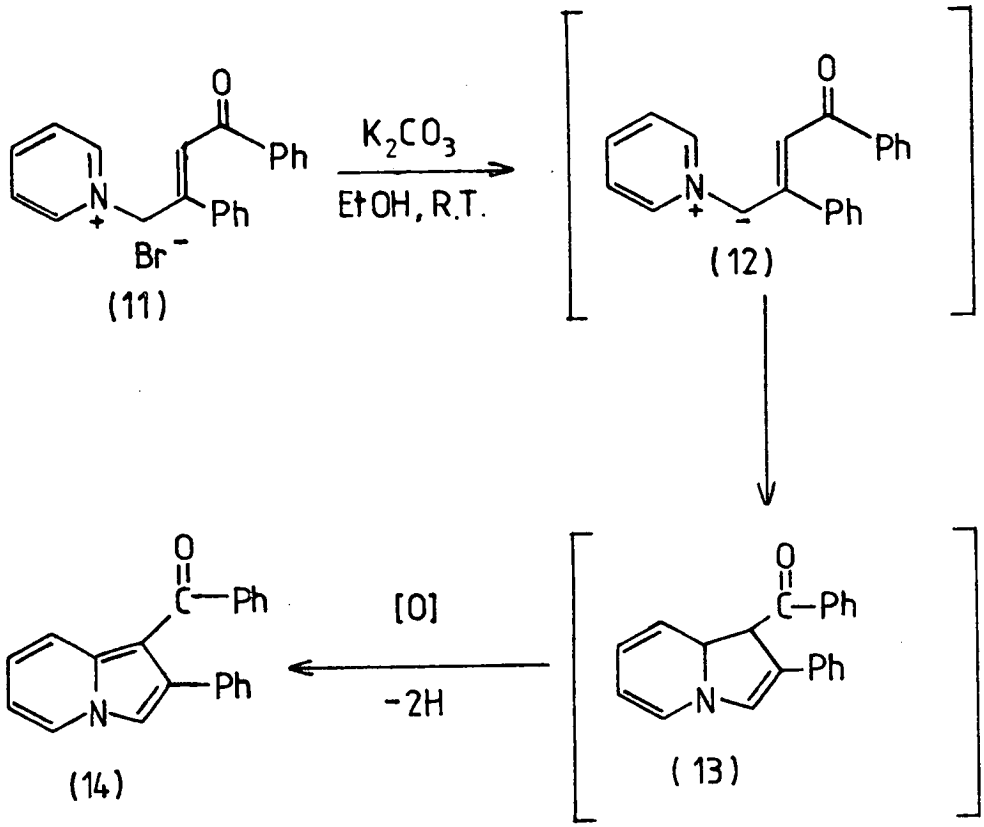


Figure 5

1,3-Dipoles of both propargyl-allenyl and allyl type when conjugated with a double bond are capable of 1,5-electrocyclisations (6π) to form charge free unsaturated five-membered rings, for example the formation of 1,3,4-oxadiazole from the carbonitrile imine[29] (Figure 6). At least eight allyl type of 1,3-dipoles and four propargyl-allenyl type 1,3-dipoles (nitrile ylides, nitrile imines, diazoalkanes and azides) are known to undergo reactions of this type.[29,67]

Figure 6

The conjugated double bond in these systems has included C=C, C=S, C=N and C=O. 1,5-Electrocyclisation of 1,3-dipoles has been used with great success in the synthesis of many monocyclic and fused unsaturated, aromatic and heteroaromatic ring systems which have been the subject of excellent reviews.[29, 31] In many cases the primary cyclisation product may undergo rearrangement or oxidation to more thermodynamically stable aromatic compounds. For example, the azomethine ylide (12) generated by base-induced elimination of hydrogen bromide from the pyridinium bromide (11) underwent a 1,5-electrocyclisation to the dihydroindolizine (13) which was not isolable but spontaneously oxidised to the stable aromatic indolizine (14) in 90% yield.[30]

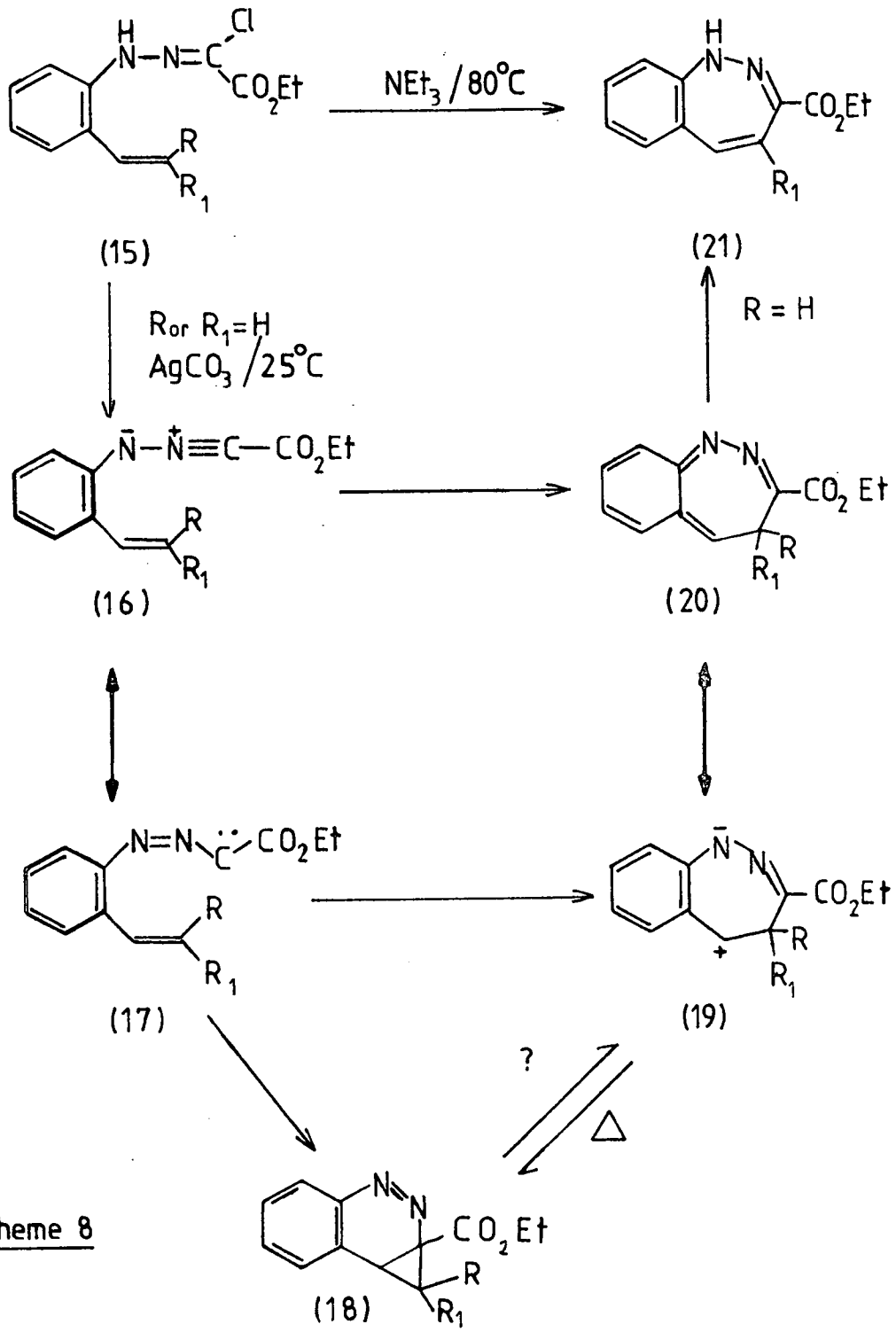


Scheme 7

1,7-Electrocyclisation is the least well studied type of electrocyclic reaction of 1,3-dipoles. It involves the 8π-electron cyclisation of an α,β:γ,δ-unsaturated unit conjugated to a 1,3-dipole, and at present only three propargyl-allenyl type dipoles (nitrile imines, nitrile ylides and diazoalkanes) and only one allyl type dipole (carbonyl ylides) have been shown to undergo such electrocyclisations. Diazoalkane and nitrile ylide 1,5-and 1,7-electrocyclisations will be discussed in detail later.

The formation of the 1,2-benzodiazepines (21) from α,β:γ,δ-unsaturated nitrile imines (16) can be rationalised as a 1,7-electrocyclisation reaction.[32,33] These diazepines are obtained when the reaction is carried out at 80°C and when one of the terminal groups of the alkene is hydrogen. Their

formation could result from a direct 1,7-electrocyclisation to (20) followed by a [1,5]sigmatropic hydrogen shift to (21). However when the reaction is carried out at room temperature using silver carbonate as the base the cyclopropa[c]cinnolines



Scheme 8

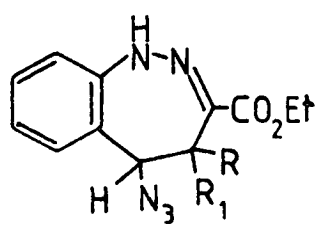
(18) may be isolated in high yield. These may be converted into the 1*H*-1,2-benzodiazepines (21) on heating provided that R or R_1=H. Formation of the cyclopropa[c]cinnoline is stereospecific, the *E* starting nitrile imine giving only the *exo* product.

The isolation of the cyclopropa[c]cinnoline intermediate (18) in the low temperature reaction and its subsequent rearrangement to the 1*H*-1,2-benzodiazepine raise some doubts that a simple 1,7-electrocyclic reaction is the primary step in the above scheme (Scheme 8). However, evidence for a nitrile imine precursor was obtained by trapping of the 1,3-dipole (16) with methyl acrylate, and so an alternative mode of reaction involving the 1,3-dipolar species was postulated. The mechanism favoured involves the 1,1-intramolecular cycloaddition of the carbene form of the nitrile imine (17) to form the cyclopropane ring. Precedent for this mechanism exists as nitrile imines have been shown to undergo 1,1-intramolecular cycloaddition to non conjugated double bonds, *via* the carbenic resonance form, when certain geometric constraints are imposed.[33, 35] The formation of (18) would be stereospecific and account for the formation of specific *exo*+*endo* isomers as it closely parallels the stereospecific addition of singlet carbenes to olefins.[34] The cyclopropa[c]cinnoline (18) could then ring open by an electrocyclic ring opening to give the non aromatic intermediate (20) followed by a [1,5]sigmatropic hydrogen shift to give (21).

An alternative mechanism has been suggested for the generation of (18) by stepwise nucleophilic attack of the terminal double bond on the electron-deficient carbon of the

nitrile imine (17) to generate a seven-membered ring dipole which contains a benzylic carbonium ion as well as an azallyl anion moiety. This is however mechanistically equivalent to the 1,7-electrocyclisation discussed earlier with (19) simply a canonical form of (20). Collapse of this intermediate can be viewed as a disrotatory 1,6-electrocyclisation process similar to that in the rearrangement of diazacycloheptatrienes to diazanorcaradienes.[36] As long as the 1,6-electrocyclisation is fast relative to ring flipping then the 1,1-cycloaddition will proceed with retention of configuration.

Evidence exists for the involvement of the intermediate (19/20) in the formation of the cyclopropa[c]cinnoline ring by the fact that it can be trapped with added nucleophiles such as azide or acetate to give, for example, 5-azido-4,5-dihydro-1*H*-1,2-benzodiazepines (22)[37,38].

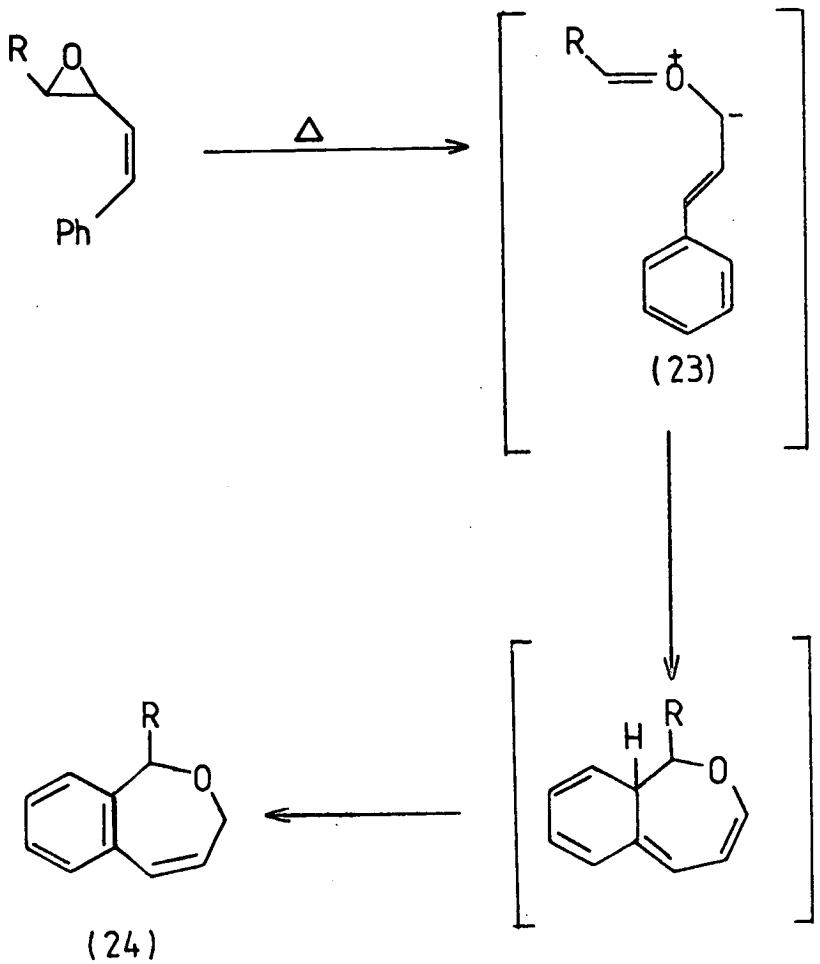


(22)

Thus the mechanism at present is not clear but it is thought that the primary step is more likely to be *via* a stereospecific 1,1-cycloaddition followed by ring expansion to (20), rather than a 1,7-electrocyclisation. This is discussed in greater detail in the Discussion section.

The only example of allyl type dipoles undergoing 1,7-electrocyclisation is reported by Eberbach[39-41]. Several

styryloxiranes were thermally transformed to the carbonyl ylides (23) which underwent a 1,7-8π electrocyclisation followed by [1,5]sigmatropic hydrogen shift to 2,7-dihydro-3,4-benz-oxepines (24) (Scheme 9).



Scheme 9

2.) DIAZOALKANES

2.1) Properties and Synthesis of Diazoalkanes

Diazoalkanes are 1,3-dipolar species best represented as a resonance hybrid, comprising linear structures with opposing dipoles (see Section 1, p. 2). The first known diazoalkane was diazoacetic ester prepared by Curtius[42] in 1883 by treatment of glycine ethyl ester hydrochloride with potassium nitrite.

$$C_2H_5CO_2CH_2\overset{+}{N}H_3\bar{C}l \xrightarrow{KNO_2} C_2H_5CO_2CH{=}N_2 + KCl + H_2O$$

The simplest diazoalkane, diazomethane (CH_2N_2) is a highly toxic, yellow gas, explosive at room temperature. It has been shown to have a linear, planar structure by electron diffraction[43] and microwave spectroscopy[44]. The resonance hybrid structure is supported by bond lengths ($\rangle C \underset{}{\overset{1.300}{}} N \overset{1.139}{} N$) and ^{13}C n.m.r. spectroscopy[45] shows that the carbon has a high electron density (δ23.1), showing a large contribution from structures with a negative charge on carbon.

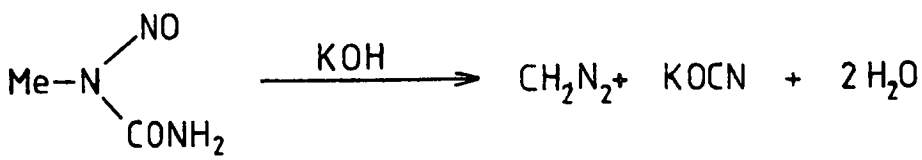
The thermal stability of higher homologues depends markedly on the nature of substituents. Conjugating substituents, regardless of whether they are electron releasing or electron withdrawing, increase stability. Non-conjugating electron withdrawing substituents increase stability as they favour a resonance structure having a formal carbanion ($R_2\bar{C}\text{-}\overset{+}{N}_2$), whereas non-conjugating electron releasing substituents decrease stability as they favour a formal positive charge on carbon ($R_2\text{-}\overset{+}{C}\text{-}\bar{N}_2$). Consequently, although diazomethane and diazoethane are unstable

gases under normal atmospheric conditions, diazoalkanes having carbonyl, aryl, nitrile or fluorinated substituents are more stable and may be handled conveniently as liquids or solids.

Synthesis

The original method of Curtius[42], the diazotisation of amines, requires a strongly electron withdrawing substituent on the α-carbon of the amine, and also an α hydrogen.

The classical method of preparation of diazoalkanes involves treatment of a nitroso compound of the general formula $R.CH_2.N(NO).X$ with a suitable base to yield the diazomethane $RCH{-}N_2$. For example diazomethane is readily prepared by treating *N*-nitroso-*N*-methylurea (25) with base.[46]



(25)

Disubstituted diazo alkanes can be prepared by the oxidation of ketone hydrazones (26) with a variety of reagents including manganese dioxide[47], lead tetra-acetate[48], and mercuric oxide.[49]

(26)

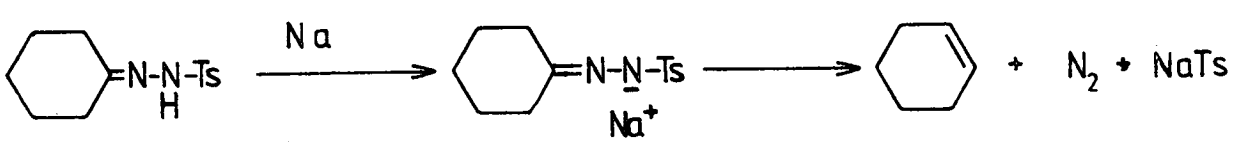
Hydrazones can also be converted into diazoalkanes by treatment with toluene-*p*-sulphonyl azide[50].

(26)

The method used in this research for preparation of diazoalkanes involves the base induced decomposition of tosylhydrazones which is discussed in detail below.

Base Induced Decomposition of Tosylhydrazones

It was shown by Bamford and Stevens[51] that heating of non-enolisable tosylhydrazones with base gave diazo compounds or products of their decomposition e.g. olefins.

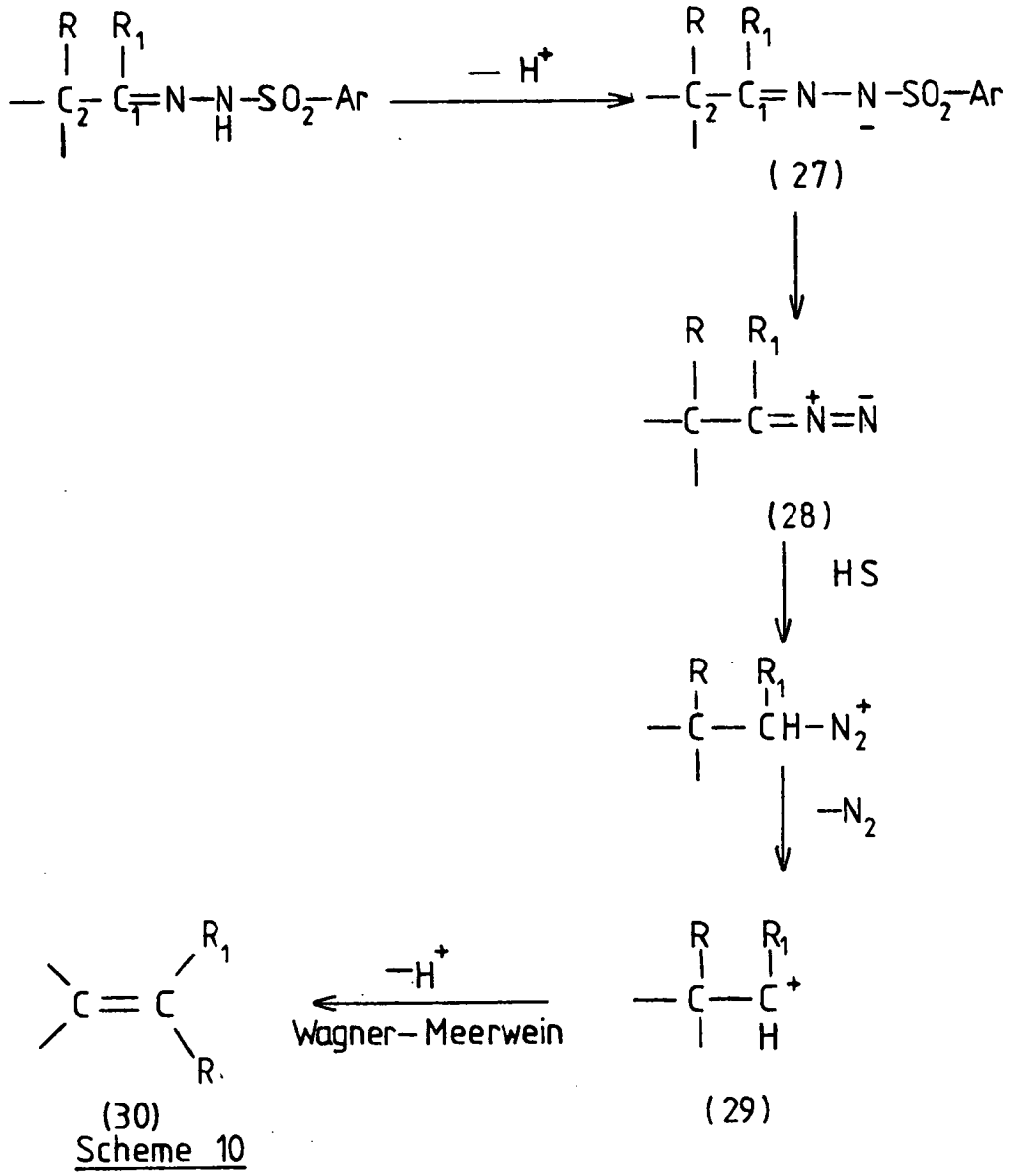


At lower temperatures substantial yields of the diazo-compounds could be obtained, from the tosylhydrazones of aromatic aldehydes and ketones.

The mechanism of the Bamford-Stevens reaction has been intensively studied and several reviews have appeared.[53-56] A large number of parameters are important, including the ability of the solvent to donate and accept protons and the nature and concentration of base.

The rate determining step of tosylhydrazone decomposition was shown by Whiting[57] to be the unimolecular elimination of *p*-toluenesulphinyl anion from the anion of the tosylhydrazone (27) to give an aliphatic diazo compound (28). It was also shown that in protic solvents protonation of the diazoalkane (at C-1) can occur followed by loss of nitrogen to give a carbonium ion which may then undergo a Wagner-Meerwein migration of a group from C-2 and loss of H^+ to give an olefin[57] (Scheme 10).

In addition Shapiro and co-workers[58] investigated the effect of base concentration and concluded that when a deficiency of base is used the unreacted tosylhydrazone acts as a proton donor so that an equilibrium between the diazonium cation and the diazocompound is set up which lies on the side of the cationic species, and thus carbonium ion products predominate. When equimolar base is used the equilibrium lies on the diazoalkane side and so diazoalkane and products of their decomposition predominate.

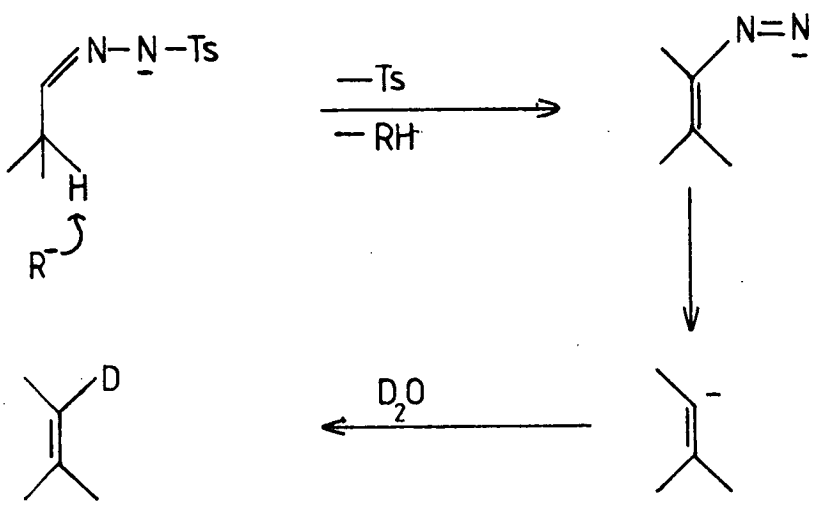


(30)

Scheme 10

Shapiro[59] and Friedmann[60] also showed that if excess strong base, such as alkyl lithium reagents, are reacted with tosylhydrazones at low temperature, then diazocompounds were not involved but that an entirely different mechanism operated (Scheme 11). Both workers showed that tosylhydrazones with α-hydrogen atoms gave good yields of alkenes. Deuterium was

incorporated into the product when the reaction was quenched with deuterium oxide, in accord with the mechanism shown (Scheme 11). The existence of the vinyl carbanion intermediate was confirmed by Shapiro[61] by chemically trapping the intermediate from fluorenone tosylhydrazone with deuterium oxide, ethyl bromide and carbon dioxide, to give 9,9-disubstituted fluorenes. This reaction has since been much used as a source of vinyl carbanions.



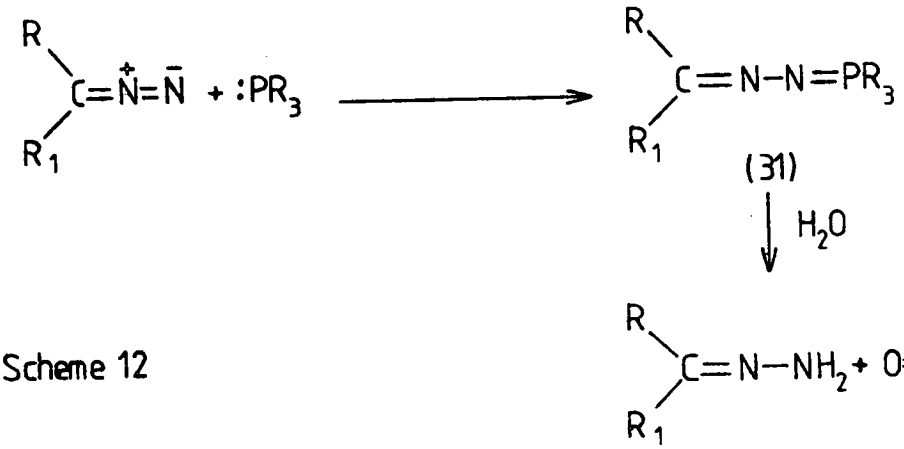
Scheme 11

An alternative to thermal generation is the decomposition of arylsulphonylhydrazone salts by ultraviolet irradiation to give diazoalkanes. This is known as the photic Bamford-Stevens reaction and recently the first isolation of a diazo intermediate from this photic reaction has been reported.[52]

Reactions

Diazoalkanes can sometimes be observed in reactions by their red coloration. They can be chemically trapped by their

reaction with alkylphosphines[62] forming phosphazines which on hydrolysis gave a hydrazone and phosphine oxide (Scheme 12).



Scheme 12

The last forty years has seen much interest in diazoalkane chemistry which has been reviewed[63,64]. Much of this interest has derived from the ability of diazoalkanes to form carbenes *via* loss of nitrogen. However, another important aspect of diazoalkene chemistry is their ability to react without loss of nitrogen, undergoing "intermolecular" or "intramolecular" 1,3-dipolar cycloaddition.

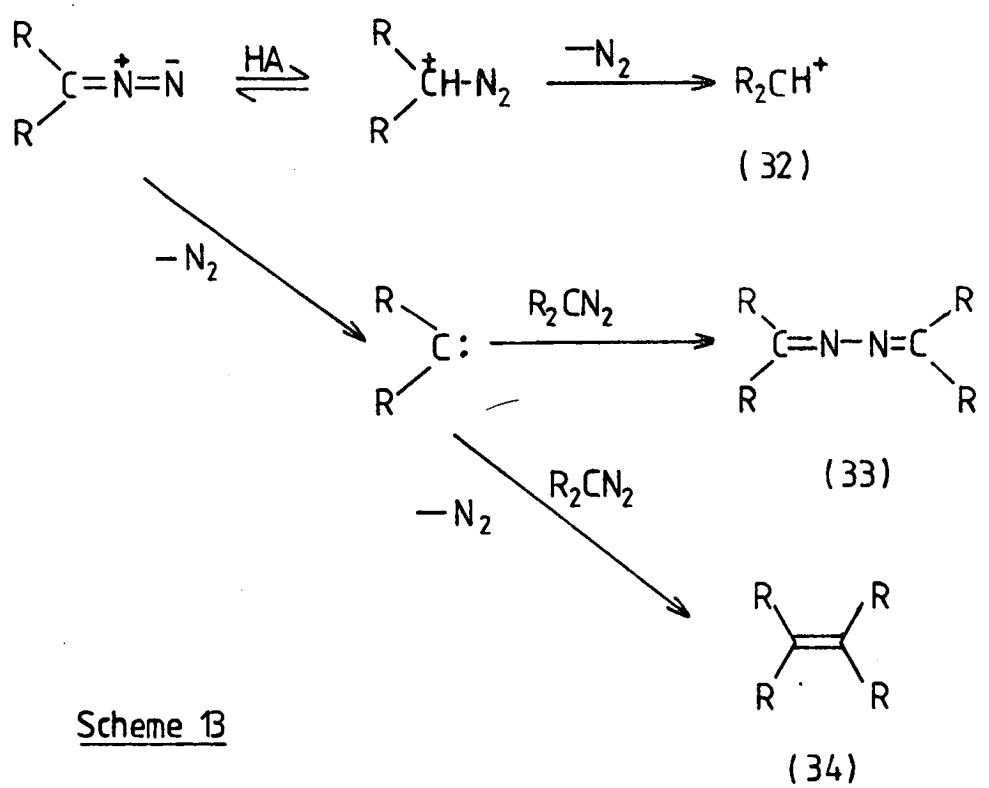
2.2) Carbene Formation

Carbenes are highly reactive, neutral species (R_2C:) in which carbon is attached to two groups by covalent bonds and has two non-bonding electrons. These may have parallel spins and occupy different orbitals (triplet state) or be spin paired (singlet state).

Carbenes practically all have lifetimes considerably less than 1 second, and can undergo a wide variety of reactions, including additions to olefins, aromatic systems, and other

double and triple bond systems; insertions into carbon-hydrogen bonds; abstraction of hydrogen; rearrangements and dimerisation.

The reactions of carbenes have been fully documented[55,56] and carbenes are now recognised as the most common intermediates in the photochemical and thermal decompositions of diazoalkanes. One of the uncertainties of the photic Bamford-Stevens route to carbenes is that some of the products may be formed directly by reactions of the excited diazoalkane rather than *via* the carbene.[52] This slight complication is absent in the production of carbenes by the thermolysis of diazoalkanes, but there are three common side-reactions of the ground state diazoalkane which interfere with carbene generation (Scheme 13). Firstly diazoalkanes are susceptible to protonation and carbenium ion production *via* loss of nitrogen. Also carbene attack on the diazoalkane can occur, both with retention of nitrogen to give the azine (33) or with loss of nitrogen to give a dimer (34), actual dimerisation being statistically unlikely.

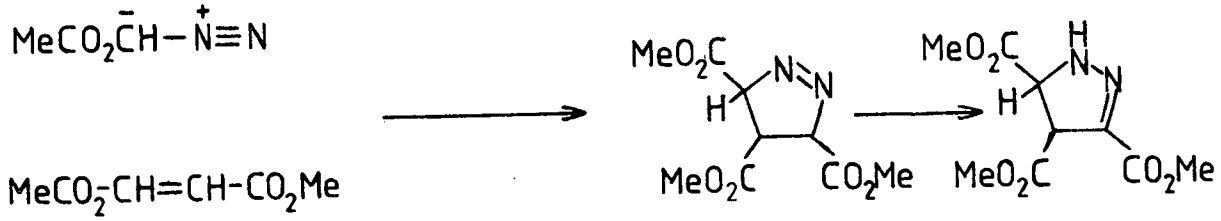


Scheme 13

In addition, the diazoalkane can add as a 1,3-dipole to any alkene or alkyne present to give pyrazolines or pyrazoles which may subsequently extrude nitrogen to give what are apparently carbene-derived products.

2.3) Intermolecular 1,3-Dipolar Cycloadditions

Formation of five-membered ring cycloadducts has been known since 1888[65] when Bucher observed the addition of diazoalkanes to α,β-unsaturated esters to form 1-pyrazoline (35) which underwent rearrangement to the more stable 2-pyrazoline (36). Diazoalkanes readily react with sites of unsaturation to give five-membered rings which frequently undergo rearrangements, oxidation or extrusion reactions to give more stable, often aromatic, products.

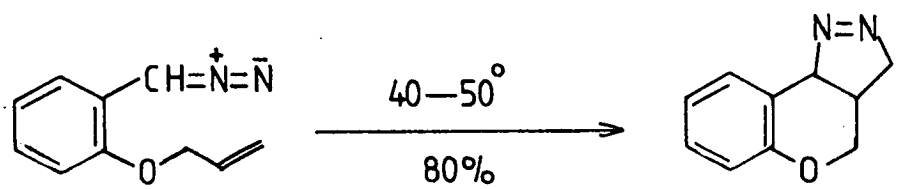


Scheme 14 (35) (36)

Diazoalkanes are known to undergo intermolecular 1,3-cycloaddition with alkenes[1,2] to form pyrazolines, alkynes[14,78] to form pyrazoles and other unsaturated functions[15] which will not be discussed further as they are not of direct relevance to this thesis.

2.4) Intramolecular 1,3-Dipolar Cycloaddition

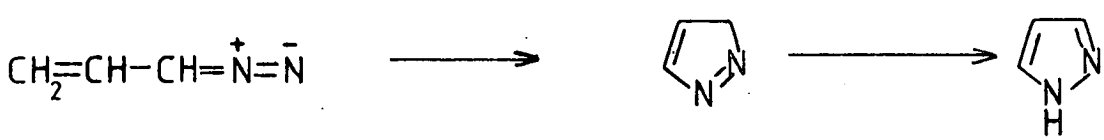
The first example of 1,3-dipolar cycloaddition was reported by Kirmse[66] who reported the synthesis of the 1-pyrazoline (37) in 80% by the thermal decomposition of the corresponding tosylhydrazone sodium salt.



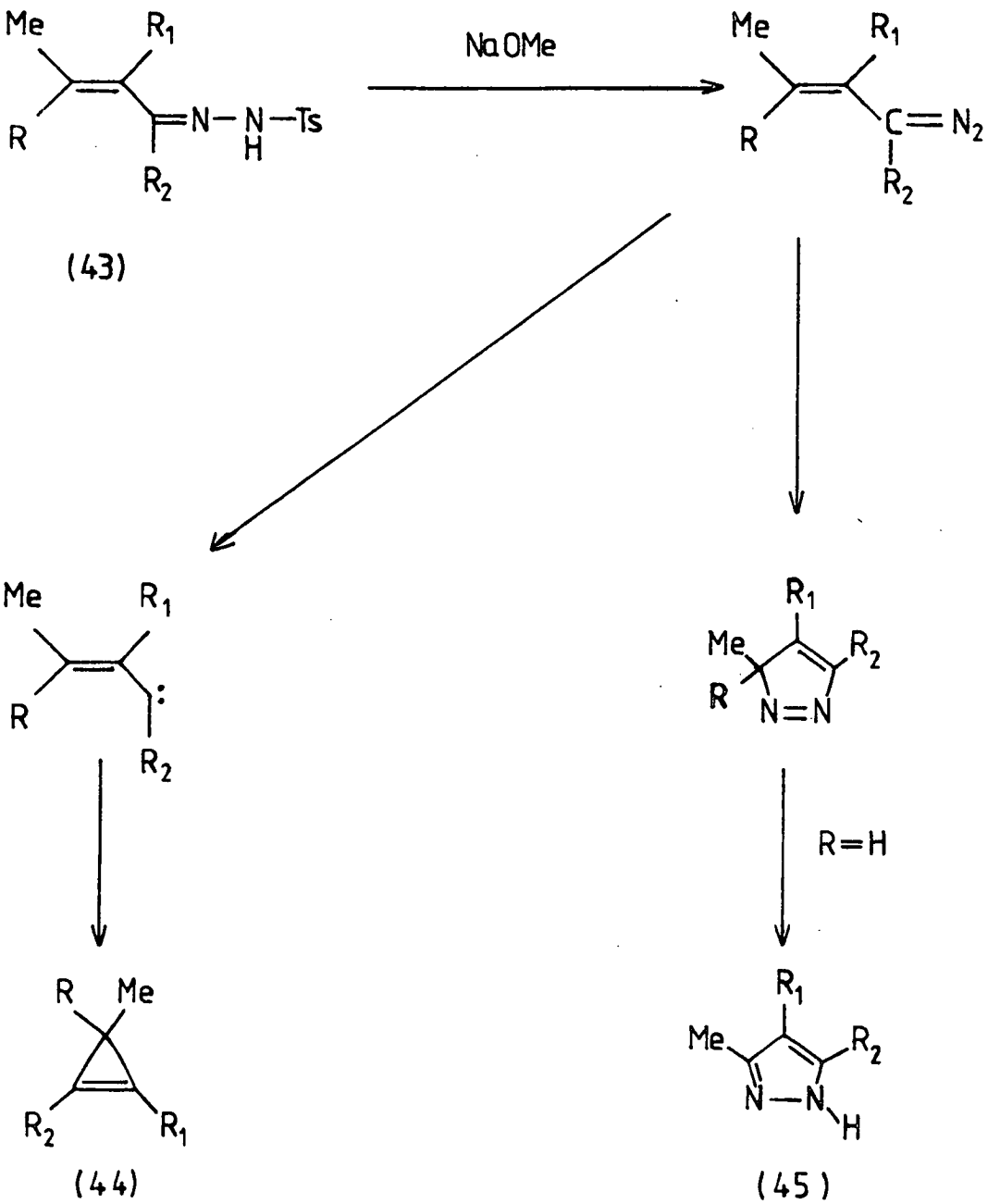
(37)

Many other examples of intramolecular 1,3-dipolar cycloaddition [3+2→5] of diazo alkanes to carbon-carbon double bonds, to form fused five membered rings have been reported.[16,67]

Conjugated diazoalkanes also undergo 1,3-dipolar electrocyclisation reactions. The first such reaction was reported by both Adamson and Kenner[68] and Hurd and Lui[69] who showed that 3-diazopropene (38) reacts slowly at room temperature to give the 3*H*-pyrazole (39) which undergoes a [1,5] hydrogen shift to give the isolated 1*H*-pyrazole (40).



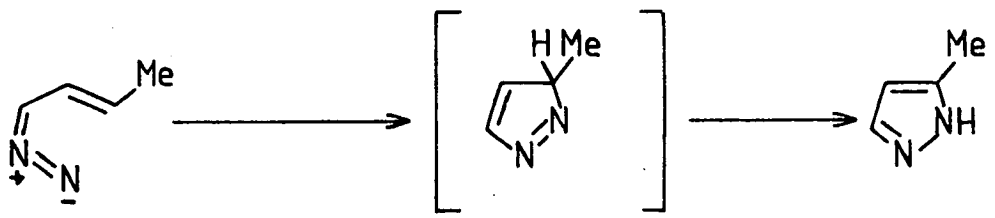
(38) (39) (40)



Compound	R	R_1	R_2	Yield (44%)	Yield (45%)
A	Me	Me	H	72	-
B	Me	H	Me	39	-
C	Me	H	H	50	-
D	H	Me	H	4	60
E	H	Me	Me	1.5	21
F	H	H	H	3	-

Scheme 15

The mechanism was investigated by Ledwith and Parry[70] who postulated the intermediacy of the 3*H*-pyrazole (39) on the basis that light of wavelength 3100-3800Å accelerated the cyclisation and as the diazoalkene itself is transparent in this region it cannot be the primary absorbing species. Adamson and Kenner[68] also reported that the red colour of an etheral solution of *trans*-1-diazo-2-butene (41) faded slowly at room temperature, the product being later identified[71] as 3(5)-methylpyrazole (42).

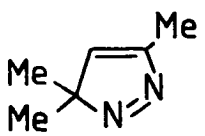


(41) (42)

In 1963, Closs, Closs and Boll[72] reported the formation of pyrazoles from the thermal decomposition of the tosylhydrazone salts of α,β-unsaturated carbonyl compounds. The decompositions of tosylhydrazones of type (43) (Scheme 15) in aprotic media at 160-220°C using sodium methoxide as base gave vinyldiazomethanes which subsequently gave alkyl substituted cyclopropenes (44), and in some cases pyrazoles (45).

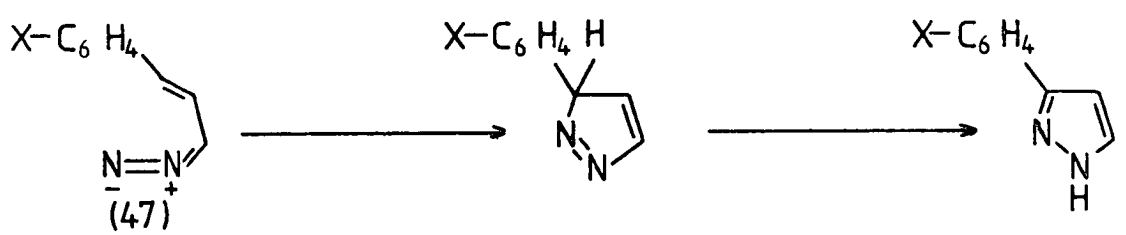
The possibility that the 3*H*-pyrazole could be an intermediate in cyclopropene formation was rejected as 3,3,5-trimethylpyrazole (46) was stable under the reaction conditions which formed cyclopropenes. This compound, with no hydrogens in the 3-position, was stable up to 180°C and did not isomerise or lose nitrogen. However, it did form a cyclopropene under

photolytic conditions *via* an electrocyclic ring opening to vinyldiazomethane followed by loss of nitrogen and cyclisation of the resulting carbene.[73]



(46)

It was thus deduced that diazoalkenes were intermediates in the formation of cyclopropenes, which was proved by isolation of the diazoalkenes from 43(A) and 43(B) by reducing the reaction temperature to 70-90°C. On subsequent pyrolysis these diazoalkenes gave cyclopropenes as before. It was also concluded by Hart and Brewbaker[74] that cyclisation of diazoalkenes (47) to pyrazoles was indeed an intramolecular, concerted 1,3-dipolar cycloaddition, as the reaction rate was increased by aryl conjugation of the double bond and showed insensitivity to substituents in the aryl ring.



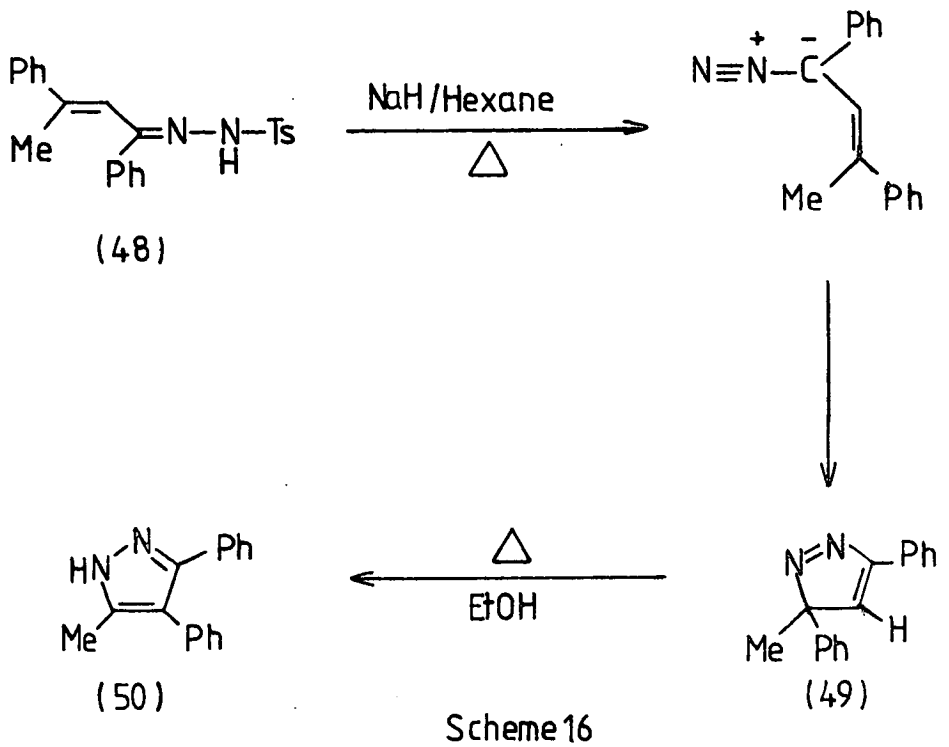
(47)

X = *m* NO_2, *p* Cl, *p* Me

The nature of the products obtained is highly dependent upon the structure of the tosylhydrazone. The difference in

behaviour in forming either pyrazole or hydrocarbon was postulated as being due to the degree of substitution at the β carbon of the tosylhydrazone. The yield of hydrocarbon is good where the β carbon is fully substituted with alkyl groups which sterically hinder cyclisation to the 3*H*-pyrazole and also accelerate elimination of nitrogen by electron release.

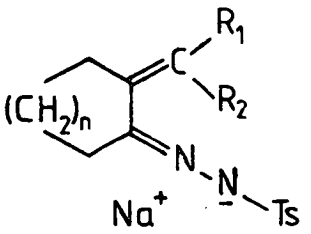
It was also shown that thermolysis in hexane in the presence of sodium hydride of β disubstituted tosylhydrazones (48) gave 3*H*-pyrazoles[75] (49). However these could be isomerised to 1*H*-pyrazoles (50) by heating in a protic solvent if one of the groups was migratable (i.e. Phenyl) (Scheme 16).



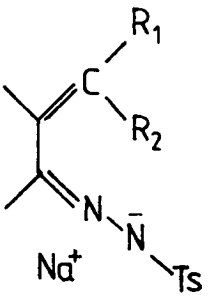
Scheme 16

1,5-Electrocyclisations of diazoalkanes to C=N, C=S and other carbon-carbon double bonds have been reviewed.[29,31]

Sharp and his co-workers[76] have investigated the electrocyclisation reactions of α,β:γ,δ-unsaturated diazoalkanes, generated from the thermal decomposition of sodium salts of tosylhydrazones of α-methylenecycloketones (51) and acyclic unsaturated ketones (52).

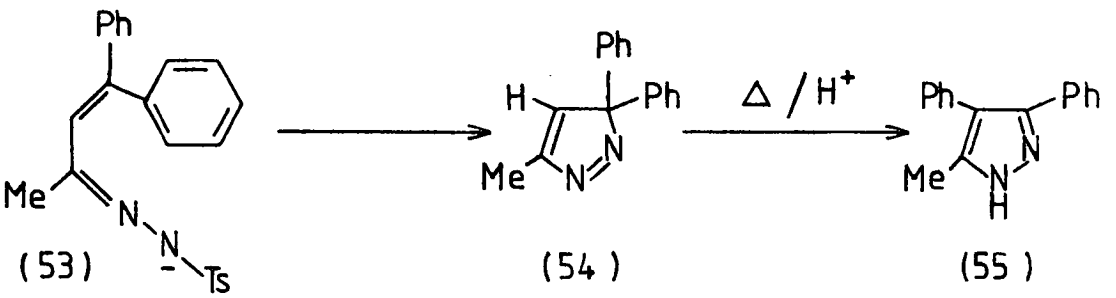


(51)



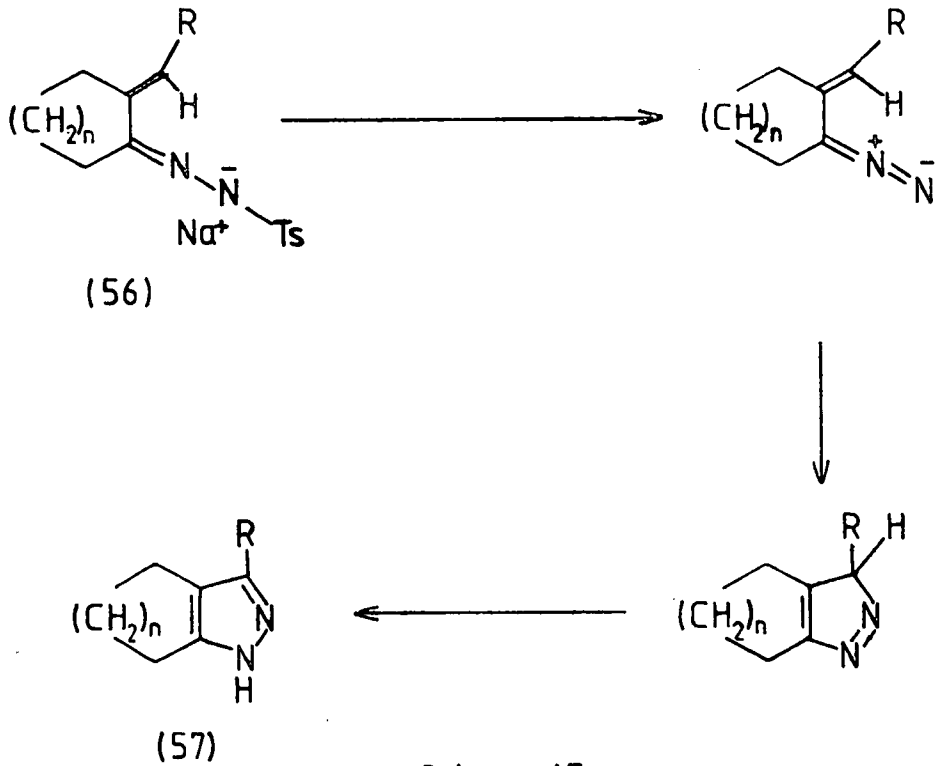
(52)

It was found that in the acyclic systems only pyrazoles were obtained, for example the cyclisation of (53) under aprotic conditions gave predominantely (54), which readily isomerised to (55) on contact with acid or on heating.



In the thermal decomposition of tosylhydrazone salts (51) the mode of reaction was found to be very dependent upon substituents R_1 and R_2 and on ring size.

The sodium salts of 2-ethylidenecyclohexanone (56; R=Me, n=2) and 2-ethylidenecyclopentanone (56; R=Me, n=1) both decomposed in aprotic solvent to give 1*H*-pyrazoles (57) (Scheme 17). In the cases where the double bond has only one *E* substituent the cyclisation showed no dependence on ring size, both the cyclopentanone and cyclohexanone derivatives giving the aromatic 1*H*-pyrazoles (60) in good yields, formed by the hydrogen migration of the less stable 3*H*-isomer (59).

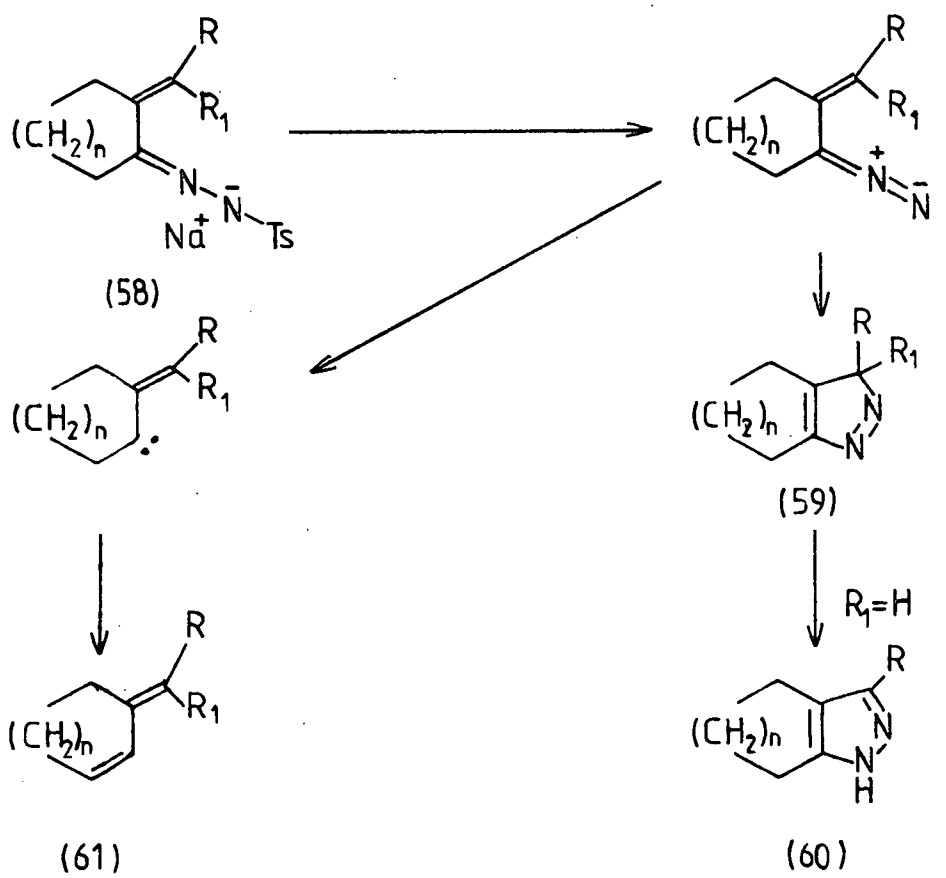


(56)

(57)

Scheme 17

However, when the double bond has two alkyl substituents the cyclohexanone derivatives (58; n=2, $R=R^1=(CH_2)_5$) gave 3*H*-



(58)

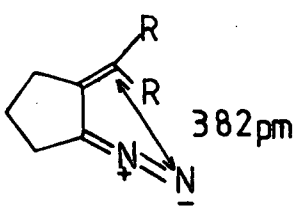
(59)

(61)

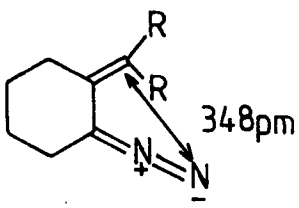
(60)

pyrazoles (59) whereas the cyclopentanone derivative (58; n=1, R =R_1=$(CH_2)_4$) gave no 3*H*-pyrazole but only carbene-derived dienes (61).

This decomposition of the cyclopentanone derivative *via* a carbenic route can be attributed to a steric affect inhibiting cyclisation rather than to an acceleration of the loss of nitrogen. For the formation of the 3*H*-pyrazole to occur the diazoalkane has to adopt a conformation in which all five atoms are coplanar, in which the diazoalkane is sufficiently distorted from its preferred linear configuration to allow cyclisation to occur. Models from Dreiding units showed a separation between the termini of the π system is about 35 pm greater in the five-membered ring (62) than in the six-membered ring (63). Therefore, the five-membered ring system would have



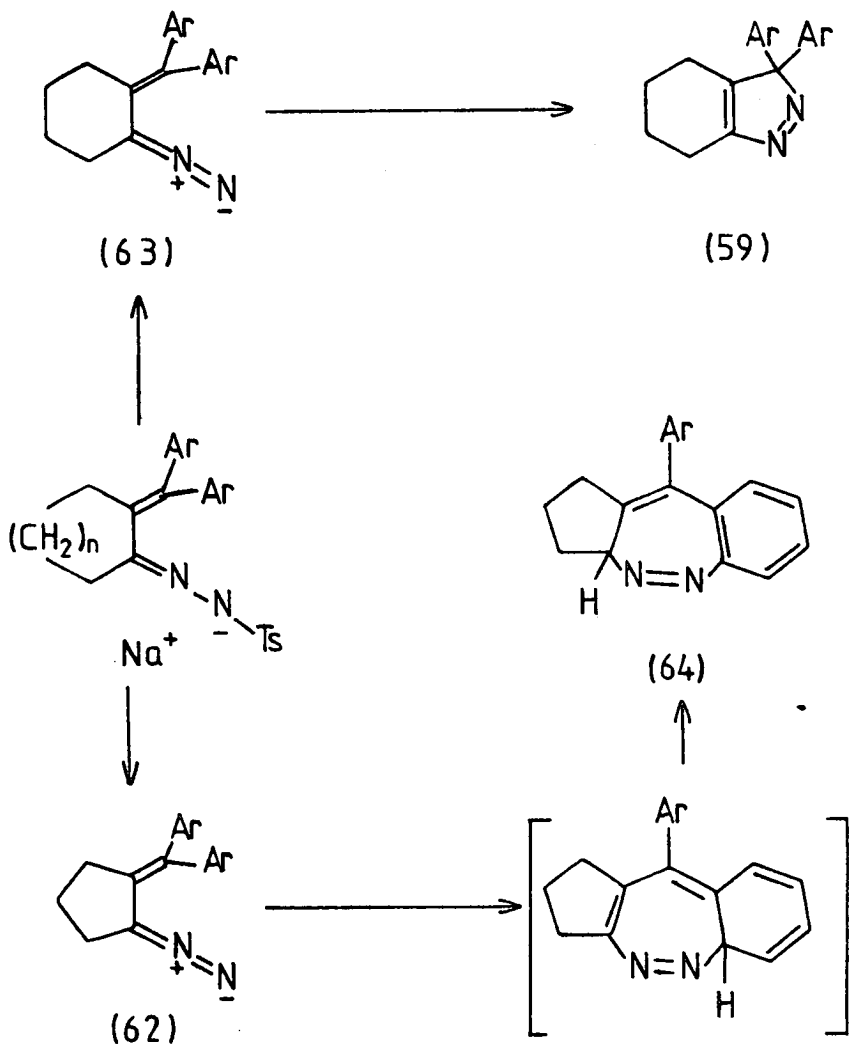
(62)



(63)

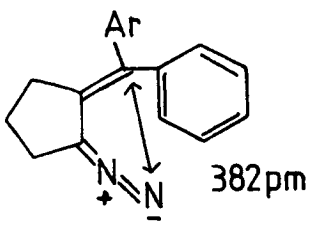
to undergo a greater bending of the diazo group from its preferred linear configuration to achieve cyclisation, and also would give a more strained 3*H*-pyrazole than that formed from the six-membered system. In the cases where 1,5-electrocyclisation is inhibited an energetically more favourable route is adopted which depends on the nature of the substituents at the terminus of the alkene. In dialkyl substituted cases carbene formation is favoured and in diaryl substituted cases the previously unknown 1,7-electrocyclisation, to give 1,2-

benzodiazepines (64) in substantial yields. (Scheme 18) is the preferred mode of reaction. The formation of 1*H*-pyrazoles (57, n=1) from mono-alkylmethylenecyclopentanone tosylhydrazones was thought to be due either to the higher stability of the aromatic final product or to the reduction in size of the *Z* substituent causing lower steric hindrance in the transition state.

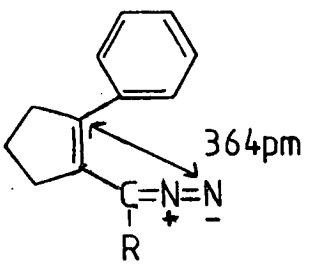


Scheme 18

These results indicated that the distance separating the diazo group and the double bond is one of the crucial factors in determining whether 1,5-or 1,7-ring-closure occurs. To prove this, Sharp[77] and co-workers investigated the reactions of the diazoalkanes derived from the tosylhydrazones of 1-acyl-2-arylcycloalkenes, (65), arguing that 3*H*-pyrazole formation would be less favoured in (62) than in (65).



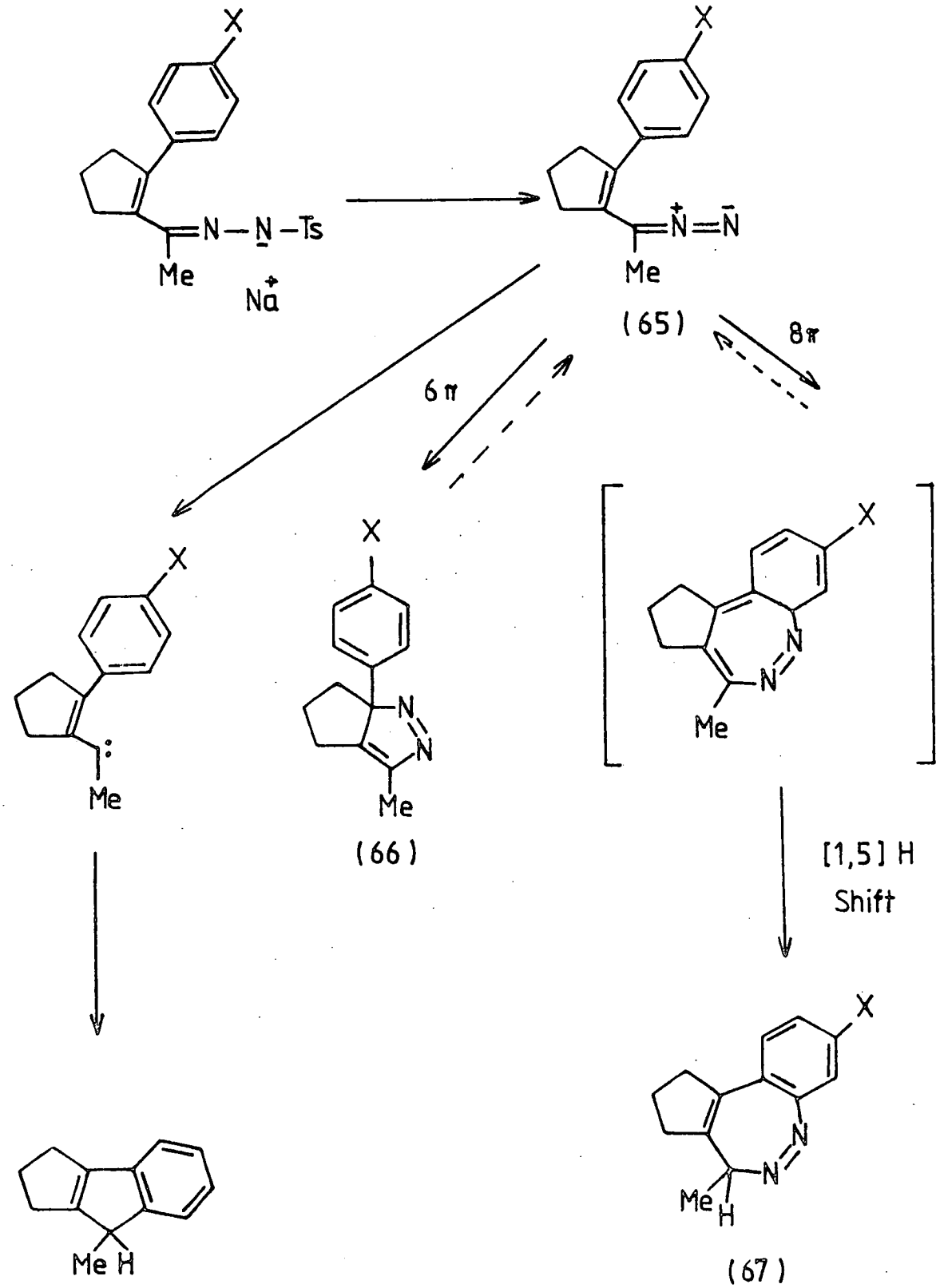
(62)



(65)

A complicating factor arises in that the diazo group is kept in conjugation with the α,β-double bond by the almost planar five membered ring in (62) whereas (65) can have free rotation about the 1,2-bond. Therefore it might be expected that both 1,5-and 1,7-ring-closure in (65) will have higher entropies of activation thus making them less competitive with carbene formation.

Where R=Me, the diazocompound (65), reacted *via* all three modes (Scheme 19), the 3*H*-pyrazole (66) to diazepine (67) ratio being high initially and decreasing as the tosylhydrazone salt was consumed. This suggested that the 6π-ring-closure was the kinetically favoured process, with the pyrazole being slowly transformed into the more stable benzodiazepine. Such a rearrangement represents a novel thermal ring transformation of 3*H*-pyrazoles rather than the usual van Alphen-Huttel

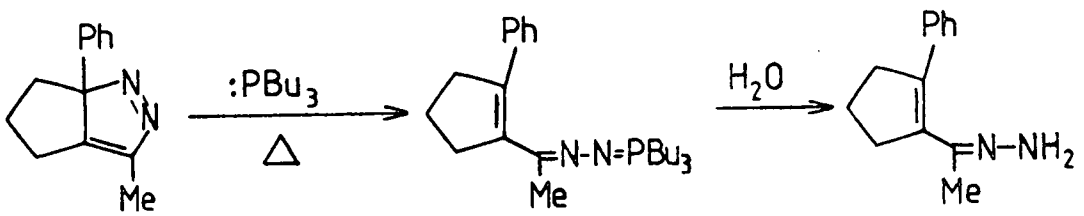


X			
H	20%	46%	32%
Me	20	43	37
F	26	36	38

Scheme 19

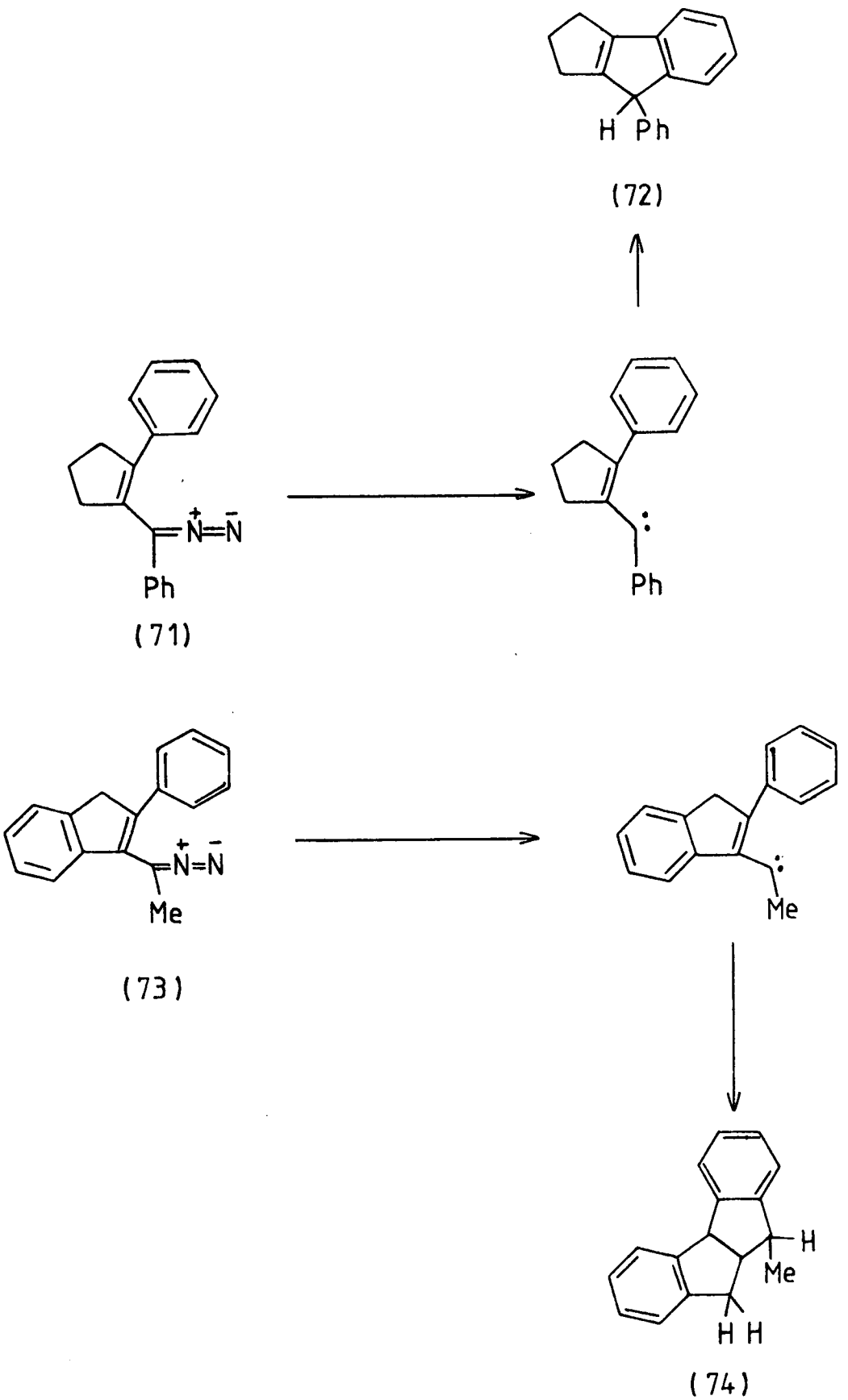
rearrangement[78,79] where one of the groups on the saturated carbon migrates to an adjacent atom giving either a 1*H*- or 4*H*-pyrazole. The yields are shown in Scheme 19 are those obtained after reactions only sufficient to ensure complete consumption of the tosylhydrazone salts.

The proposed mechanism was supported by the thermolysis of the 3*H*-pyrazole (66) at 80°C which produced both diazepine (67) and the cyclopentadiene (68), suggesting that the rearrangement of 3*H*-pyrazole to diazepine does involve a reversal of the 6π electrocyclisation process to give the initial diazocompound. Although the equilibrium between the pyrazole and the diazocompound will be heavily on the side of the pyrazole, the reaction will be driven over to the right by the irreversible sigmatropic hydrogen shift giving the diazepine and the irreversible loss of nitrogen giving the cyclopentaindene. Support for the intermediacy of the diazo compound was obtained by thermolysis of the 3*H*-pyrazole in the presence of tributylphosphine which gave the phosphazine (69), which on hydrolytic work-up gave the isolated hydrazone (70).



(66) (69) (70)

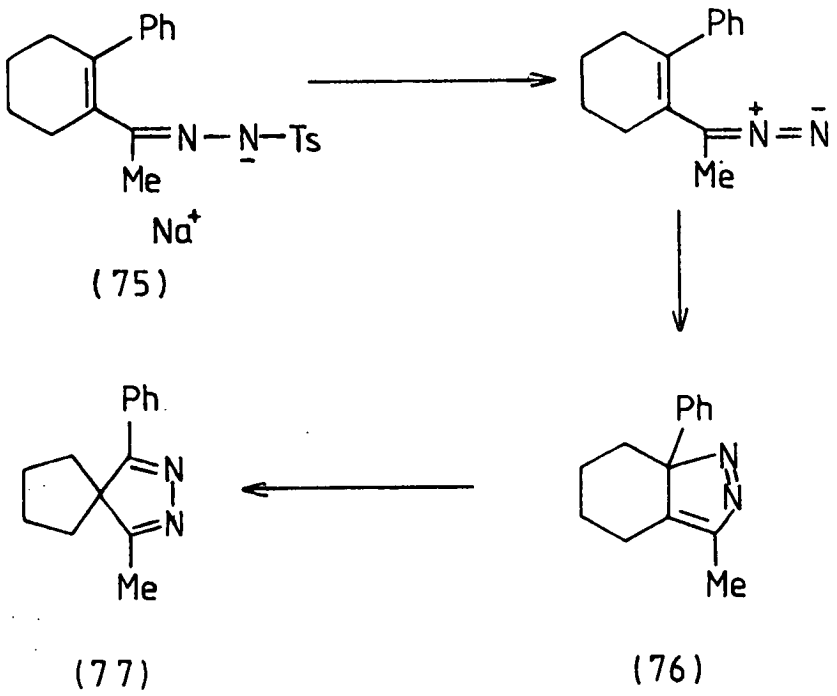
The partitioning of the reaction between the electrocyclisation and carbenic modes is greatly affected by minor structural modifications. Replacement of the methyl group by a phenyl group (71) resulted in complete dominance of the



Scheme 20

carbenic reaction giving (72) (Scheme 20). This would appear to be due to the effect of conjugation stabilising the carbene rather than a steric effect of the phenyl group in inhibiting conjugation between the diazo-group and the alkene double bonds as a similar effect was observed in conjugating the alkene bond with a fused benzene ring (73) giving hydrocarbon (74). The competing electrocyclisation was not favoured by reducing the size of the group from methyl to hydrogen, as this resulted in a multicomponent reaction where only the corresponding azine could be identified.

The effect of the cyclopentyl ring in restraining pyrazole formation and promoting diazepine formation is confirmed by comparison with the cyclohexyl analogue (75) whose cyclisation gave only 3*H*-pyrazole (76), more thermally stable than the 3*H*-pyrazole (66). However, on prolonged heating (76) decomposed by "normal" van Alphen-Huttel rearrangement *via* an alkyl shift to give the 4*H*-pyrazole (77). (Scheme 21).

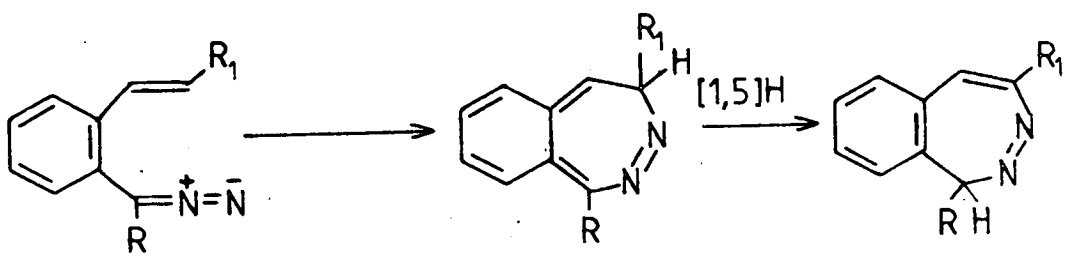


Scheme 21

In the cyclopentyl case, the fact that (66) rearranges to give (67) rather than undergoing a van Alphen-Huttel rearrangement can be rationalised on steric grounds as the greater ring strain in (66) lowers the activation energy for ring opening to (65). Group migrations are also inhibited in (66) and (i) it can be seen from a Dreiding model that the transition state for a van Alphen-Huttel[1,5]shift of the aryl group is inaccessible due to severe van der Waal's interactions between the CH_2 and the *ortho* hydrogen atoms of the phenyl group and (ii) an alkyl shift is inhibited by steric destabilisation of the spirocyclobutane product. Thus the alternative rearrangement to the diazepine is the preferred process.

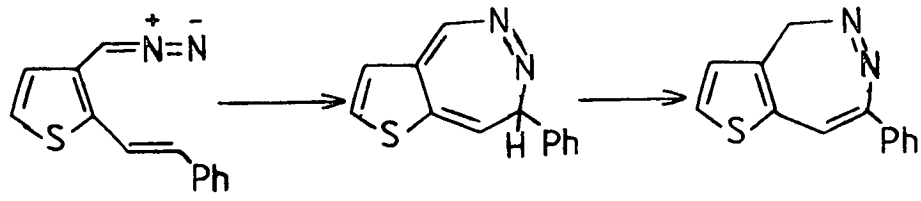
1,2-Benzodiazepines are thus only formed by the 1,7-ring closure of α,β:γ,δ-unsaturated diazoalkanes with α,β-olefinic and γ,δ-aromatic unsaturation when structural features are

present which inhibit the alternate 1,5-closure to pyrazoles. α,β:γ,δ- Unsaturated diazoalkanes with α,β-aromatic and γ,δ-olefinic unsaturation (78) however readily undergo 1,7-ring closure to give a range of 1*H*-2,3-benzodiazepines (80) in good yields.[80] Diazoalkanes of the type (78) were not susceptible to partioning of reaction into 1,5-ring closure or carbenic modes, but underwent 1,7-ring closure exclusively to give the 4*H*-2,3-benzodiazepine intermediates (79) which rearomatised to the products (80) *via* a [1,5] sigmatropic hydrogen migration, a similar mechanism to that involved in formation of 1,2-benzodiazepines.

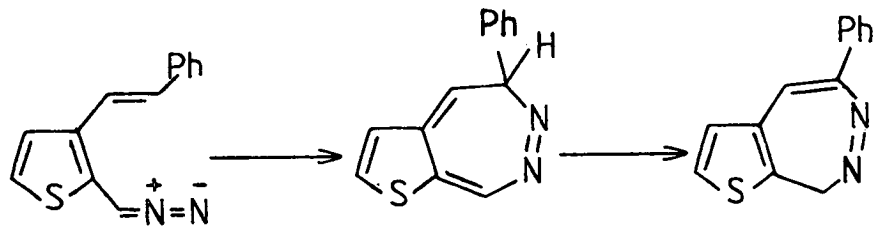


(78) (79) (80)

Similar results were obtained with α,β:γ,δ-unsaturated diazoalkanes when the α,β-unsaturation was part of a hetero-aromatic system i.e. 2,3 bond of thiophene (81,84) which readily underwent 1,7-ring closure to thieno[3*H*-1,2]diaze-pines (83,86),[81] *via* the 3*H*-diazepine intermediates (82,85).



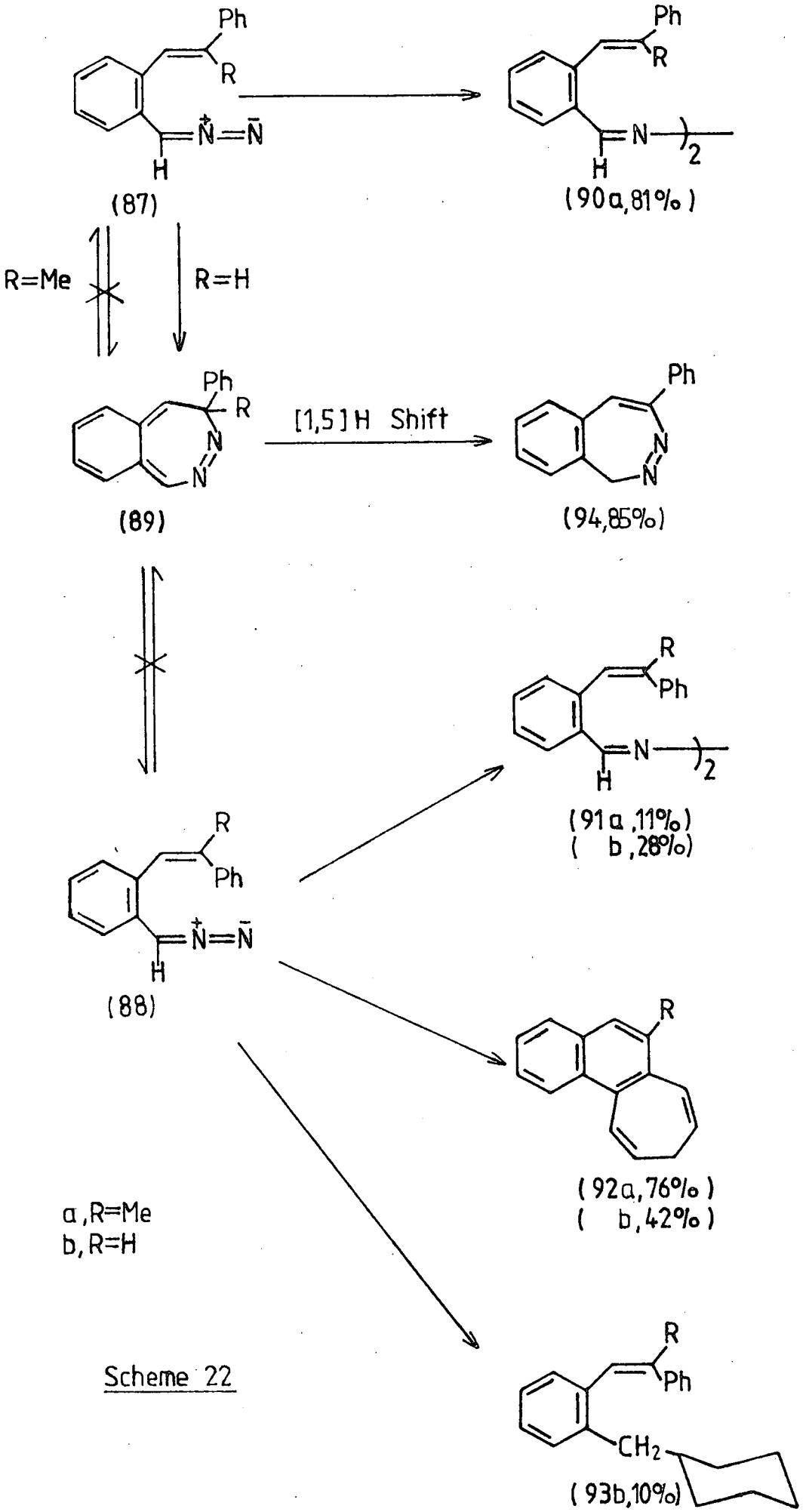
(81) (82) (83)



(84) (85) (86)

However, when the α,β-unsaturation was the ^{3},^{4} bond of thiophene 1,7-electrocyclisation did not occur and only carbene derived products, azines, carbene "dimers" and solvent insertion products, were isolated. This failure to undergo electrocyclisation is probably due to 3,4 bond having insufficient double-bond character to allow an electrocyclisation process to occur.

However, in the reactions of compounds of type (87,88) it was shown that 1,7-electrocyclisation is inhibited if a *Z* substituent other than hydrogen is present on the double bond.[82, 83] Diazoalkanes of the type (87a) and (88) do not undergo 1,7 electrocyclisation but give only carbene derived products, (90a) and (91a,92a) respectively. The *E*-2-phenylpropenyl isomer (87a) gave only the *E* azine (90a) in high yield, whereas the *Z* isomer (88a) formed the 9*H*-cyclohepta[a]naphthalene (92a) by intramolecular reaction, and gave very little of the


Ph
R
N
N
H
(87)
(90a, 81%)
R=Me
R=H
[1,5] H Shift
(89)
(94, 85%)
(91a, 11%)
(b, 28%)
(88)
(92a, 76%)
(b, 42%)
a, R=Me
b, R=H
(93b, 10%)

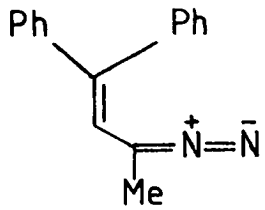
Scheme 22

azine (91a).

These results suggest that the initial electrocyclisation of (87a,88a) to the common intermediate (89a) does not occur, prior to the product forming steps. If ring closure to (89a) were to occur similar reaction products would be expected, as this would allow interconversion of (88a) to the more thermodynamically stable (87a).

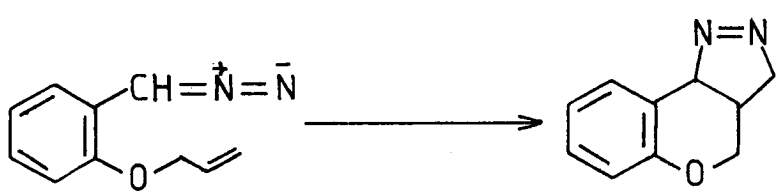
Proof that steric hindrance alone was preventing 1,7-electrocyclisation in the diazoalkane was obtained by investigating the *Z* substituted isomers (88b). Scheme 22. The *Z* isomer did not undergo 1,7-electrocyclisation but underwent carbene type reactions to give (91b,92b and 93), whereas the *E* isomer underwent normal 1,7-electrocyclisation to (89b) followed by hydrogen migration to benzodiazepine (94). If (88b) had undergone electrocyclisation to the common intermediate (89b) then benzodiazepine (94) would have been isolated. The absence of benzodiazepine (94) is proof that it is the cyclisation step to (89) which is inhibited rather than failure of the intermediate (89) to undergo rearrangements by group migration.

It is interesting that the balance between the electrocyclisation and carbenic reaction alternatives in the decomposition of these diazo compounds is much finer than for 3-diazoalkenes, e.g. (95), the 6π electron 1,5-cyclisation of the latter to give 3*H*-pyrazoles is not generally inhibited by *Z* methyl or phenyl substituents.[76]



(95)

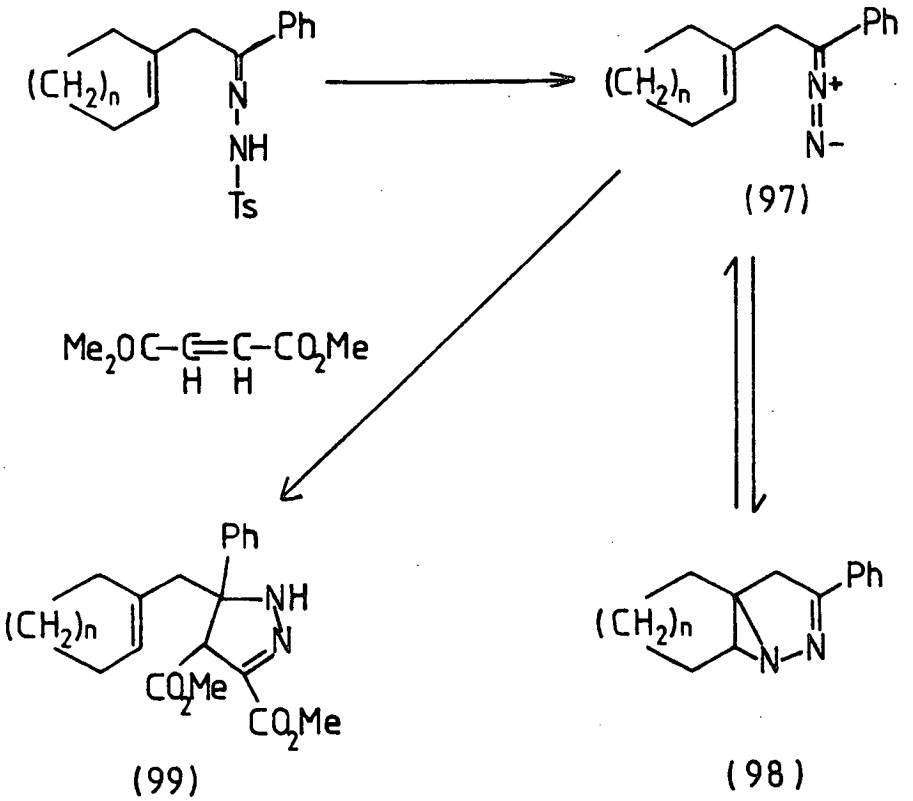
Some interesting work has been reported recently on the reaction of diazoalkenes in which the diazo-group is not conjugated with the alkene. In cases where the double bond and the diazo group can attain the required "parallel planes" transition state for [3+2] cycloaddition then this is the preferred mode of reaction. For example, the 2-allyloxyl-phenyldiazomethane (96) undergoes [3+2] intramolecular cyclo-addition to the 1-pyrazoline (37).



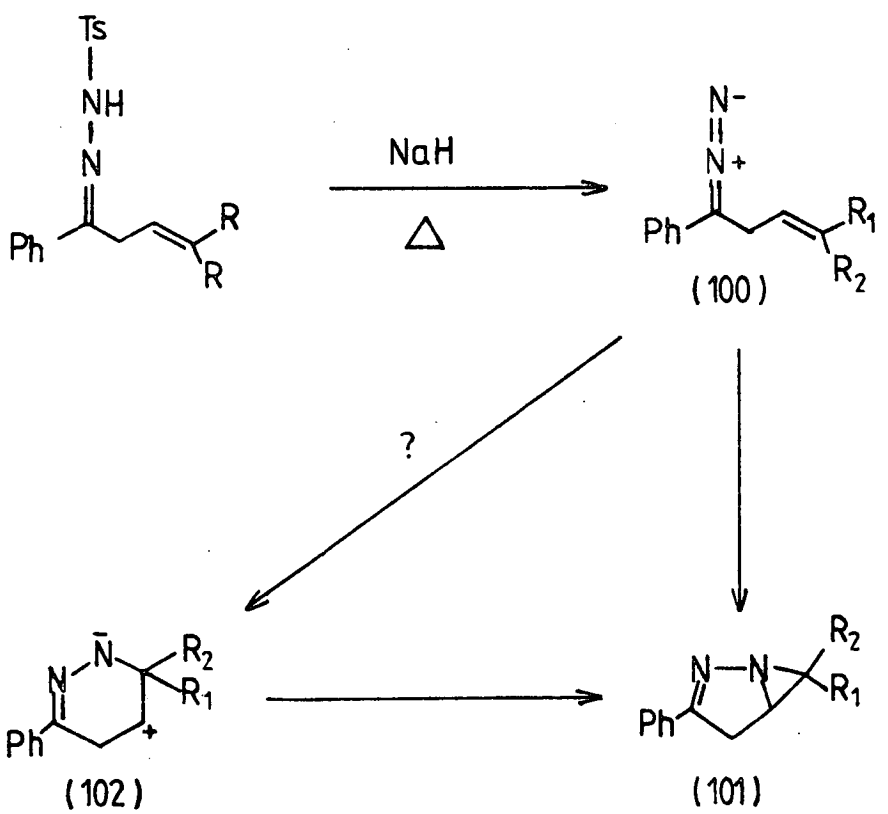
(96) (37)

However in cases where the chain linking the alkene and the dipole is short this mode of reaction is not possible. It has recently been shown that diazoalkenes of the type (97) and (100) are converted to (98) and (101) when kept at room temperature for several hours.[85-88]

Thermolysis of the sodium salts of the appropriate tosylhydrazone in carbon tetrachloride gave the initial



Scheme 23

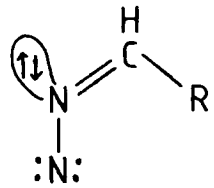


Scheme 24

diazoalkane (97), which could be trapped chemically to give (99). Allowing the solutions of (97) to cool to room temperature gives the 1,1-cycloadducts, 1,2-diazabicyclo[3.1.0]hex-2-enes (98), a completely reversible reaction by heating at 80°C. (Scheme 23).

Thermolysis of sodium salts of corresponding tosylhydrazones gave the diazoalkane (100) which underwent 1,1-cycloaddition to (101). This ring closure was stereospecific, the *E* isomer (100; R_1=CH_3) giving only the *exo* isomer (101; R_1=CH_3) and the *Z* isomer (100; R_1=H) gave 95% *endo* isomer (101; R_1=H). (Scheme 24).

In the above systems (97, 100), the normal "two-plane" orientation of the diazo group and the allyl π system is impossible, as a result of geometrical restrictions imposed, and the attack of the terminal nitrogen atom of the diazo group on the neighbouring double bond instead occurs. Two reasonable mechanistic options for the 1,1-cycloaddition have been proposed, either a concerted reaction formally involving a 'nitrene' form of the diazocompound (103) or a stepwise pathway. The concerted path would parallel the stereospecific addition of a singlet nitrene to olefins which proceeds with retention of stereochemistry about the double bond. Alternatively a stepwise nucleophilic attack of the terminal double bond on the electron deficient nitrogen atom of the diazoalkene could generate a six-membered ring dipole (102) which then collapses to generate the isolated product (101). As long as this closure step is fast relative to ring flipping then the 1,1-cycloaddition would proceed with retention of the stereochemistry of the double bond.



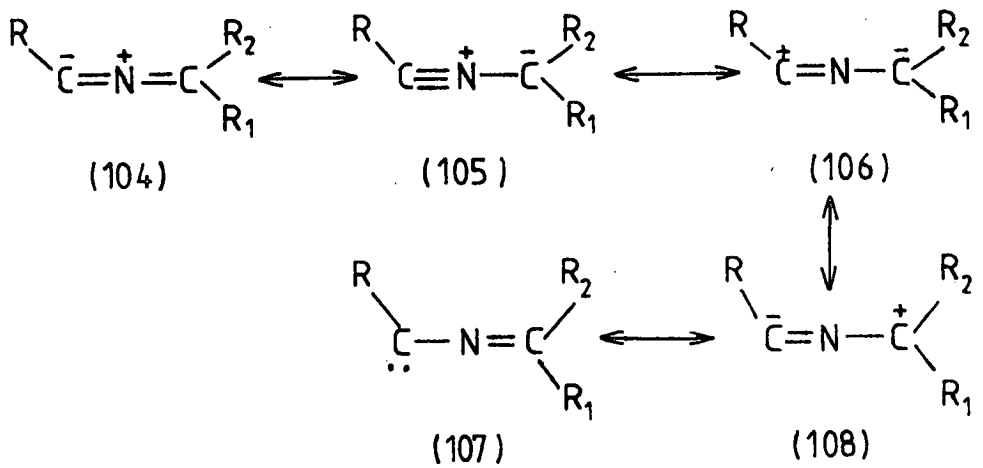
(103)

3.) NITRILE YLIDES

3.1) Structure

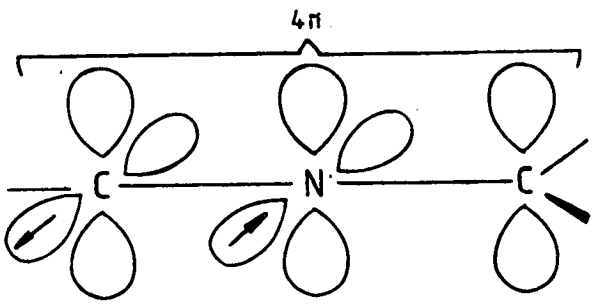
Nitrile ylides belong to the class of 1,3-dipoles known as nitrilium betaines; like diazoalkenes these have a central nitrogen atom and an orthogonal double bond. However they are less stable than diazoalkenes and are not normally isolable although transient red colours due to their presence can be seen in reactions carried out at room temperature. The nitrile ylide (112) has been isolated in a matrix at -185°C and its U.V. spectrum obtained.

The electronic structure and shape of nitrile ylides has been a source of some uncertainty. They can be envisaged as resonance hybrids of the canonical structures (104)-(108) shown below with the octet structures (104) and (105) being the major contributors.



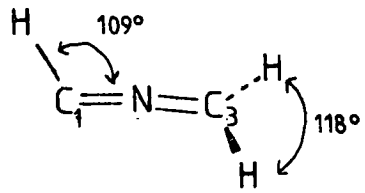
(104) (105) (106) (107) (108)

Huisgen suggested many years ago that they would have a preferred linear and planar conformation (109) like diazoalkenes as this would maximise the allyl resonance and give maximum overlap for the orthogonal double bond.[1] Huisgen also stated that the bent geometric form would be of lesser importance.



(109)

Until 1973 MO calculations on nitrile ylides were based on this fixed linear geometry but had given orbital coefficients which did not accord with Houks FMO method predicting regio-selectivity. Houk[90] deduced that these calculations must be wrong and did further MO calculations with geometry optimisation. These *ab initio* calculations indicate that the geometry of the nitrile ylide is appreciably different from that suggested by Huisgen. Salem[89] also concluded that the lowest energy ground state geometry of the nitrile ylide has a HCN angle of 156.7° and being ∿18 kcal/mol more stable than the linear form. Houk's calculations showed that the bent nitrile ylide geometry is favoured over the linear, thus indicating that the most stable form resembles a bent allenyl anion rather than a linear propargyl anion. The HOMO and SLUMO of the bent ylide bear a strong resemblance to the HOMO and LUMO of a singlet carbene. Houk's calculations show that the bent nitrile ylide HOMO is heavily localised at C-1, as is also shown by protonation at this position,[91] but still resembles the normal three-orbital, four π electron system of 1,3-dipoles. This refined model enables rationalisation of the bimolecular nitrile ylide cycloadditions, as well as all other known reactions of nitrile ylides.



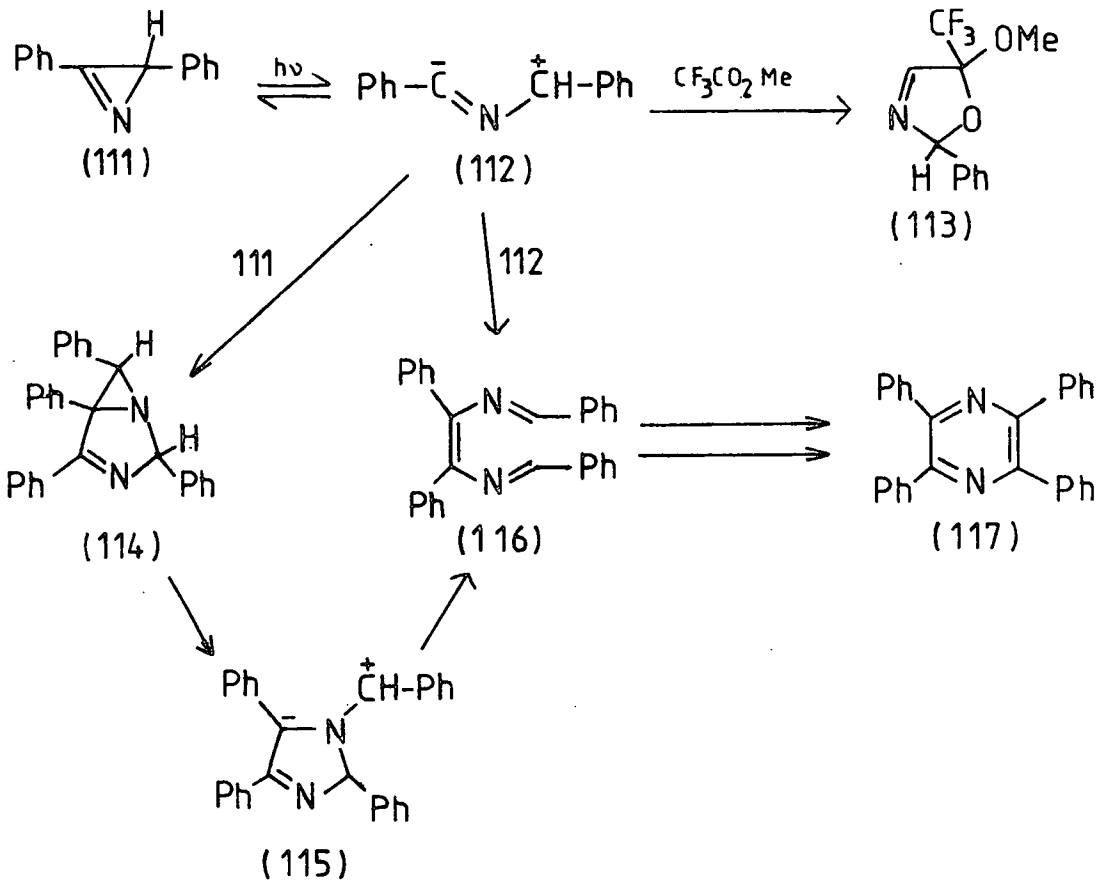
(110)

Electron acceptors at C-3 stabilise the planar species relative to the bent species and electron donors favour the bent allenyl form. 1-Aryl and 3-alkyl or aryl substituted nitrile ylides were also calculated to prefer the bent form.

3.2) Synthesis of Nitrile Ylides

Although many methods of synthesis of nitrile ylides are known the most thoroughly investigated method of generation is *via* the photolysis of 2*H*-azirines. For example, irradiation of the 2*H*-azirine (111), in a rigid matrix at -185°C,[92] gave the nitrile ylide (112) which was observed as an ultraviolet absorption (*ca* 350 nm). This absorption decreased on warming to -160°C in presence of methyl trifluoracetate indicating that a cycloadduct (113) had formed from the initially generated nitrile ylide (112) (Scheme 25).

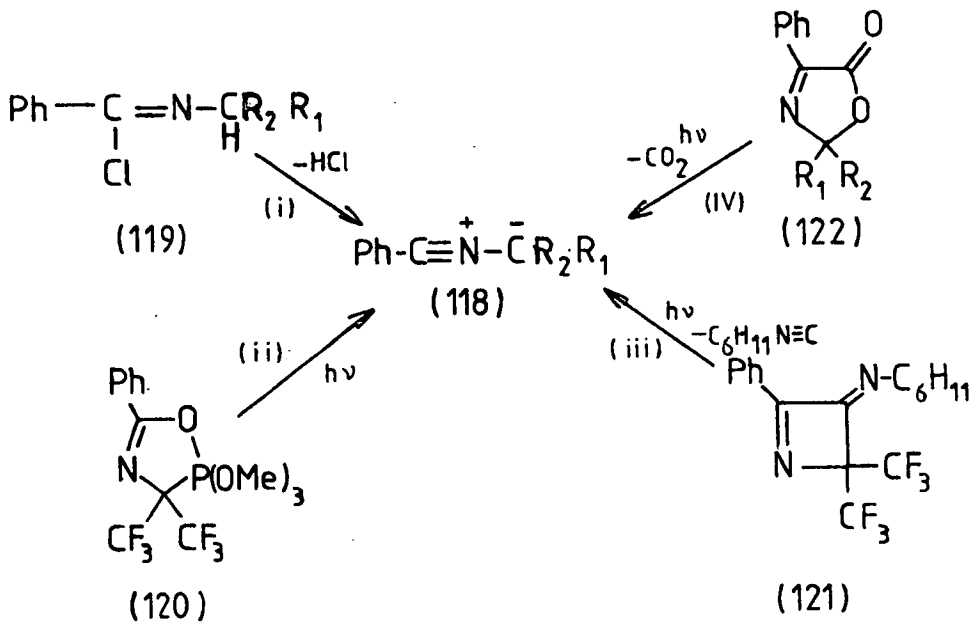
It was proved that the nitrile ylide can react with the starting 2*H*-azirine to give the bicyclic compound (114) *via* [3+2→5] mechanism which rearranges to (115) which ring opens to (116). It was also proved that the nitrile ylide (112) can undergo head to head dimerisation to (116) directly which then undergoes an electrocyclic ring closure and subsequent oxidation to the pyrazine (117) (Scheme 25). This reaction



Scheme 25

scheme shows the most utilised route to nitrile ylides, *via* the photolysis of 2*H*-azirines, as well as demonstrating the [3+2→5] cycloaddition and dimerisation reactions typical of most 1,3-dipoles.

A number of other methods have also been used including i) treatment of imidoyl halides having an α hydrogen (119) with base,[93-95] ii) thermal or photochemical elimination of a phosphoric acid ester from 4,5-dihydro-1,3,5-oxaphospholes (120)[96,97] iii) 1,3-dipolar cycloreversion of 1-azetidines (121)[98] and iv) loss of carbon dioxide from 3-oxazolin-5-ones (122)[99]. (Scheme 26).



Scheme 26

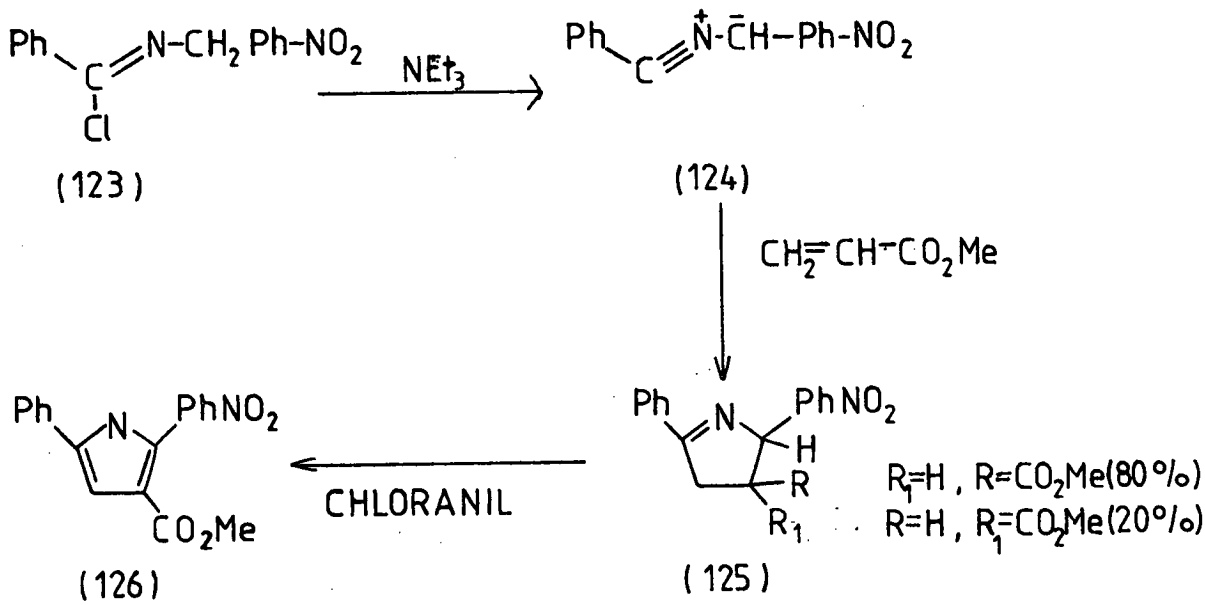
Of the above methods described to generate nitrile-ylides the photochemical generation of this 1,3-dipole from 2*H*-azirines has been the most extensively investigated method. This is probably due to the fact that an extensive range of substituted 2*H*-azirines can be readily prepared in large quantities by the photolysis of vinyl azides[100] or by the modified Neber reaction.[101] A comprehensive review of nitrile ylide formation from 2*H*-azirines has been published.[102]

3.3) Reactions of Nitrile Ylides

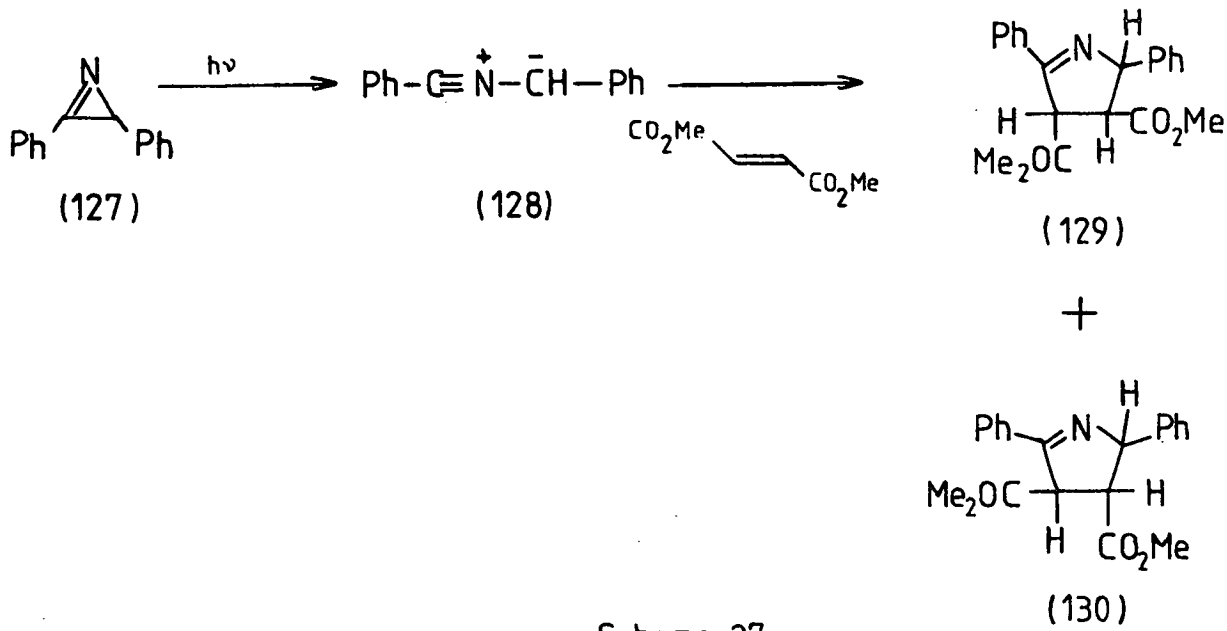
3.3.1) Intermolecular Reactions of Nitrile Ylides

Nitrile ylides undergo normal 1,3-dipolar reactions such as dimerisation[92,102] and normal 1,3-dipolar cycloadditions to double bonds to form five membered heterocycles. A large

number of these cycloadditions have been reported.[103] Thus, they react with carbon-carbon double bonds to form 1-pyrrolines (125) which can be dehydrogenated to give aromatic pyrroles.[103] For example, treating imidoyl chloride (123) with triethylamine at 0-20°C gave a deep violet solution of the nitrile ylide (124) which can be trapped with methyl acrylate to give two diasteriomeric-1-pyrrolines (125a, 125b, 58%), which can be readily aromatised to pyrrole (126) by chloranil.[93,95]



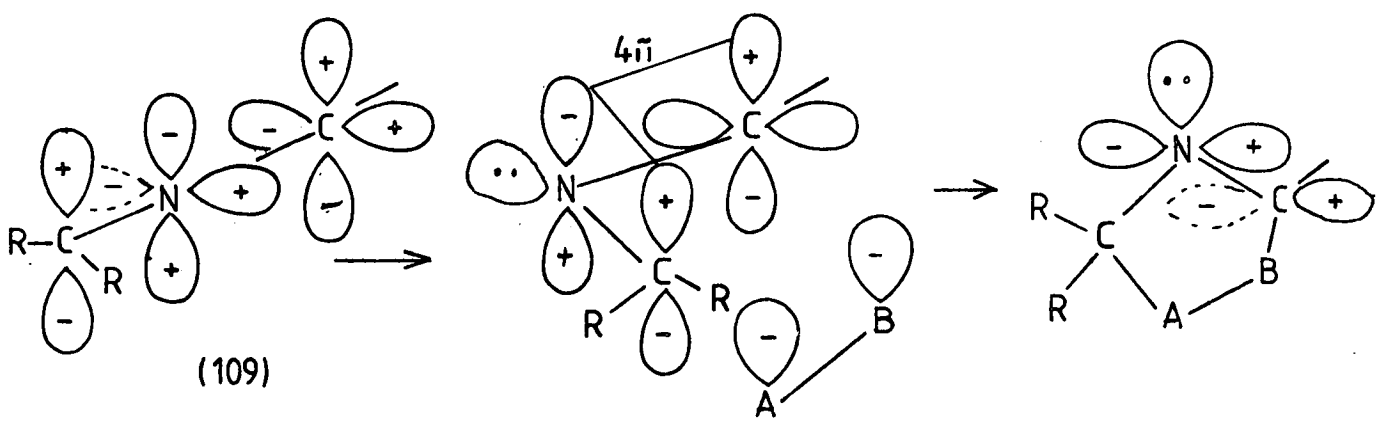
Reactions with *Z* and *E* alkenes have shown that the addition is stereospecific thus confirming a concerted formation of both new bonds.[99,104] For example, photolysis of 2,3-diphenylazirine (127) gave the nitrile ylide (128) which reacted with dimethyl fumarate to give only two pyrrolines (129,130).[104] (Scheme 27). Nitrile ylides have also been reported to undergo 1,3-dipolar cycloadditions with C=S, C=N, C=O and cumulated double bonds,[15] as well as with carbon-carbon triple bonds to



Scheme 27

give pyrroles directly.[95,102,103]

The mechanism of the 1,3-dipolar cycloadditions of nitrile ylides has been proposed to proceed *via* a "two plane" orientation complex in which the dipole and dipolarophile approach each other in parallel planes.



The above scheme depicts the orientation of complex involved in the addition of the linear nitrile ylide (109) with a dipolarophile. During the activation process the linear bond system of the nitrile ylide must bend. This

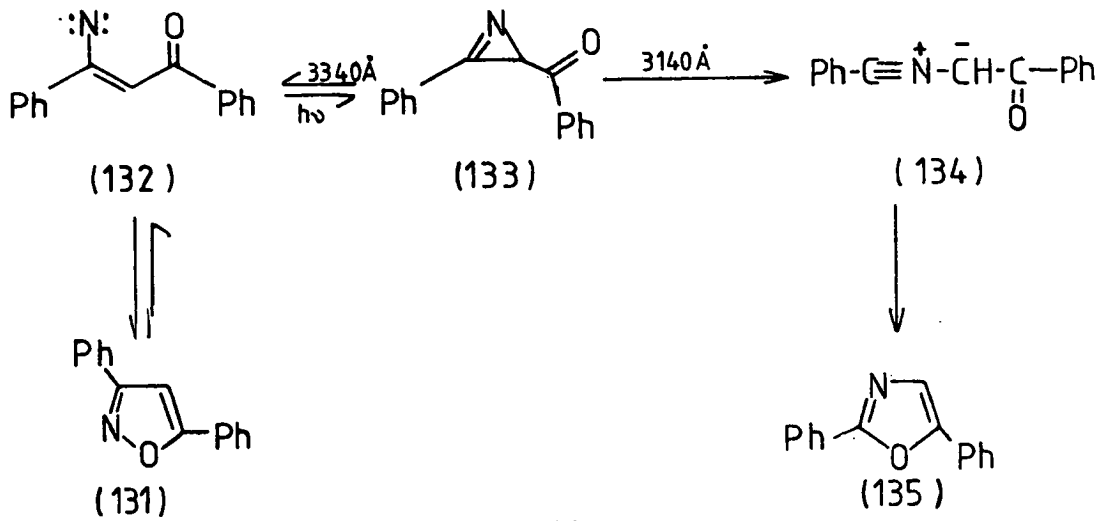
involves the disruption of the orthogonal π bond but leaves the allyl anion π system undisturbed. The loss of π bond energy is partly compensated by a gain in energy resulting from rehybridisation and accommodation of a lone pair of electrons in an orbital of high s character.

3.3.2) Intramolecular Reactions of Nitrile Ylides

Intramolecular reactions of nitrile ylides can be classed as 1,5 and 1,7 electrocyclisations and intramolecular cycloaddition. These two classes will be considered separately, for the present, although the possibility of the intramolecular cycloaddition going through initial electrocyclisation cannot be discounted.

Electrocyclisation of Nitrile Ylides

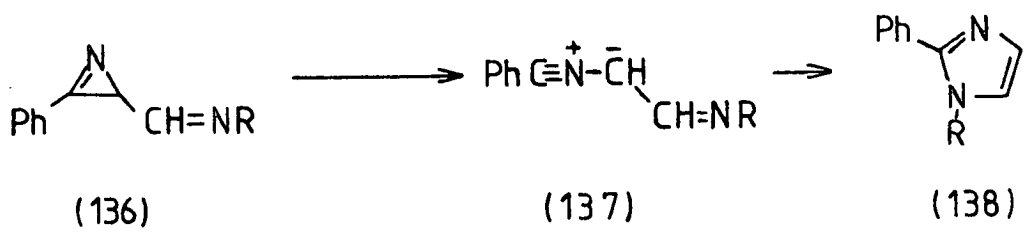
The first 1,5-electrocyclisation of nitrile ylides was observed in 1966 by Ullman and Singh.[105,106] These workers found that 3,5-diphenylisoxazole (131) isomerised to 2,5-diphenyloxazole (135) under photolysis, *via* an intermediate subsequently identified as 3-benzoyl-2-phenyl-1-azirine (133). (Scheme 28). The behaviour of the azirine (133) was controlled by the wavelength of light used, with 3340Å light (133) rearranges to the vinylnitrene (132) which subsequently rearranges to the isoxazole (131). Using shorter wavelength light C-C bond cleavage occurs to give the carbonylnitrile ylide (134) which undergoes 1,5-dipolar electrocyclisation to give the oxazole (135).



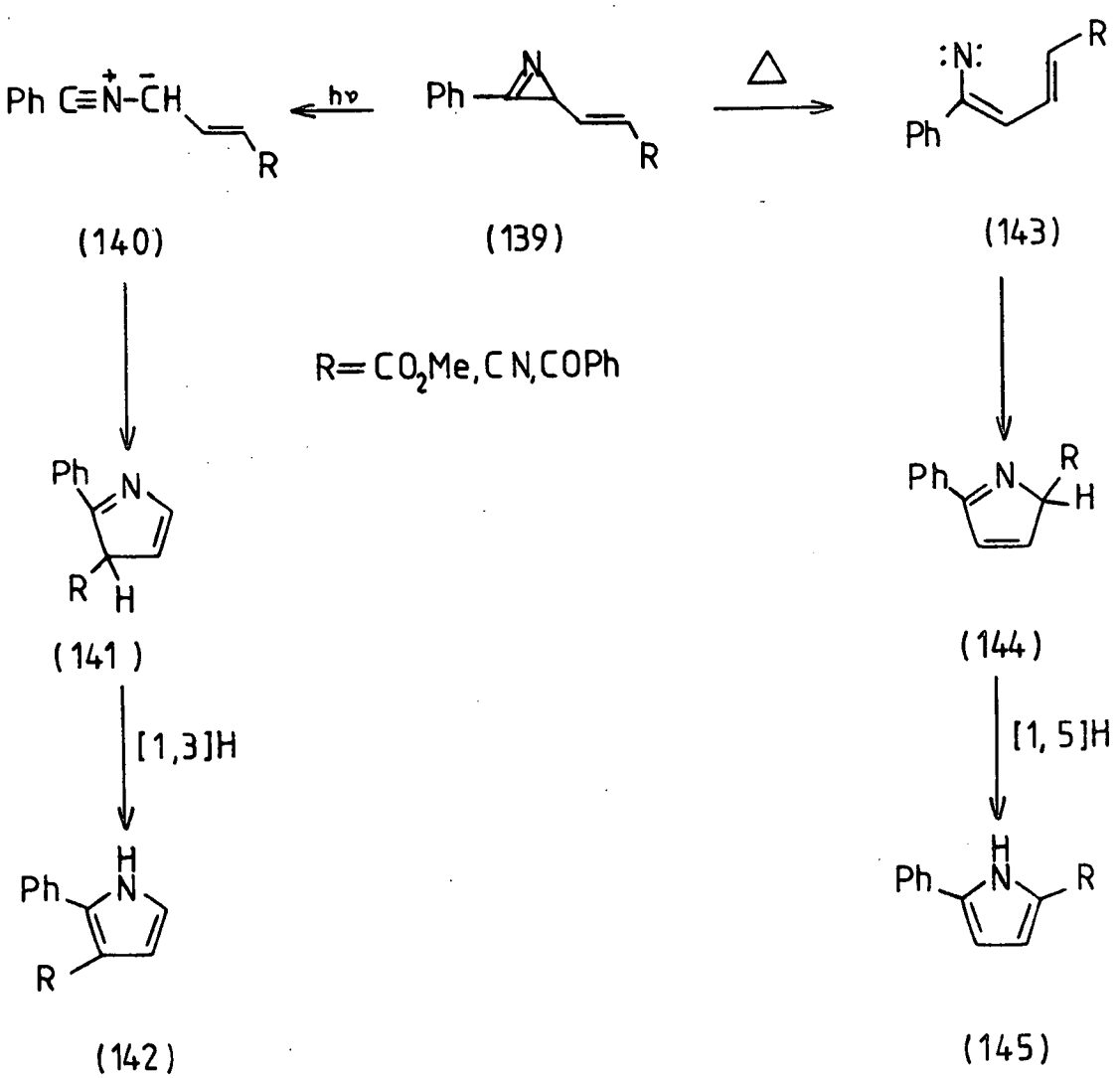
Scheme 28

Many other examples of photolytic transformation of isoxazoles into oxazoles, *via* nitrile ylides are known and these reactions have been reviewed.[29,102] It is also known that thermolysis, rather than photolysis, of 2*H*-azirines gives vinylnitrenes, and not nitrile ylides as intermediates.

1,5-Electrocyclisations of iminonitrile ylides (137) have also been reported. The azirine (136) undergoes C-C cleavage on photolysis generating the iminonitrile ylide (137) which undergoes 1,5-dipolar electrocyclisation to imidazoles (138)[108].

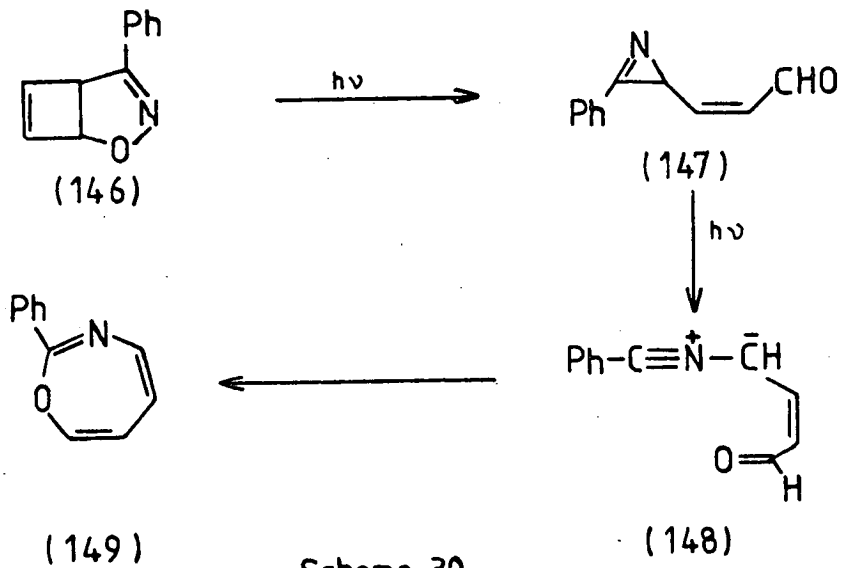


The final and most thoroughly investigated class of nitrile ylides to undergo 1,5-electrocyclisation are the vinylnitrile ylides. Photolysis of 3-vinyl-1-azirines (139) gives vinylnitrile ylides (140) followed by a 1,5-electrocyclisation to the 3*H*-pyrrole (141) which then undergoes a 1,3-sigmatropic hydrogen shift to give the 1*H*-pyrrole (142).[107] It is worthwhile to note that thermolysis of this and other azirines goes *via* C-N cleavage to give the vinylnitrene (143) which then gives the isomeric 2*H*-pyrrole (144) and hence the isomeric 1*H*-pyrrole (145) *via* a [1,5] sigmatropic hydrogen shift. (Scheme 29).



Scheme 29

Vinylnitrile ylides can also undergo 1,7-electrocyclisation if the stereochemistry of the substituted alkene side chain of the vinyl azirine is Z. It was shown that photolysis of bicyclic isoxazoline (146) resulted in oxazepin (149).[109,110] This transformation involves the isomerisation of (146) into the Z vinyl azirine (147) which ring opens to the Z vinylnitrile ylide which then undergoes 1,7-electrocyclisation on to the carbonyl group, to form oxazepin (149) (Scheme 30).



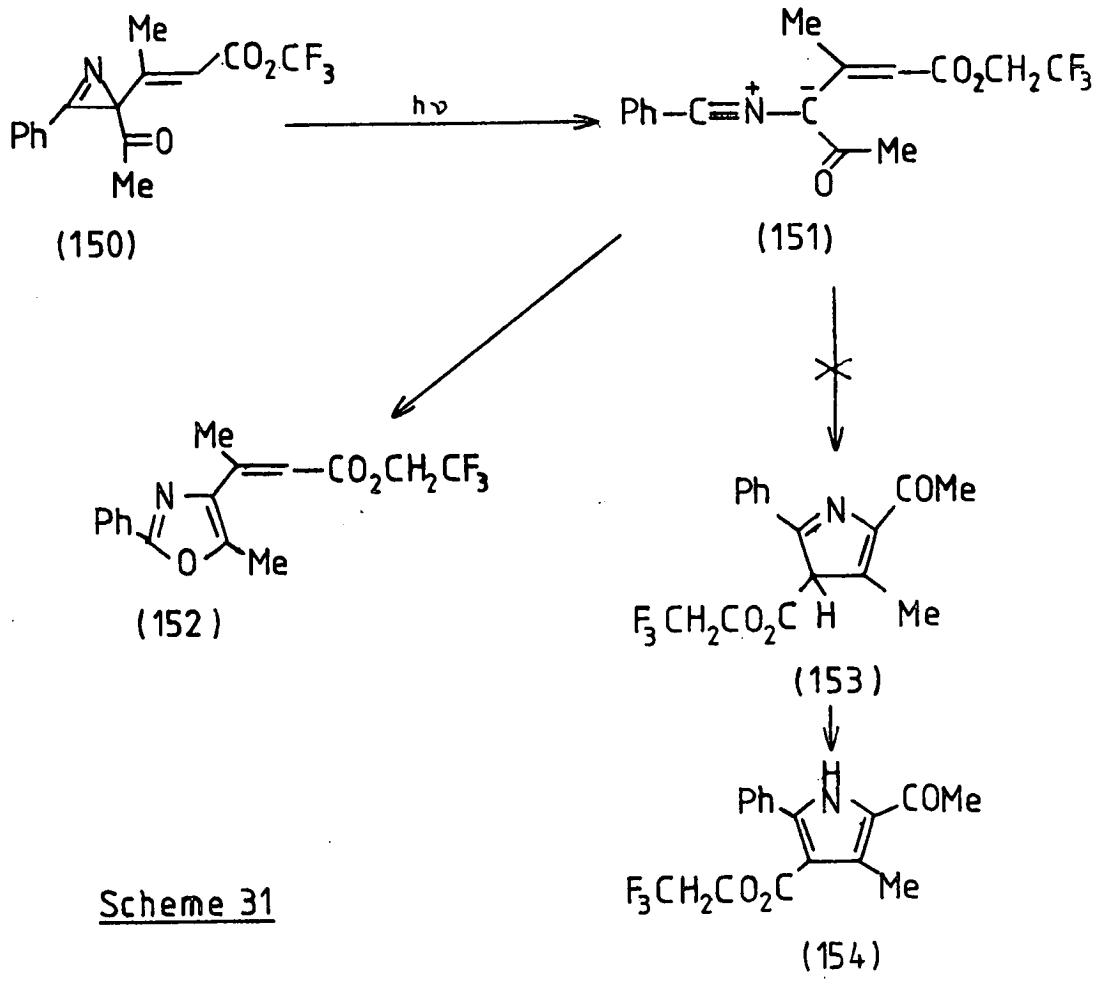
(146) (147) (148) (149)

Scheme 30

This 1,7-cyclisation only occurs with the Z isomer as it is impossible due to steric constraints for the *E* isomer to behave in this manner, and it undergoes the rearrangement described above to give a pyrrole. Other examples of the rearrangement of Z-vinyl-1-azirines to oxazepins have been reported[29] and analogous results were obtained for Z and *E* 3-styryl-1-azirines, which will be discussed later in the benzazepine section.

When a nitrile ylide bears both a vinyl and a carbonyl substituent at the trisubstituted carbon atom, two cyclisation

processes are possible, i.e. to carbon or to oxygen. Such nitrile ylides have been generated (151) and only 1,5-cyclisation to oxygen ensures yielding oxazoles rather than pyrroles. For example, irradiation of azirine (150) provides only the oxazole (152) and no pyrrole (154).[111] (Scheme 31).



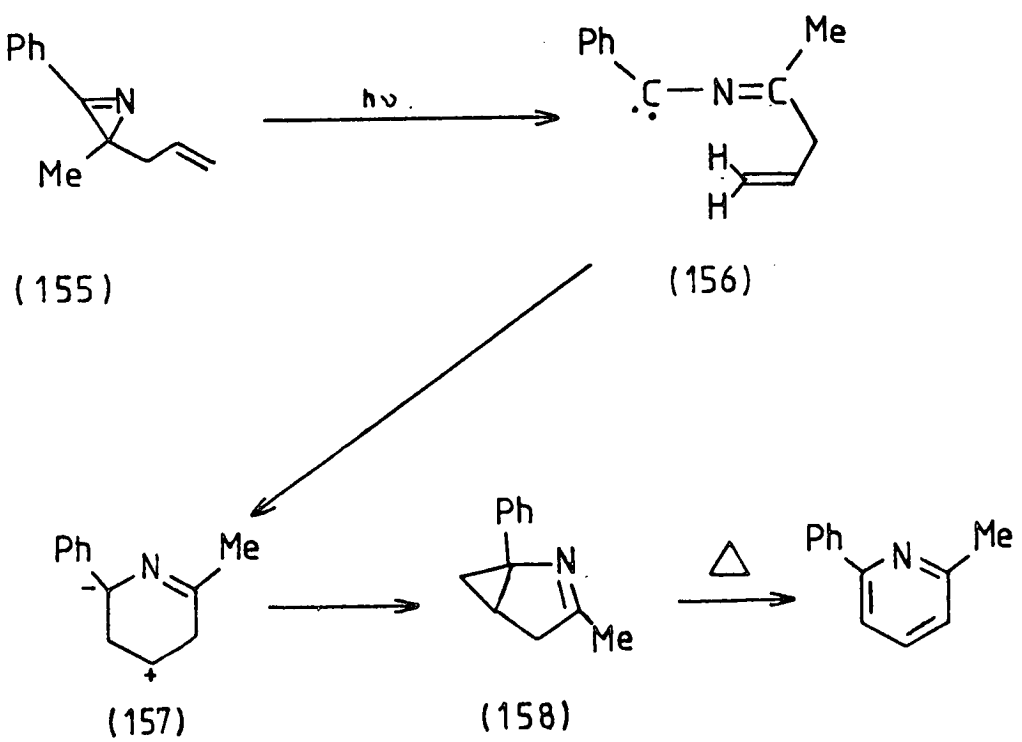
Scheme 31

Rather surprisingly vinylnitrile ylides can be trapped with external dipolarophiles, to the total exclusion of 1,5-electrocyclisations,[29] indicating that the activation energy for the intramolecular reaction must be quite high. In the reactions of carbonyl nitrile ylides 1,5-electrocyclisation is favoured over intermolecular 1,3-dipolar cycloaddition.

Conversely for vinyl nitrile ylides 1,3-dipolar cycloaddition is favoured over 1,5 and 1,7-electrocyclisation respectively.

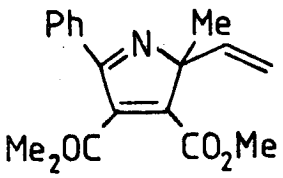
Intramolecular Cycloadditions of Nitrile Ylides

As mentioned earlier, the HOMO and SLUMO of the bent nitrile ylide bear a strong resemblance to the HOMO and LUMO of a singlet carbene. Since carbenes undergo reactions readily with double bonds, a 1,1-cycloaddition of nitrile ylides can be expected, and this was first discovered by Padwa and Carlsen.[112] When a solution of deareated 2-allyl-2-methyl-3-phenyl-2*H*-azirine (155) was irradiated in cyclohexane with light λ>280 nm a clean conversion to 3-methyl-1-phenyl-2-azabicyclo[3.1.0]hex-2-ene (158) was observed. (Scheme 32).



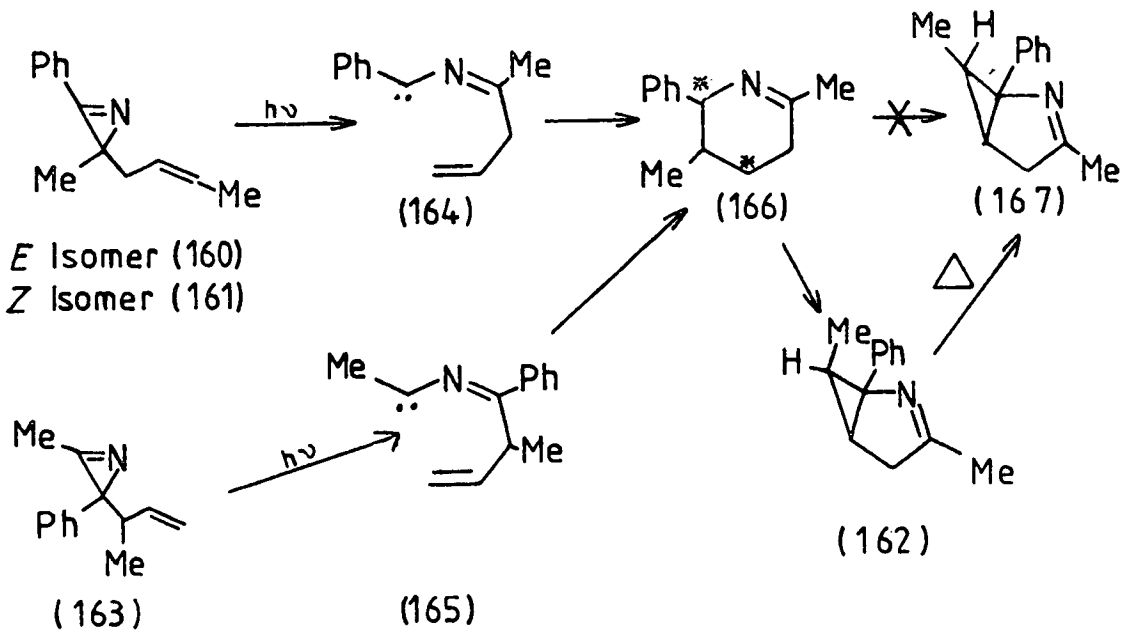
Scheme 32

The formation of the azabicyclohexenes (158) from the irradiation of azirine (155) clearly proceeds *via* a nitrile ylide since the formation of these compounds is entirely suppressed when the irradiation is carried out in the presence of a dipolarophile. For example, when dimethylacetylenedicarboxylate is used, cycloadduct (159) was the only isolated product.



(159)

An unusual aspect of the intramolecular photocyclisation of 2-allyl substituted 2*H*-azirines arose during a study of the photochemistry of *E* and *Z*-2-(2-butenyl)-2-methyl-3-phenyl-2*H*-azirine (160,161). Irradiation of (160) gave one product (>95%) which was identified as *endo*-3,6-dimethyl-1-phenyl-2-azabicyclo[3.1.0]hex-2-ene (162). The formation of the thermodynamically less favoured *endo* isomer corresponds to complete inversion of stereochemistry of the π system. Photolysis of the *Z* isomer also gave (162) and it was shown that no isomerisation of azirine (160,161) occurred during photolysis. Irradiation of 2-(1-methylallyl)-3-methyl-2-phenyl-2*H*-azirine (163) also gave (162) as the only product. The *endo* isomer (162) epimerised to the *exo* isomer (167) on standing at room temperature.



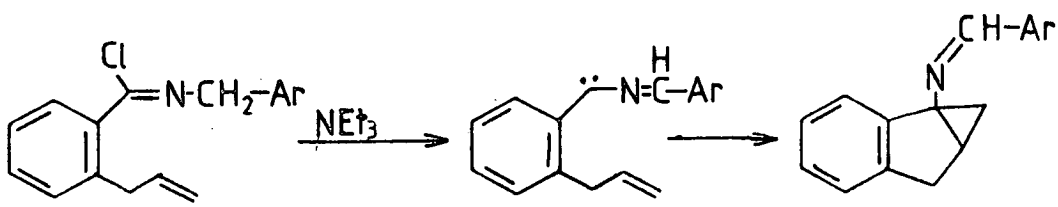
Scheme 33

The mechanism proposed to rationalise these results involves the ring opening of azirine (160) to nitrile ylide (164) best represented by the bent (carbene-like) form. Attack of the carbene on the double bond generates a six-membered trimethylene derivative (166) which collapses to form the azabicyclo species (162). This intermediate collapses to the thermodynamically less favoured product (162) as a severe torsional barrier results during ring closure to the thermodynamically more stable product (167), whereas collapse to (162) moves the phenyl and methyl further apart. Photolysis of azirine (163) results in the same product (162) formed by ring collapse of common intermediate (166).

1,1-Cycloaddition occurs in the above examples as the dipole and dipolarophile are unable to approach each other in the parallel plane approach necessary for 1,3-dipolar cyclo-

additions to occur. Thus, the bent nitrile ylide, the "carbene-like" form attacks the double bond forming a dipolar or diradical intermediate (166) which then undergoes ring collapse to the three-membered ring systems (158,162). The cycloaddition proceeds in a nonconcerted manner and bears a strong resemblance to the stepwise-diradical mechanism proposed for 1,3-dipolar cycloadditions.[5,7]

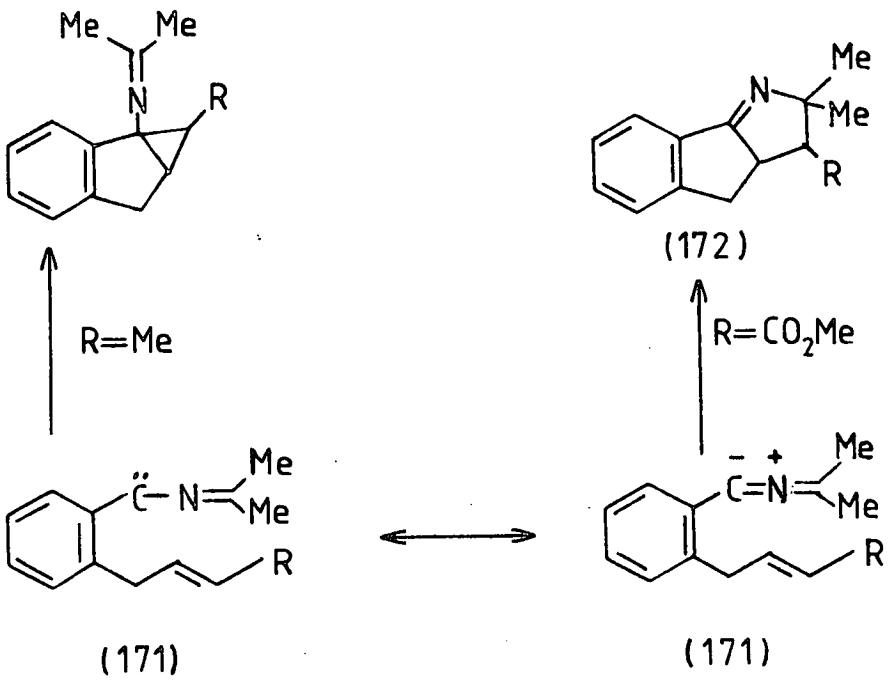
Several other examples of 1,1-cycloaddition of nitrile ylides have been reported.[113,114] For example the non-photolytically generating nitrile ylide (169), generated from imidoyl chloride (168) gave exclusive 1,1-cycloaddition to benzobicyclo[3.1.0]hex-2-ene (170).



(168) (169) (170)

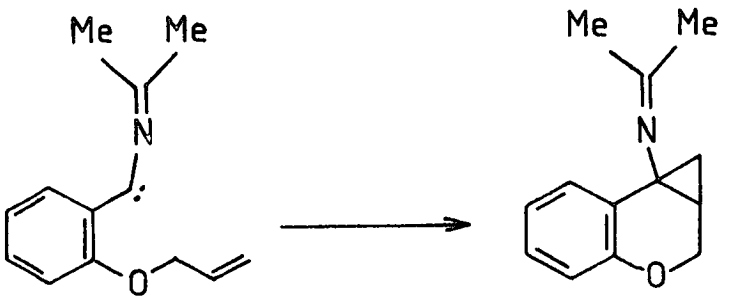
The mode of cyclisation is strongly dependent upon whether the normal parallel planes transition state for[3+2]cycloaddition is sterically inhibited, but it also depends on the substituents present.[102,113]

Thus, (171; R=Me) reacts clearly *via* 1,1-cycloaddition but the presence of an electron withdrawing substituent on the double bond (171; R=CO_2Me) lowers the dipolarophile LUMO and so increases the rate of 1,3-cycloaddition, relative to that of 1,1-cycloaddition, so that (172) becomes the only isolated product.[102]



The substituents of the 1,3-dipole moiety also affects the mode of cycloaddition. If the nitrile ylide bears electron donating groups (i.e. alkyl) on the C-3 carbon then this enforces bending of the nitrile ylide to form a species such as (173). Bending results in making C_1 of the nitrile ylide more carbene-like, in that essentially an in-plane lone pair (HOMO) and an out-of-plane vacant orbital (SLUMO) are present. Bending of the nitrile ylide decreases the possibility of 1,3-dipolar cycloadditions, since the parallel planes' geometry is unattainable, and increases the electrophilicity of C-1. Both these effects cause only 1,1-cycloaddition to occur for this dimethylated nitrile ylide, whereas the mono-methylated species gives both 1,1- and 1,3-adducts. Thus, when the nitrile ylide is flattened 1,3-dipolar cycloaddition is favoured, but upon bending, 1,1-cycloaddition becomes of

increasing importance.



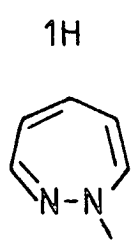
(173)

4.) 1,2-DIAZEPINES

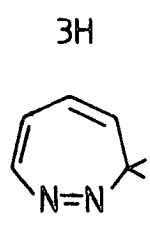
4.1) Introduction

1,2-Diazepines are monocyclic, seven-membered rings containing two adjacent nitrogen atoms. The chemistry and synthesis of these systems has been extensively reviewed.[115-120]

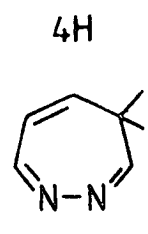
The unsaturated 1,2-diazepines are subdivided according to the position of the saturated atom in the seven-membered ring.



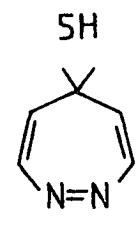
(174)



(175)



(176)



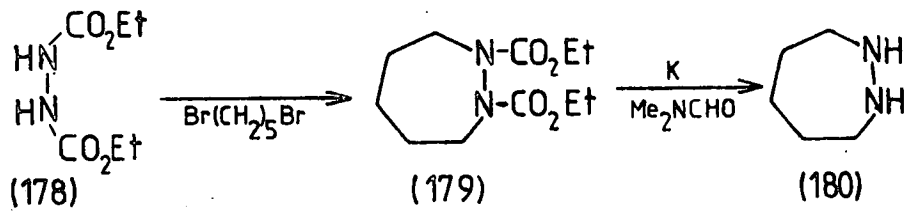
(177)

These unsaturated systems adopt a flexible, boat shaped conformation analogous to cycloheptatriene and n.m.r. has been used to study the energetics of these ring systems. The most characteristic feature of the chemistry of 1,2-diazepines is their ability to undergo ring transformations under thermal photochemical, acidic and basic conditions.

A great amount of literature has been published on the synthesis and reactions of the 1*H*, 4*H* and 5*H* 1,2-diazepines, but these systems will not be discussed as they are not of direct relevance. This introductory section will only be concerned with the synthesis and reactions of 3*H*-1,2-diazepines.

4.2) Synthesis

The parent fully saturated system (180) has been prepared, by hydrolysis of the product of the reaction 1,2-dicarboethoxy-hydrazine (178) with 1,5-dibromopentane, in dimethylformamide in the presence of potassium.[121]



(178) (179) (180)

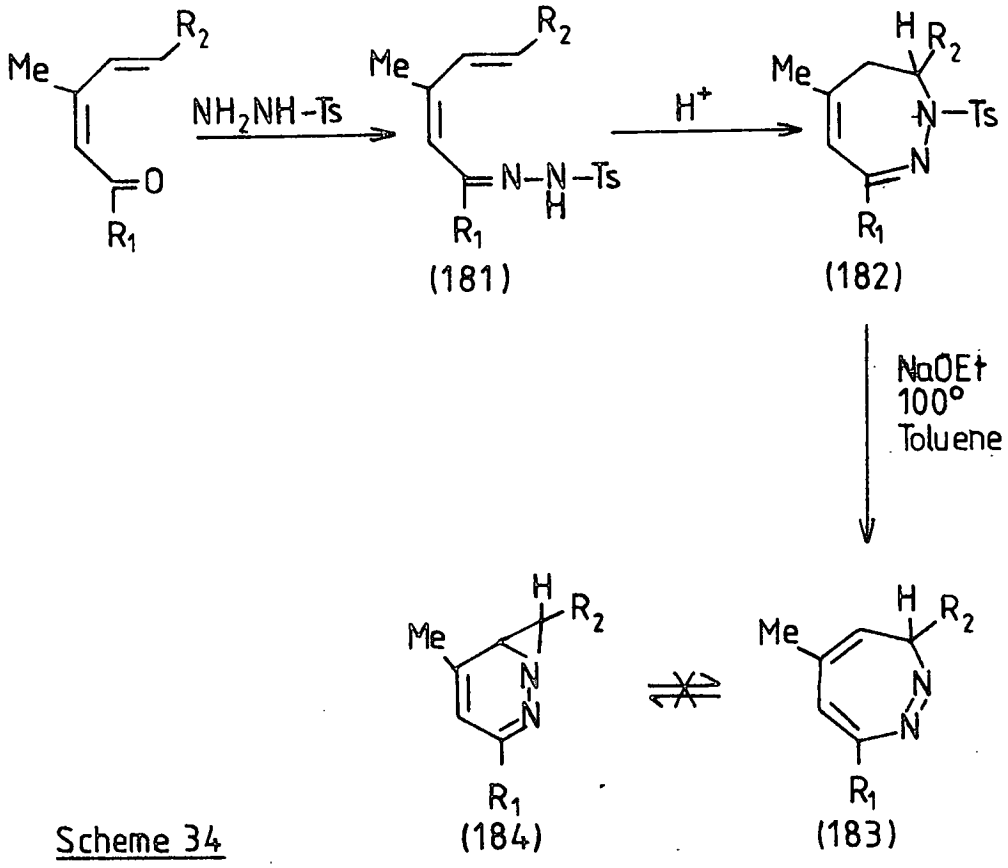
The first examples of 3*H*-1,2-diazepines were synthesised by Sharp and co-workers.[77] It was shown that α,β:γ,δ-unsaturated diazocompounds (62), derived from the tosylhydrazones of 2-methylene cyclopentanone, could undergo 1,7-electrocyclisations to give 3*H*-1,2-benzodiazepines (64), *via* the non-benzoid isomer which rearomatised to give the final product. This was the first route to 3*H*-1,2-diazepines, and was found only to occur when steric factors disfavoured the alternate 6π 1,5-electro-cyclisation to pyrazoles. It was subsequently shown that 3*H*-1,2-benzodiazepines of the structure (67) could be formed by an analogous route. (See section 2.4, page 34).

Further studies have shown that the 1,7-intramolecular electrocyclisation of conjugated diazoalkenes can result in 3*H*-1,2-diazepines as final products. It was shown that α,β:γ,δ-unsaturated diazo compounds having α,β - aromatic and γ,δ-olefinic unsaturation readily underwent 1,7-electrocyclisa-

tion to give the non-benzoic intermediates which underwent a[1,5]sigmatropic hydrogen shift to give the isolated 1*H*-2,3-benzodiazepines (80)[80] and thieno[3*H*-1,2]diazepines (83,86)[81] in good yields. (See section 2.4, page 40).

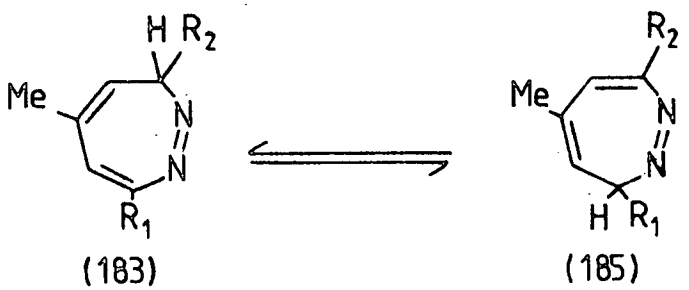
The only known route to monocyclic 3*H*-1,2-diazepines is by the base-induced elimination of toluene-*p*-sulphinic acid from 3,4-dihydro-2-tosyl-1,2-diazepines. Prolonged treatment of an α,β:γ,δ-unsaturated aldehydes or ketones with *p*-toluene-sulphonylhydrazine in the presence of catalytic amounts of strong acids, sulphuric acid or hydrochloric acid, leads to the 3,4-dihydro-2-tosyl-1,2-diazepines[122] (182). It is notable that in this cyclisation both *E* and *Z* dienones react to give the 3,4-dihydro-2-tosyl-1,2-diazepines and it was shown that two mechanisms for formation of (182) were operating: a slow cyclisation of the *Z* tosylhydrazone, and a fast acid-catalysed reaction in which protonation of the tosylhydrazone allows *E*→*Z* conversion before ring closure. It should also be noted that the ring closure step is substituent dependent and in some cases, notably R_2=aryl, the tosylhydrazone (181) could not be cyclised. (Scheme 34).

Treatment of the 3,4-dihydro-2-tosyl-1,2-diazepines (182) with sodium ethoxide in toluene at *ca* 100°C[123] provides a high-yielding route to 3*H*-1,2-diazepines (183), which exists in this form and not the tautomeric diazanorcaradiene (184) that the 5*H*-1,2-diazepine is known to exist as.[124]



Scheme 34

In these reactions the primary product (183) was not always the only product isolated; in two cases the product was an equilibrium mixture of the two isomers (183) and (185).

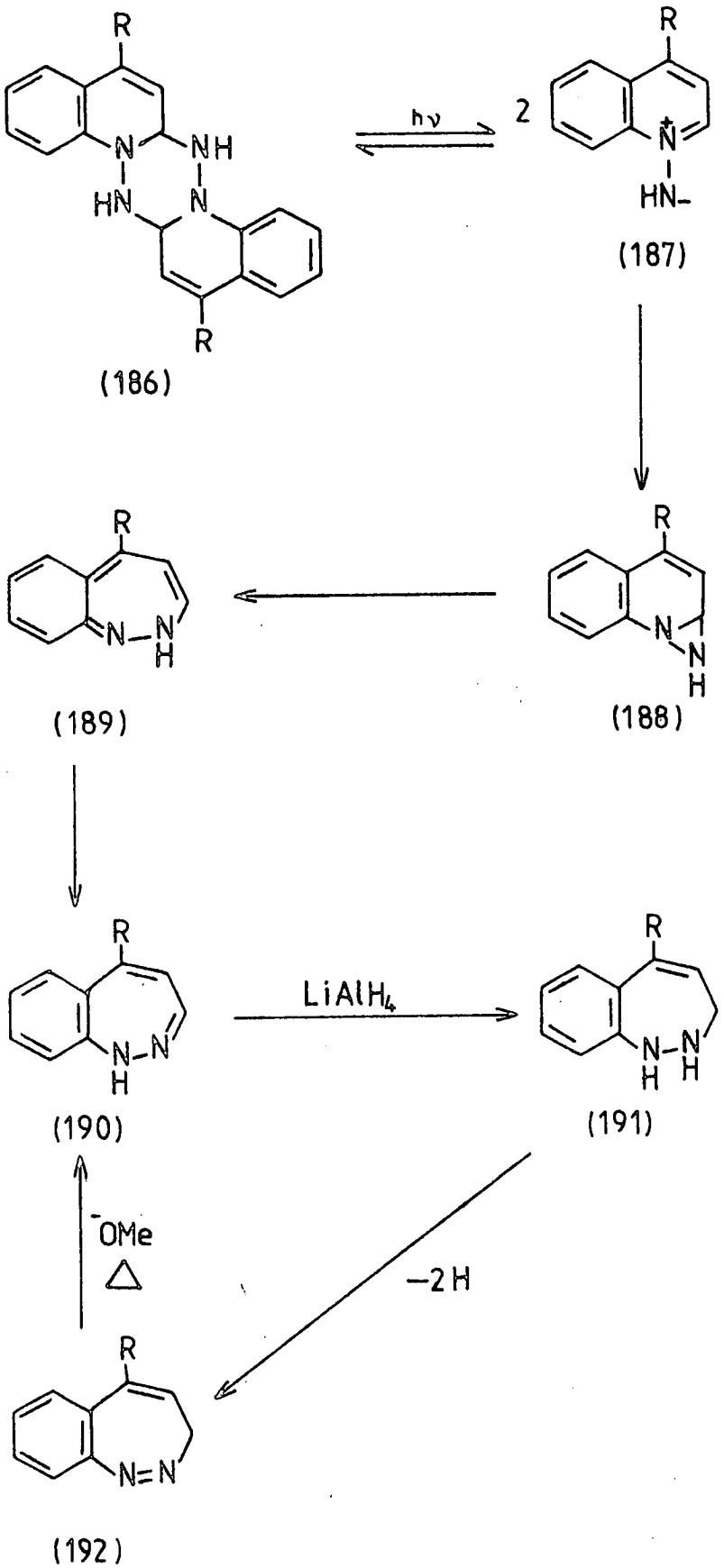


These isomers interconvert by [1,5] sigmatropic hydrogen shifts, very rapidly at the reaction temperature and fast enough at room temperature to make isolation of pure samples

of each isomer impossible. Pure samples could be obtained by high speed liquid chromatography at $0^{o}C$, which reverted back to an equilibrium mixture over *ca* 2 h at $0^{o}C$. A kinetic study showed that the hydrogen shift is *ca* 10^{10} faster than in the analogous cycloheptatriene.

The only other known fused 3*H*-1,2-diazepines are the 3*H*-1,2-benzodiazepines (192) reported by Tsuchiya.[125] These were prepared from the isomerisation of the known 1*H* isomers which were prepared in moderate yields by photolysis of *N*-iminoquinolium ylide dimers (186). The process for the formation of the 1*H* isomers (190) is thought to involve the equilibration to the ylides (187) followed by isomerisation to the diazirine intermediate (188) which subsequently undergoes a cycloreversion to (189) which tautomerises to the 1*H*-1,2-benzodiazepines (190).

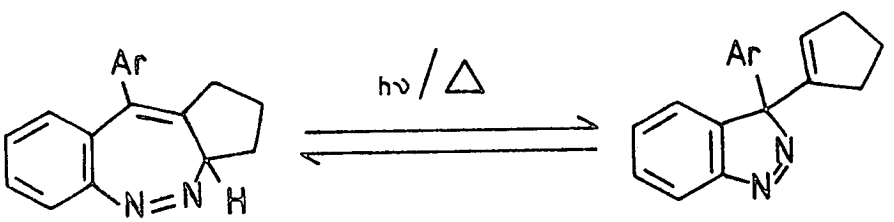
Treatment of the 1*H*-1,2-benzodiazepine (190) with lithium aluminium hydride gave the dihydro 1,2-benzodiazepine (191) which was dehydrogenated with 4-phenyl-1,2,4-triazoline-3,5-dione to give the 3*H*-1,2-benzodiazepines (192) in moderate yields.[126] (Scheme 35). The 3*H* isomers readily tautomerised to the 1*H* isomer on heating or treatment with base.


R
NH
HN
N
(186)
hν
2
R
N
HN–
(187)
R
N
N
H
(188)
R
N–N
H
(189)
R
N–N
H
(190)
LiAlH4
R
N–N
H H
(191)
-OMe
△
–2 H
R
N=N
(192)

Scheme 35

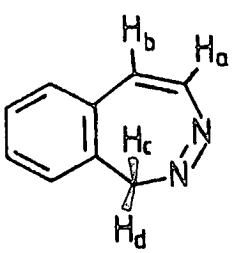
4.3) Reactions of 3*H*-1,2-Diazepines

3*H*-1,2-Diazepines (64) undergo a thermally or photochemically induced reversible transformation to 3-alkenyl-3*H*-indazoles (193), *via* a formal 1,3-migration of the azo group.[127,128] This 3*H*-indazole then readily extrudes nitrogen to give a complex mixture of hydrocarbons, derived from a carbene or diradical intermediate.



(64) (193)

The benzodiazepines (80) are crystalline, light sensitive structures which readily lose nitrogen in the mass spectrometer, a feature typical of cyclic azo-compounds. They exhibit temperature dependence ^{1}H n.m.r. For example in the parent system (80; R=R$_1$=H) apart from the aromatic multiplet the low temperature spectrum (-50°C) shows four doublets, each one integrating to one proton, decoupling experiments showing coupling between the a-b pair and the c-d pair. An examination of the temperature dependence of the spectrum showed that the



(80, R=R$_1$=H)

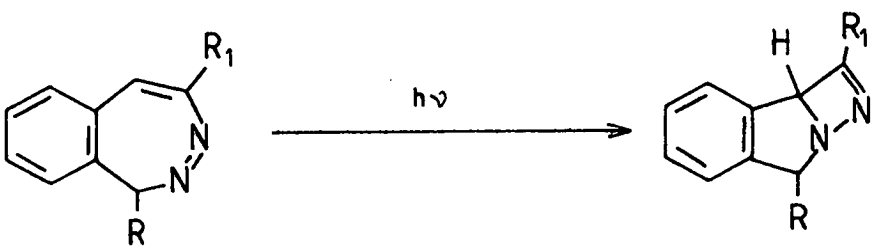
c and d doublets broadened with increasing temperature eventually undergoing coalescence to give a singlet. The protons c and d had a very large chemical shift difference (*ca* 3.4 p.p.m.). This large difference in chemical shift is due to differing deshielding exhibited by the azo group on each proton. This difference is accounted for by investigating a Dreiding model of the molecule, which shows that H_d is almost in the plane of the azo-group and H_c lies well above the plane. (It has been shown that protons in the plane of an azo group are deshielded relative to those above or below their plane[129].) Thus the deshielded doublet of the c-d pair was assigned to H_d and the less deshielded doublet assigned to H_c.

The variable temperature dependence of the ^1H n.m.r. is explained in terms of ring inversion of the diazepine ring system, similar temperature dependence had been observed for 4*H*-1,2-diazepines. At higher temperatures ring inversion was occurring rapidly giving H_c and H_d as an average signal i.e. a singlet and at low temperatures the diazepine ring was fixed in one rigid conformation giving the two non-equivalent protons observed. When substitution at the C-3 of the diazepine occurred the substituent always adopted the least hindered *exo* position and no variable temperature effect could be observed. The structure of the 1*H*-2,3-benzodiazepines was also confirmed by an X-ray structure analysis.

The energy barrier to ring conversion was calculated, from the coalescence temperature, to be *ca* 72 kJ mol^{-1}. The thieno[3*H*-1,2]diazepines (83,86) exhibit similar temperature dependent ^1H n.m.r. but have a lower $\Delta G_{\ddagger}$ (*ca* 67 kJ mol^{-1}) as

the 3*H*-diazepine ring is slightly more flexible in these cases.

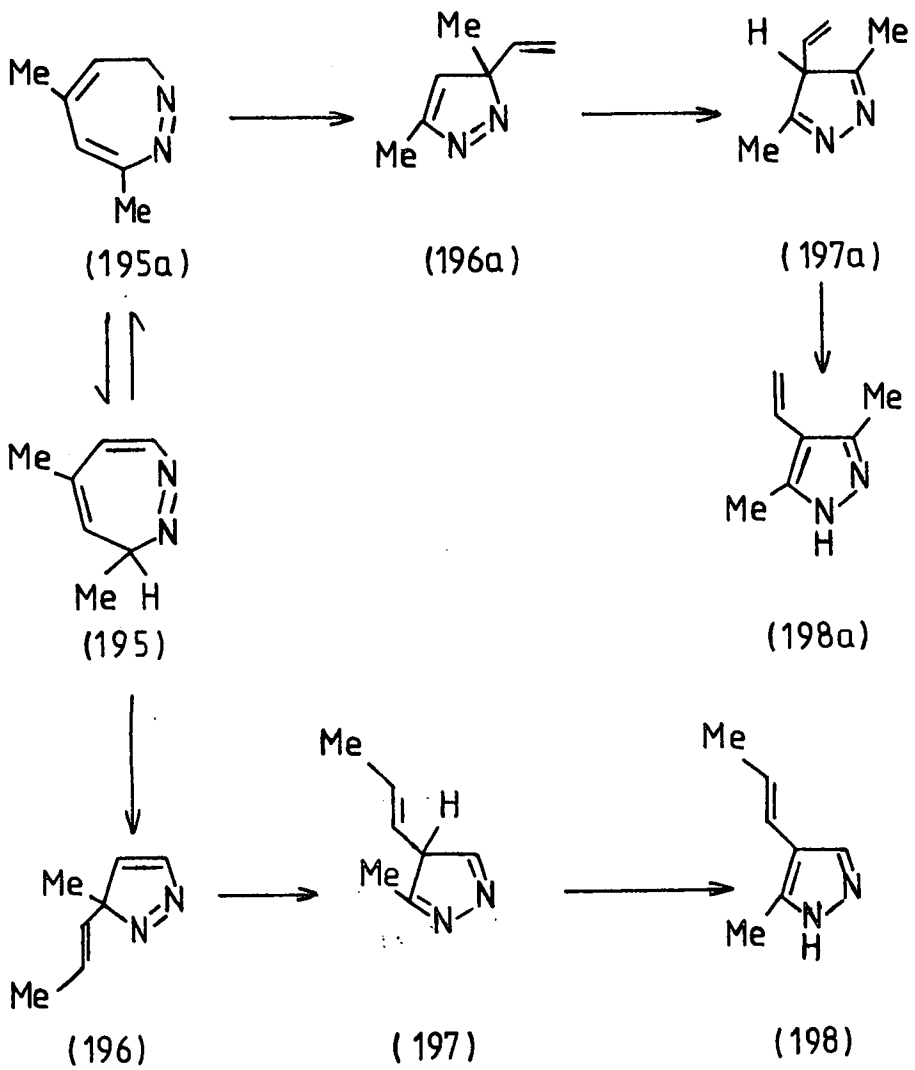
The 1*H*-2,3-benzodiazepines (80) are readily isomerised by light to the tricyclic compounds (194) by an internal $2\pi+2\pi$ cycloaddition.[130] These compounds are stable, although loss of nitrogen to give indenes is observed on heating, and similar results were observed for the thieno[3*H*-1,2]diazepines[81] and the monocyclic 3*H*-1,2-benzazepines.[131]



(80) (194)

The 3*H*-1,2-diazepines have similar spectral properties[80] to those of 1*H*-2,3-benzodiazepines, e.g. the monocyclic 3*H*-1,2-diazepines readily lose nitrogen in the mass spectrometer. The ^{1}H n.m.r. spectra were much like those of similarly substituted 1*H*-2,3-benzodiazepines. For example in (183; R_1=Ph, R_2=H) the chemical shifts of two protons attached to the saturated ring carbon had a characteristically wide chemical-shift separation (*ca* 3.9 p.p.m.). The ^{13}C n.m.r. had a saturated carbon at 66.7 p.p.m. which appeared as a doublet of doublets in a single off resonance decoupling study. This position for C-3, the saturated carbon attached to the azo group, is strongly deshielded and observed in a range (65.7-77.4 p.p.m.) similar to that reported for benzodiazepines,[76,77] having adjacent nitrogens.

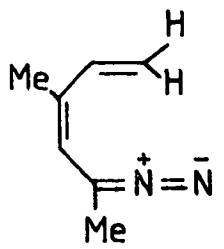
On thermolysis 3*H*-1,2-diazepines undergo a thermally induced ring contraction to 4-alkenyl-1*H*-pyrazoles *via* a formal 1,3-azo group migration and further rearrangements[132]. In non-symmetrical 3*H*-1,2-diazepines a rapid interconversion of the two isomers (195,195a) occurs *via* a[1,5]sigmatropic hydrogen shift and thus pyrolysis can proceed *via* cleavage of the 2,3-bond in either (195) or (195a) or both. The reaction can be rationalised as a multi-step process in which the initial azo-group migrates to give an unstable 3-alkenyl-3-methyl-3*H*-pyrazole (196,196a) which undergoes a van Alphen-



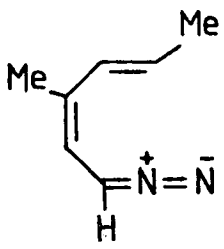
Scheme 36

Huttel rearrangement to the 4*H*-pyrazoles (197,197a) followed by a very fast proton shift to nitrogen to give the 1*H*-pyrazoles (198,198a) (Scheme 36).

The mechanism of the initial ring contraction step is unclear, but involves the formal 1,3-migration of an azo group, either by a dipolar or diradical intermediate. It was suggested that the radical mechanism seems unlikely and that ring opening to a diazoalkane (199,199a) followed by 6π electrocyclisation to (196,196a) is the more probable mechanism.



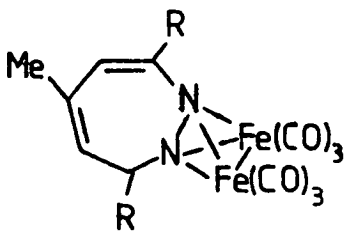
(199a)



(199)

3*H*-1,2-Diazepines have been shown to form 1:1 complexes (200) with diiron nonacarbonyl.[133] This complexation much reduces the activation for diazepine ring inversion and destroys the strong activating effect of the azo group on the rate of 1,5-sigmatrophic hydrogen migrations.[136] The separation of each isomer of the iron complexes could be achieved in some cases whereas separation of the parent diazepine had been impossible.

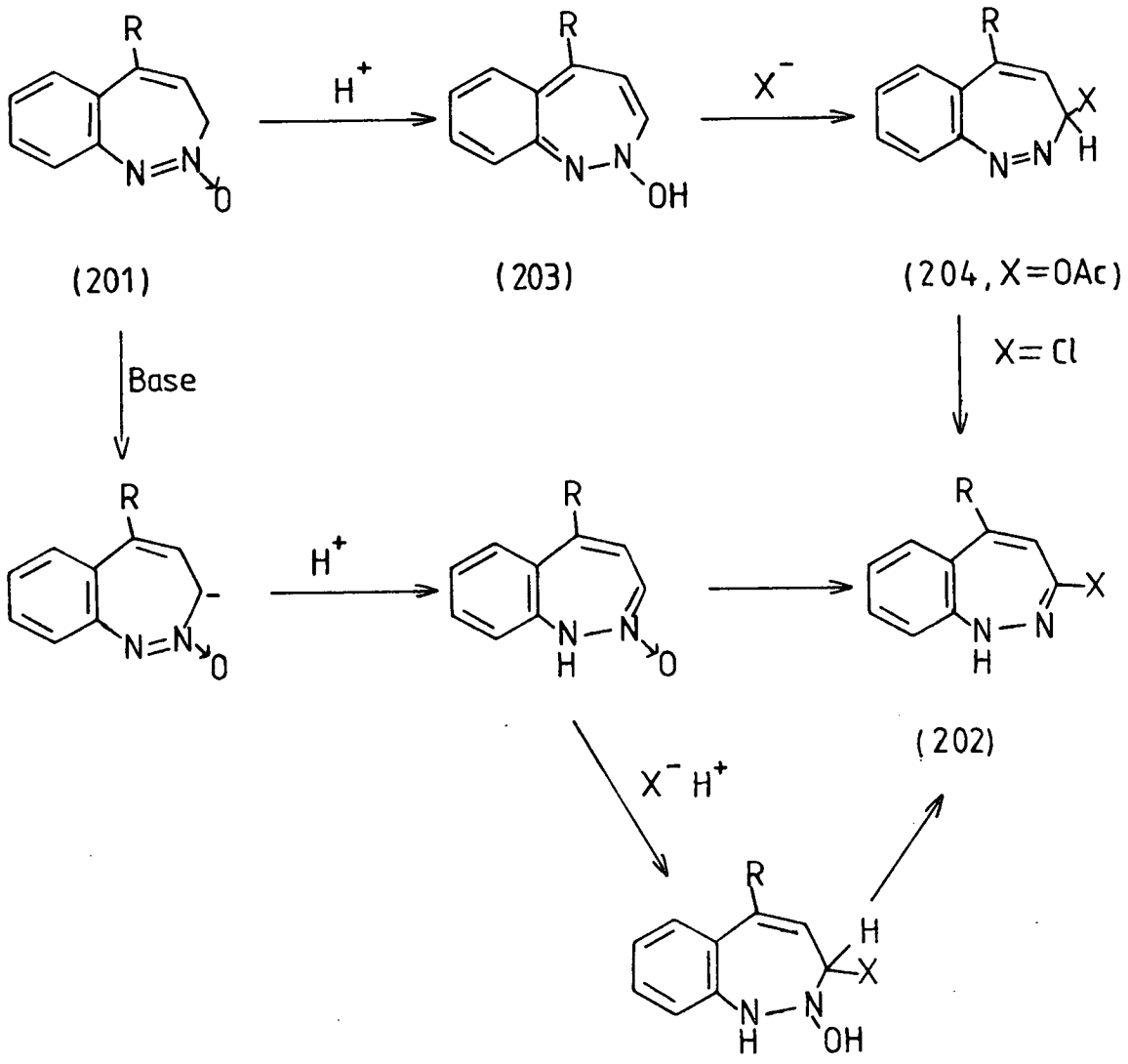
The n.m.r. spectra of 3*H*-1,2-benzodiazepines (192) show a similar temperature dependence to 1*H*-2,3-benzodiazepines, consistent with temperature dependent inversion of a diazepine ring. The C-3 methylene protons showed analogous behaviour



(200)

to 1*H*-2,3-benzodiazepines, both protons being equivalent at high temperatures (100°C) and at lower temperatures (-80°C) being separated by 3.6 p.p.m. The energy barrier to ring inversion was found to be lower than that of the 1*H*-2,3-benzodiazepines.

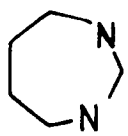
On photolysis the 3*H*-1,2-benzodiazepines (192) give 1*H*-indazoles and indenes probably *via* a 3*H*-pyrazole, in a process similar to previously reported compounds of this type.[126] Treatment of 3*H*-1,2-benzodiazepines (192) with *m*-chloroperbenzoic acid gave two *N*-oxides, the *N*-2:*N*-1 ratio =3:1. The resulting *N*-2-oxide (201) was converted into 3-functionalised 1*H*-1,2-benzodiazepine (202) on treatment with base. Treatment with acid however resulted in 3-functionalised 3*H*-1,2-benzodiazepines (204) which were isolable in some cases[134] (Scheme 37).



Scheme 37

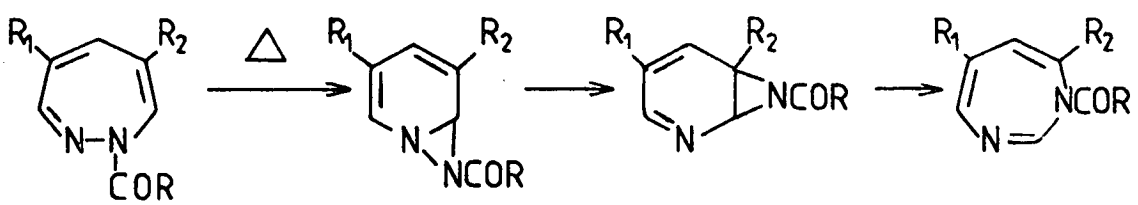
5.1) 1,3-Diazepines

1,3-Diazepines are monocyclcic, seven-membered rings containing two nitrogen atoms (205) which are separated by one carbon atom. The 1,3-diazepines have received less attention than their 1,2-isomers, but their synthesis and chemistry has been reviewed.[117,118,120]



(205)

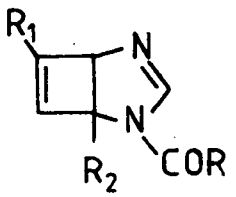
Recently the first route to the fully unsaturated system (208) was reported.[135-137] Thermal decomposition of 1-acyl-1,2-diazepines (206), having specific ring substitution, gives the diazanorcaradiene (207) which undergoes a walk rearrangement, followed by ring opening to give the 1,3-diazepine (208).



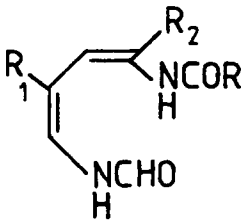
(206) (207) (208)

Not much is known about the reactivity of fully unsaturated 1,3-diazepine systems, but it has been shown that (208) undergoes a thermally reversible photoisomerisation to the bicyclic product (209),[135] and that it hydrolyses readily with water

and acids to the open chain system (210).[143]

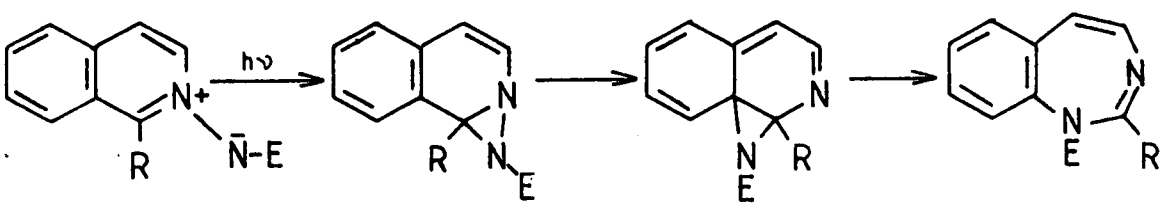


(209)



(210)

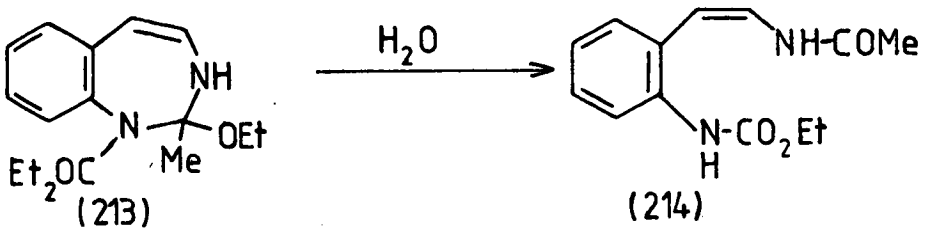
The fully unsaturated 1*H*-1,3-benzodiazepine (212) is formed in a similar process by a photoreaction of the 1-substituted isoquinoline *N*-imide (211).[137] The same principle



(211) (212)

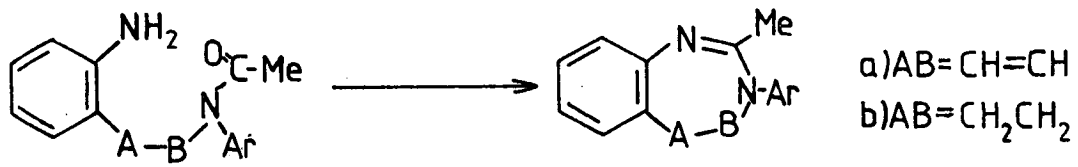
has also been applied to the preparation of thieno-, furo- and pyrrolo-fused 1,3-diazepines.[136] and 3*H*-1,3-benzodiazepines from quinoline-*N*-imides.[142]

Treatment of (212; R=Me) with ethanol in the presence of acetic acid gave the adduct (213) which hydrolysed readily to give the ring opened product (214). This hydrolysis step is a common reaction of 1,3-diazepines having the unstable saturated -NR-CR_2-NH- linkage, and is responsible for the instability of these systems.[137]



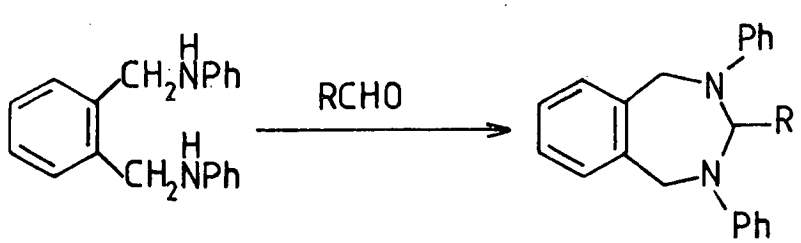
(213) (214)

Unsaturated 1,3-benzodiazepines (216) have also been prepared by ring closure of systems of type (215), by dehydration with molecular phosphorus oxychloride and phosphorus tribromide.[138]



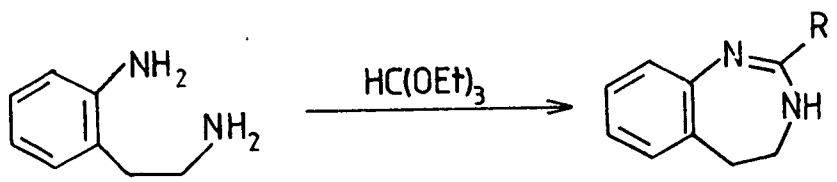
(215) (216)

The most widely used routes to 1,3-diazepines are those involving reaction of diamino compounds (217,219) with 1,1-bis-electrophilic reagents. This route gives easy access to 1,3 and 2,4-benzodiazepines, e.g. reaction of (217) with formaldehyde gives the saturated 2,4-benzodiazepine (218).[139]



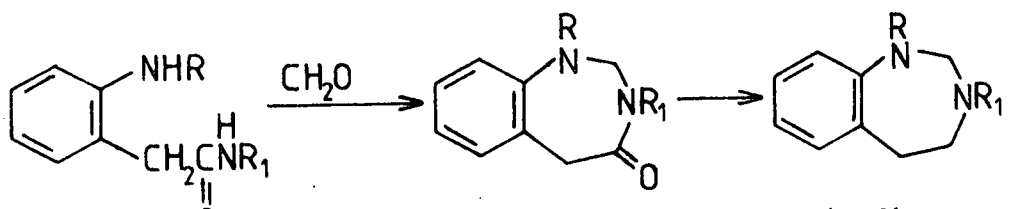
(217) (218)

Condensation of 1,4-diamines with a variety of carboxylic acid derivatives e.g. imidate esters and orthoformic esters produces the cyclic amidine linkage (-N=C-R(NH)-) and this route has led to monocyclic systems[120] and 1,3-benzodiazepines.[118] For example reaction of (219) with ethyl orthoformate gives the 1,3-benzodiazepine (220).



(219) (220, R=H)

Reduction of 1,3-benzodiazepin-4-ones (221) with lithium aluminium hydride also gives the fully saturated 1,3-benzodiazepines (222).[140]

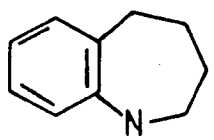


(221) (222)

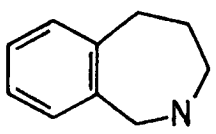
The completely saturated 1,3-diazepines all have the unstable fully saturated $-NHCH_2NH-$ linkage, which results in a very limited stability in this series of compounds. For example, (222; R=H, R_1=Me) could only be isolated as its maleate salt as the free base decomposed spontaneously.[141] The C=N bond of unsaturated 1,3-benzodiazepines is also readily hydrolysed to systems such as (213) which contain this unstable linkage and thus these systems are also unstable.

6.) BENZAZEPINES

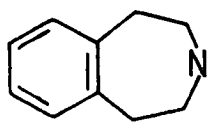
Benzazepines are bicyclic compounds consisting of an azepine ring, fused to a benzene ring. Annulation of a benzene ring to the azepine ring can be achieved in three different ways, to give three isomers (223-225).



1-Benzazepine (223)



2-Benzazepine (224)

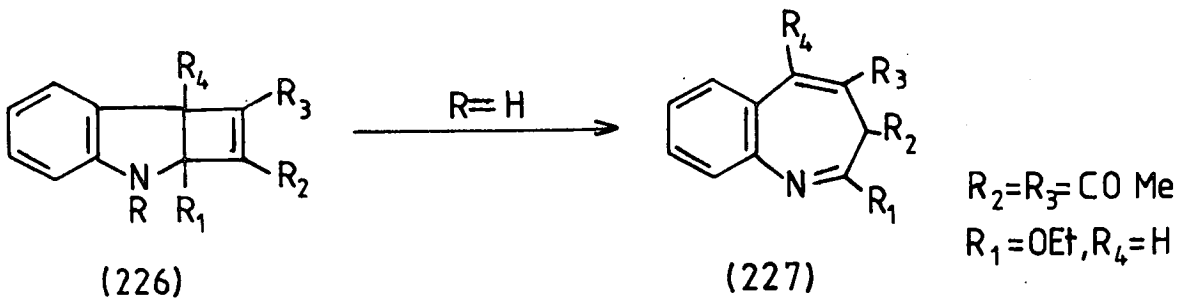


3-Benzazepine (225)

Derivatives of the benzazepines have been of interest to medicinal chemists for their wide range of biological activity. Reviews on the synthesis and reactivity of benzazepines have been published and these deal mostly with the well-known hydro and oxo derivatives.[144-146]

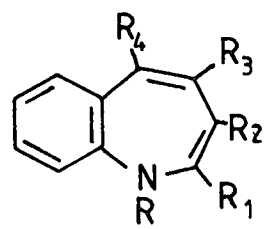
The fully unsaturated derivatives of all three benzazepines have now been synthesised and the routes to the 3- and 1-isomers are discussed below.

The 3*H*-1-benzazepine (227) has been prepared by the ring expansion of the 2-ethoxyindole-dimethyl acetylenedicarboxylate Diels-Alder adduct (226). When this reaction was carried out with a *N*-substituted indole the only reaction product was the 1*H*-1-benzazepine isomer.[147] The 1-acetyl-1-benzazepine derivative (228, R=Ac, R^1=R^2=H, R^3=CO_2Me, R^4=piperidine) has also been obtained by the ring expansion of analogous intermediates (226; R=Ac, R^1=R^2=H, R^3=CO_2Me, R^4=piperidine), which could be



(226) (227)

isolated and whose structures were confirmed by n.m.r.[148] A number of *N*-acylated derivatives e.g. (226; R=R-C=O, $R^1=R^2=R^3=R^4=H$) have also been prepared *via* the photocycloaddition of methyl acrylate to 1-benzoylindole followed by hydrolysis and oxidative decarboxylation with lead tetraacetate, these decomposed at 250-280°C to give 1-acyl-1*H*-1-benzazepines (228; R=R-C=O, $R^1=R^2=R^3=R^4=H$) as a major product.[149]

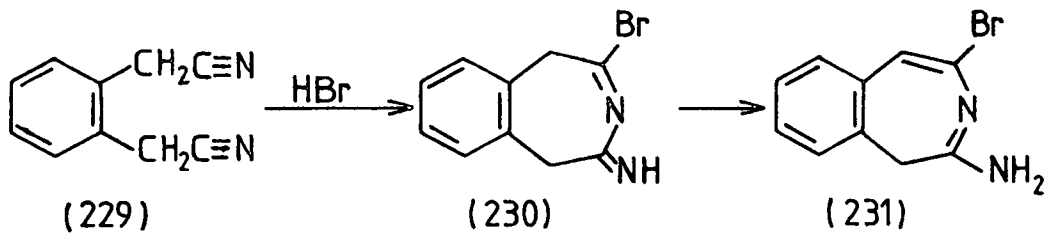


(228)

More heavily substituted *N*-methyl analogues have also been prepared directly by the photocycloaddition of dimethyl acetylenedicarboxylate to *N*-methylindoles, it was shown that these undergo both thermal and photochemical rearrangements to 1*H*-1-benzazepines, but that this rearrangement is prevented by a methylene bridge across the fusion position.[150]

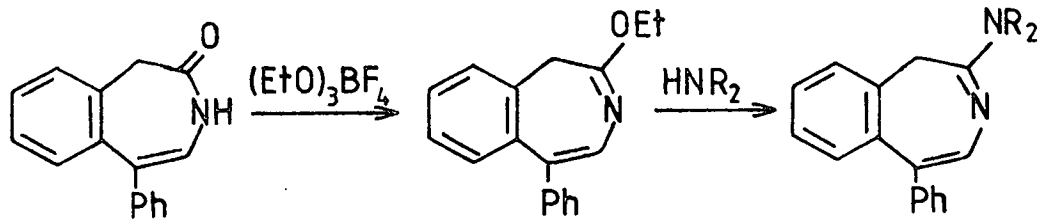
Unsaturated 3-benzazepines have also been prepared from compound (229) upon treatment with hydrogen bromide in acetic acid.[151] The intramolecular electrophilic attack of one nitrile group upon the other gives (230) which tautomerises to

the 2-amino-1*H*-tautomer (231).



(229) (230) (231)

It has been shown that 1*H*-3-benzazepin-2-amines are pharmacologically active, and synthetic routes to these compounds have been reported.[152] Thus, the 1,3-dihydro-2*H*-3-benzazepin-2-one (232) was prepared in four steps from homoveratroyl chloride and phenacylamine. Treatment of (232) with triethyloxonium fluoroborate gave the imino-ether (233) which on heating with ammonia or dimethylamine gave the desired 1*H*-3-benzazepin-2-amine (234).



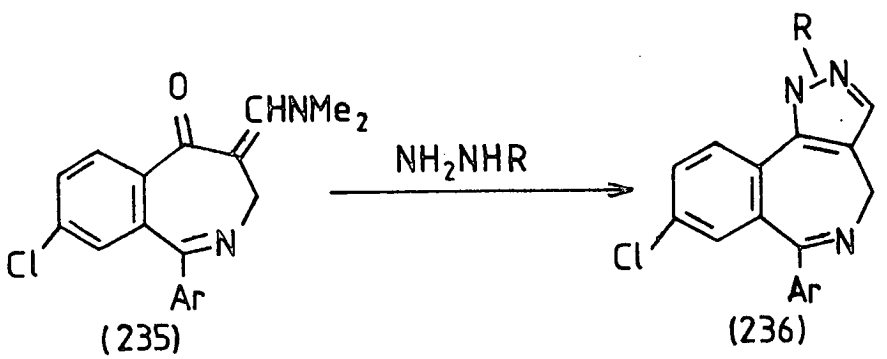
(232) (233) (234)

6.1) 2-Benzazepines

Many examples of di- and tetra-hydro 2-benzazepines have been reported and these are reviewed by Kasparek.[145] These derivatives were prepared by von Braun, intramolecular Friedel-Crafts, and Bishler-Napieralski reactions on suitably mono- or

o-di-substituted benzenes.

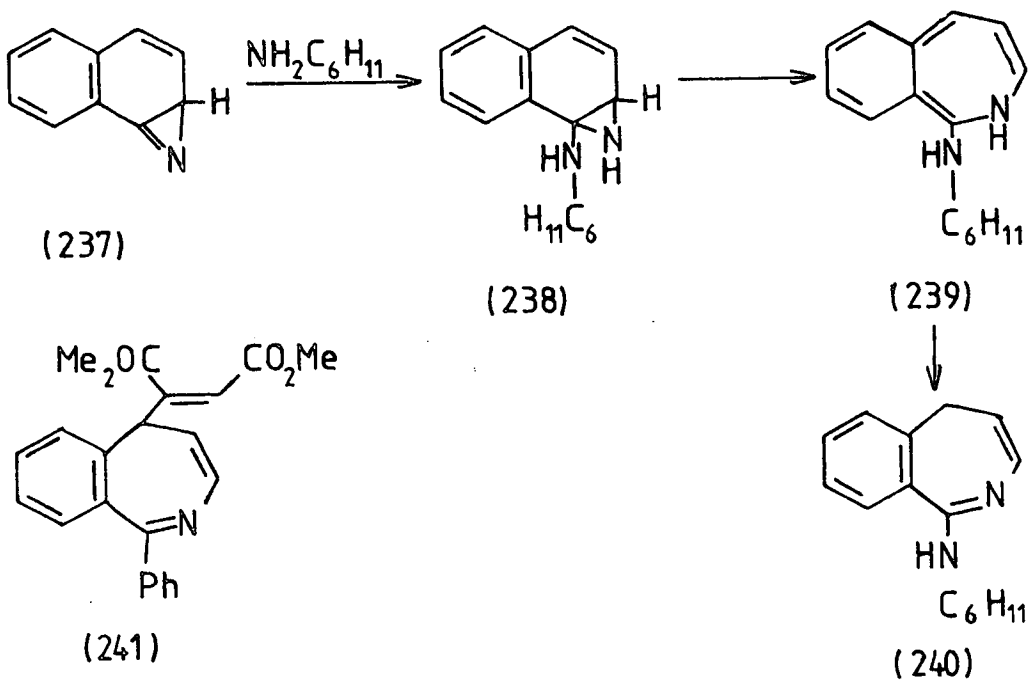
There are comparatively few references to the parent unsaturated 2-benzazepines reported, but several examples of unsaturated 2-benzazepines fused to another aromatic ring are reported.[153-156] For example, examination of the literature shows that industrial laboratories are reporting a number of pyrazolo[4,3-c]benzazepines (236) as anti-depressants and anxiolytics. The pyrazolobenzazepine (236) was prepared by condensing (235), obtained from 5-chloro-*o*-toluic acid in eight steps, with hydrazines.[153-155]



Of the non-fused 2-benzazepines the 2*H*- and 4*H*-isomers are the least stable as they both contain a non-benzoid carbocyclic ring, and no compounds of these types have been isolated. Of the remaining three unsaturated 2-benzazepine isomers only a few examples of 5*H*- and 1*H*-isomers appear in the literature with the 3*H*-isomer being the best documented.

Only one synthetic route to 5*H*-2-benzazepines has been reported, involving the photolysis of α-azidoarenes in primary amines.[157] Thus photolysis of α-azidonaphthalene in hexylamine leads to the 1-amino-5*H*-2-benzazepine (240) in low yield. The reaction mechanism is thought to involve the formation of (238) by nucleophilic attack on the 2*H*-azirine (237) followed

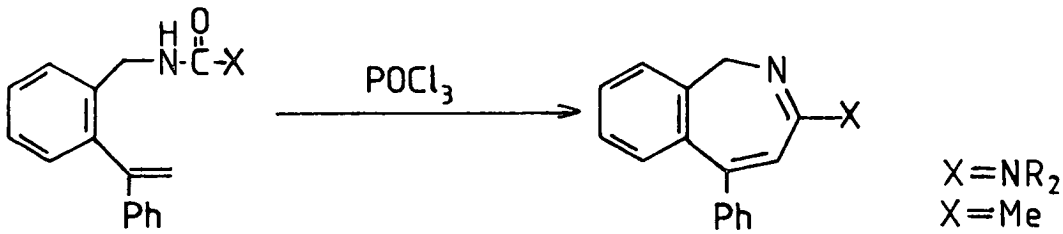
by ring expansion to the non-aromatic 2*H*-2-benzazepine which then tautomerises to the stable 5*H*-isomer (240). Photolysis of 5- and 8-azidoquinolines leads to 5*H*-pyridoazepines by an analogous mechanism.



The only other reported 5*H*-2-benzazepine is (241) obtained by heating dimethylacetylene dicarboxylate with 1-phenyl-3*H*-2-benzazepine.[158]

The synthesis of fully unsaturated 1*H*-2-benzazepines has been carried out by Gast and co-workers.[159] Treatment of trisubstituted urea derivatives (242), derived from 2-(β-styryl)-benzylamines, resulted in cyclisation to 3-amino-5-phenyl-1*H*-2-benzazepines (243) in moderate yields.

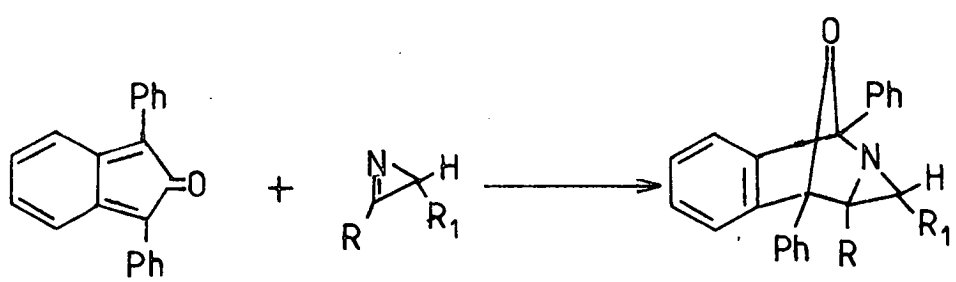
These 1*H*-2-benzazepines (243; X=NR_2) could be hydrolysed to the corresponding 2-benzazepin-3-ones and also reduced



(242) (243)

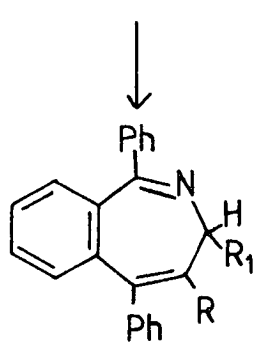
with sodium borohydride to the 2,3-dihydro-1*H*-2-benzazepines. The proton n.m.r. showed that the C-1 protons absorbed at *ca* 4.4 p.p.m. as a broad singlet (X=Me), and as an AB system at *ca* 4.0 and 4.5 p.p.m., J *ca* 10Hz at 20°C which becomes a broad singlet at higher temperatures ($X=NMe_2$).

Several examples of 3*H*-2-benzazepines have been synthesised by Hœssner and Anderson, by utilising the cycloaddition reactions of 2*H*-azirines with dienones.[160] Thermal decomposition of terminal vinyl azides in the presence of 1,3-diphenylinden-2-one, in refluxing xylene, lead to the formation of the highly crystalline 3*H*-2-benzazepines in high yields.



(244) (245)

a R=Ph, R^1=H
b R=Ph, R^1=Me
c $R=R^1$=Ph
d $R=R^1$=Me
e $R=R^1$=Et



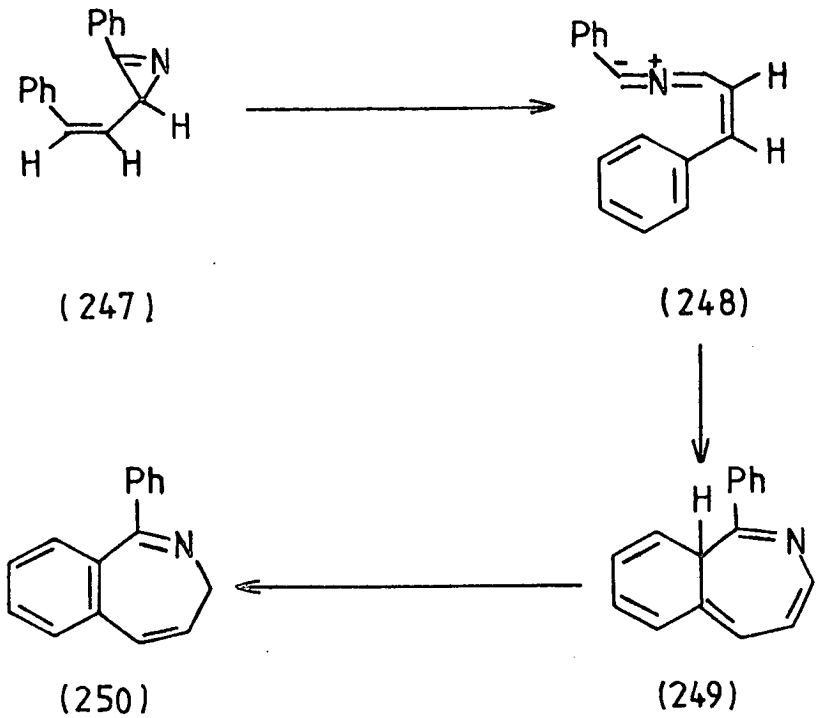
(246)

The mechanism of this reaction is thought to involve the initial Diels-Alder type addition of the azirine and the cyclone (244) to give the intermediate (245) which then undergoes loss of carbon monoxide *via* participation of the aziridine carbon-nitrogen bond. 3*H*-Azepines and phenanthro-2*H*-azepines were also prepared by analogous routes.

The 3*H*-2-benzazepines formed were stable to isomerisation when treated with base or heat. The proton n.m.r. of (246a) at 25°C showed the C-3 protons as two doublets, δ3.60 (d, J10Hz, eq.H) and 4.94 (d, 10Hz, ax.H), indicating a slow inversion of the azepine ring at this temperature.

Access to 3*H*-benzazepines is also available by the photorearrangement of *Z*-3-phenyl-2-styryl-2*H*-azirines[107,158] (247). Irradiation of the 2*H*-azirine (247) generates the nitrile ylide (248) which undergoes a 1,7-electrocyclisation to the non-benzoid structure (249) which undergoes a rapid [1,5]sigmatropic hydrogen migration restoring the aromaticity of the benzene ring of the isolated 3*H*-2-benzazepine (250).

The proton spectra of the 3*H*-2-benzazepine (250) showed only one absorption for C-3 protons at ambient temperatures indicating a fairly rapid ring inversion, in this compound. The equivalence of the methylene protons conflicted with the non-equivalence found in previous systems (246a) at similar temperatures. However, similarly prepared 3*H*-2-naphthazepines showed the C-3 protons as non-equivalent at room temperature giving absorptions at δ2.80 (dd J=18, 6Hz) and 3.25 (dd, J=18, 6Hz). Irradiation of the corresponding *E*-isomer of the 2*H*-azirine did not produce any benzazepine, as the 1,7-electrocyclisation is prevented by



(247) (248)

(250) (249)

steric restrictions, but gave 2,3-diphenylpyrrole *via* a 1,5-electrocyclisation.

A 3*H*-2-benzazepine was also claimed to be a minor product (5%) in the photolysis of diethoxycarbonyl isoquinolinium ylide[161] although the ^{1}H n.m.r. shift of the imine proton (δ6.71) was not as deshielded as would be expected and no subsequent reports confirming this structure have been published.

DISCUSSION

Page No

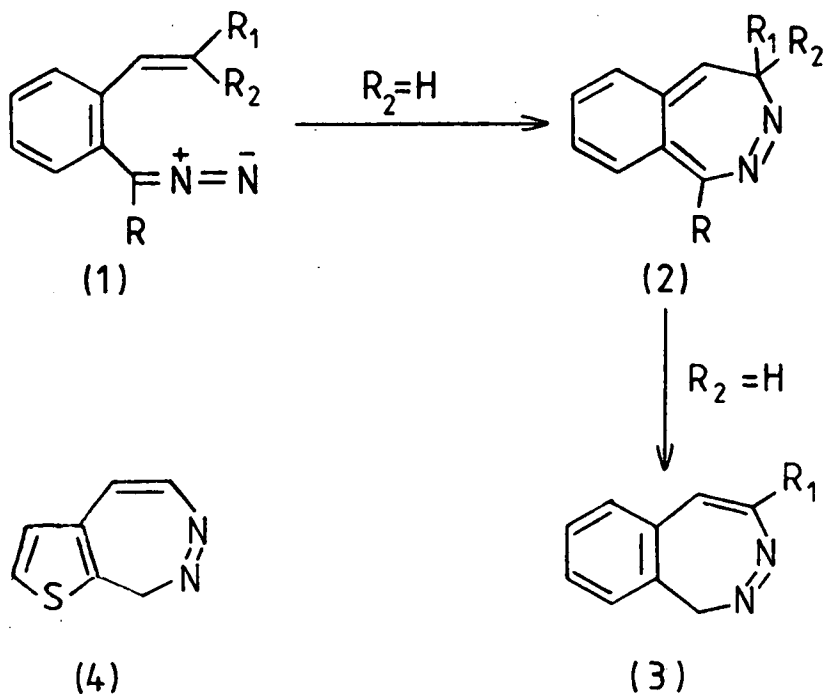
SECTION 2

INTRAMOLECULAR REACTIONS OF α,β:γ,δ-UNSATURATED NITRILE YLIDES

DISCUSSION

Programme of Research

It has been known for some time that α,β:γ,δ-unsaturated diazoalkanes, having α,β-aromatic unsaturation, (1) undergo 1,7-electrocyclisation to give,for example,1*H*-2,3-benzodiazepines (3) and thieno[3*H*-1,2]diazepines (4) as shown in Scheme 1.

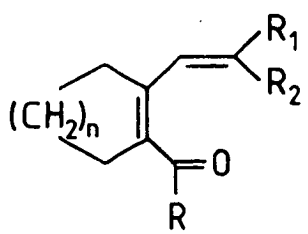


Scheme 1

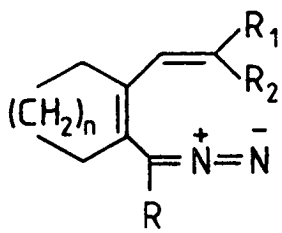
The object of this research was to ascertain whether this principle could also be used to prepare monocyclic 3*H*-1,2-diazepines from precursors having α,β-and γ,δ-olefinic bonds. The first objective was to study systems having a cycloalkenyl α,β-double bond (6) which would ensure the

required Z relationship of the γ,δ-double bond and the diazo function.

Thus, it was the target of the project to find routes to the α,β:γ,δ-unsaturated carbonyl compounds (5) which could be converted to the corresponding diazocompounds (6) *via* the tosylhydrazones.



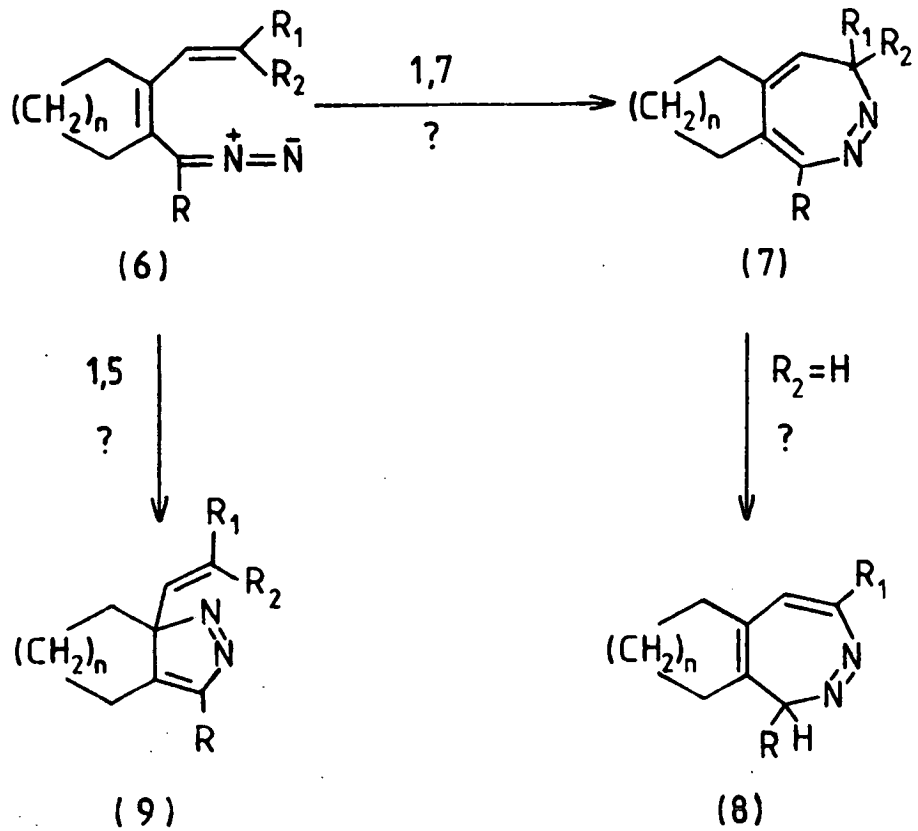
(5)



(6)

The primary object of this project was to find out whether these systems would react *via* an 8π electron 1,7-cyclisation or *via* a 6π electron 1,5-cyclisation, to give 3-vinyl pyrazoles (9) (Scheme 2), or by some other route. It has been shown in the aromatic systems e.g. (1) that the introduction of the Zδ substituents R_2=Me, Ph and CO_2Et inhibited 1,7-electrocyclisation and we wished to find out whether the introduction of similar substituents would also alter the mode of reactivity of the diazoalkanes (6).

It was also hoped to generate analogous systems with an acyclic α,β-double bond and to investigate the effect of *E* and Z stereochemistry of this bond on their mode of intramolecular reaction.



(6) (7) (9) (8)

Scheme 2

A further potential area of interest was to investigate whether the principle of 1,7-electrocyclisation could be extended to other conjugated 1,3-dipoles, with a view to developing the syntheses of novel seven-membered heterocycles.

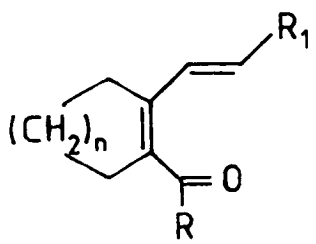
SECTION 1

INTRAMOLECULAR REACTIONS OF α,β:γ,δ-UNSATURATED DIAZO-COMPOUNDS

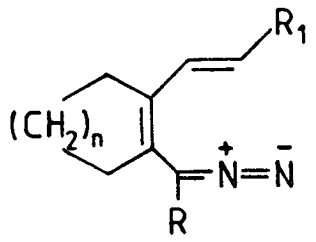
1.1) With cycloalkenyl α,β-double bonds

1.1.1) Synthesis of 1-alkenyl-2-carbonylcycloalkenes

The target diazo-compounds (6) were to be derived from the *p*-toluenesulphonylhydrazone precursors prepared from the compounds (5).

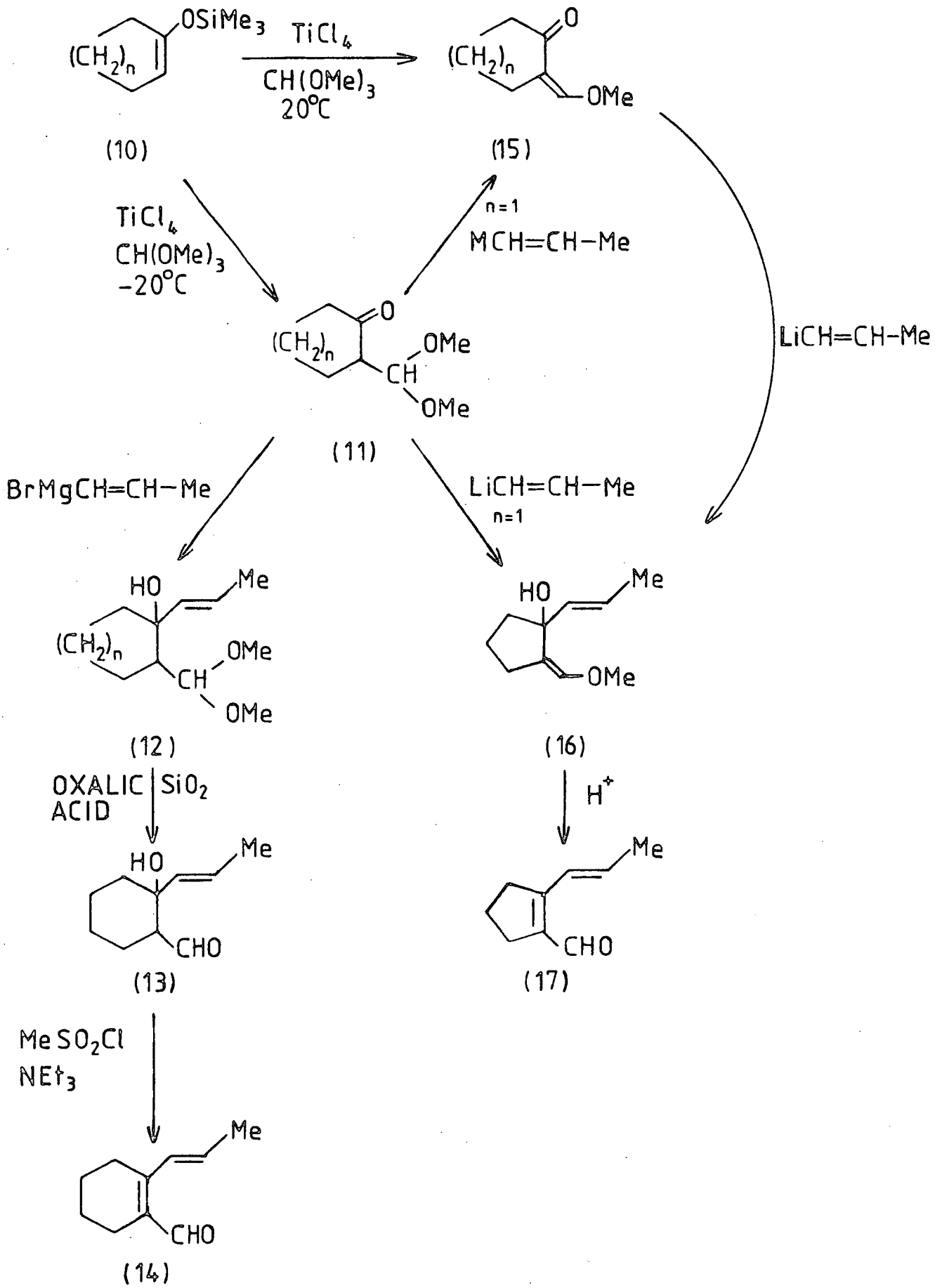


(5)



(6)

Therefore the initial priority was a synthesis of these carbonyl compounds. The first method used for their preparation involved the introduction of γ,δ-unsaturation by the Grignard reaction of 1-bromoalkenes with protected β-ketoaldehydes eg (11) Scheme 3. The latter were prepared by the reaction of trimethyl silyl enol ethers (10) with trimethyl orthoformate in the presence of titanium tetrachloride. The syntheses of these compounds were found to be more difficult than envisaged from the experimental details of Mukaiyama[162]. When this reaction was first carried out an inseparable mixture of the acetal (11) and another unreported compound (15) was obtained. By varying the reaction conditions it was found that either the desired acetal or enol ether (15) could be formed as the sole reaction product. Thus hydrolysis of the reaction mixture at


OSiMe3
TiCl4
CH(OMe)3
20°C
(CH2)n
O
OMe
(10)
(15)
TiCl4
CH(OMe)3
-20°C
n=1
MCH=CH-Me
LiCH=CH-Me
OMe
CH
(11)
BrMgCH=CH-Me
LiCH=CH-Me
n=1
HO
Me
(12)
(16)
OXALIC ACID
SiO2
H+
CHO
(13)
(17)
MeSO2Cl
NEt3
(14)

Scheme 3

room temperature with rapidly stirred base resulted in the isolation of compound (15), whereas hydrolysis of the reaction mixture under similar conditions at <-20°C resulted in the formation of the required dimethyl acetal of the 1-formyl cycloketone (11). Heating the acetal (11) did not produce any enol ether so it seems that the loss of methanol to give the enol ether arose during hydrolysis of the titanium complex and not from the acetal itself.

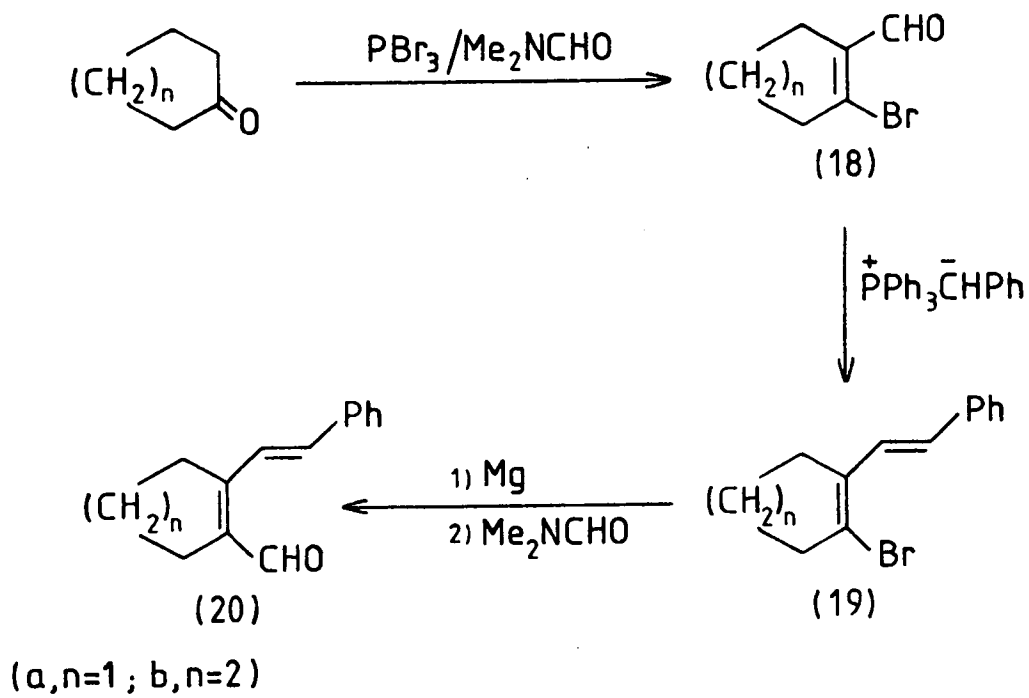
Synthesis of the α,β:γ,δ-unsaturated aldehyde (14) was to be achieved by reaction of a vinyl Grignard reagent with the acetal to give the alcohol (12) which would be subsequently deprotected to give the β-hydroxy-γ,δ-unsaturated aldehyde (13) by the use of silica gel and oxalic acid.[163] This was to be followed by dehydration by the method of Corey and Enders[164] to give the α,β:γ,δ-unsaturated aldehyde. This route was followed concurrently by co-workers and gave the cyclohexanone derivative in good yield (Scheme 3). However, when the cyclopentanone derivative (11, n=1) was reacted with the Grignard of 1-bromopropene a product was isolated which was formed by the reaction of two molecules of the Grignard reagent with the starting acetal. This product was not identified but its molecular weight was determined by mass spectroscopy. Low temperature (-78°C) reaction of the Grignard reagent with the acetal gave the alcohol (12, n=1) in very low yield. These results seemed to indicate that the acetal was extruding methanol under the reaction conditions to give the enol ether (15) which then underwent attack, by another molecule of the Grignard reagent, at the enol ether double bond. It was thought that use of an alkyl lithium reagent would avoid this

problem, as by precedent any enol ether formed during the reaction would subsequently undergo 1,2-addition of the lithium reagent at the carbonyl group to give the alcohol (16) rather than undergo the 1,4-addition which is favoured by Grignard reagents. However, use of the lithium reagent resulted mainly in formation of the enol ether (15, n=1) and a very low yield of the alcohol (16). Presumably the methanol formed with the enol ether destroyed the remaining lithium reagent. Thus it would have been necessary to use at least two fold excess of alkyl lithium reagent in order to effect the reaction with the acetal (11).

The α,β:γ,δ-unsaturated aldehyde (17) was finally synthesised in moderate yield *via* the reaction of the lithium reagent, formed from lithium metal and 1-bromopropene, with the enol ether (15) to give the alcohol (16). This was not isolated but treated with aqueous hydrochloric acid to effect dehydration of the α,β-bond and to remove the enol ether functionality.

Because of the problems outlined above and because of the difficulty in obtaining the required vinyl bromides it was decided to devise another synthetic route to the α,β:γ,δ-unsaturated carbonyl compounds. A review of the literature uncovered the synthesis of β-bromoacraldehydes (18). These were considered to be suitable starting materials as they had functional groups on the double bond of the ring which would allow the introduction of both the γ,δ-unsaturation and the carbonyl group. These unstable β-bromoacraldehydes (18a, 18b) were prepared in moderate yields by Arnold's route[165] which involved a Vilsmeier-Haack reaction between the adduct of phosphorous tribromide and dimethylformamide and the

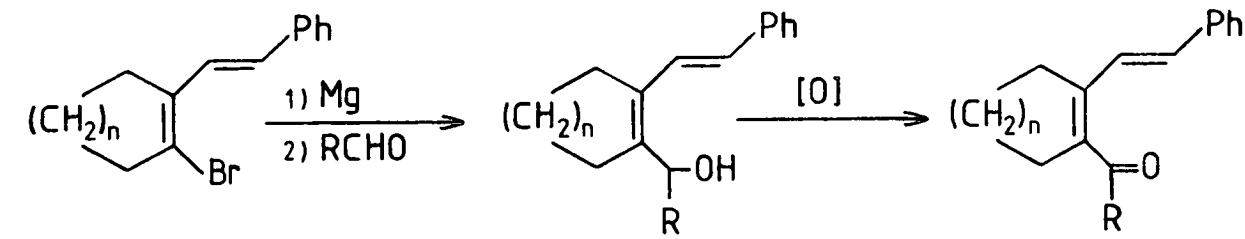
appropriate ketone. They underwent a Wittig reaction with benzyltriphenylphosphonium bromide to introduce the phenylethenyl group at position 2 giving a mixture of *E* and *Z* isomers. The major *E* isomers (19a,19b) were isolated by m.p.l.c. Grignard reagents prepared from (19a,19b) were reacted with dimethylformamide and subsequent hydrolysis gave the desired aldehydes (20a,20b) (Scheme 4).



Scheme 4

The corresponding ketones were prepared by the reaction of the Grignard reagents of (19a,19b) with the appropriate aldehyde to give alcohols (21) which were oxidised to the corresponding ketones (22). Thus reaction of (19a,19b) gave the desired alcohols (21a,21b) in good yields. However, the oxidation of these alcohols gave problems and could only be effected in very low yields by Jones oxidation using chromium

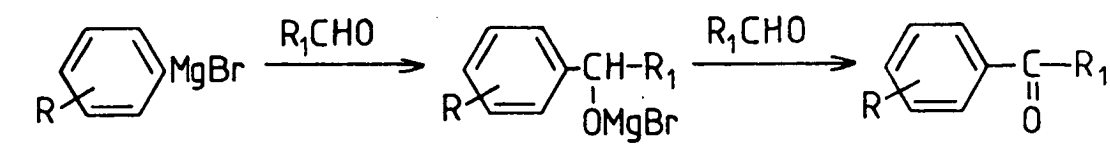
trioxide in pyridine. A range of oxidising agents was tried but the best, barium manganate, gave (22, n=2, R=Me) in only 30% yield. The low yield in these reactions was probably due to oxidation of the γ,δ-bond.



(a,n=1; b,n=2)

(19) (21) (22)

When the Grignard reagent of (19a) was reacted with 1.5x molar excess of *p*-tolualdehyde both the alcohol (21a, R=*p*Me C_6H_4) (49%) and the ketone (22a, R=*p*Me C_6H_4) (36%) were isolated. It was again found that these alcohols could only be oxidised in poor yields with chromium trioxide in pyridine. Precedent for the formation of the ketones during the Grignard reaction was found in a report by Short,[166] who isolated ketones from the reaction of the Grignard reagent of bromo-*N*,*N*-dialkylbenzyl amines with benzaldehydes. It was proposed that their formation involved the oxidation of (23) by any carbonyl compound present to give the isolated ketone, in a reaction analogous to an Oppenauer oxidation.



R=NR_2CH_2 (23) + R_1CH_2OMgBr

This oxidation process involved any excess *p*-tolualdehyde present being reduced to *p*-methylbenzyl alcohol which proved difficult to separate from the desired alcohol (21). It was decided to react the Grignard reagent of (19b) with only one equivalent of *p*-tolualdehyde and to effect any subsequent oxidation by the addition of a simple carbonyl compound, whose reduced form could be easily removed. Thus reaction of the Grignard reagent of (19b) with one equivalent *p*-tolualdehyde followed by the addition of dry acetone, prior to hydrolysis, gave both the alcohol (21b, R=*p*Me C_6H_4) and the ketone (22b, R=*p*Me C_6H_4), in 42 and 22% yield respectively.

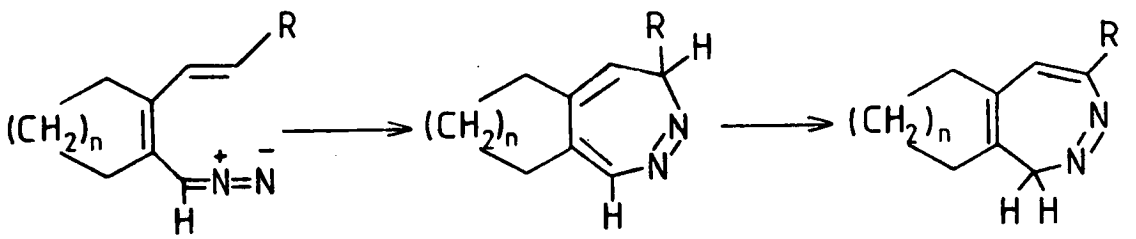
1.1.2) Decomposition of tosylhydrazone sodium salts

The carbonyl compounds, with one exception, were converted by condensation with *p*-toluenesulphonylhydrazide, into the corresponding *p*-toluenesulphonylhydrazones. The ketone (22b, R=*p*Me C_6H_4) could not be converted into its *p*-toluenesulphonylhydrazone under a variety of reaction conditions. The *p*-toluenesulphonylhydrazones were used to generate the required diazo-compounds *via* the Bamford-Stevens reaction.[51]

Conversion of the tosylhydrazones to the sodium salts was carried out by stirring at room temperature in super-dry ethanol containing 0.95 molar equivalents of sodium ethoxide. A deficiency of base was used so as not to cause any base catalysed reactions of the primary products. The decomposition of this series of *p*-toluenesulphonylhydrazone salts was carried out in dry, boiling cyclohexane for the minimum time required to consume all of the starting material. The products were isolated by filtering off the sodium-*p*-toluenesulphinate which

had precipitated during the reaction, removing the solvent by evaporation under reduced pressure, and separating the resulting residue by chromatography.

The reactions of the diazo compounds (24a), (24b) and (24c) exactly parallel those of the aryl analogues[80] (1, R_2=H) giving the cyclopenta- and cyclohexa[3*H*-1,2]diazepines (26a), (26b) and (26c) respectively in high yields, thus providing a route to these previously unknown heterocyclic systems.



a) n=1, R=Ph ; b) n=1, R=Me ; c) n=2, R=Ph

(24) (25) (26)

The formation of (26) can be rationalised in terms of a primary 1,7-electrocyclisation to give the non-isolable intermediates (25). These subsequently isomerised by a rapid [1,5] sigmatropic hydrogen shift to give the isolated products (26) thus bringing the substituent R into conjugation with the α,β:γ,δ-unsaturation as well as moving the two exocyclic double bonds to the more stable endocyclic positions. In these three cases no products were obtained from the possible competing 1,5-electrocyclisation or carbenic reactions.

The mass spectra of these fused-1,2-3*H*-diazepines (26) showed only a small peak due to the parent ion and a base peak of (P-28), which was shown to be due to loss of N_2, by exact mass measurements. This facile loss of N_2 from the parent

^{1}H N.m.r. of 4-phenyl-1*H*-6,7,8,9-tetrahydrocyclohexa[d][1,2]diazepine

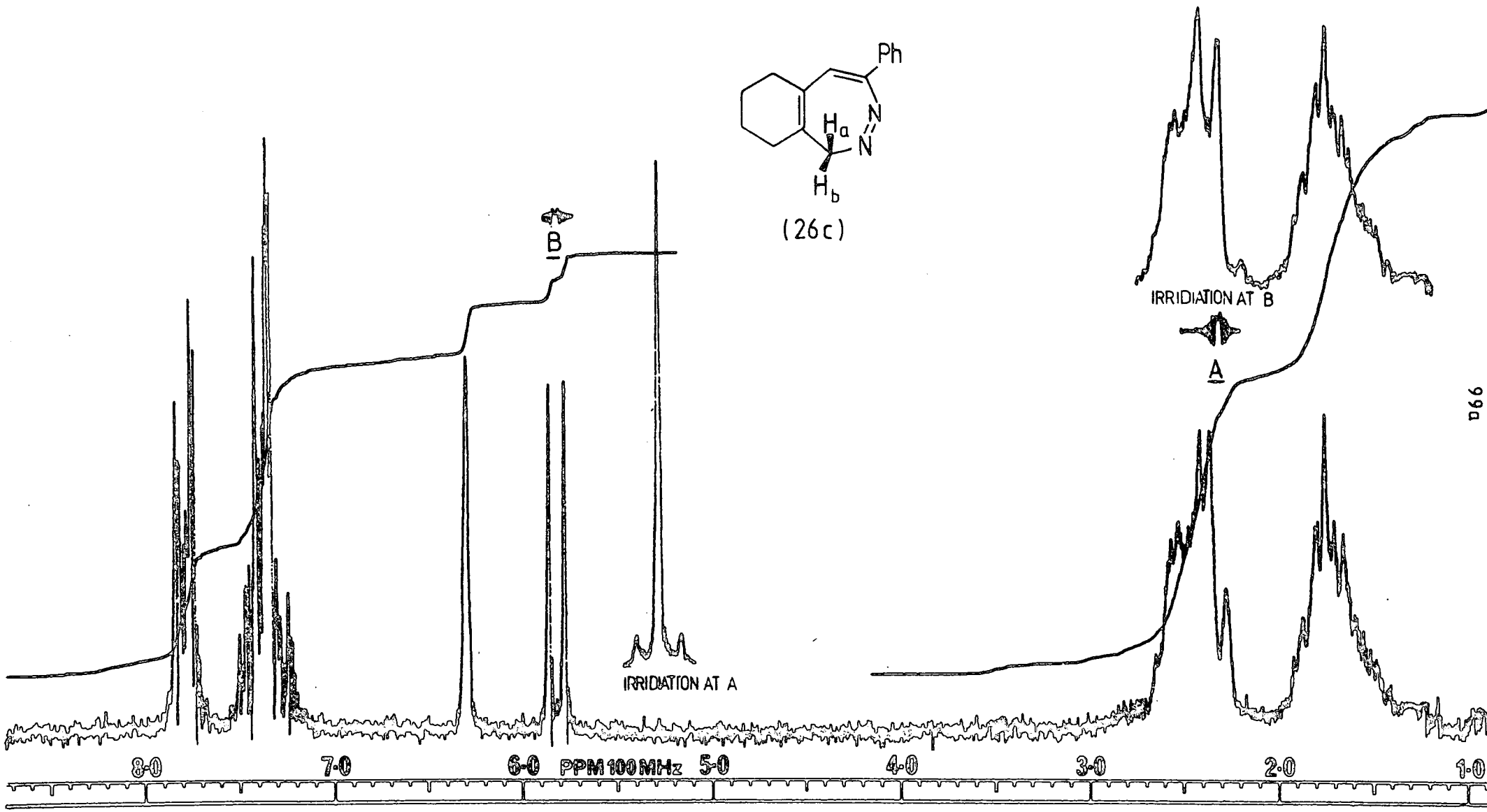


Figure 5

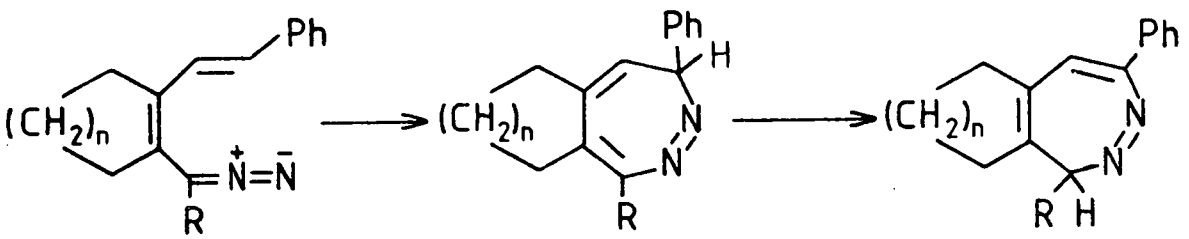
ion is typical of cyclic azo compounds. These compounds (26) exhibit n.m.r. spectra similar to the analogous 1*H*-2,3-benzodiazepines[80] (3) whose ^{1}H n.m.r. spectra showed that where there were two hydrogen substituents (*exo* and *endo*) at position 1 in the diazepine ring, they had widely separated chemical shifts (*ca*.3.6 p.p.m.). Similar results were observed for the analogous cyclopenta- and cyclohexa[3*H*-1,2]diazepines, for example (26c) as shown in Figure 5.

Here, H_a (*endo*) absorbed at *ca* δ2.25 and H_b (*exo*) absorbed at δ5.82, as a doublet J=8Hz which collapsed to a singlet on irradiation at δ2.25. This large difference arises from the deshielding effect that the adjacent azo group has on α-protons which lie in the -C-N=N- plane, as the *exo* proton does in this case. An examination of the temperature dependence of the spectrum showed that the H_b doublet broadened with increasing temperature although the coalescence temperature could not be obtained before decomposition occurred.

The ^{13}C n.m.r. spectra also supported the structure of compounds (26). For example, the spectrum of (26c) showed a saturated carbon atom absorption at 71.6 p.p.m. which appeared as a doublet of doublets in a single frequency off resonance decoupled (s.f.o.r.d.) spectra confirming the presence of a carbon bearing two non-equivalent hydrogen atoms. The absorption of this carbon atom in this deshielded position is similar to the absorption found for C-1 of other fused 3*H*-1,2-diazepines e.g. 1*H*-2,3-benzodiazepines[80] (3) and thieno-[3*H*-1,2]diazepines[81] (4).

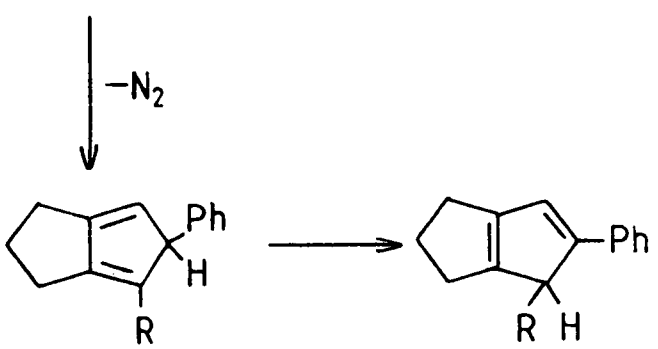
The diazoalkanes derived from ketones rather than aldehydes were also investigated (27). Thermolysis of (27a) gave

a single product as a yellow oil which was subsequently identified as (29a) by its mass spectrum and its ^{1}H and ^{13}C n.m.r. spectra. The ^{13}C n.m.r. spectra had a saturated carbon carrying only one proton, as shown by s.f.o.r.d. spectra, at 74.7 p.p.m., a similar shift as that found for (26c). Differentiation between structures (28a) and (29a) (Scheme 6) was achieved by investigation of the ^{1}H n.m.r. spectra. The methyl group absorption appeared as a doublet (δ2.02, J6.4Hz) and the proton on C-1 appeared as a broad quartet (δ2.12). This



a) n=2, R=Me ; b) n=1, R=Me ; c) n=1, R=*p*MeAr

(27) (28) (29)



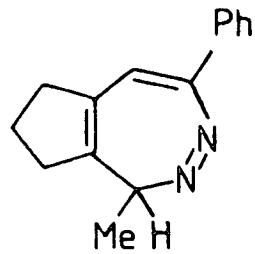
(30) (31)

Scheme 6

splitting is consistent with a proton and a methyl group on the same carbon atom and proves that (29a) is the isolated product rather than (28a) which would have the Me at C-1 as a singlet.

The thermolysis of diazoalkane (27b) also produced a yellow oil as the only isolated product. The mass spectrum

a) ^{1}H N.m.r. spectra of 1-methyl-4-phenyl-1*H*-6,7,8-trihydrocyclopenta[d][1,2]diazepine



(29b)

b) On addition of 10 mg Eu (fod)$_3$

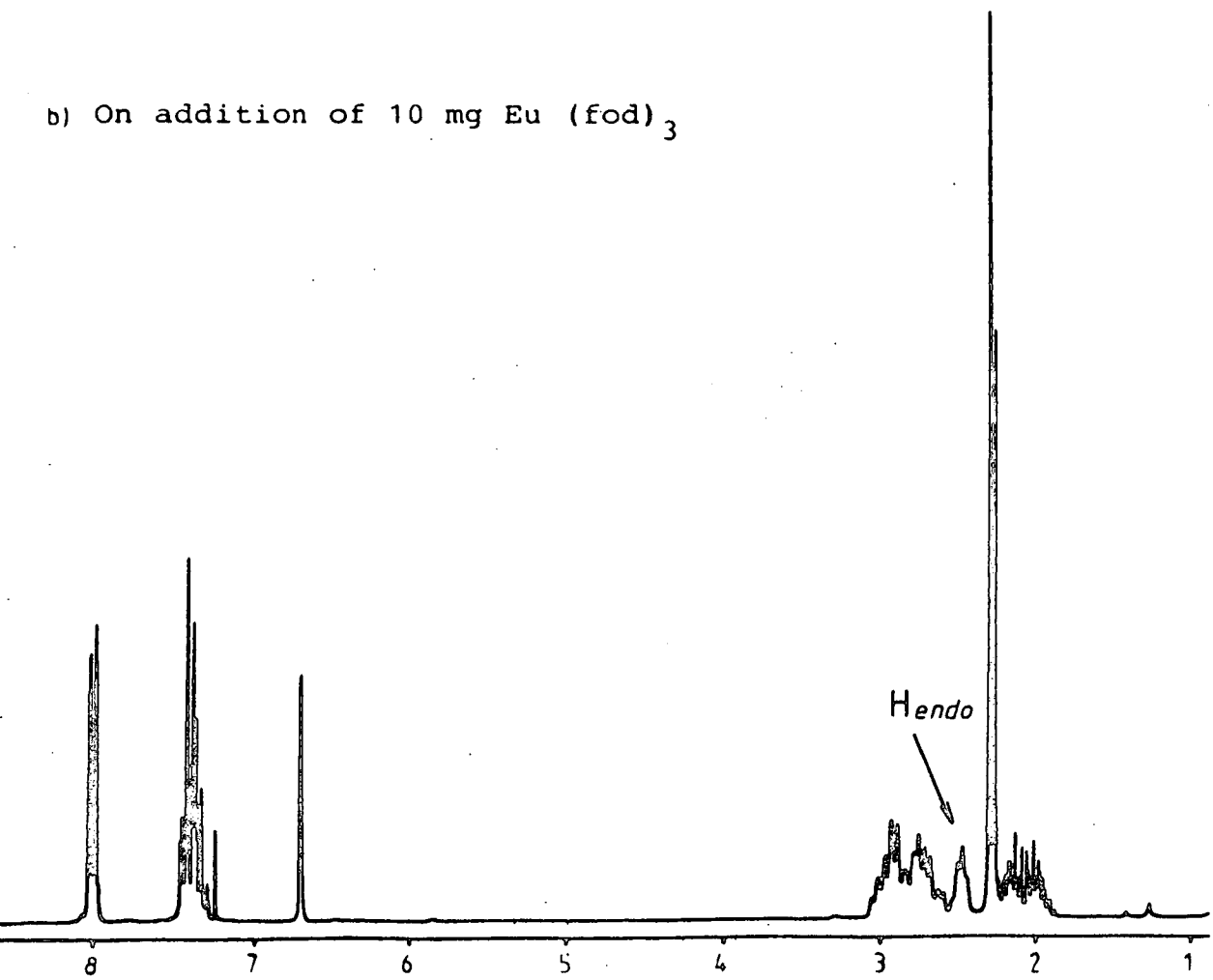
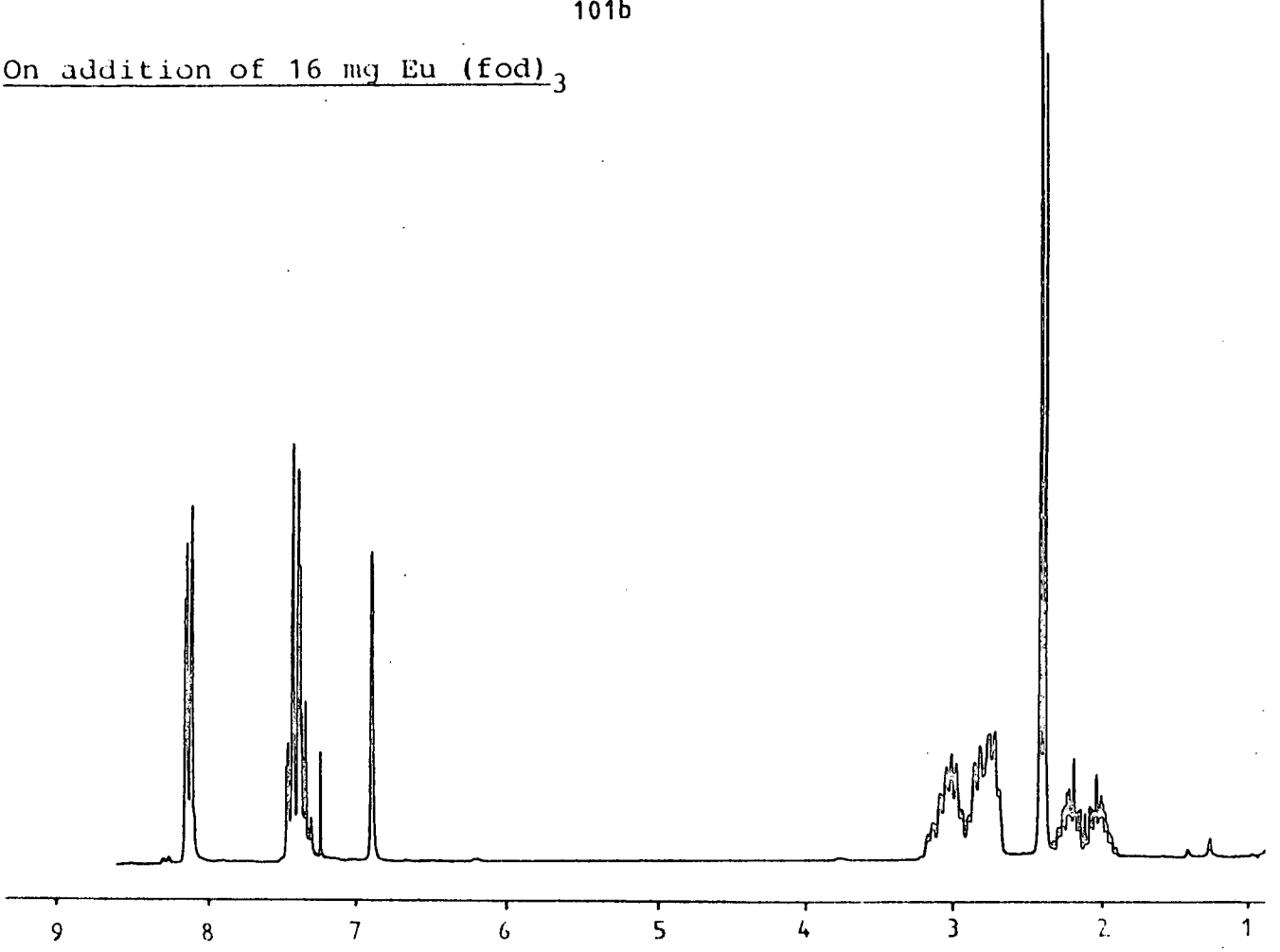
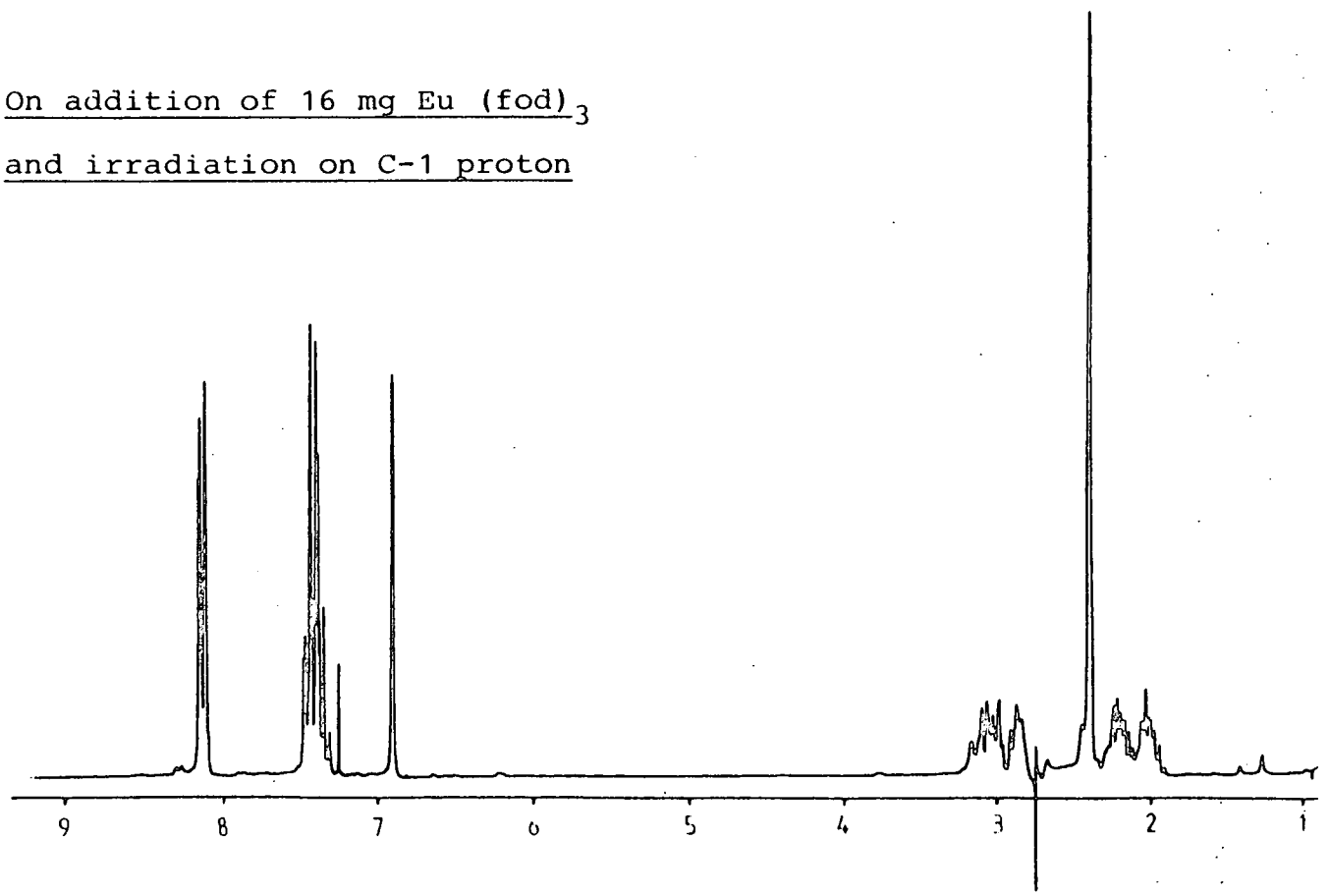


Figure 7

c) On addition of 16 mg Eu (fod)$_3$



d) On addition of 16 mg Eu (fod)$_3$
and irradiation on C-1 proton



of this compound had a very small parent ion and a base peak at P-28, indicating a cyclic azo structure consistent with (28b) or (29b). Investigation of the ^{1}H n.m.r. spectra showed that, even at high field (360MHz), the methyl group did not have any discernable coupling. It was at first thought that this absence of coupling indicated that the isolated product was (28b). The ^{13}C n.m.r. showed an absorption (72.8 p.p.m.) corresponding to a deshielded saturated carbon bearing only one proton, as shown by s.f.o.r.d,, which would be consistent with either C-4 of (28b) or C-1 of (29b). However in the fully coupled ^{13}C n.m.r. spectrum this signal appeared as a doublet of quartets. The CH couplings, 142 and 4.9Hz are consistent for *C-H* and *-C-C-H* coupling constants respectively.[167] This result seemed to indicate the presence of a H-C-Me grouping and that the product was (29b), in direct contrast to the result indicated by the proton spectra. (Figure 7a).

The only reason which rationalises the absence of coupling between the *endo* proton and the methyl of (29b) is accidental coincidence of their chemical shifts. If this was the case, it was believed that the addition of a chemical shift reagent would enable the two signals to be separated. Thus after the addition of 10 mg of Eu $(fod)_3$, the *endo* proton appeared as a broad quartet, adjacent to a doublet due to the methyl group (Figure 7b). Further addition of Eu $(fod)_3$, resulted in the *endo* proton being shifted to a higher frequency into the cyclopentyl absorptions (Figure 7c). This increased chemical shift difference allowed decoupling of this signal without simultaneous irradiation of the methyl group. This resulted in collapse of the methyl doublet to a singlet,

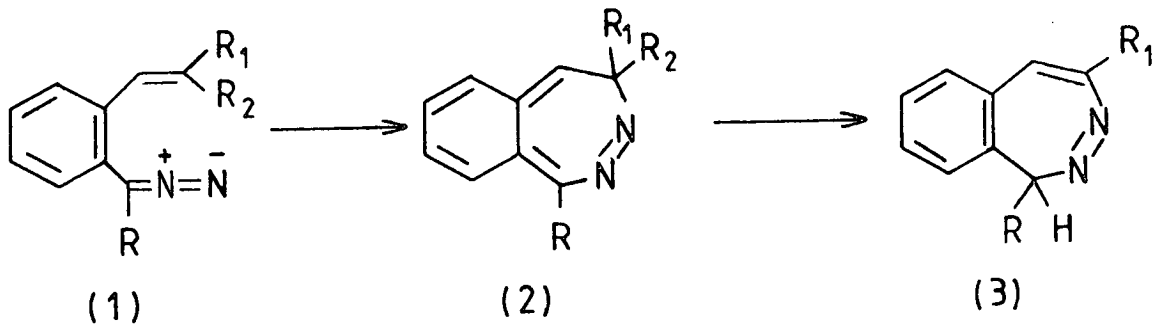
(Figure 7d) confirming the presence of a H-C-CH_3 moiety and positively identifying the product as (29b).

The thermolysis of diazoalkane (27c) produced two products. The minor product (9%) was identified by comparison of its mass spectral, ^1H and ^{13}C n.m.r. data as being the cyclopentyl [3*H*-1,2]diazepine (29c). The major product (40%) was identified as a 2-phenyl-3-*p*-tolyl-3,4,5,6-tetrahydropentalene (31). This was formed from the carbene derived from (27c) *via* cyclisation to the γ,δ-double bond to give (30) followed by a [1,5]hydrogen shift forming (31). (Scheme 6).

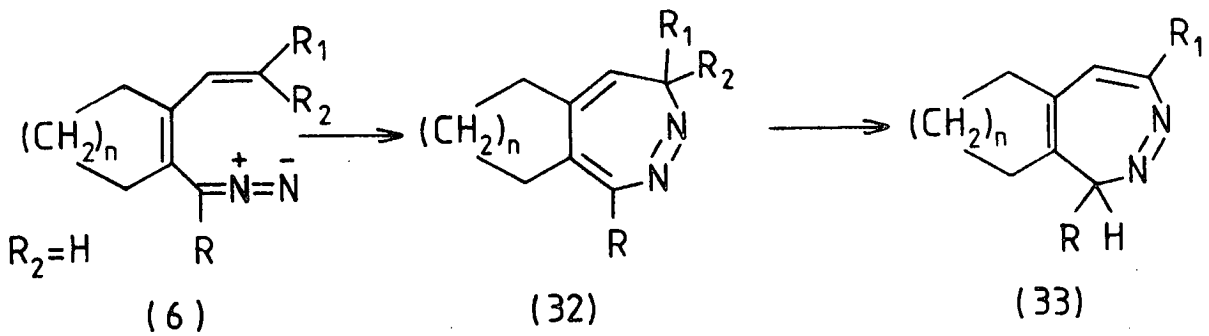
The high proportion of carbene derived product was not unexpected as a similar effect had been demonstrated earlier in a related system (see Introduction p.36). It was suggested that the carbene was stabilised by conjugation with the aryl group thus making its formation a more favoured process with respect to the competing electrocyclisation.

It is worthy of note that in all these cyclisations the primary product (32) was not isolated but rearranged *via* a [1,5] sigmatropic hydrogen shift to give (33). A similar rearrangement was observed in the analogous aromatic system eg (1) which results in the restoration of the aromaticity of the fused benzene ring of (3).

In the cyclisation of these cyclopentyl and cyclohexyl diazo-compounds (6) the strong driving force of restoration of aromaticity is no longer present but the analogous [1,5] shift is still observed to give (33).



(1) (2) (3)



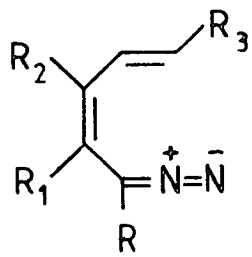
(6) (32) (33)

[1,5]Sigmatropic hydrogen shifts of this type are known to be fast thus allowing the rapid formation of the more thermodynamically stable (33) in which R_1 is now conjugated and which lacks the destabilising exocyclic double bonds of (32).

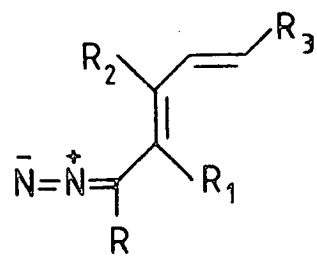
1.2) With acyclic α,β-double bonds

1.2.1) Synthesis of 1-carbonyl α,β:γ,δ-unsaturated compounds

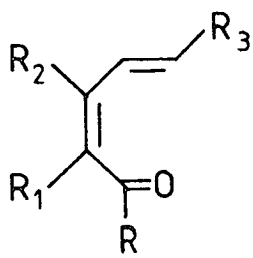
The target diazo-compounds (34) and (35) were as usual to be derived from the corresponding *p*-toluenesulphonylhydrazones prepared from the corresponding carbonyl compounds (36) and (37).



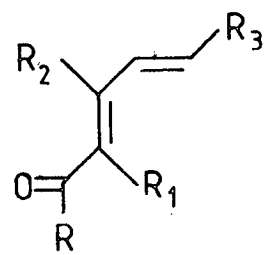
(34)



(35)



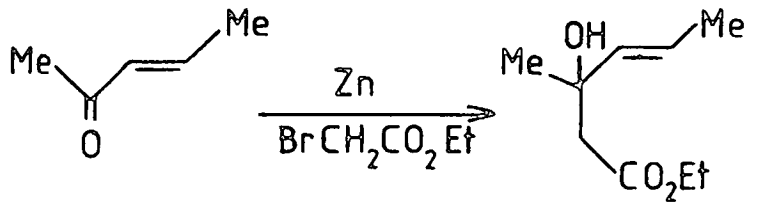
(36)



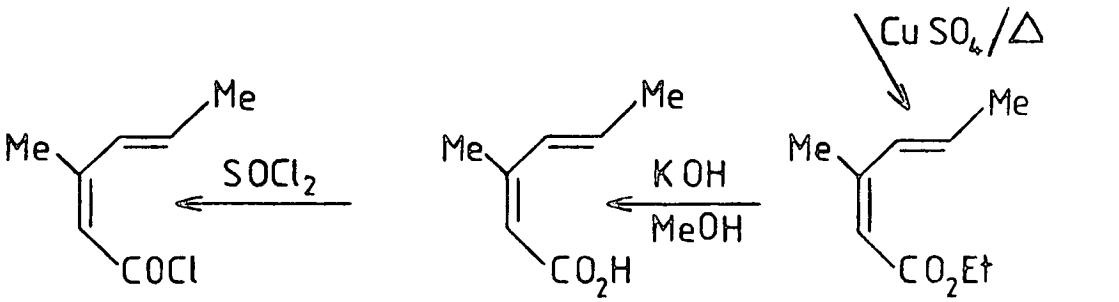
(37)

The first route to these compounds is shown in Scheme 8.

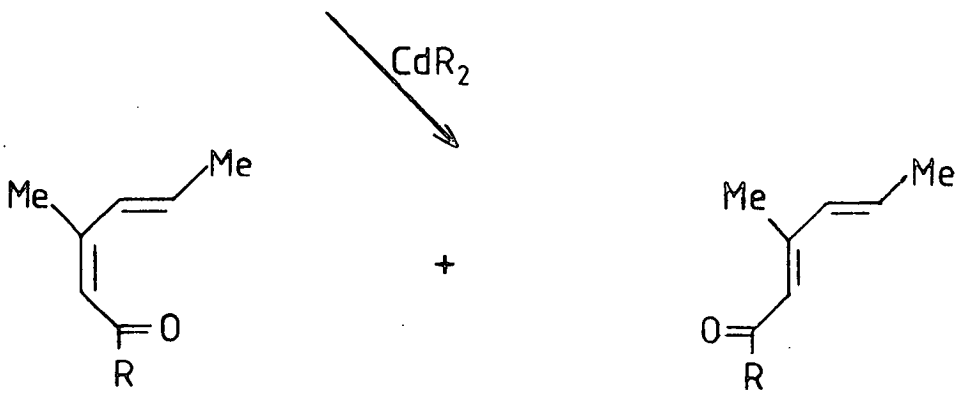
Pent-3-en-2-one (38) was prepared by the aldol reaction of acetaldehyde, acetone and sodium hydroxide. A Reformatsky reaction between ethyl α-bromoacetate and pent-3-en-2-one gave the hydroxyester (39), which was subsequently dehydrated by slow distillation from anhydrous copper sulphate to give the dienic ester (40) as a mixture of *E,E* and *Z,E* isomers. Hydrolysis of this ester with potassium hydroxide gave the acid (41) which was treated with thionyl chloride to give the acid chloride (42). Subsequent reaction of this acid chloride with an organocadmium reagent, prepared from the alkyl Grignard reagent and anhydrous cadmium chloride, gave the desired ketone again as a mixture of *Z,E* and *E,E* isomers (1:2).



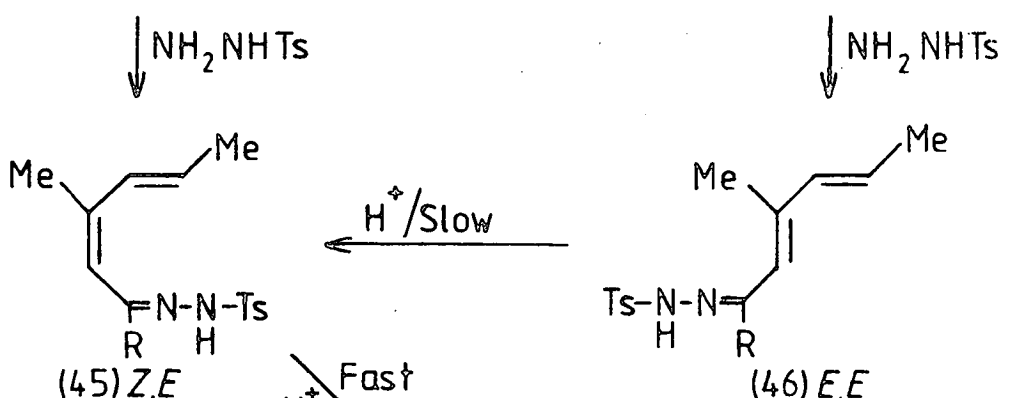
(38) (39)



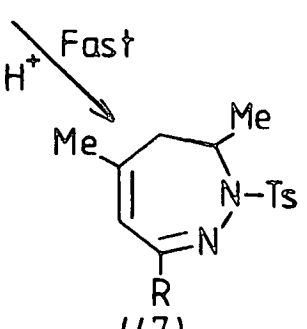
(42) *Z,E* and *E,E* (41) *Z,E* and *E,E* (40) *Z,E* and *E,E*



(43) *Z,E* (44) *E,E*



(45) *Z,E* (46) *E,E*

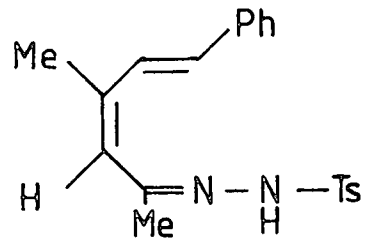


(47)

R = Me_2CH

Scheme 8

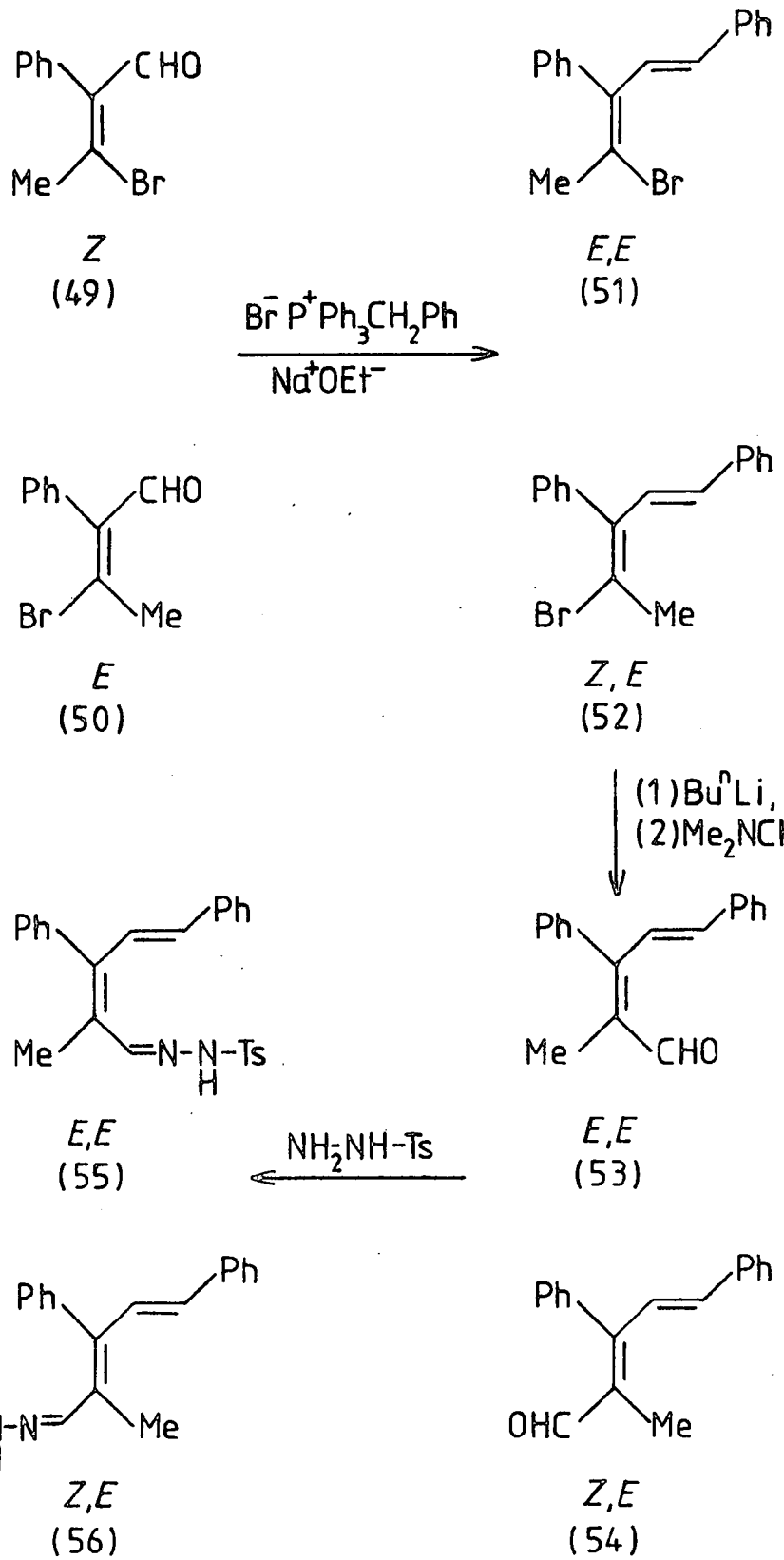
Prolonged treatment of the ketones (43,44) with *p*-toluenesulphonylhydrazide in the presence of concentrated hydrochloric acid gave both corresponding *p*-toluenesulphonylhydrazones (45,46). However, under the reaction conditions the *E,E* isomer (46) slowly isomerised to the *Z,E* isomer (45) which was rapidly transformed into the corresponding 2-tosyldiazepine (47). Working-up of the reaction mixture before the isomerisation of (46) to (45) was complete enabled the isolation of 2-tosyldiazepine (47) and pure *E,E* tosylhydrazone (46). The tosylhydrazone (48) was also synthesised by an analogous route as a mixture of *Z,E* and *E,E* isomers.



(48)

The inability to separate the *E,E* and *Z,E* isomers of the carbonyl compounds and difficulty in obtaining and identifying the pure *E,E* isomer (46) was a major disadvantage of this synthetic route. It was highly desirable to be able to obtain and identify both isomers as this would allow the investigation of the effect of the stereochemistry upon the mode of reactivity of the diazoalkanes.

Thus in order to obtain both isomers an alternative synthetic route was sought involving some intermediate whose *E* and *Z* isomers at the α,β-double bond were sufficiently dissimilar to allow complete separation by chromatography. It was decided to attempt an extension of the β-bromoacraldehyde route which had been so effective for the cyclic analogues (Scheme 4).


Ph
CHO
Me
Br
Z
(49)
Br⁻ P⁺Ph3CH2Ph
Na⁺OEt⁻
Ph
Ph
Me
Br
E,E
(51)
Ph
CHO
Br
Me
E
(50)
Ph
Ph
Br
Me
Z, E
(52)
(1) BuⁿLi, -120°C
(2) Me2NCHO
Ph
Ph
Me
N-N-Ts
H
E,E
(55)
NH2NH-Ts
Ph
Ph
Me
CHO
E,E
(53)
Ph
Ts-N-N
H
Me
Z,E
(56)
Ph
Ph
OHC
Me
Z,E
(54)

Scheme 9

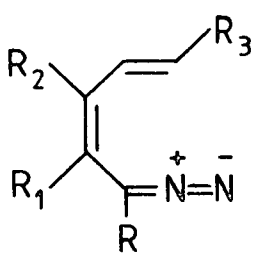
Thus it was found that ~~the reaction of~~ the adduct of phosphorus tribromide with dimethylformamide reacted with benzyl methyl ketone to give a mixture of *E* and *Z* β-bromoacraldehydes in moderate yield . Unlike the original preparation of Arnold[165] the products were not isolated by distillation but rather by m.p.l.c. which enabled complete separation of both isomers.

The two isomers were identified by their ^{1}H n.m.r. spectra, and each characterised separately. The *Z* isomer (49) had a methyl absorption at δ2.43 compared with the methyl of the *E* isomer (50), which had an absorption at δ2.93. The *Z* isomer methyl had an absorption at lower frequency as the methyl group of this isomer is in the shielding region of the aromatic ring. Also the aldehyde proton of the *Z* isomer absorbed at higher frequency (δ10.25) compared to that of the *E* isomer (δ10.06) as it is more deshielded by this *Z* bromine atom.

The two β-bromoacraldehydes were then separately converted to the corresponding α,β:γ,δ-unsaturated bromo-compounds *via* a Wittig reaction with benzyltriphenylphosphonium bromide. These reactions gave mainly *E* isomers about the phenylethenyl double bond. The small amounts of *Z* isomers were removed by m.p.l.c. to give pure *E,E* and *E,Z* isomers (51),(52). Attempts to generate Grignard reagents proved unsuccessful but it was found that the organolithium derivatives could be formed by metal-halogen exchange at -120→-80°C using *n*-butyllithium. Subsequent reaction with dimethylformamide at -80°C, followed by hydrolysis gave the corresponding aldehydes in good yields (53),(54). These aldehydes were readily converted by their condensation with *p*-toluenesulphonylhydrazide into their corresponding *p*-toluenesulphonylhydrazones (55),(56) (Scheme 9).

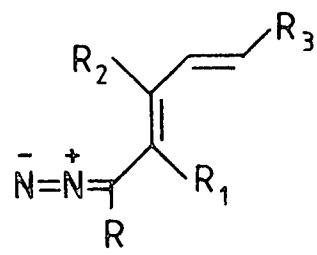
1.2.2) Decomposition of tosylhydrazone sodium salts

The diazoalkanes were generated by the Bamford-Stevens reaction of the sodium salts of tosylhydrazones as described for the cyclic analogues (24,27). For reasons of clarity individual assignment of each double bond will not be shown in the remainder of this thesis. The acyclic isomers having the diazo moiety and γ,δ-double bond on the same side of the α,β-double bond will be regarded as the *Z* isomer (57) and the other isomer having the diazo moiety and γ,δ-unsaturation on the opposite side will be regarded as the *E* isomer (58).



Z

(57)

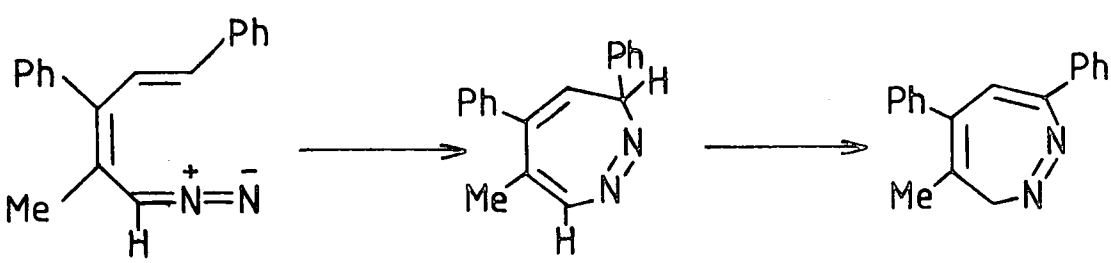


E

(58)

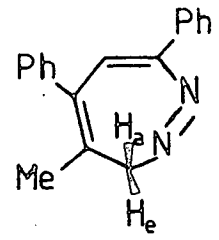
1.2.2.1) Cyclisation of the Z diazoalkane (57, $R^1 \neq H$)

The reaction of the Z diazoalkane (59) gave only a single product as a yellow oil which was identified as being 4-methyl-5,7-diphenyl-3*H*-1,2-diazepine (61).



(59) (60) (61)

^{13}C N.m.r. spectrum of 4-methyl-5,7-diphenyl-3*H*-[1,2]-diazepine



(61)

Figure 10b

^{1}H N.m.r. spectrum of 4-methyl-5,7-diphenyl-3*H*-[1,2]-diazepine

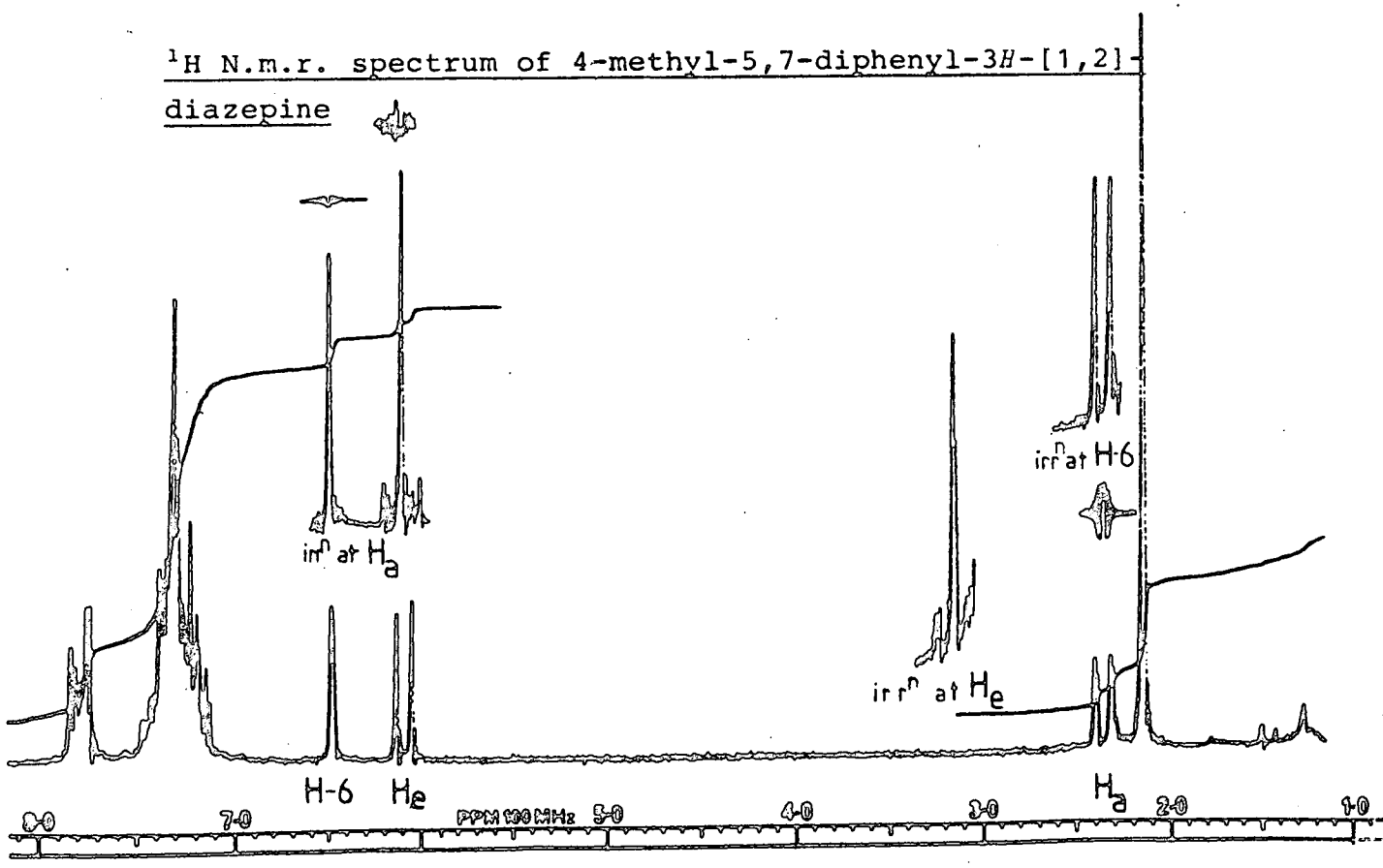
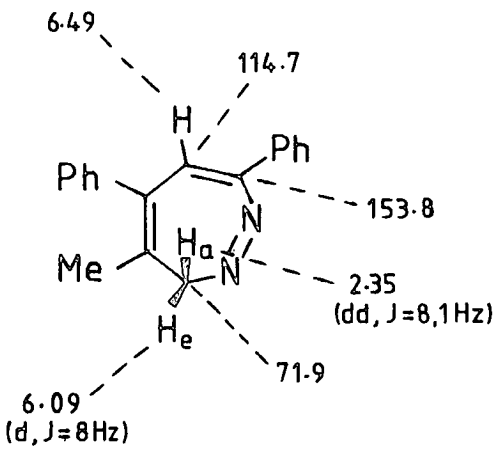


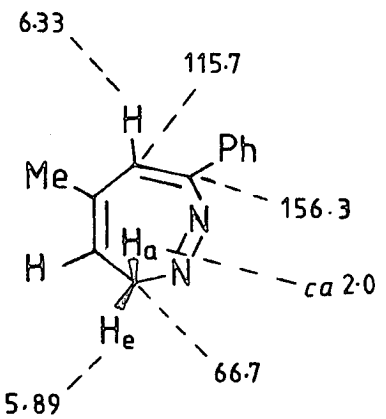
Figure 10a

The structure of this monocyclic diazepine was established by comparison of its spectral data with other 3*H*-1,2-diazepines, synthesised by Sharp *et al* by elimination of toluene-*p*-sulphinic acid from 3,4-dihydro-2-tosyl-1,2-diazepines.[123]

The mass spectra of (61) showed major fragmentation *via* loss of N_2 and also confirmed that the structure had formula $C_{18}H_{16}N_2$. ^1H n.m.r. spectra did not indicate a NH present and this was subsequently confirmed by infra-red spectroscopy. The ^1H and ^{13}C n.m.r. spectra had signals characteristic of other 3*H*-1,2-diazepines, for example (62).



(61)

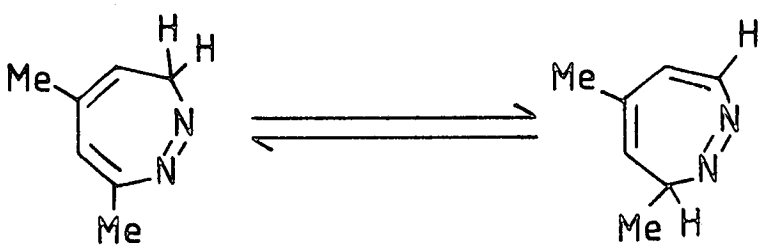


(62)

The large chemical shift separation of the protons of the C-3 carbon was due to the previously reported deshielding affect of the azo group on the equatorial proton. These protons, Ha and He, clearly appeared as two doublets which were proved to be coupled to each other by spin-decoupling experiments. Proton Ha also exhibited a small five bond coupling to the proton attached to C-6 (Figure 10a). ^{13}C N.m.r. spectra showed the C-3 carbon, which is adjacent to the azo group, to be strongly deshielded. In the non-decoupled spectra this

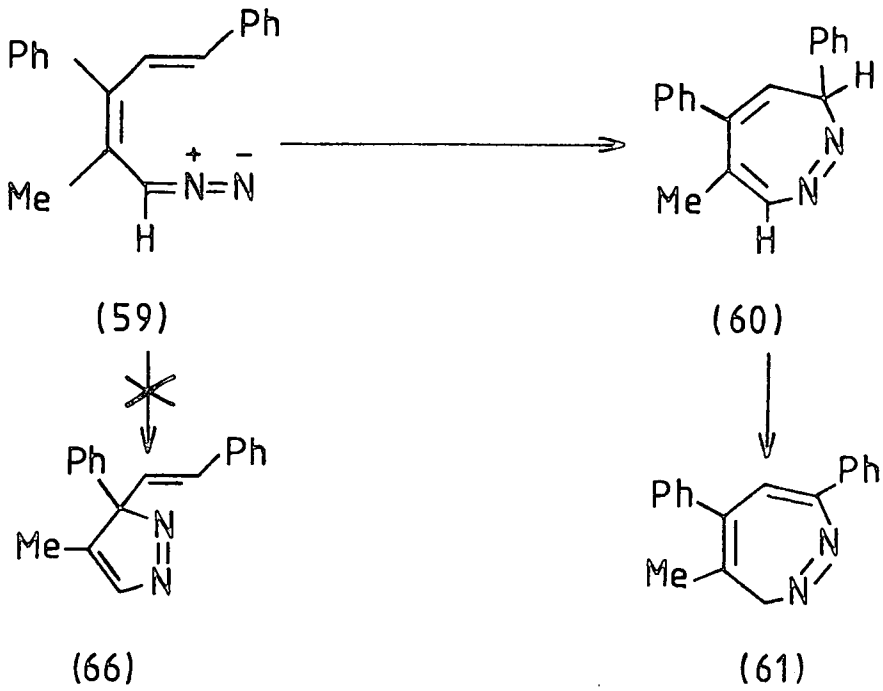
signal appears as a doublet of doublets as expected for a CH_2 bearing two non-equivalent protons (Figure 10b).

It should be noted that this 3*H*-1,2-diazepine only exists as the one isomer (61) unlike the previously reported examples which could exist as an equilibrium mixture, for example (63, 64). The existence of the product as the isomer (61) only was due to the considerable preference of a phenyl group to be in conjugation with the diene moiety therefore resulting in (61) having a much greater stability than (60). In contrast a methyl group does not have such a large preference for being in conjugation and this allows the existence of some (*ca.*15%) of the less stable isomers (64).



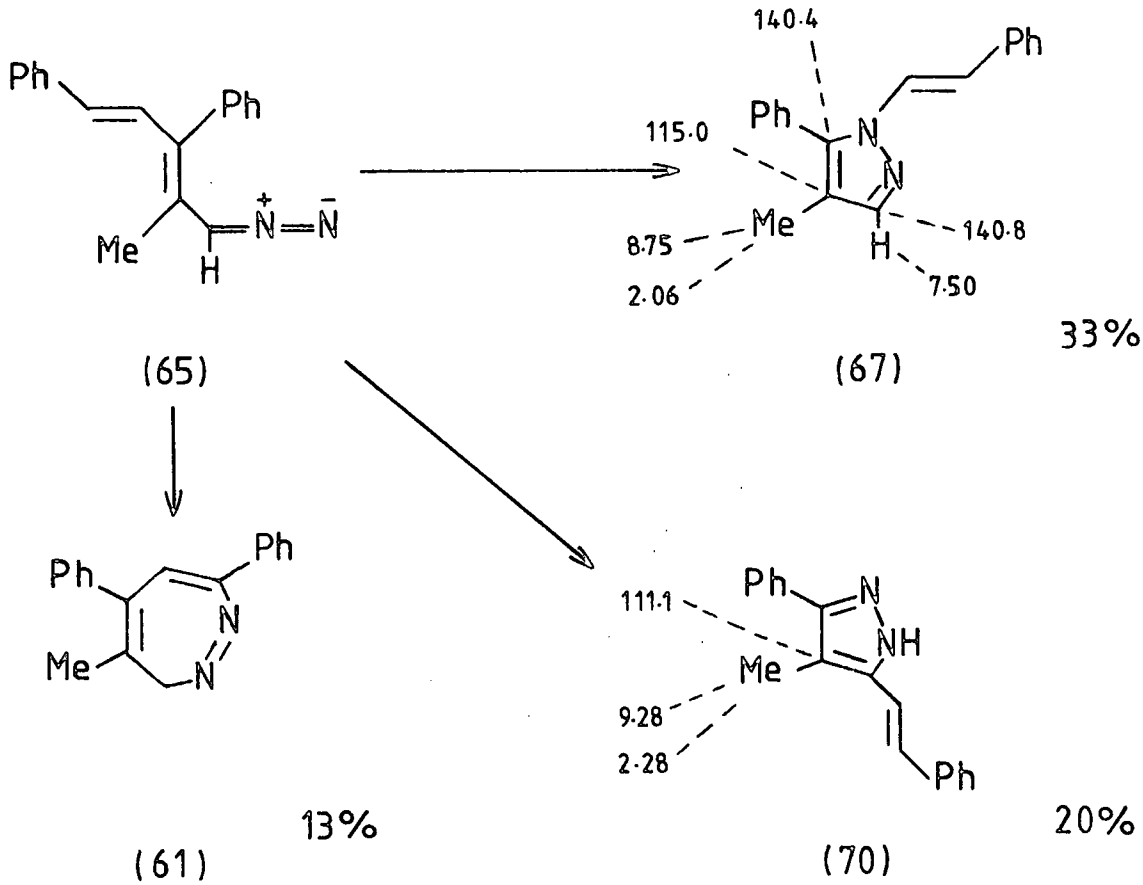
(63) (64)

The mechanism of formation of (61) apparently follows the route observed earlier for the analogues with fused rings in the α,β-position and shows the same strong preference for 1,7-over 1,5-cyclisation. No evidence was observed for the pyrazole (66) or any isomers derived from it by group migration.



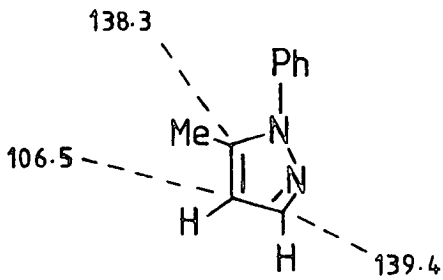
1.2.2.2 Cyclisation of the *E* diazoalkane (58, $R^1 \neq H$)

Whereas the reaction of the *Z* diazoalkane (59) proceeded *via* only 1,7-electrocyclisation to give 3*H*-1,2-diazepine (61) the reaction of the isomeric *E* diazoalkane (65) was more complex. The reaction of (65) gave a mixture containing three products, pyrazoles (67) and (70) and the previously isolated diazepine (61), in 33, 20 and 13% yield respectively.

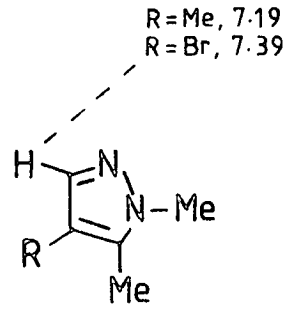


Structures of the cyclisation products: 4-methyl-5-phenyl-1-(*E*-phenylethenyl)pyrazole (67).-

Mass spectrometry indicated that the pyrazole (67) had the formula $C_{18}H_{16}N_2$ and also showed M^+ as the base peak indicating a stable aromatic structure. ^{13}C N.m.r. spectroscopy showed a shielded quaternary carbon (115.0 p.p.m.), C-3 (140.8 p.p.m., shown to be a CH by s.f.o.r.d.) and the expected aromatic and methyl signals. The chemical shift of this quaternary carbon (C-4) and the C-3 carbon were similar to values observed for other 1-substituted pyrazoles, for example (71).[168]



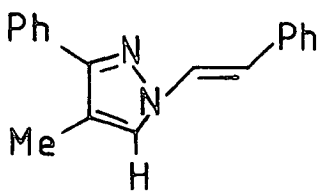
(71)



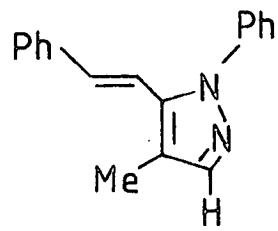
(72, R=Me)
(73, R=Br)

^{1}H N.m.r. spectra showed the presence of the phenylethenyl unsaturation as an AB pattern (δ6.26, 6.66; J11Hz), and also a singlet (δ7.50). This singlet absorption corresponds closely to the value for the ring proton of other 1,4,5 trisubstituted pyrazoles, for example (72,73).[169] ^{1}H N.m.r. spectra did not indicate an NH and its absence was subsequently confirmed by infra-red spectroscopy.

This spectral data was consistent with the N-substituted pyrazole (67) as well as the possible isomeric structures (74) and (75).



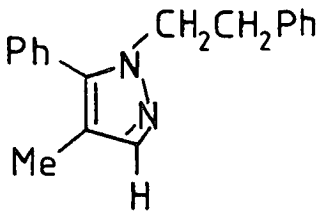
(74)



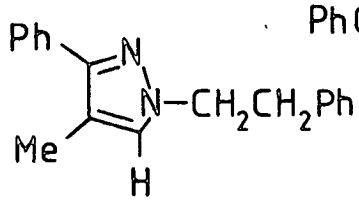
(75)

It was not possible to differentiate between the structures (67), (74) and (75) by spectroscopic means alone and this necessitated the hydrogenation of (67) followed by the preparation

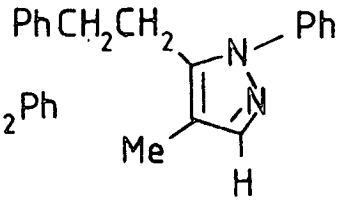
of the reduced compounds (76) (77) and (78) for comparison.



(76)

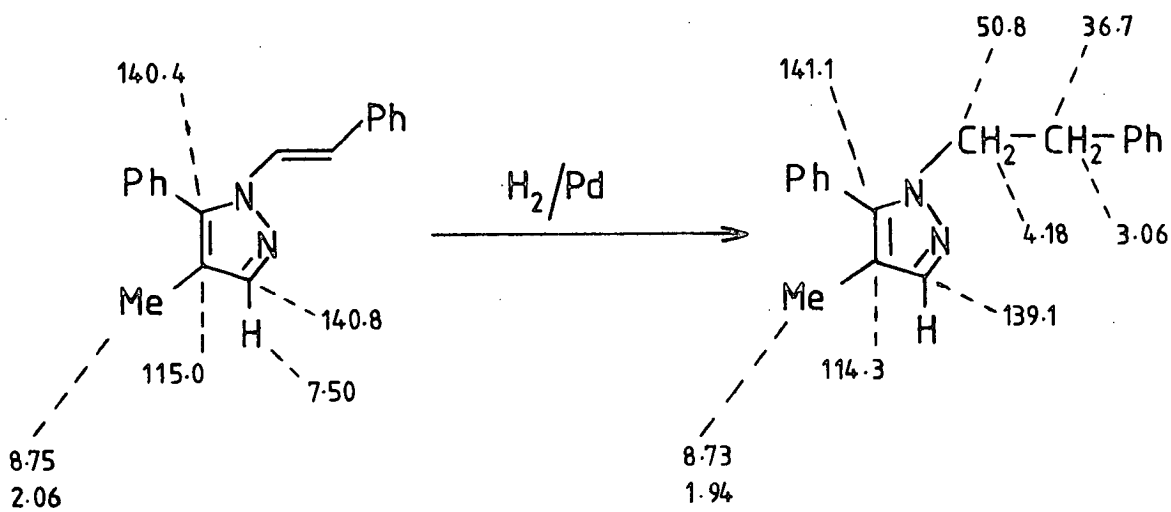


(77)



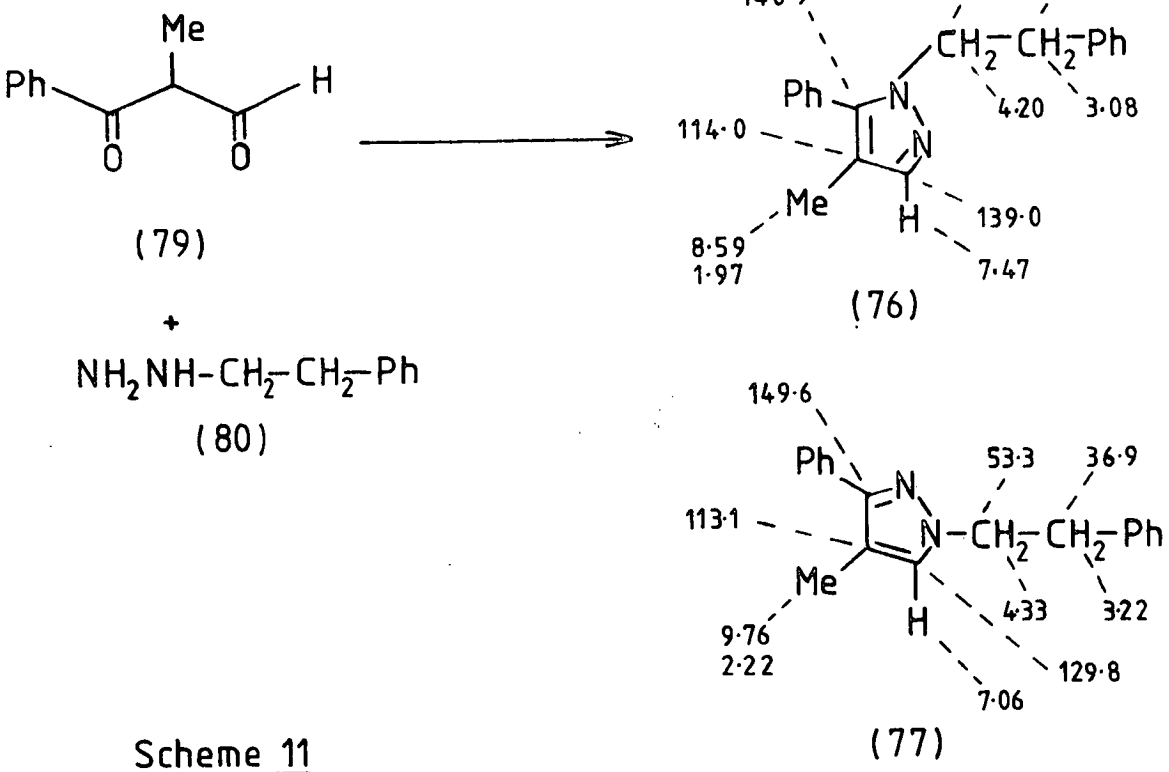
(78)

Thus hydrogenation of 4-methyl-5-phenyl-1-(*E*-phenyl ethenyl)pyrazole (67) gave 4-methyl-5-phenyl-1-phenethyl-pyrazole (76). The spectral data of this product was consistent with structure (76). It should be noted that in both ^{1}H and ^{13}C n.m.r. spectra one of the CH_2 absorptions is significantly deshielded (δ4.18, 50.8 p.p.m. for C-α compared to δ3.06 and 36.7 p.p.m. for C-β). This effect was attributed to the C-α of phenethyl side chain being attached to the electronegative nitrogen of the pyrazole ring.



(67) (76)

It was subsequently found that both isomers (76) and (77) could be synthesised, separated and positively identified from one synthetic route (Scheme 11). Thus, 2-benzoylpropanal (79), prepared by the acylation of propiophenone with ethyl formate by the method of Aspart-Pascot and Lematre,[170] was condensed with β-phenethylhydrazine (80) to give both isomers (76) and (77) in 36% and 17% yields respectively. The two isomers were separated by m.p.l.c. and characterised separately.

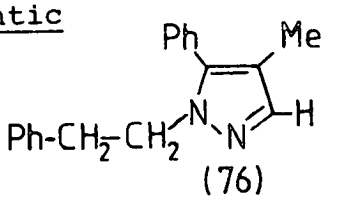


Scheme 11

The ^{1}H and ^{13}C n.m.r. spectra of both isomers (76) and (77) showed one CH_2 unit as being deshielded thereby confirming that this effect, previously observed in the product from the hydrogenation of (67), was indeed due to the phenethyl group being attached to nitrogen. Both compounds had very similar mass spectra and infra-red spectra confirmed that NH were absent in both cases. Preliminary assignment of each isomer was based on the ^{1}H and ^{13}C n.m.r. spectra. Isomer (76) had the

N.O.E. Difference ^1H nmr Spectra of Authentic Pyrazoles

1) 4-Methyl-5-phenyl-1-phenethyl-1*H*-pyrazole



(76)

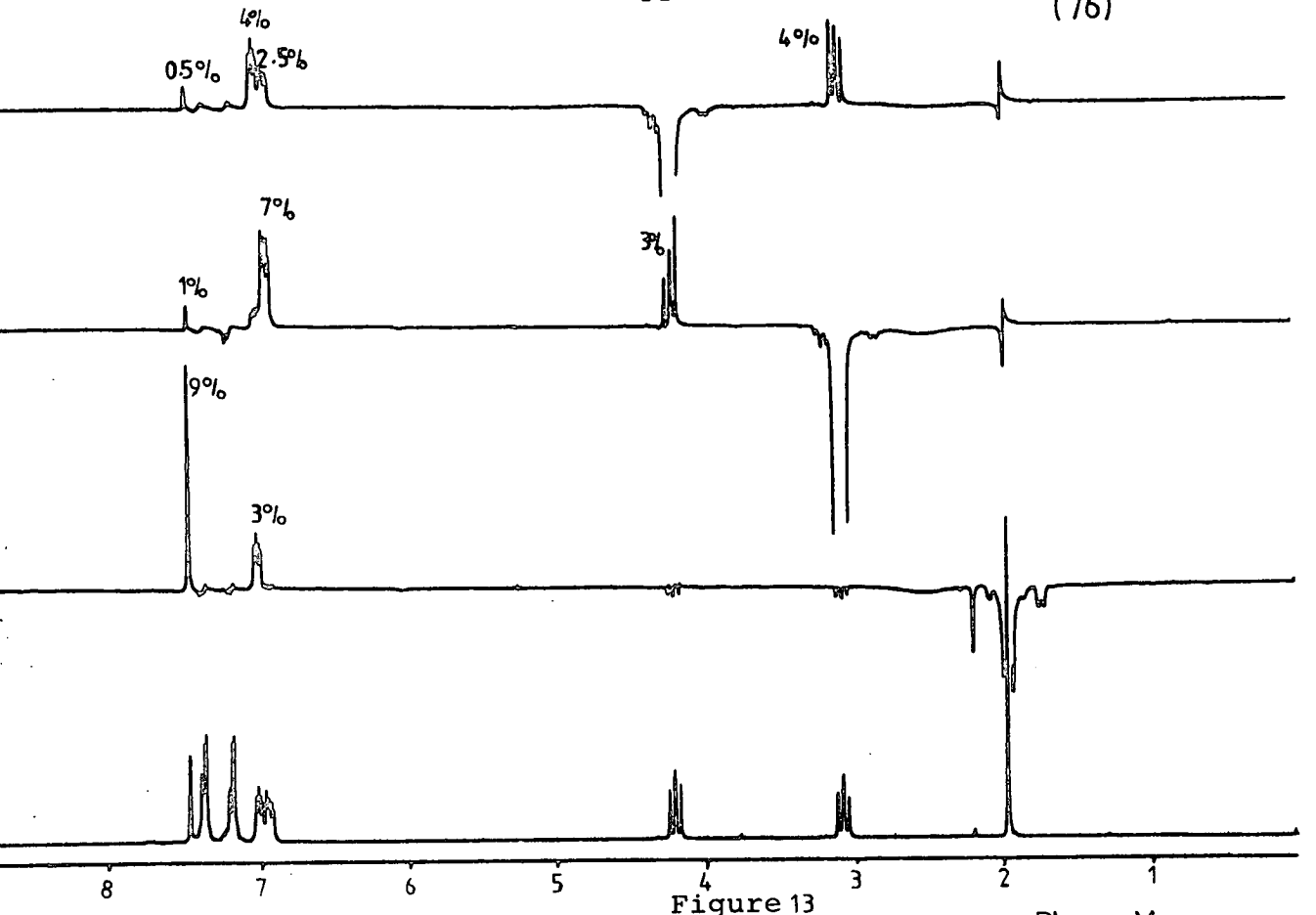
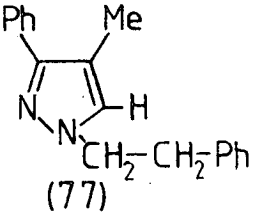


Figure 13

2) 4-Methyl-3-phenyl-1-phenethyl-1*H*-pyrazole



(77)

Figure 12

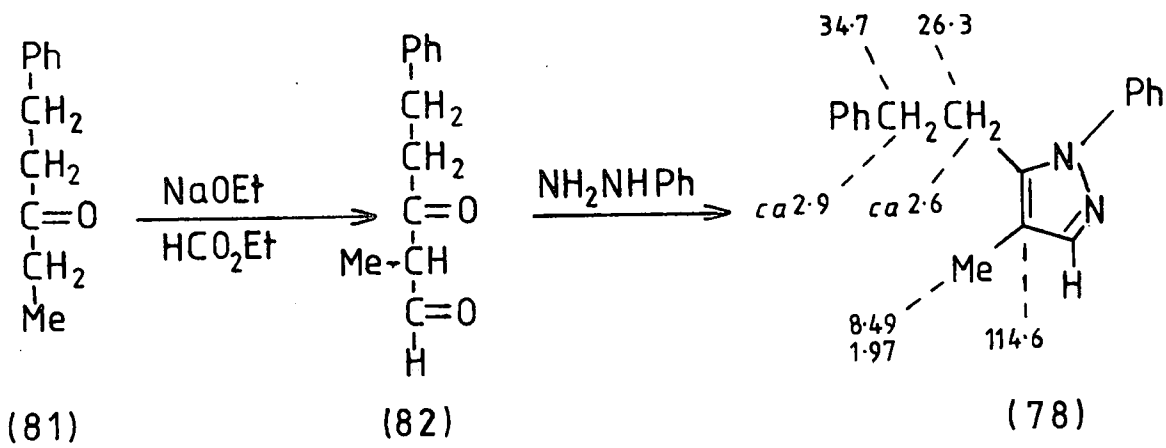
more deshielded ring proton (δ7.47) and C-3 carbon (139.0 p.p.m.), with respect to isomer (77), as would be expected for the isomer having a formal imine type bond in the pyrazole ring.

Although, the ^{1}H n.m.r. shifts of the $-CH_2CH_2-$ protons were too similar to aid in the identification of each isomer, it was found that use of Nuclear Overhauser Enhancement (N.O.E.) of these protons enabled each isomer to be positively identified. In isomer (77) irradiation at the β CH_2 and α CH_2 resulted in 2% and 7% enhancement respectively of the pyrazole ring proton, (Figure 12). This large N.O.E. effect of isomer (77) was in contrast to the small enhancement found in isomer (76), irradiation on β CH_2 and α CH_2 resulted in 1% and 0.5% enhancement respectively of the pyrazole ring proton (Figure 13). The relatively large effect in isomer (77) is a consequence of the protons of the CH_2CH_2 group, α CH_2 especially, being physically close to the pyrazole ring proton, with respect to isomer (76). Thus this enabled isomers (76) and (77) to be distinguished and confirmed as structures shown.

This assignment is in agreement with the ratio of isomers formed in the independent synthesis. The NH_2 of the hydrazine unit would be expected to attack at the aldehyde moiety more readily than the ketone carbonyl group of (79) thereby giving more (76) than (77). The product formed from the hydrogenation of (67) was found to give mass spectral, ^{1}H and ^{13}C n.m.r. data identical to that of compound (76). Thus, it was proved conclusively that product isolated from the reaction of (65) was 4-methyl-5-phenyl-1-(*E*-phenylethenyl)pyrazole (67).

It was also shown that the isolated product was not

structure (75) as the hydrogenated derivative was unambiguously synthesised as shown below. Thus, acylation of 1-phenylpentan-3-one (81) with ethyl formate gave 2-methyl-3-oxo-5-phenylpentanal (82). Subsequent condensation of this diketone with phenylhydrazine gave only one pyrazole, 4-methyl-5-phenethyl-1-phenyl-1*H*-pyrazole (78). This isomer is assumed to be the isolated product as nucleophilic attack of the NH_2 group of the phenylhydrazine will occur at the aldehyde rather than the ketone moiety of the diketone (82).

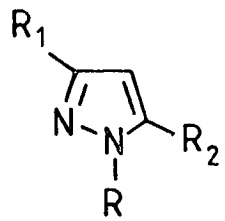


(81) (82) (78)

This pyrazole (78) did not have the same deshielded ^1H and ^{13}C n.m.r. signals found for the product of hydrogenation of (67).

Structure of the cyclisation product: 4-methyl-3-phenyl-5-(*E*-2-phenylethenyl)pyrazole (70).

Elemental analysis and mass spectrometry showed that (70) had the formula $C_{18}H_{16}N_2$. ^{13}C N.m.r. spectra showed a shielded quaternary carbon (111.1 p.p.m.), the methyl absorption (9.28 p.p.m.) and unresolved aromatic and olefinic signals. This shielded quaternary carbon shift is characteristic of the pyrazole ring system,[171] for example (83).

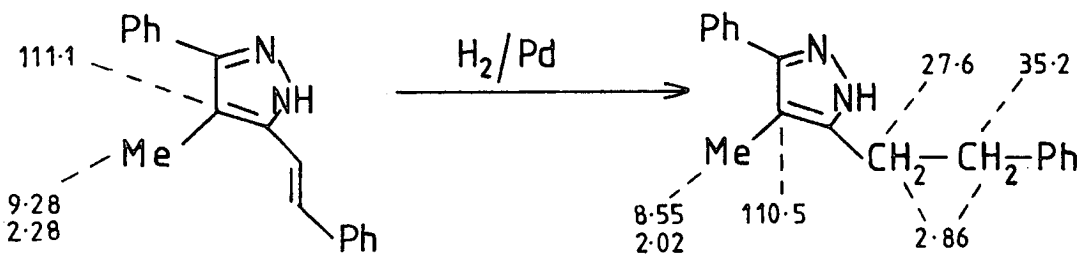


(83)

$R = R_1 = R_2 = H$; C-4 = 106·0
$R = R_2 = H$, $R_1 = Me$; C-4 = 106·0
$R = R_2 = Me$; $R_1 = Ph$; C-4 = 102·0

The infra-red and ^1H n.m.r. spectra both showed absorptions due to the N-H group. However, in the ^1H n.m.r. spectra the signals due to the olefinic protons were not resolved from the aromatic signals. The structure of (70) was confirmed by hydrogenation followed by preparation of an authentic sample.

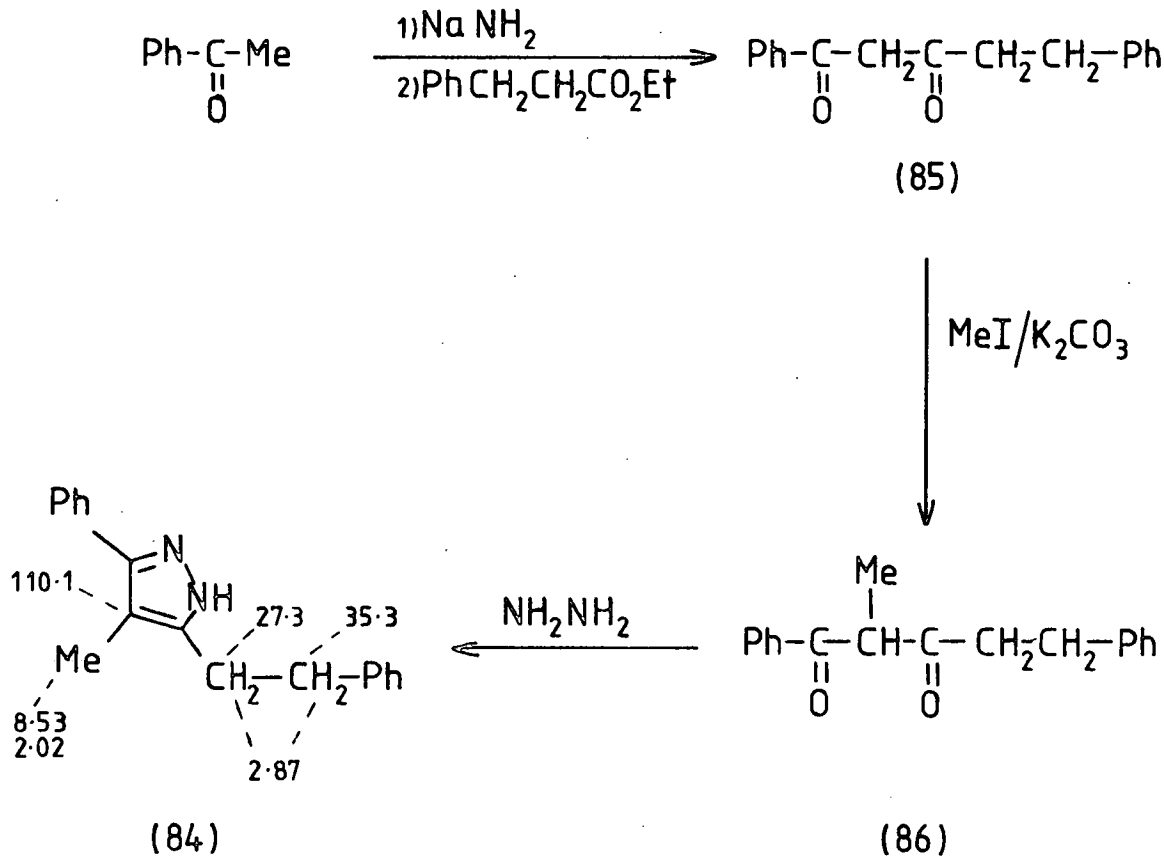
Hydrogenation of (70) gave 4-methyl-3-phenyl-5-phenethyl-pyrazole (84). The unambiguous synthesis of (84) was carried



(70) (84)

out as shown in Scheme 14. Claisen acylation of acetophenone with ethyl 3-phenylpropionate gave the diketone (85) and subsequent methylation, with methyl iodide and potassium carbonate, gave the desired diketone (86). This diketone was then reacted with hydrazine hydrate to give the pyrazole (84) in good yield. This authentic pyrazole was characterised and found to have identical melting point and spectral characteristics

to the sample obtained from the hydrogenation of (70). Thus, it was conclusively proved that the product isolated from the reaction of (65) was indeed 4-methyl-3-phenyl-5-(*E*-2-phenylethenyl)pyrazole (70).

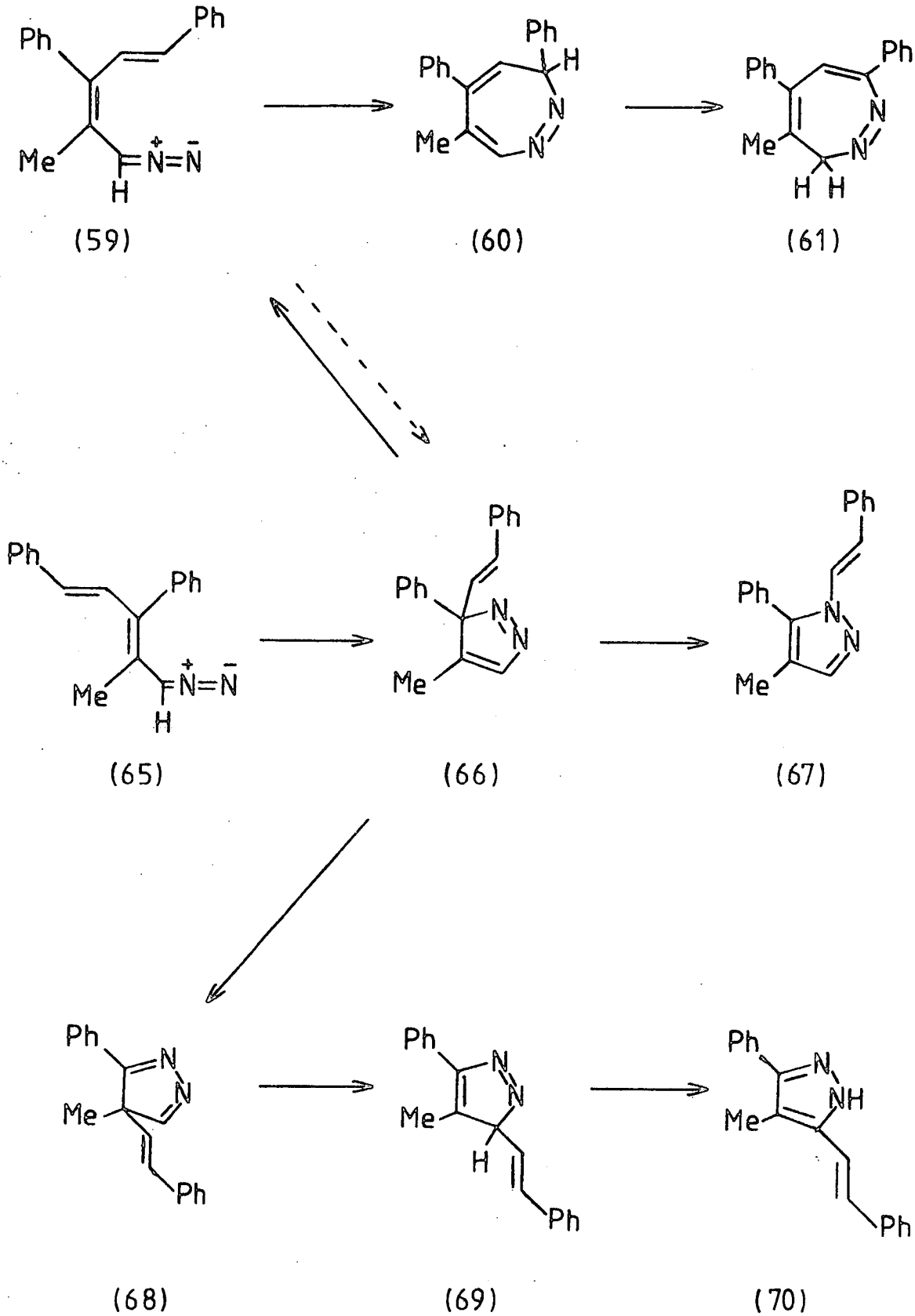


(84) (86)

Scheme 14

Mechanism of formation of cyclisation products from reaction of the *E*-diazoalkane (58, $R^1 \neq H$)

The mechanism proposed to account for the formation of (61), (67) and (70) from the reaction of the *E* diazoalkane (65) is shown in Scheme 15. These products are all formed from a common intermediate, the 3*H*-pyrazole (66) which is formed by a 1,5-electrocyclisation process. This 3*H*-pyrazole intermediate can rearrange by several possible pathways to give the isolated products.


Ph
Ph
Me
H
Ph
Ph
Me
H
Ph
Ph
Me
H H
(59)
(60)
(61)
Ph
Ph
Me
H
Ph
Ph
Me
Ph
Ph
Me
(65)
(66)
(67)
Ph
Me
Ph
Ph
Me
H
Ph
Ph
Me
NH
Ph
(68)
(69)
(70)

Scheme 15

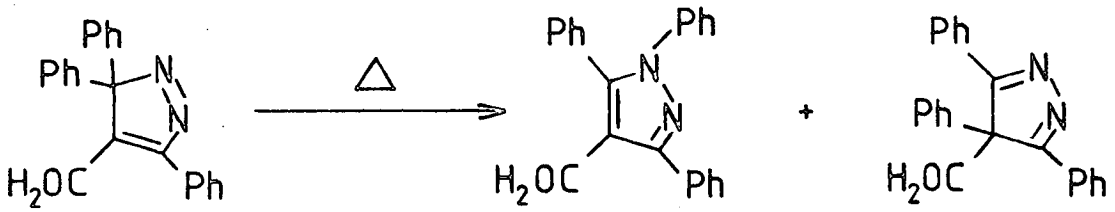
A [1,5] sigmatropic shift of one of the groups at C-3 can occur, either to nitrogen or carbon. A shift of the phenyl group to nitrogen would have resulted in formation of the previously proposed structure (75). However, the observed [1,5] shift to nitrogen is that of the phenylethenyl group to give the isolated product (67). This is the most favourable process as it results in a stable aromatic product *via* one rearrangement.

The 3*H*-pyrazole (66) also underwent a van Alphen-Huttel rearrangement *via* a [1,5] sigmatropic shift of the phenylethenyl group to give the 4*H*-pyrazole (68). However, as this intermediate is not aromatic it subsequently undergoes a further [1,5] sigmatropic shift of the phenylethenyl group to give the 3*H*-pyrazole (69). Such a rearrangement is reasonable as it is well known that the migratory aptitude of alkyl groups ie Me at C-4 is small with respect to that of unsaturated groups.[132,172] This 3*H*-pyrazole would readily aromatise by hydrogen shift to give the isolated pyrazole (70).

The final product obtained from the reaction of (65) was the 3*H*-1,2-diazepine (61). This product is formed by the 3*H*-pyrazole (66) undergoing a retro-1,5-electrocyclisation to give the *Z* isomer (59) of the diazoalkane. This *Z* diazoalkane immediately undergoes a 1,7-electrocyclisation to give (60) which readily isomerised to (61) as discussed earlier. The possibility of (61) arising from an initial formation of (60), from the corresponding *Z* tosylhydrazone, was discounted as ^{1}H and ^{13}C n.m.r. did not show any of the *Z* isomer of the tosylhydrazone to be present in the starting *E* tosylhydrazone. Isolation of (61) infers that the 1,5-electrocyclisation is a

reversible process, which competes with normal van Alphen-Huttel rearrangements of 3*H*-pyrazoles, and this conclusion parallels the observation of previously observed 3*H*-pyrazoles. (See p.35).

It is interesting to note that the 3*H*-pyrazole (66) undergoes two separate rearrangements *via* 1,5 -alkenyl shift to both carbon and nitrogen. Previous work had shown that the migrating tendencies in such pyrazoles depend much on the nature of the migrating group. In many cases a migration to carbon only is observed e.g. (96)→(97) while in others the substituent migrates to both carbon and nitrogen.[173] For example the 3*H*-pyrazole (87) which is disubstituted at C-3 undergoes [1,5] phenyl shifts to nitrogen and carbon giving (88) and (89) respectively.[174]

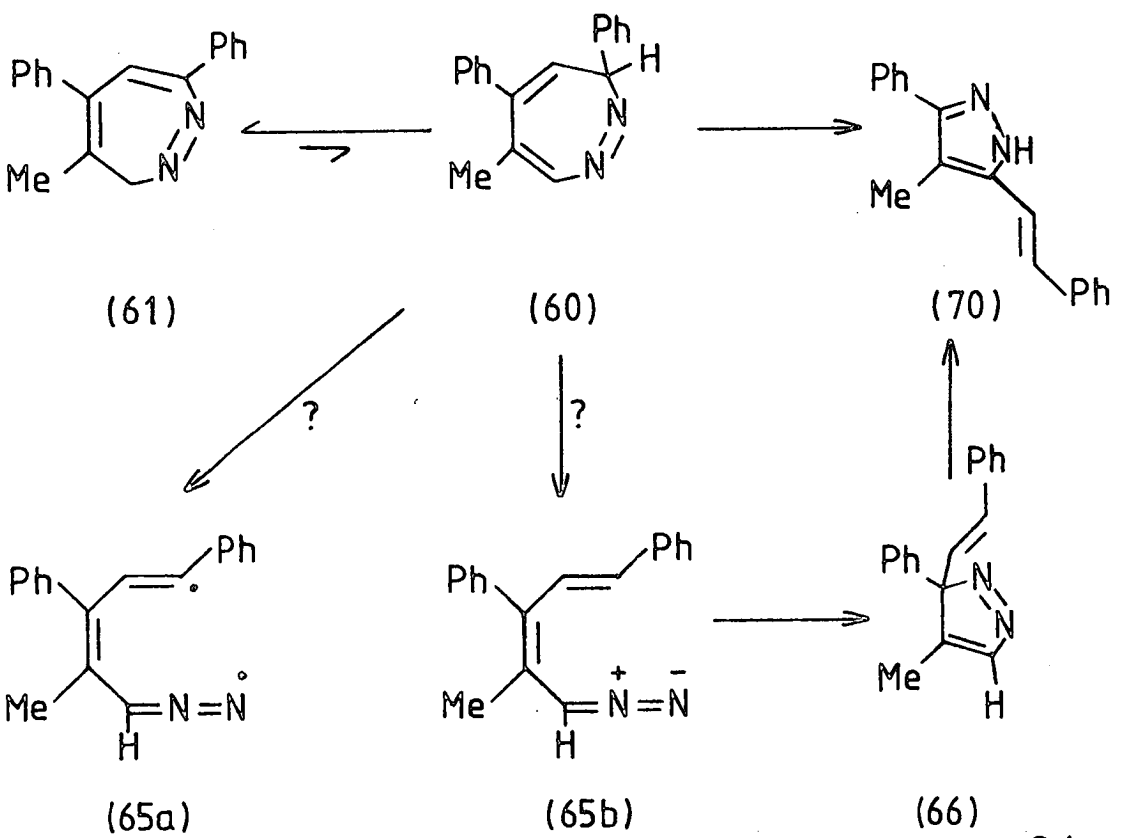


(87) (88) (89)

The migration of the phenylethenyl group of (66) to both carbon and nitrogen is thus not surprising as it has been suggested that the more unstable the 3*H*-pyrazole intermediate, or the greater the migratory aptitude of the groups at C-3, the more pronounced the tendency for migration to nitrogen rather than to carbon.[173] The 3*H*-pyrazole (66) is disubstituted at C-3 with bulky substituents and thus will be more sterically crowded, therefore less stable than other less crowded disubstituted 3*H*-pyrazoles, for example (96), and so

both types of migration could be expected for (66). It is also worthy of note that the reaction of (65) in higher boiling toluene gives a different ratio of products; (70):(67):(61), 61%:7%:6%. This result would indicate that the [1,5]phenyl-ethenyl shift to carbon becomes more favoured, than the corresponding shift to nitrogen, with increasing temperature.

The thermolysis of the 3*H*-1,2-diazepine (61) in toluene resulted in the isolation of the N-H pyrazole (70) in good yield. This structure was confirmed by comparison of its spectral data and melting point with that of the identical product obtained from the cyclisation of the *E* diazoalkane (65).



Scheme 16

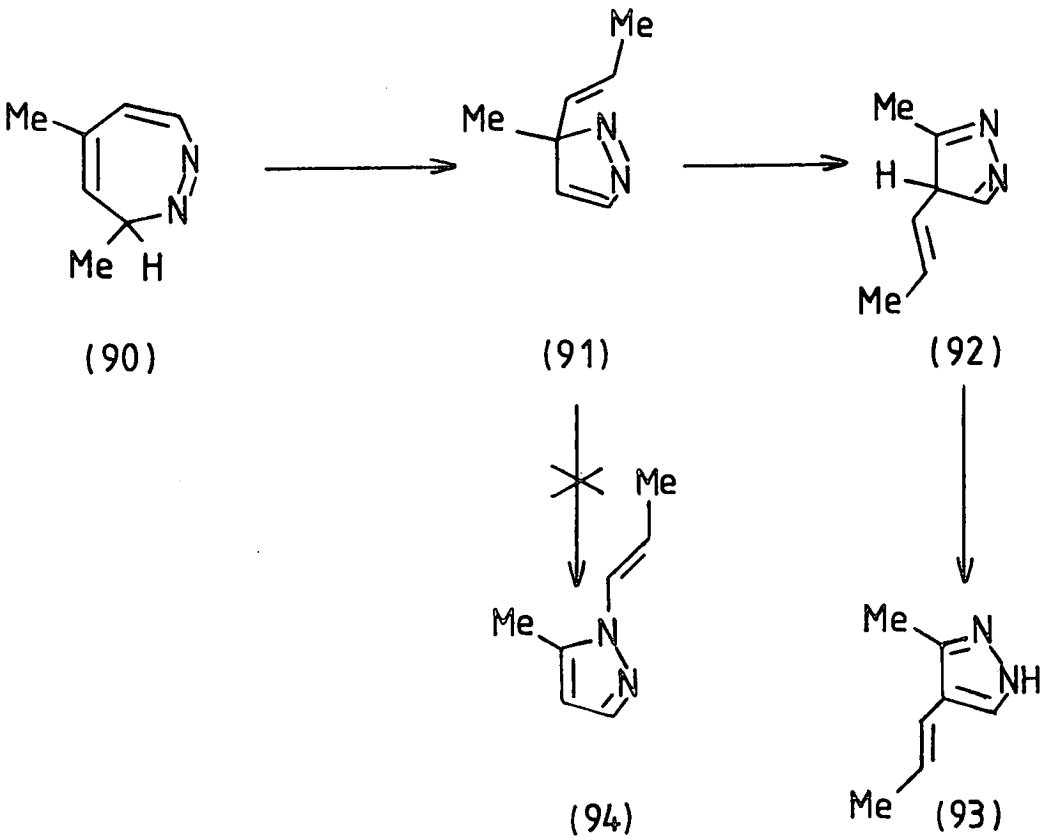
The mechanism proposed for the thermal decomposition of (61) involves the rearrangement to the 3*H*-pyrazole (66) *via* (60) and (65) (Scheme 16). The involvement of a 3*H*-pyrazole intermediate has been postulated by earlier workers as an

intermediate in the pyrolysis of 3*H*-1,2-diazepines. (See p.73).

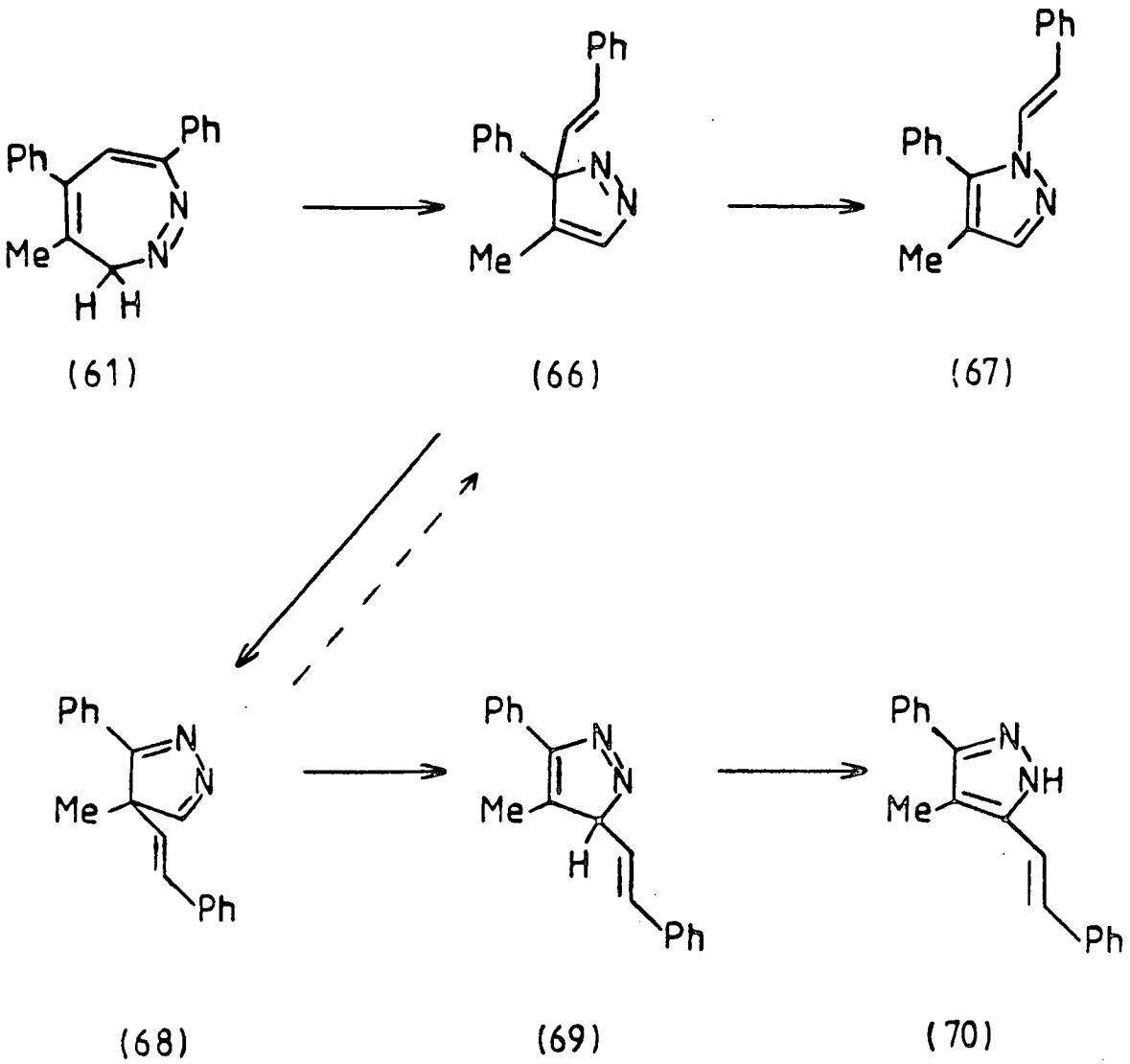
It is known that [1,5]hydrogen shifts in 3*H*-1,2-diazepines are very rapid even at room temperature and it is proposed that the decomposition of the (60) / (61) system occurs *via* C-N bond cleavage in (60). Previous work has shown that a similar phenomenon occurs in related systems.[132] This ring cleavage could be a homolysis or an electrocyclic opening to either (65a) or (65b) which subsequently cyclise to give (66). The decomposition of the 3*H*-pyrazole (66) can then occur *via* a [1,5]sigmatropic shift to carbon to give (68), and subsequently (70), rather than the alternative shift to nitrogen. This exclusive formation of (70) from the thermolysis of (61) is in agreement with the high selectivity for migration to carbon exhibited in the reaction of diazoalkane (65) at the same temperature (110°C) and indicates the involvement of a common intermediate (66).

The temperature dependence of the mode of [1,5]sigmatropic shift can be rationalised. It is known that [1,5]alkenyl shifts to carbon to give 3*H*-pyrazoles is a much faster shift compared with the [1,5] shift to nitrogen, as seen by the preferential formation of (92) rather than (94).[132] The 3*H*-pyrazole is readily transferred into the 4*H*-pyrazole (92) which then undergoes a fast hydrogen migration to give (93) only when a hydrogen is present at the C-4 position of the 4*H*-pyrazole (92).

Replacement of the hydrogen at C-4 by a non-migratable group such as the methyl group of (68) will result in the migration of the less mobile phenylethenyl group to give (69).



Thus the conversion of (68) to (69) will be much slower than (92) to (93) which enables the 4*H*-pyrazole (68) to revert back to (66) and subsequently to the *N*-phenylethenylpyrazole (67). Increasing the reaction temperature will result in a more rapid conversion of (68) to (69). This results in less effective competition by the reversal step to give (66) and thus the formation of (69) and subsequently (70) is favoured under these conditions.



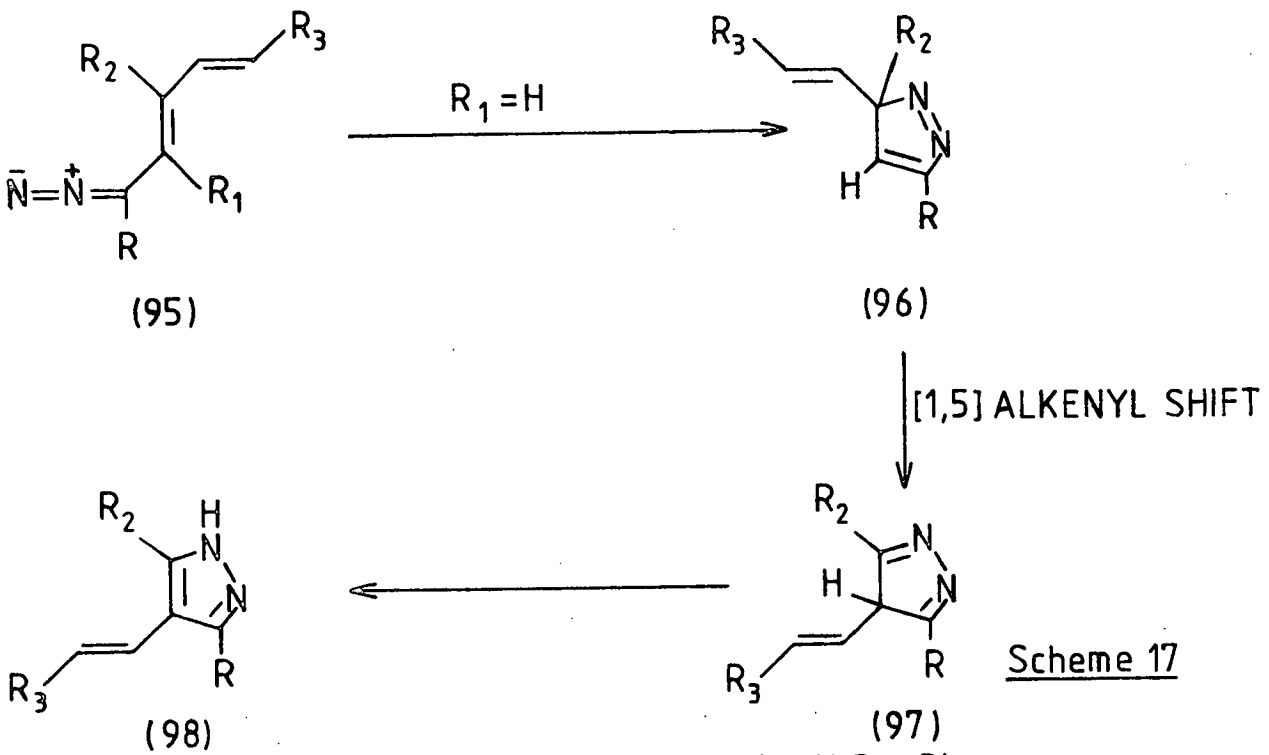
(61) (66) (67)

(68) (69) (70)

1.2.2.3 Reaction of *E* diazoalkanes (58, R^1=H)

Reaction of the *E* diazoalkanes (95a, 95b) gave a single product in each case, which were subsequently identified as the 4-alkenylpyrazoles (98a,98b).

The isolated products were identified as 1*H*-pyrazoles by ^{13}C and ^{1}H n.m.r., infra-red and mass spectral data. The ^{13}C n.m.r. spectra showed only aromatic absorptions and no other saturated carbon atoms were present, except for those expected for the R substituents. The absorptions at 111.7 p.p.m. (98a) and 113.0 p.p.m. (98b) were similar to those reported for other NH pyrazoles.[132] Further confirmation of structure (98b) was obtained in that only nine signals

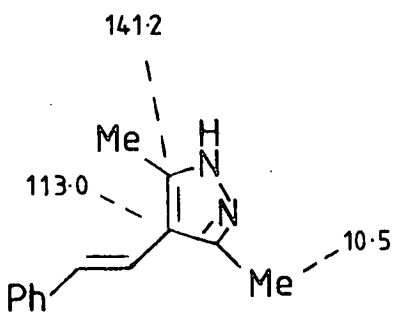


(95) (96) (97) (98)

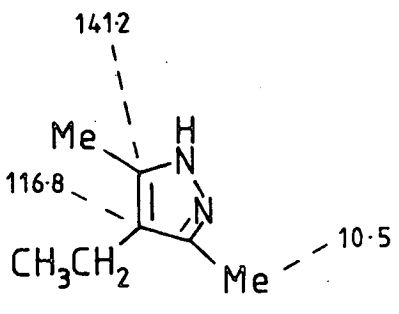
Scheme 17

a) R = Me_2CH, R_1=H, R_2=R_3=Me ; b) R=R_2=Me, R_1=H, R_3=Ph

were observed as expected for the proposed symmetrical pyrazole. The absorptions for (98b) also correlated well with those reported for symmetrical pyrazole (99).[132]



(98b)



(99)

Evidence that the γ,δ-double bond of (98a,b) was still intact, and that 1,7-electrocyclisation had not occurred, was provided by the ^{1}H n.m.r. data. In both cases the olefinic regions could be clearly seen, as two doublet of quartets

(δ5.70, J16Hz, 6.2Hz; δ6.27, J16Hz, 1.4Hz) for (98a) and as an AB pattern (J=16.5Hz) for (98b). The proton n.m.r. of (98a) also showed the presence of an N-H as did the infra-red spectra of both (98a) and (98b). In both cases the mass spectra showed M^+ as the base peak with fragmentation *via* loss of the R groups indicating a stable aromatic ring.

The 1*H*-pyrazoles are formed by a 1,5-electrocyclisation of the diazoalkanes (95a,95b) to give the 3*H*-pyrazole (96a,96b) which readily undergoes a van Alphen-Huttel rearrangement of the unsaturated side-chain to C-4 to give the 4*H*-pyrazoles (97a,97b). These 4*H*-pyrazoles then undergo a facile aromatisation, by hydrogen migration, to give the aromatic 1*H*-pyrazoles (98a,98b).

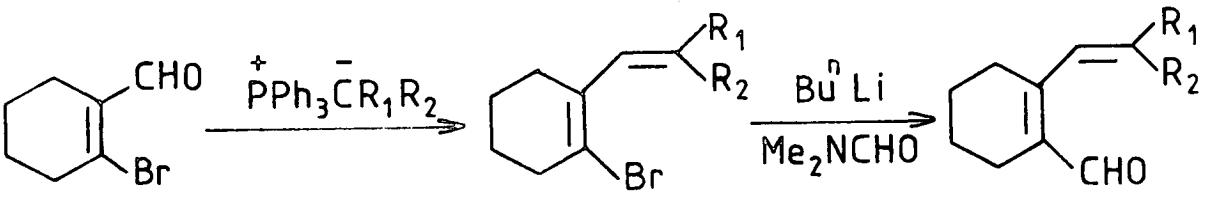
To summarise the work of this section, the mode of reactivity of electrocyclisations of α,β:γ,δ-unsaturated diazoalkanes is dependent on geometrical factors. When a *Z* diazoalkane is reacted it undergoes immediate 1,7-electrocyclisation only to a give a diazepine. However, when a *E* diazoalkane is reacted only 1,5-electrocyclisation is observed, to give pyrazole derived products, as the δ termini for the preferred 1,7-electrocyclisation mode of reaction and the diazoalkane are separated by too large a distance. The mechanism of diazepine formation is discussed in more detail later (p.138).

1.3) Substrates with a Zδ substituent other than hydrogen

1.3.1) Synthesis of α,β:γ,δ-unsaturated aldehydes having a Zδ substituent other than hydrogen

It has been shown by Munro that *o*-alkenylaryldiazoalkanes having a Z hydrogen atom (1, R_2=H) undergo 8π electron 1,7-electrocyclisation to give 1*H*-2,3-benzodiazepines.[80] However, introduction of a Zδ substituent eg. methyl or phenyl, completely blocks this mode of cyclisation. These diazoalkanes react *via* loss of nitrogen to give carbene derived products only and do not undergo the alternative 6π electron 1,5-electrocyclisation.[82,83]

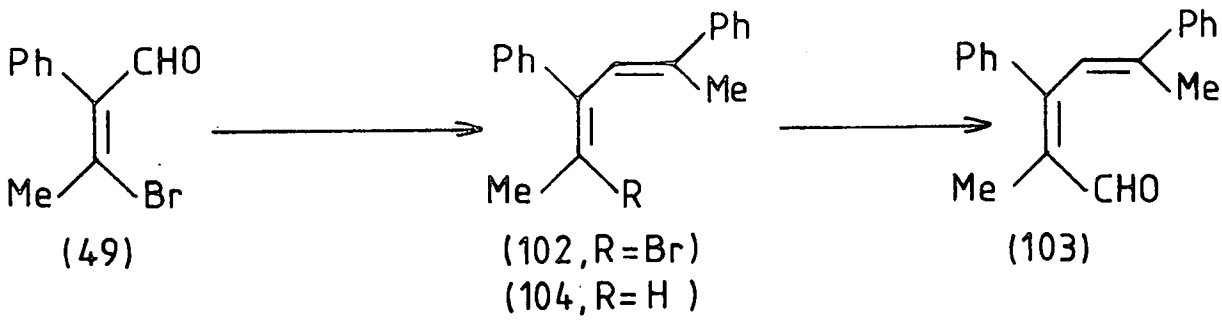
As demonstrated in previous sections diazoalkanes with only α,β-and γ,δ-unsaturation also undergo 1,7-electrocyclisation, if the geometry of the diazoalkane is Z. It was of interest to ascertain if the introduction of a Z substituent at the δ position would prevent 1,7-electrocyclisation in these diazoalkanes. Thus, the aldehyde (101) was prepared by a route similar to that used for (20). The β-bromoacraldehyde (18b) was reacted with the ylide derived from the corresponding triphenylphosphonium salt, to give the α,β:γ,δ-unsaturated bromo compounds (100a,b). The organolithium reagent of (100a,b), formed *via* metal-halogen exchange, on reaction with dimethylformamide followed by hydrolysis gave the desired aldehydes in moderate yields. This lithiation reaction was carried out at low temperature (-78°C) to prevent butylation of the organolithium derivative occurring, by its reaction with *n*-butylbromide formed during the reaction. This resulted in slow lithiation and the recovery of some starting material in the reaction of (100a).



a) $R_1 = R_2 = Me$; b) $R_1 = Ph, R_2 = Me$

(18b) (100) (101)

The acyclic compound (103) was synthesised by an analogous procedure to that used in the preparation of aldehyde (53). The Wittig reaction of the *Z* β-bromoacraldehyde (49) with the ylide, generated from α-methylbenzyltriphenylphosphonium bromide and *n*-butyllithium, gave the desired α,β:γ,δ-unsaturated bromo compound (102) in good yield. The preparation of (103) was again accomplished *via* the reaction of the organolithium derivative with dimethylformamide. In this case the addition of *n*-butyllithium at -78°C gave an intense red colour, but subsequent quenching with dimethylformamide after 30 minutes did not give any of the desired aldehyde. The product which was formed was tentatively identified as 2,4-diphenyl-2,4-hexadiene (104) on the basis of mass spectral and ^1H n.m.r. data. As this reaction was carried out under anhydrous conditions it seemed likely that the proton which replaces the bromine originates from the δ Me. This proton would be readily abstracted as it would involve a stable six-membered intermediate, and the $CH_2^{\ominus}$ subsequently generated would not react with dimethylformamide, at -78°C, but would protonate on work up to give (104).



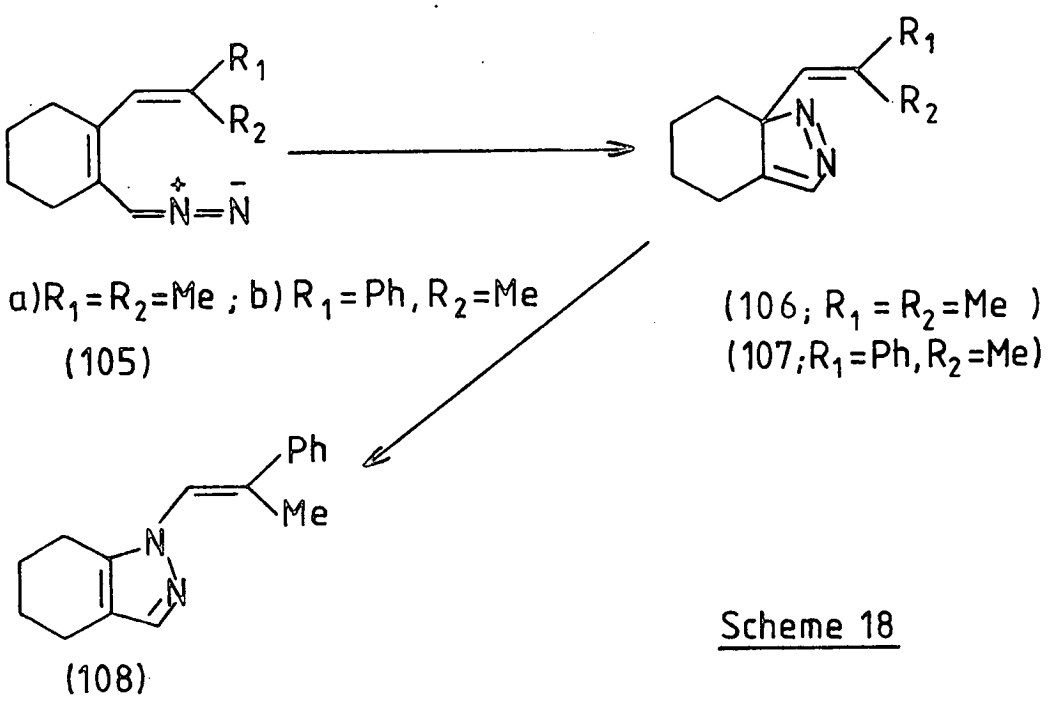
(49) (102, R=Br) (104, R=H) (103)

This rearrangement was prevented by carrying out the addition of *n*-butyllithium at -120°C, followed by rapid quenching of the vinyl-lithium derivative with a large excess of dimethylformamide. This procedure enabled the synthesis of the derived aldehyde (103) to be accomplished in good yields.

1.3.2) Decomposition of tosylhydrazone sodium salts

Conversion of the precursory aldehydes (101a,b) and (103) to the tosylhydrazones and hence to the sodium salts was carried out using standard methods. The reaction of (105a) gave extensive polymerisation and a multicomponent reaction mixture from which only one identifiable product was isolated. This product was isolated in 11% yield and identified by its spectral properties as being 7a-(2-methylpropenyl)-4,5,6,7-tetrahydroindazole (106). The reaction of (105b) gave a less complex reaction mixture containing two identifiable products i) 7a-(*E*-2-phenylpropenyl)-4,5,6,7-tetrahydroindazole (107) in 42% yield and ii) 1-(*E*-2-phenylpropenyl)-4,5,6,7-tetrahydroindazole (108) in 9% yield. (Scheme 18).

Thus, these δ disubstituted diazoalkanes (105a,b) did not undergo 1,7-electrocyclisation. Instead, they reacted



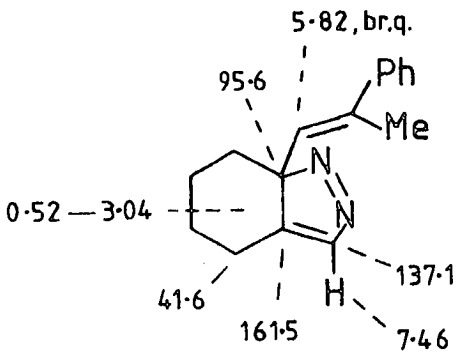
Scheme 18

via the alternative 6π electron 1,5-electrocyclisation to give the 7a*H*-tetrahydroindazole (106,107). In the case of the 7a*H*-tetrahydroindazole (107) a [1,5]alkenyl shift occurs to give the more stable aromatic 1*H*-tetrahydroindazole (108). This was confirmed by subsequent thermolysis of (107) in refluxing 1,2-dimethoxyethane which gave the rearranged product (108).

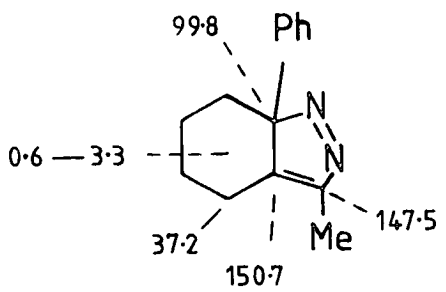
The tetrahydro-7a*H*-indazoles were identified on the basis of their spectral data. The 7a*H*-tetrahydroindazole (106) was shown by mass spectrometry to have the formula $C_{11}H_{16}N_2$. ^1H N.m.r. spectra did not indicate the presence of an NH and this was subsequently confirmed by infra-red spectroscopy. ^1H N.m.r. spectra confirmed the presence of the isopropenyl olefinic proton as a broad signal (δ5.29) and the presence of one deshielded proton (δ7.34, d, J1.5Hz), which was assigned as the H-3 proton. ^1H N.m.r. spectra also showed a shielded proton absorption (δ0.40-0.60) characteristic of the absorptions

observed for one of the cyclohexyl protons of 7a*H*-tetrahydroindazoles (109).[77] ^{13}C N.m.r. spectra showed the expected two methyl and isopropenyl signals. Also present were i) the CH_2 signals including one deshielded signal (41.4 p.p.m.) ii) a deshielded olefinic carbon (161.5 p.p.m.) and iii) a deshielded saturated quaternary carbon absorption (95.6 p.p.m.). These three ^{13}C n.m.r. absorptions closely paralleled the absorptions observed for previously synthesised 7a*H*-tetrahydroindazoles (109).

The structure of (107) had similar ^1H and ^{13}C n.m.r. spectral characteristics to (106) and (109). Mass spectrometry and elemental analysis confirmed its formula as $C_{16}H_{18}N_2$ and ^1H n.m.r. and infra-red spectroscopy confirmed the absence of an NH.

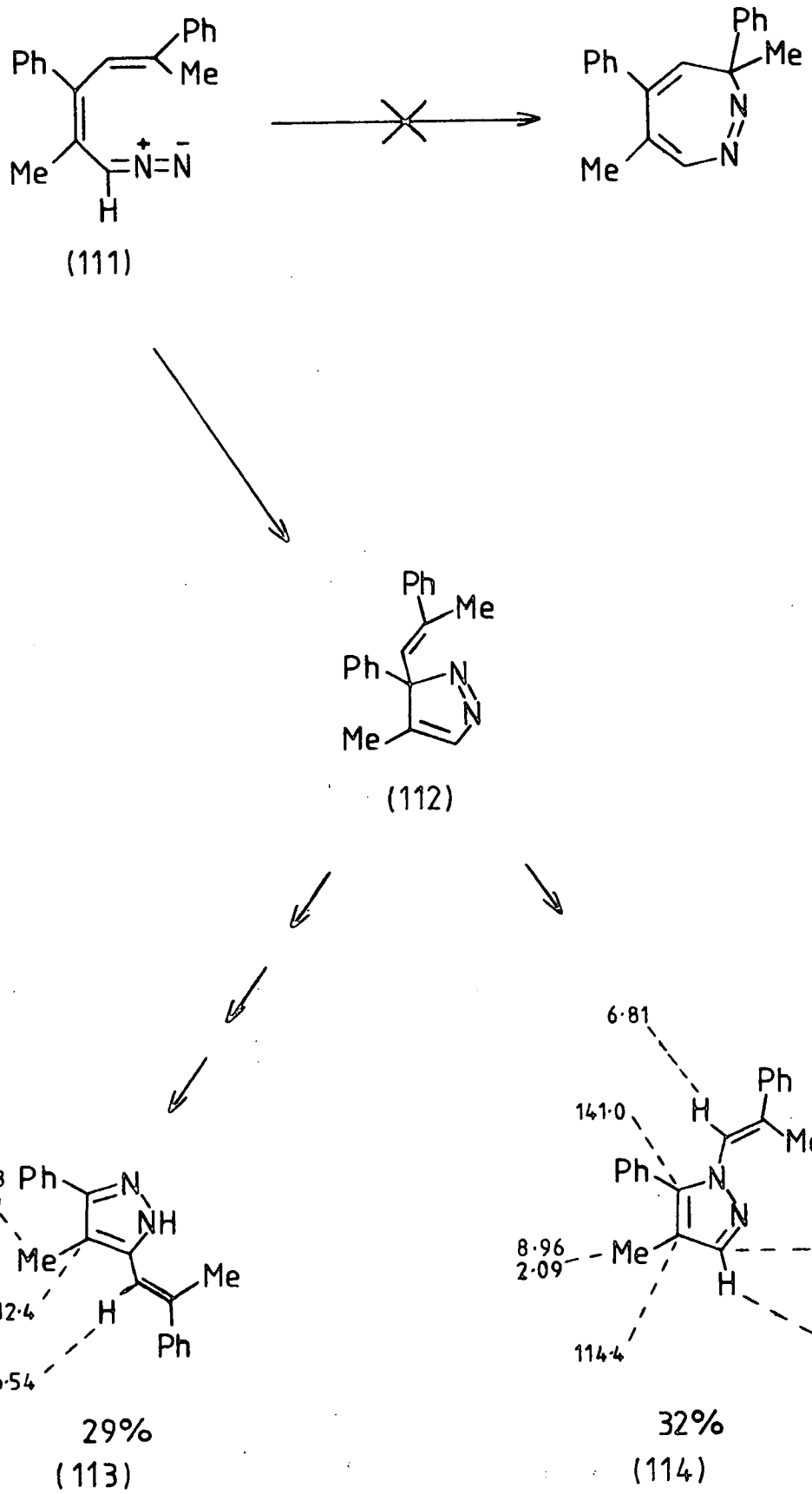


(107)



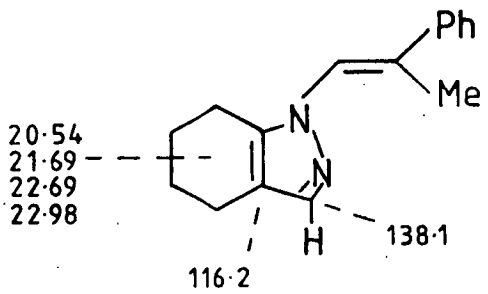
(109)

The structure of the 1-alkenyltetrahydroindazole (108) was also established from its spectral data. The ^1H n.m.r. spectra showed an olefinic absorption present as a quartet (δ6.85, J1.4 Hz), the methyl doublet (δ2.35, J1.4Hz) and cyclohexyl ring absorptions (δ1.25-1.86 and 2.50-2.60). ^{13}C N.m.r. spectra showed the Me, aromatic and C-3 (138.1 p.p.m.) absorptions as

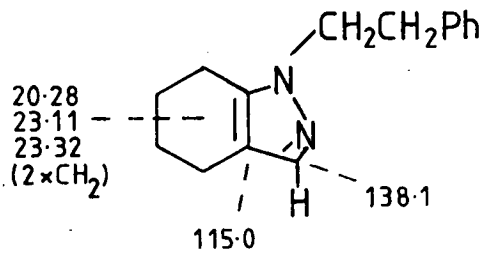

Ph
Me
Ph
Me
N
N
H
(111)
Ph
Me
Ph
N
N
Me
(112)
9·23
2·19
Ph
N
NH
Me
Me
112·4
H
Ph
6·54
29%
(113)
6·81
141·0
H
Ph
Me
Ph
N
N
8·96
2·09
Me
−140·5
H
114·4
7·55
32%
(114)

Scheme 19

well as four CH_2 signals (20.5, 21.7, 22.7, 23.0). The quaternary carbons absorbed at 116.2, 132.0, 139.2 and 141.5 p.p.m. These absorptions indicated that the structure was a 1-substituted tetrahydroindazole rather than a 7a*H*-substituted isomer. Further support for this structure was obtained by comparison with 1-phenethyl-4,5,6,7-tetrahydroindazole (110) prepared from the reaction of 1-formylcyclohexanone with β-phenethylhydrazine.



(108)



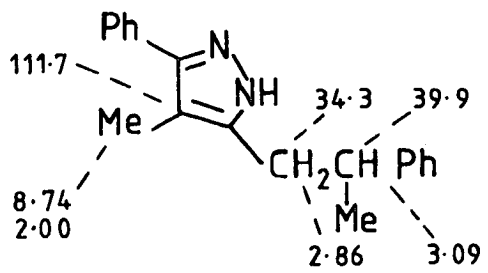
(110)

Similarly, ~~reaction of~~ the monocyclic δ disubstituted diazoalkane (111) did not undergo 1,7-electrocyclisation, but underwent the alternative 1,5 - 6π electron electrocyclisation to give pyrazole derived products *via* the 3*H*-pyrazole intermediate (112). This 3*H*-pyrazole intermediate underwent identical rearrangements to the previously reported 3-phenyl-3-phenylethenyl-3*H*-pyrazole (66). Thus, the isolated products were i) 4-methyl-3-phenyl-5-(*E*-2-phenylpropenyl)pyrazole (113) in 29% yield and ii) 4-methyl-5-phenyl-1-(*E*-2-phenylpropenyl)-pyrazole (114) in 32% yield. (Scheme 19).

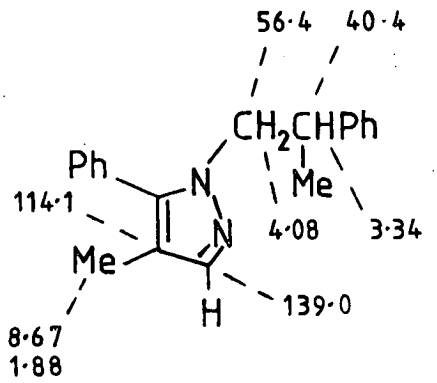
Elemental analysis and mass spectroscopy confirmed that the NH pyrazole (113) had the formula $C_{19}H_{18}N_2$. Its structure

was established from its spectral data which was found to be very similar to that of the analogous compound (70) (page 112). Further proof of the structure was obtained by the hydrogenation of a sample to give (115) which has formula $C_{19}H_{20}N_2$ thereby confirming the presence of an olefinic bond in (113). The spectra data of (115) was found to be very similar to that of the analogous compound (84) (page 118).

Similarly, the mass spectra confirmed that (114) had the formula $C_{19}H_{18}N_2$, and both ^1H n.m.r. and infra-red spectra did not show the presence of NH. Subsequent hydrogenation of (114) gave (116) and both these compounds had very similar spectra to the analogous compounds (67) and (76) respectively (p.112 and 114).



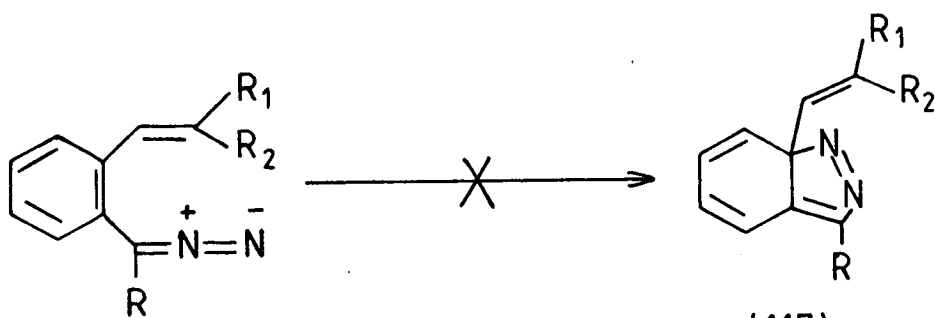
(115)



(116)

From the results of the above reactions of δ disubstituted diazoalkane it is clear that the introduction of a Z substituent completely inhibits 1,7-electrocyclisation. However, in these cases the diazoalkanes undergo the alternative 1,5-electrocyclisation mode of reaction, to give pyrazole derived products. It is interesting to note that in the previously reported σ-alkenylaryldiazoalkanes where 1,7-electrocyclisation

is inhibited only carbene derived products are formed. It is believed that the failure of these aromatic analogues to undergo 1,5-electrocyclisation is due to the fact that this would involve the formation of a non-aromatic intermediate (117). The more thermodynamically favoured process is *via* loss of nitrogen to give the corresponding carbenes, as this process has a lower activation energy as it does not involve the disruption of the benzene ring aromaticity. In the cases of olefinic α,β:γ,δ-unsaturated diazoalkanes (105) and (111) there is no equivalent loss of aromaticity if 1,5-electrocyclisation occurs and thus the activation energy is much lower, resulting in this process being the predominate mode of reaction.

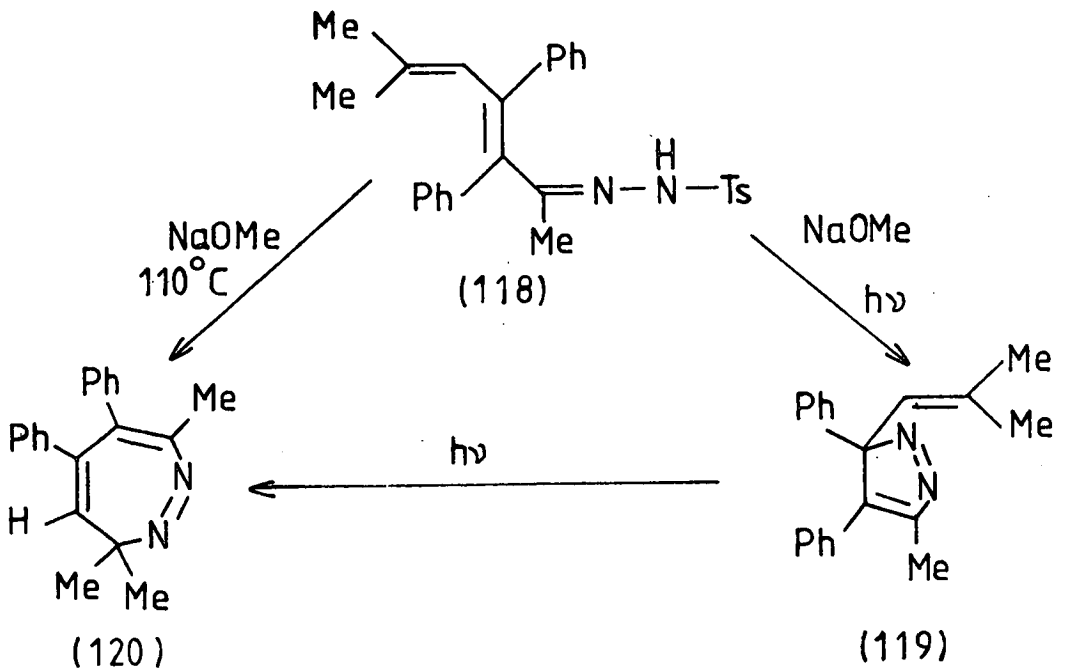


(117)

These results show that the presence of a *Z* methyl group at the cyclisation site of (105) and (111) effectively blocks the 1,7 ring closure mechanism which is the dominant reaction path for analogues (24) (27) (59) which possess a *Z* hydrogen.

Our many results on the reactions of δ disubstituted α,β:γ,δ-unsaturated diazoalkanes are a contradiction to the one reported example.[175] It was claimed that the sensitised photolysis of the sodium salt *E*-3,4-diphenyl-6-methyl-3,5-heptadien-2-one tosylhydrazone (118) in T.H.F. gave the isolable 3*H*-pyrazole (119). Subsequent photolysis of this proposed

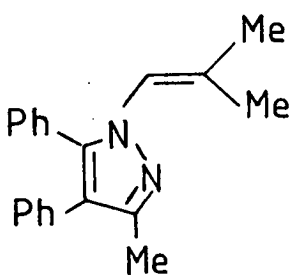
3*H*-pyrazole gave many products one of which was claimed to be 5,6-diphenyl-3,3,7-trimethyl-3*H*-1,2-diazepine (120). This product was also claimed to be isolated in 84% yield from the pyrolysis, at 110°C for 8 h, of the sodium salt of the tosylhydrazone (118).



However, we believe there is much doubt about the structural assignment of these products (118-120); i) although the 3*H*-pyrazole (119) had ^{1}H n.m.r. and mass spectral data, consistent with its proposed structure from the evidence present in the paper, it did not have the expected ^{13}C n.m.r. ie. no deshielded saturated carbon characteristic of 3*H*-pyrazoles (*ca.* 90-105 p.p.m.) was evident, but rather a relatively shielded signal (13.1, 21.0, 27.1 and 47.3 p.p.m.) was present. Thus the compound obtained cannot be (119) but must be some isomer product. ii) Photolysis of the reported 3*H*-1,2-diazepine did not result in any observed reaction, which is indeed very surprising as every previously reported structure of this type

very readily undergo an internal $2\pi + 2\pi$ cycloaddition. iii) No comment is made of the proposed 3*H*-1,2-diazepine losing nitrogen in the mass spectrometer, a feature exhibited by all other compounds of this type, and no ^{13}C n.m.r. data for the tosylhydrazone and diazepine are presented whereas this data was present for all other new compounds reported in this publication. iv) It is very unlikely that the reported diazepine would be stable for 8 h at 110°C without undergoing previously reported rearrangements to pyrazoles, known to occur under these conditions.

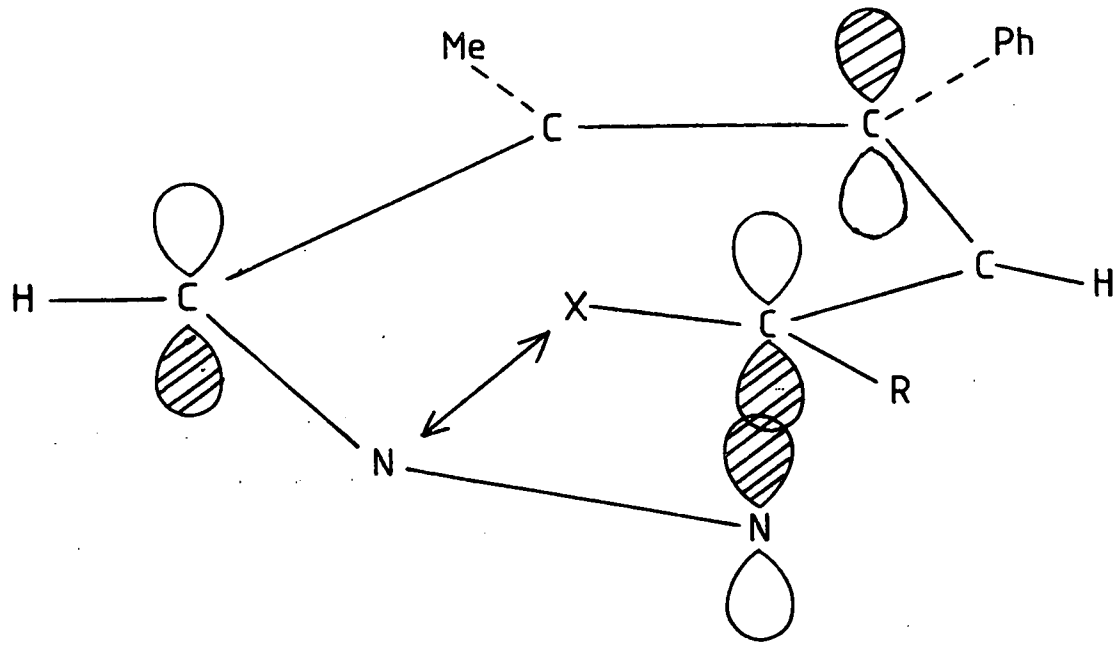
From our own results it would be very surprising if the thermal decomposition of the sodium salt of (118) did undergo 1,7-electrocyclisation, as it i) possesses a *Z* substituent and ii) the tosylhydrazone precursor is in the *E* confirmation and both these factors have been shown by us to result in 1,5 rather than 1,7-electrocyclisation. The above factors make it likely that the product isolated was not the 3*H*-1,2-diazepine (120) but more likely a product derived from 1,5-electrocyclisation, most probably the 1-isobutenylpyrazole (121).



(121)

Mechanism of 1,7-cyclisation

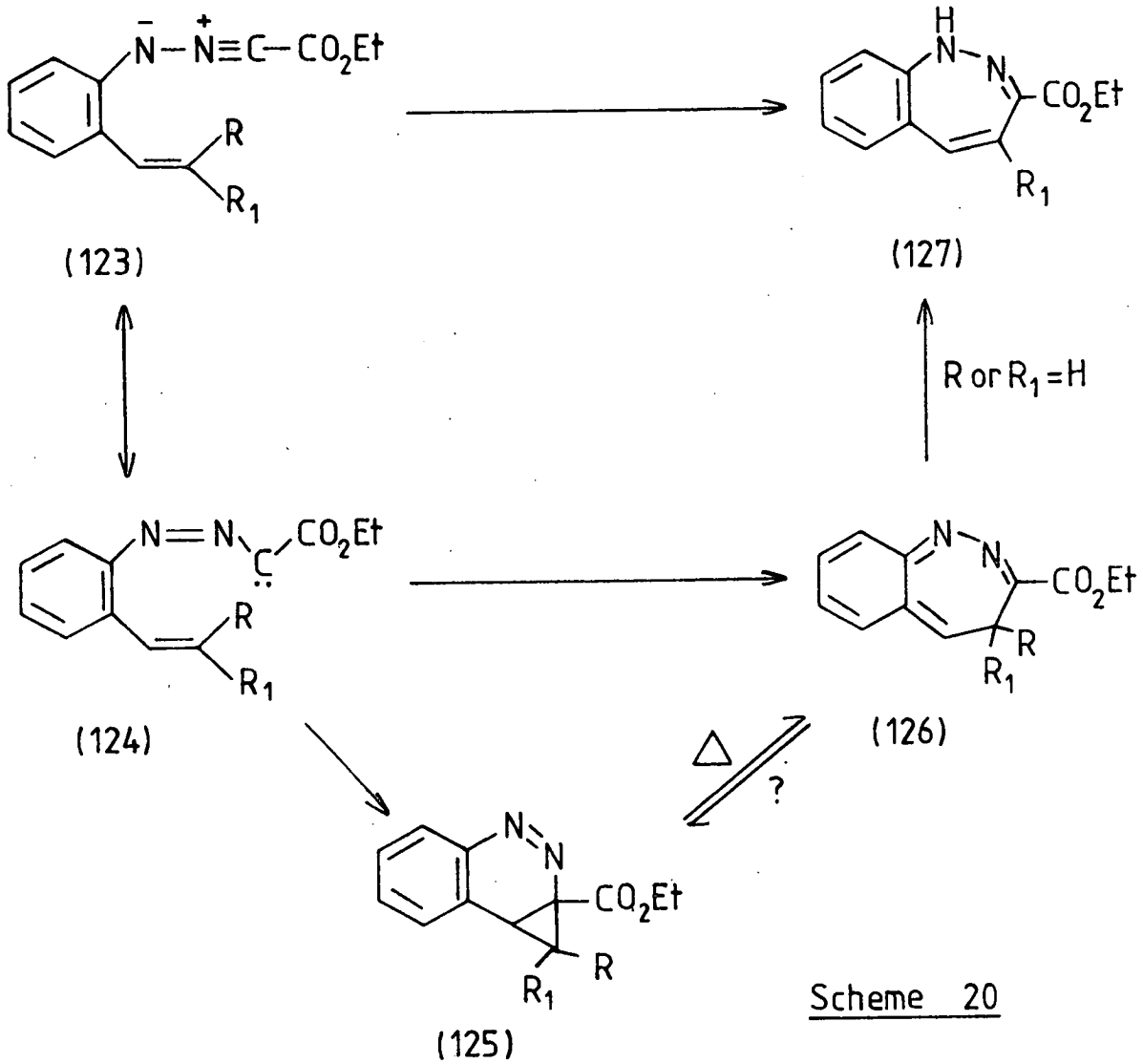
To explain the blocking effect of a Z substituent on the 1,7-electrocyclisation it is necessary to consider the mechanism and nature of the transition state for the ring closure step. It is believed that it is an 8π electron 1,7-electrocyclisation process and that the transition state is of the form (122). Such a transition state brings the terminal atoms into a bonding overlap and requires no angular distortion at the trigonal carbon atoms and the minimum distortion of the diazo group from its preferred linear geometry.[176,177] In such a transition state the steric interaction (↔ in 122) between the Z group X and N-2 of the diazo group is small when X=H but models show that the larger Z methyl comes into significant interaction with N-2. This would raise the energy of the transition state either by inhibiting overlap between the orbitals at the two reaction termini or by causing the terminal carbon atom to twist so that the conjugation required for an electrocyclisation process would be lost.



(122)

However, in view of work carried out on related systems the question of whether 1,7-electrocyclisation is the primary step in the conversion of (6) and (59) to (33) and (61) respectively, has to be raised. Nitrilium betaines isoelectronic with (6) undergo reactions which are in some respects very similar. These nitrile imines (123, R or R_1=H), when heated at 80°C readily undergo cyclisation to give 1*H*-1,2-benzodiazepines (127).[32-33] This conversion also depends on the presence of a hydrogen atom on the terminal carbon of the alkene but unlike the diazo system it may be in either *Z* or *E* positions. When (123) is generated at room temperature, however, it reacts to give the cyclopropa[c]cinnoline system (125) *via* a stereospecific 1,1-cycloaddition process which is not inhibited by the presence of *Z* methyl[33] or phenyl[178] groups. Heating (125) at 80°C effects conversion to the benzodiazepine system (127) provided R or R_1 is hydrogen. The reactions of

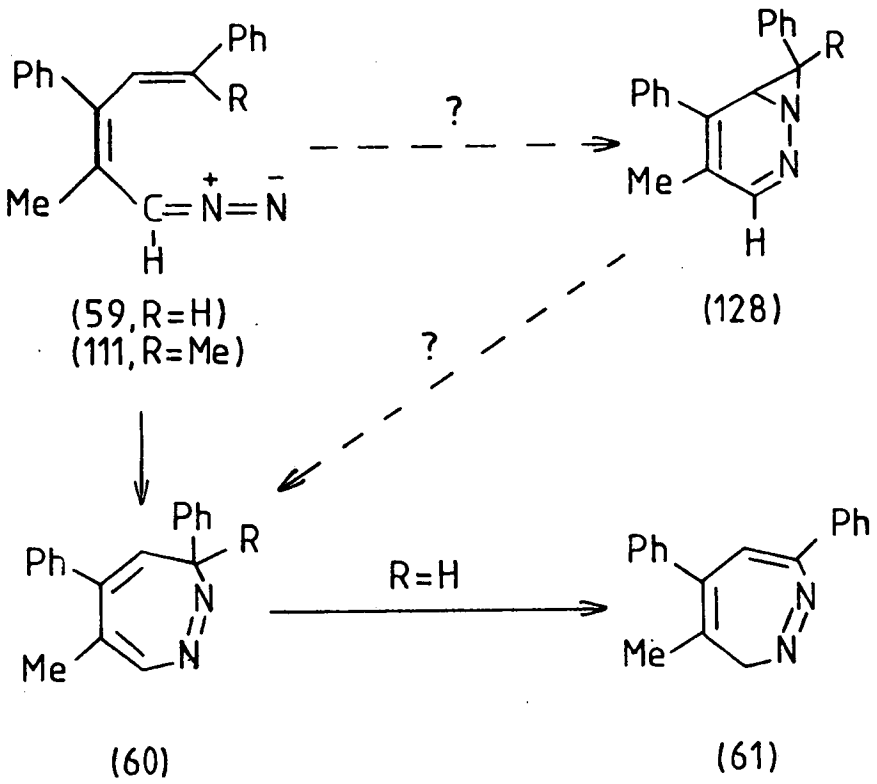
the nitrile imine can thus be rationalised on the basis of a primary 1,1-cycloaddition step giving (125) rather than at a 1,7-electrocyclisation giving (126) directly (see Introduction, p.13).



Scheme 20

In view of this the possibility has to be considered that the conversion of the diazo-compound (59) into the 3*H*-1,2-diazepines (61) (Scheme 21), also involves a primary 1,1-cycloaddition to give (128), followed by electrocyclic ring opening to give (60) and finally a [1,5] hydrogen shift giving the isolated product. Particularly so since recent work[85,86,88] has shown that diazocompounds <u>can</u> react *via* stereospecific

1,1-cycloadditions (see Introduction, p.43). As these 1,1-cycloadditions are reported to be reversible it would be expected that we would not isolate the analogous species (128) from the reactions of the diazo compound (59) which was carried out at 80°C. This though does not rule out 1,1-cycloaddition as the primary step when R = H. However there is no support for it. The 1,1-cycloadditions of nitrile imines are not deterred by the presence of *Z* methyl or phenyl groups and similarly the 1,1-cycloadducts have been prepared from diazo-compounds having a *Z* substituent.[85-88] That being so one would expect similar characteristics for the 1,1-cycloadditions of (111) so that the diazoalkane should give (128, R=Me). Under the reaction conditions it seems likely that the diazanorcaradiene structure (128, R=Me) would undergo cleavage of the C-N bond to give the 3*H*-1,2-diazepine (60, R=Me), as this type of monocyclic structure is preferred rather than the bicyclic structure. A further indication that the diazanor-caradiene structure (128, R=Me) would undergo ring cleavage to (60) was the observation that the analogous structure (125) undergoes cleavage of a stronger C-C bond to give the unstable non-aromatic intermediate (126). It seems reasonable that if this ring cleavage occurs the analogous cleavage of the weaker C-N bond of (128, R=Me) should also occur under similar reaction conditions.

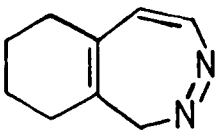


Scheme 21

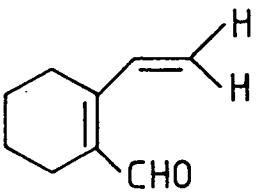
As shown previously the product of reaction of diazoalkane (111) are products derived from 1,5-electrocyclisation ie (113) and (114). The absence of any 1,2-diazepine would tend to indicate that the 1,1-cycloaddition mode of reaction is not the primary step in 1,7-electrocyclisations. It is however possible that 1,1-cycloaddition is the primary process in the conversion of (6) and (59) to (33) and (61) respectively, but if this is so it is much more sensitive to steric hindrance than in the 1,1-cycloaddition of diazoalkanes (see Introduction, page 43) and in the reactions of the nitrile imines (123).

1.4) Cyclisation of 1-diazomethyl-2-vinylcyclohexene

Since the synthesis of several substituted cyclopenta- and cyclohexa-3*H*[d][1,2]diazepines had been accomplished *via* the thermolysis of α,β:γ,δ-unsaturated diazoalkanes it was thought possible that this route may provide access to the parent systems. It was therefore decided to attempt the synthesis of 1*H*-6,7,8,9-tetrahydrocyclohexa[d][1,2]diazepine (134).



(134)

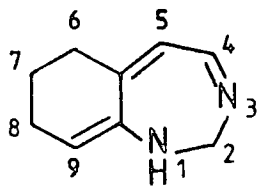


(101c)

Thus, the first priority was the synthesis of the desired aldehyde (101c). This was synthesised by a similar route to that used for compounds (101a,b). The β-bromoacraldehyde (18b) was reacted with the required ylide, generated from methyltriphenylphosphonium iodide and lithium diisopropylamide (L.D.A.), to give the α,β:γ,δ-unsaturated bromo compound (100c); this compound could only be isolated when L.D.A. was used as base, rather than *n*-butyllithium, as otherwise separation from the butyl residues proved impossible. The organolithium reagent was generated by the addition of *n*-butyllithium to (100c) at -110°C, which after reaction with D.M.F. and subsequent hydrolysis gave the aldehyde (101c). This aldehyde was unstable, undergoing rapid polymerisation on chromatography and thus the tosylhydrazone was synthesised by addition of

^{1}H N.m.r. of 1*H*-2,6,7,8-tetrahydrocyclohexa[d][1,3]diazepine

a) 298K



(130)

Figure 22

b) 183K

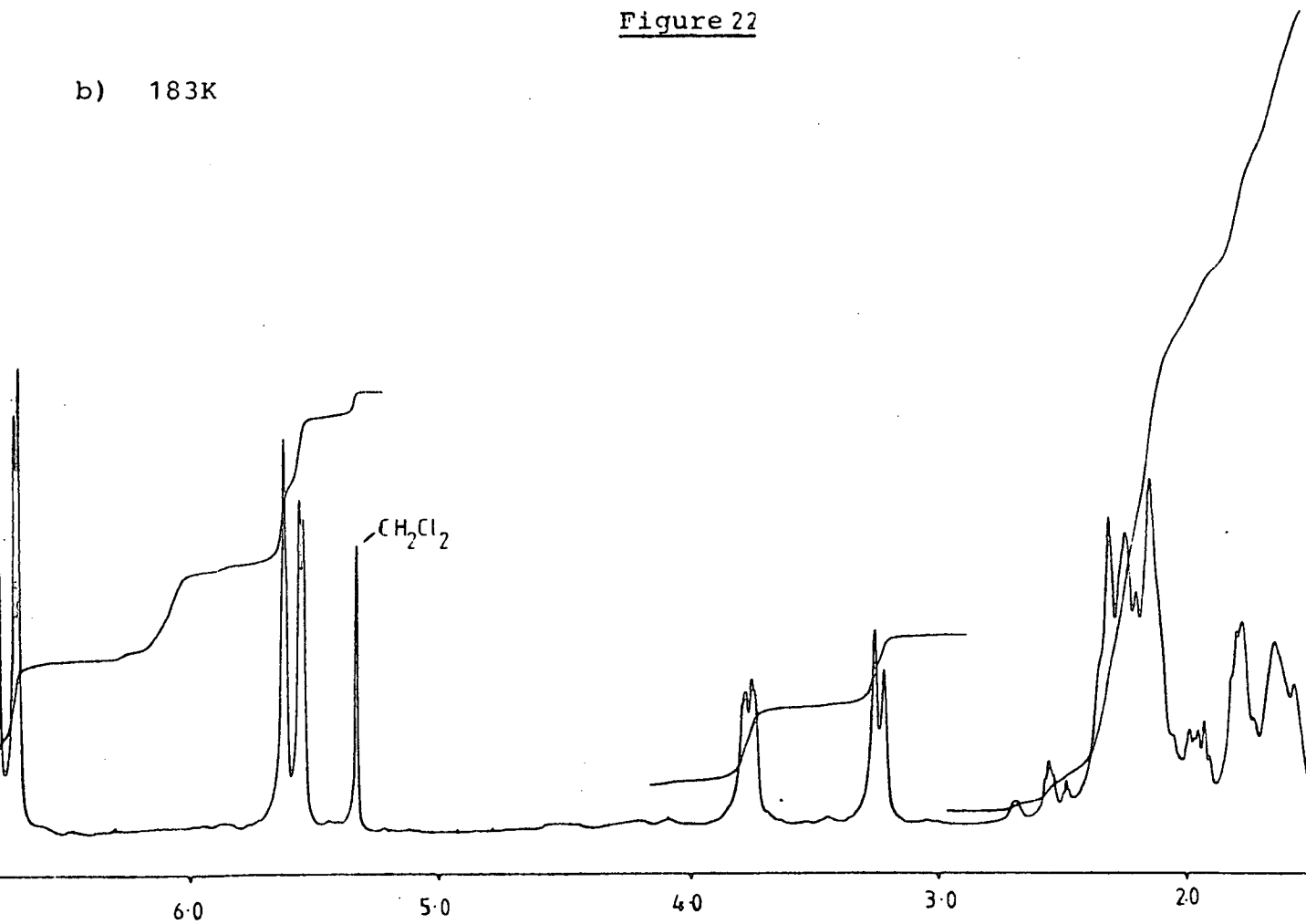


Figure 23

p-toluenesulphonylhydrazide directly to the unpurified reaction mixture and the subsequent conversion of the aldehyde monitored by t.l.c. The resulting tosylhydrazone was isolated by chromatography as unstable, light sensitive crystals which rapidly decomposed unless reacted immediately.

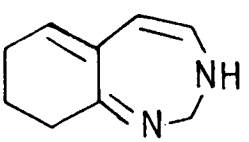
The sodium salt of the tosylhydrazone was prepared in the usual manner and heated in refluxing cyclohexane for 3 h, until the red coloration had disappeared and t.l.c. indicated no remaining tosylhydrazone. T.l.c. and ^{1}H n.m.r. of the reaction mixture indicated one major product but attempted purification by preparative t.l.c. (silica or alumina) gave extensive decomposition, which continued on standing at 0°C. This product was eventually isolated as a clear oil by flash-chromatography under dry nitrogen, in the absence of light. This oil was dissolved in dry $CDCl_3$ and sealed in a predried, nitrogen flushed n.m.r. tube, which was stored at -190°C.

Mass spectrometry showed that this product had the expected formula, $C_9H_{12}N_2$. However, high resolution ^{1}H n.m.r. (Figure 22) showed three olefinic protons, rather than the two olefinic protons which we expected for (134), and the presence of an NH. Also present were four signals each corresponding to two protons (δ1.75, quintet J6.3Hz; 2.15, q, J5.5Hz; 2.34, t of d, J6.3, 1.2Hz and 3.57, s). Decoupling experiments showed that two olefinic protons (δ6.71, d, J5.2Hz and 5.53, d, J5.2Hz) were coupled to each other. The other olefinic proton (δ5.58, t, J3.9Hz) was subsequently shown to be coupled to one of the cyclohexyl CH_2 (δ2.15, which collapsed to a triplet on irradiation at δ5.58). This observation and the multiplicity of the other CH_2s (δ1.75 and 2.34) suggested

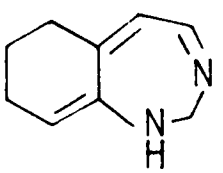
that a cyclohexane ring was no longer present but rather a 2,3-disubstituted cyclohexene ring system.

The remaining deshielded CH_2 did not show any coupling to any other protons suggesting that it was isolated from any proton bearing carbon atoms. A variable temperature investigation of this CH_2 showed that the intensity decreased on cooling until coalescence occurred (212K) and that a further cooling the CH_2 signal appears as two distinct signals (Figure 23), until at 183K an AB pattern was evident. One half of this AB pattern had a small coupling present and it was found that irradiation on the N*H* signal removed this coupling to give a normal AB pattern. These results indicated an isolated CH_2 in a flexible ring adjacent to the NH moiety.

The ^{13}C n.m.r. showed 3xCH_2 signals in positions typical for a cyclohexene ring (22.5, 25.4 and 32.8 p.p.m.) and a deshielded CH_2 (55.1 p.p.m.), three olefinic carbons each bearing one proton (117.2, 129.2 and 137.6 p.p.m.) and two quaternary carbons (135.4 and 144.8 p.p.m.). The above evidence was consistent with two possible structures, the cyclohexa[d][1,3]diazepines (129) or (130).

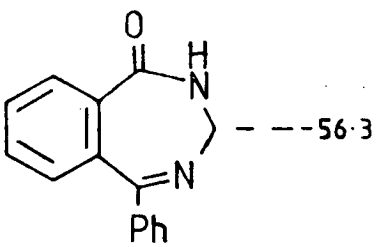


(129)



(130)

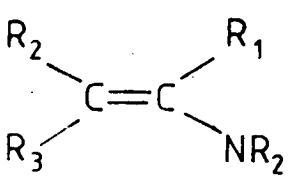
The position of the diazepine C-2 carbon in the ^{13}C n.m.r. (55.1 p.p.m.) was very deshielded for a saturated CH_2. However, this value is very similar to the 2,4-benzodiazepin-1-one (131) which is the most similar compound, whose ^{13}C n.m.r. is reported,[179] containing a CH_2 situated between an imine nitrogen and an NH, in a seven-membered ring.



(131)

Of these two possible structures (129) was initially considered more likely as this compound would have the most deshielded carbon (C-9a) as a quaternary signal, which was consistent with the observed ^{13}C n.m.r. spectra, whereas the other possible structure (130) would not be expected to have the most deshielded carbon (C-4) as a quaternary, but rather as a =C-H.

However, it was known that quaternary enamine carbons, such as C-9a of (130), absorb in the region observed for the most deshielded carbon. For example, in compound (132) the quaternary carbon atom absorbs between (140-147 p.p.m.).[180]

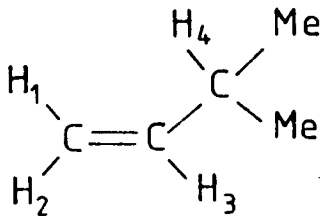


(132)

R_1=Me, R_2=Me, R_3=H, NR_2 = Pyrrolindino
R_1=Et, R_2=Me, R_3=H, NR_2 = Pyrrolindino

This value for the quaternary enamine carbons would suggest that the deshielded carbon in the observed spectra would probably correspond to C-9a of both (129) and (130).

Support for the structure (130) was obtained from the fact that a coupling of 1.2Hz was evident in the ^1H n.m.r. spectra from one of the olefinic protons to the CH_2 furthest from the cyclohexene double bond. It seemed unlikely that C-9 protons and the C-5 proton of (129) would have a five bond coupling of this magnitude through a cross-conjugated system as is proposed for this structure. However, it is well known that couplings are common between Z protons of alkyl substituted olefinic systems such as that present between C-5 and C-6 of (130). For example, the coupling between the H_1 proton and the H_4 proton of 3-methylbutene is of the magnitude of 1.2Hz.[167]



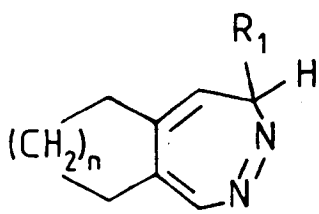
$J_{1,4}$=1·2Hz

Thus, ^1H n.m.r. would suggest that (130) is the more likely structure. However, if this is so then the C-4 carbon is in an unexpectedly shielded position for an imine carbon. Conjugation is known to shield carbons of this type,[181] but not to such an extent, but the effects of extended conjugation on ^{13}C n.m.r. absorptions of imines is not well documented.

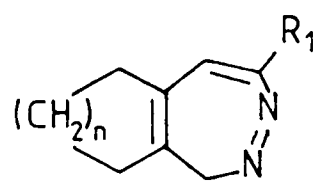
From the above spectral data it is evident that the expected cyclohexa[d][1,2]diazepine (134) is not the isolated product, from the reaction of (105c). Although it is not

possible to differentiate whether the product is structure (129) or the tautomeric structure (130) it is fairly certain that the product is a tetrahydrocyclohexa[d][1,3]diazepine system. The formation of such a system can be easily rationalised from a mechanism which involves the expected product (134) (Scheme 24).

It seems likely that the diazoalkene (105c) will undergo the previously observed 1,7-electrocyclisation to give the cyclohexa[d][1,2]diazepine (133) which contains two exocyclic double bonds. This product will undergo the expected rapid [1,5]hydrogen migration to give the more stable isomer (134), which in this case has no substituent at the terminus of the diene unit of the 1,2-diazepine ring. It was proposed earlier that it is the conjugation of the diene system with a substituent which results in the greater stability of systems such as (33) and (61) with respect to (32) and (60). Thus, as this stabilising effect is absent in (134) this results in this product having a much lower stability than the analogous compounds (33).

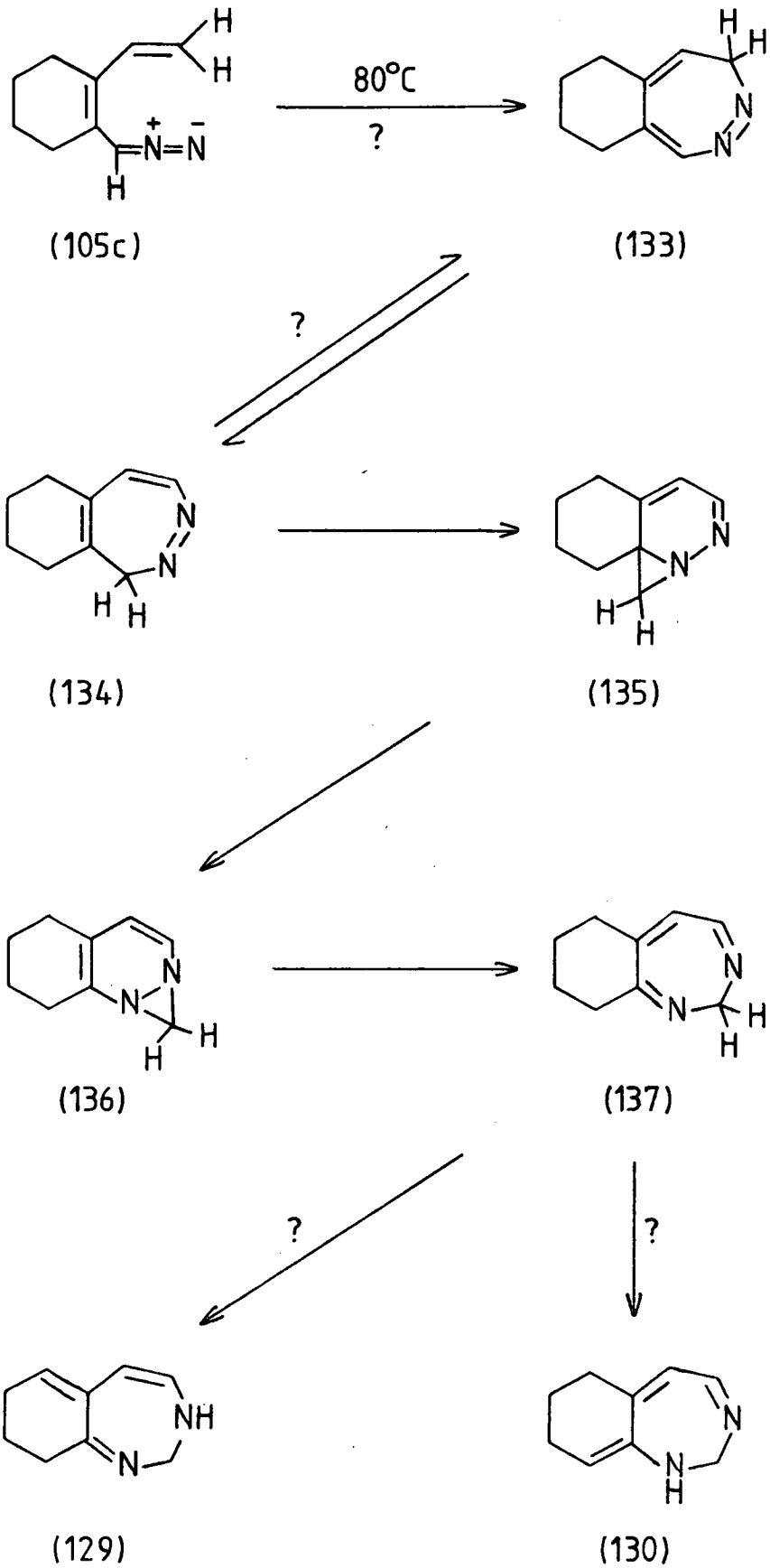


(32)



(33)

This reduced stability results in this compound undergoing the previously discussed diazacycloheptadiene → diazanorcaradiene isomerisation, which eliminates the unstable azo



(105c) (133) (134) (135) (136) (137) (129) (130)

Scheme 24

linkage, to give (135). A subsequent walk rearrangement of the methylene group of (135) gives the tricyclic structure (136), thereby resulting in the more stable endocyclic double bond isomer. Walk rearrangements of the methylene groups of diazanorcaradiene system are known to occur under thermal conditions,[182,183] and thus it would not seem unreasonable to propose such a migration in the above rearrangement. The weak N-N bond of the diaziridine ring of (136) would readily undergo cleavage to give the cyclohexa[d][1,3]diazepine system (137). This system can then tautomerise to give either product (129) or (130) although it is not clear which isomer is actually formed.

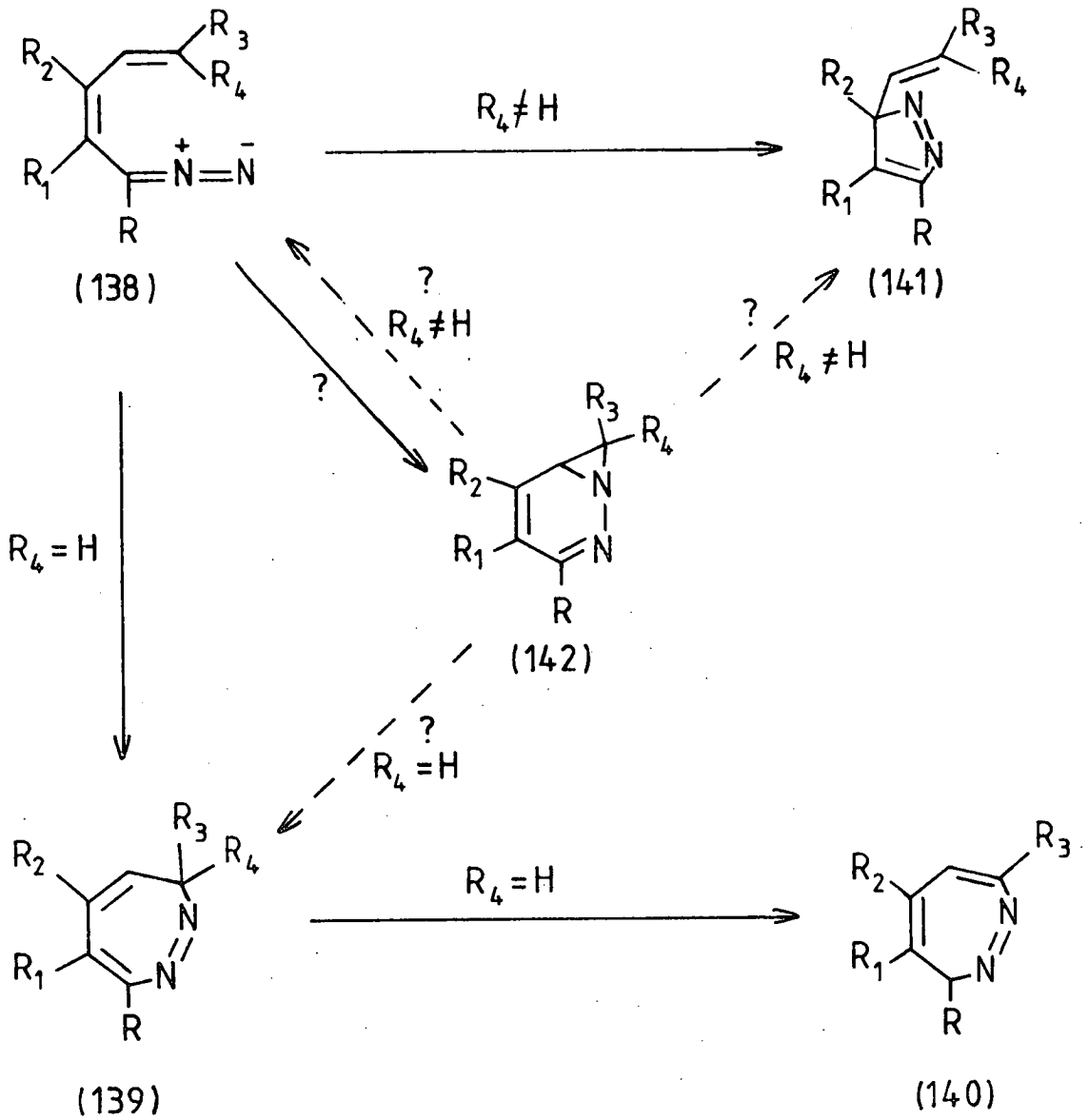
Thus, it is clear that the parent 1*H*-6,7,8,9-tetrahydrocyclohexa[d][1,2]diazepine (134) is much less stable than the 4-substituted analogues (33) and undergoes a complex series of rearrangements before reaching the isolated product (129) or (130), which itself has very limited stability.

1.5) Photolytic decomposition of tosylhydrazone lithium salts

The results from the previous sections indicate that the electrocyclisation of α,β:γ,δ-unsaturated diazocompounds - under thermal conditions - gives 1,7-electrocyclisation unless inhibiting factors prevented this mode of reaction, in which case 1,5-electrocyclisation occurs.

However in both these modes of cyclisation the products which were isolated were not the primary products. In cases where 1,5-mode of cyclisation occurs the primary product was thought to be a 3*H*-pyrazole (141) which readily underwent alkenyl group migrations to give aromatic pyrazoles. In examples where 1,7-electrocyclisation is known to occur the primary product is thought to be a 3-substituted-3*H*-1,2-diazepine (139), which undergoes a rapid [1,5]sigmatropic hydrogen shift to give 3*H*-1,2-diazepines (140) having the substituent (R_3) in conjugation with the diene moiety.

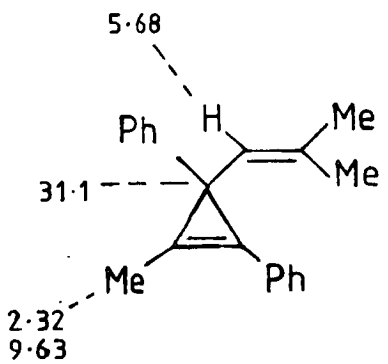
However, as discussed previously, it is possible that a diazanorcaradiene structure (142) may be formed initially *via* 1,1-cycloaddition of the diazoalkane. This intermediate could ring expand to give (139) or rearrange to (141) possibly *via* a retroelectrocyclisation to (138). Thus, it was desirable to effect the generation of the diazoalkane precursors under mild conditions so as to enable the isolation of the primary products of the two modes of cyclisations. It was, therefore, decided to investigate the course of the reactions of the acyclic diazoalkanes (59) and (111), when these were generated at low temperatures by photolytic decomposition of the tosyl-hydrazone salts.



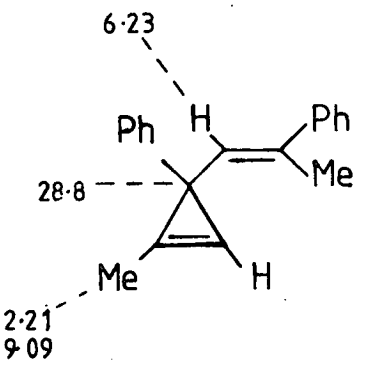
The corresponding tosylhydrazones were dissolved in dry tetrahydrofuran and reacted with one equivalent of methyllithium, at -60°C for 1 h, to give the tosylhydrazone anion. The diazoalkanes were generated by photolysis of this solution, through pyrex, at -60°C, until t.l.c. indicated that no starting tosylhydrazone remained. The solvent was removed from the solution at <30°C and the products isolated by flash chromatography.

The isolated products were subsequently identified as being 3-alkenyl-3-phenyl-1-methylcyclopropenes (146) and 4,6a-dihydro[1,2]diazeto[1,4-a]pyrroles (147 and 148). These compounds were identified by their spectral data and by comparison with analogous compounds.

It has been shown that photolysis of α,β:γ,δ-unsaturated diazoalkenes give various carbene derived products including 3-alkenylcyclopropenes.[175,184,185] The spectral data for these reported compounds, for example (143), which were also prepared by these workers by independent routes, compared favourably with the examples isolated from the reaction of (59) and (111).

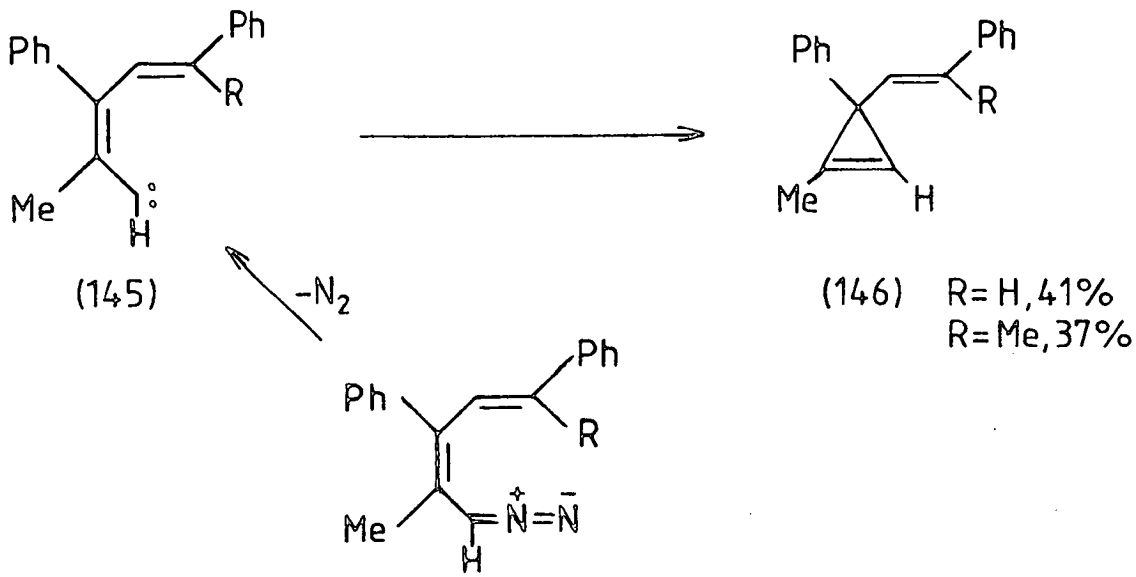


(143)

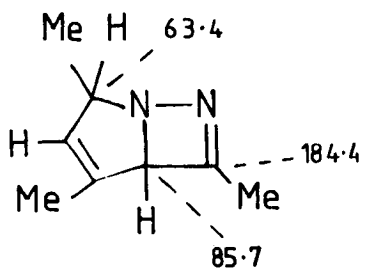


(146)

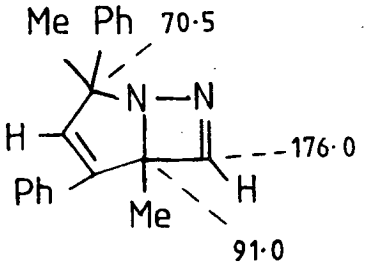
The 4,6a-dihydro[1,2]diazeto[1,4-a]pyrroles had very similar spectral properties to the analogous compounds, for example (144), prepared from the photolysis of previously prepared 3*H*-1,2-diazepines.[186] The structure of (148) was also confirmed by its comparison to an authentic sample obtained from the photolysis of the 3*H*-1,2-diazepine (61).


Ph
Ph
R
Me
H
(145)
-N2
(146) R=H, 41%
R=Me, 37%
(59) R=H
(111) R=Me
-60°C
R=H
[1,5] H Shift
(60) R=H
(139) R=Me
(61)
2π+2π
2π+2π
(147), a) R=H, 25%
b) R Me, 25%
(148) 10%

Scheme 25



(144)



(147, R=Me)

The mechanism for the formation of these products is shown in Scheme 25. The diazoalkanes can extrude nitrogen to form the carbene (145) which undergoes electrophilic attack on the α,β-double bond to form the isolated cyclopropenes (146). The diazocompounds also undergo 1,7-cyclisation to give the 3*H*-1,2-diazepines (60) and (139) regardless of whether the δ*Z* substituent is H or Me. These subsequently undergo an intramolecular 2π + 2π cycloaddition to give the photoproducts (147). In the case where R=H (60) some hydrogen migration to (61) also occurs and this isomer also gives (148) in low yield.

The formation of (147a) as the major heterocyclic product in the photolysis of (59) clearly shows that the 3,5-diphenyl isomer (60) (not obtained in the thermal reaction) is the primary reaction product. The 'trapping' of this apparently unstable compound by photoisomerisation is possible under these conditions because the low temperature slows the [1,5]-hydrogen shift. However this migration is still fast enough to be competitive with the photoisomerisation even at -60°C as shown by the formation of (148) in 10% yield. The forma-

tion of a diazepine from (111) contrasts starkly with the total absence of 1,7-cyclisation in the thermal reaction. The reason for this is not yet understood but there are several possible explanations.

i) In the thermal reactions (Scheme 19,p.133a) there is direct competition between 1,7 and 1,5-cyclisation, the latter gives the rather unstable 3*H*-pyrazole (112) which subsequently isomerises to give the stable products (113) and (114) *via* a series of sigmatropic migrations of the alkenyl group. In the photochemical reaction at -60°C these alkenyl migrations will be very slow and so (112) will not isomerise to give (113) and (114). In addition it is well known[73] that 3*H*-pyrazoles such as (112) readily ring open under photolysis to give diazocompounds. Thus the combined effect of the photochemical conditions and low temperature is to make 1,5-cyclisation non-viable as a product-forming pathway. Once this competition is removed the 1,7-cyclisation may then be observable even though it is slower because of the hindering effect of the methyl group at the cyclisation site.

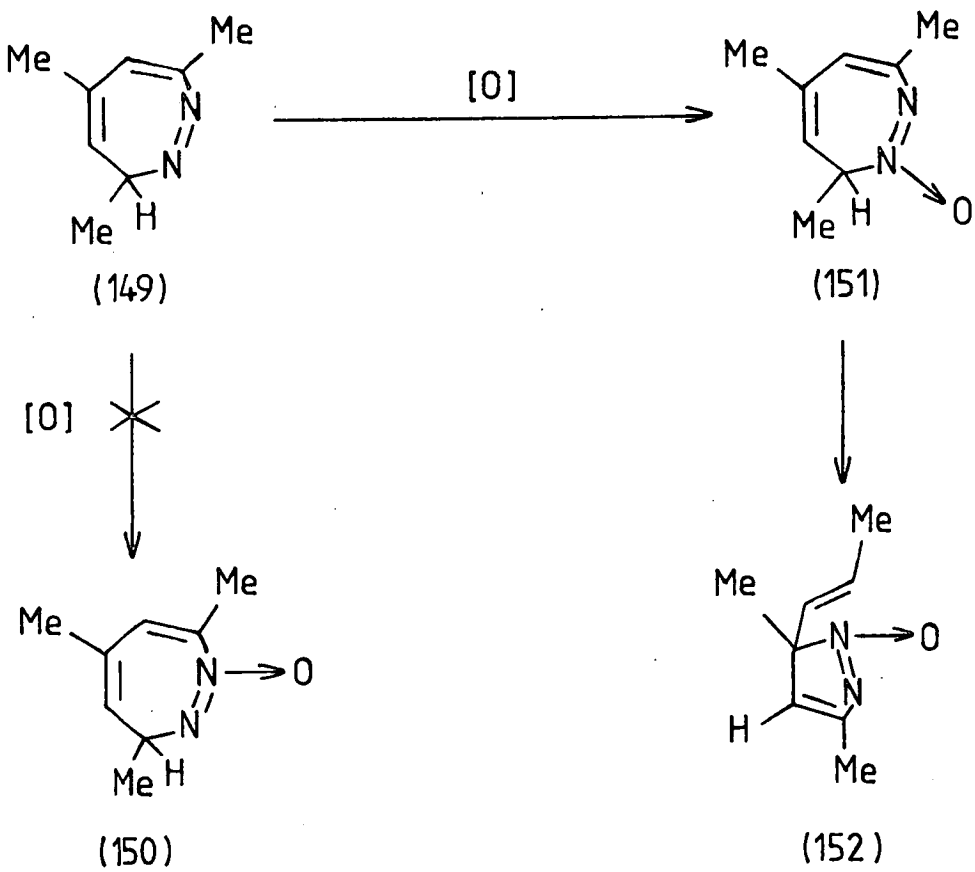
ii) The explanation above assumes that although the diazo compound is generated by photolysis it is reacting in its electronic ground state by the same mechanism as proposed for the thermal cyclisation (p.138). However it is quite likely that the diazocompound is in an electronically and/or vibrationally excited state. It has been calculated that the first and second excited states of diazomethane have CNN bond angles of 158° and 152° respectively.[187] If this is true for (111) then a different transition state geometry for cyclisation would be required from that of the thermal

cyclisation. This difference in transition states could thus explain the 1,7-cyclisation product observed in the photolytic reaction of (111).

As both (60) and (139) form the photoisomers (147a) and (147b) in approximately equal yields, it is reasonable to assume that both these isomers have similar stability. Thus, it seems likely that (139) would have been isolable in the thermal cyclisation had it been formed.

1.6) Preparation of 3*H*-1,2-diazepine *N*-oxides

Earlier work by Argo[188] had shown that 3*H*-1,2-diazepines undergo mild oxidation to give a single *N*-oxide in high yield. The structure of the product was thought to be either (150) or (151) but the site of oxidation was not definitely known. These oxides were all oils so no X-ray structure determination was possible. The oxide, subsequently shown to be (151) was also found to undergo a rearrangement readily at room temperature to give the 3*H*-pyrazole oxide (152), whereas the parent diazepine (149) slowly rearranges to the analogous 3*H*-pyrazole on prolonged heating at 110°C.



Scheme 26

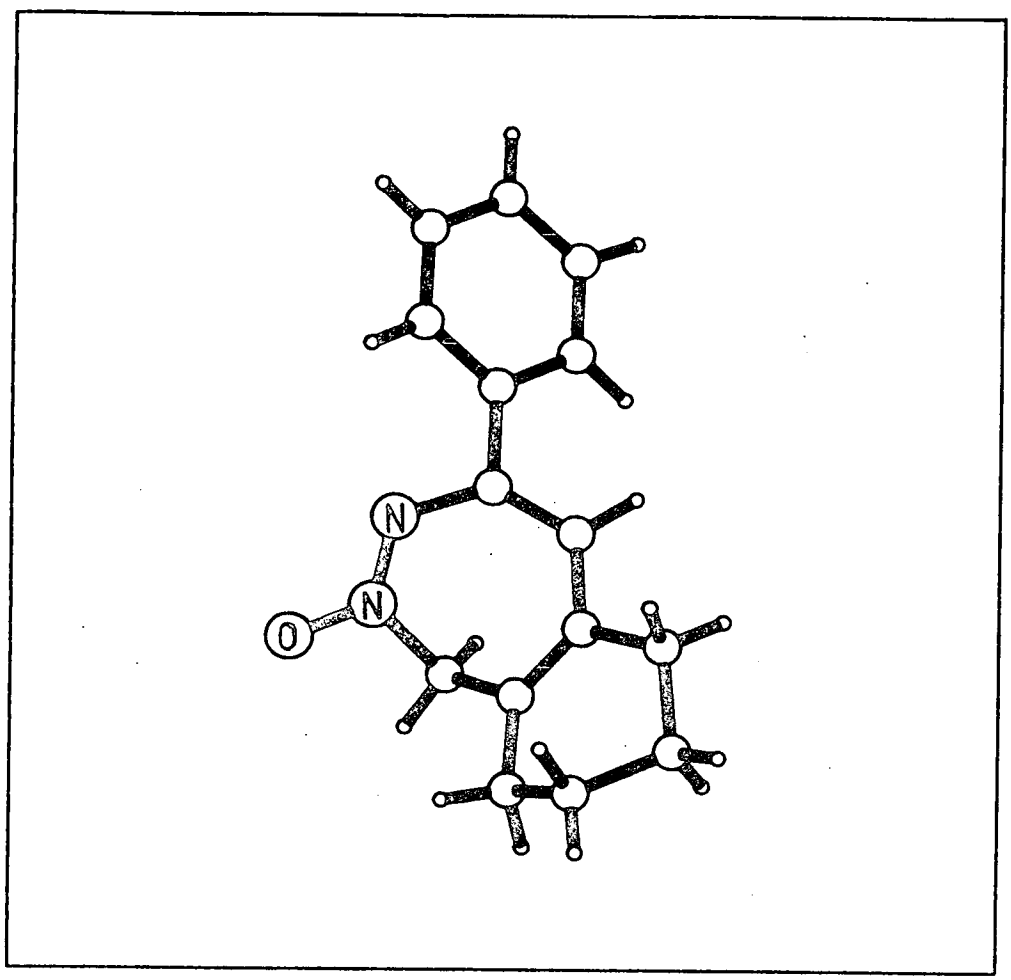
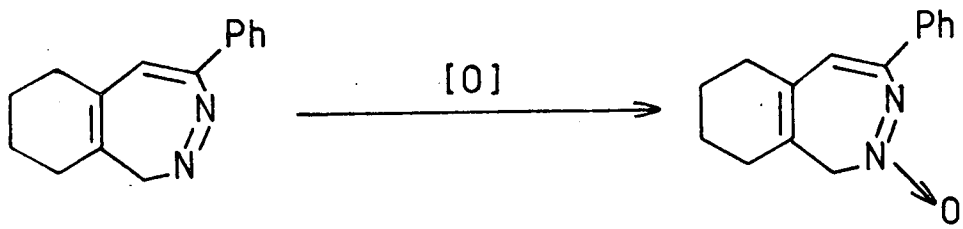


Figure 27

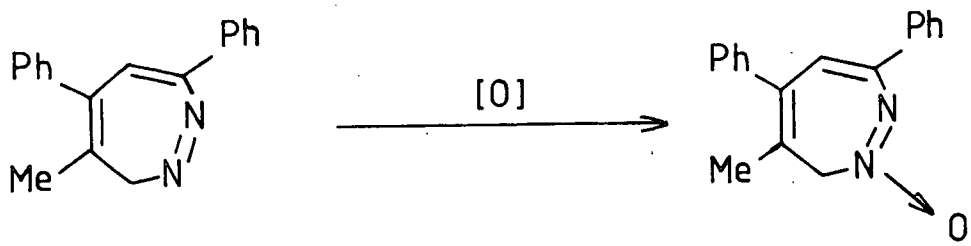
X-ray crystal structure of 4-phenyl-1*H*-6,7,8,9-tetrahydrocyclohexa[d][1,2]diazepine *N*-2 oxide.

It was thought to be of interest to examine the oxidation of the new 3*H*-1,2-diazepines prepared in this thesis with two objectives, (i) to prepare a crystalline analogue for X-ray structure determination, and (ii) to further investigate the novel ring contraction.

Thus the 3*H*-1,2-diazepines (26c) and (61) were oxidised, by treatment with an equimolar amount of *m*-chloroperbenzoic acid, to give (153) and (154) in good yields. The *N*-oxide (153) was a white crystalline solid and an X-ray structure determination subsequently showed that the oxygen atom was located on N-2 as shown (see Figure 27).

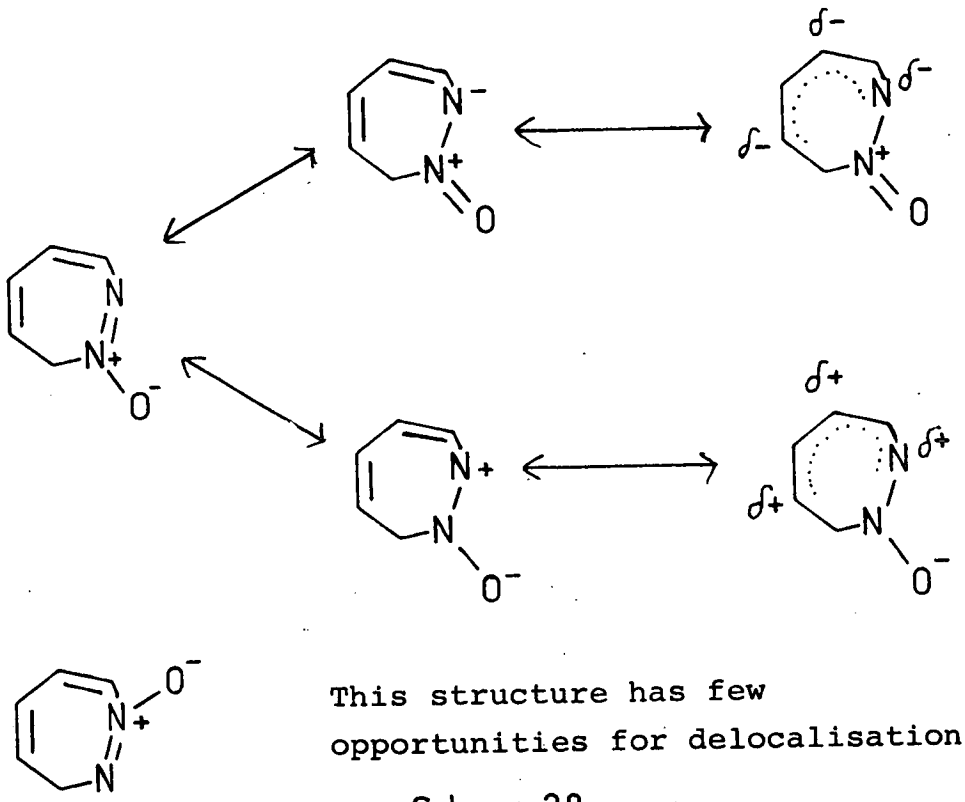


(26c) (153)



(61) (154)

In the examples above oxidation occurs only at the nitrogen atom adjacent to the saturated carbon atom. Thus, the oxidation reaction appears to follow thermodynamic control since this product has much greater charge delocalisation (Scheme 28) which should stabilise the system.

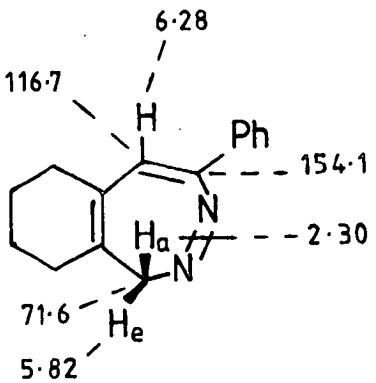


This structure has few opportunities for delocalisation

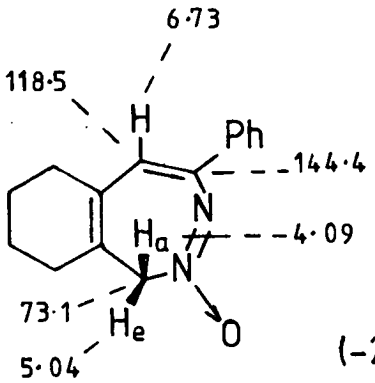
Scheme 28

The *N*-oxides (153) and (154) were shown by mass spectroscopy to have the molecular formula corresponding to the original diazepines plus one oxygen atom. These products also showed ^{1}H and ^{13}C n.m.r. spectra similar to those of their precursors (26c) and (61). It should be noted that the ^{13}C n.m.r. spectra of both *N*-oxides showed the saturated carbon atoms to be deshielded, with respect to the parent diazepine, and similarly that the other carbons adjacent to the azoxy group were more shielded.

These observed changes in shielding are in accord with results reported for acyclic azoxy compounds.[189] For example, in the ^{1}H n.m.r. the methyl protons of azomethane resonate at δ3.68, while in azoxymethane two signals are observed at δ4.05 and δ3.07. The methyl group adjacent to oxidised nitrogen atom is more deshielded whereas the other methyl

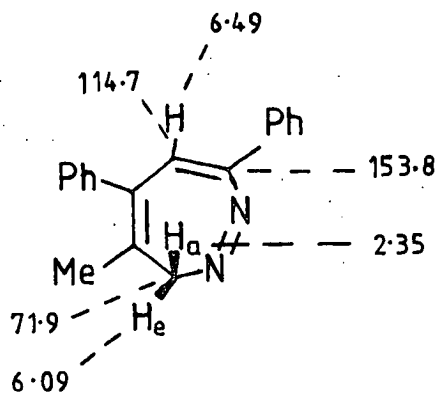


(26c)

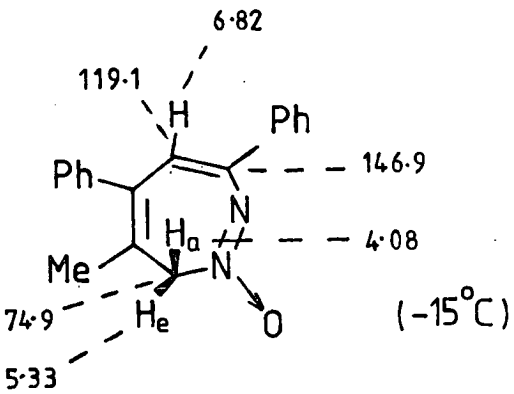


(-27°C)

(153)



(61)



(-15°C)

(154)

is less deshielded. It was also observed that the chemical shifts of the CH_2 protons of the diazepine ring were significantly affected upon oxidation. For example, in the parent diazepine (61) the axial and equatorial protons had ^1H n.m.r. absorptions at δ2.35 and 6.09 respectively, compared with δ4.08 and 5.33 for *N*-oxide (154). This shift of these protons upon oxidation can be rationalised as follows.

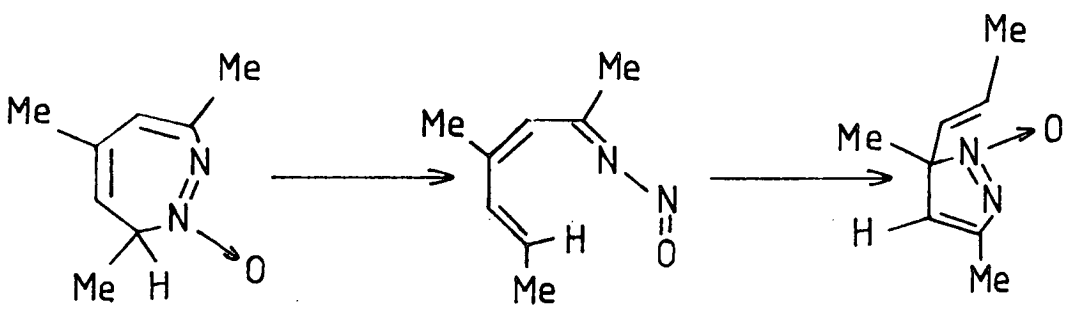
i) The azoxy group apparently has a smaller anistropic effect than the azo group, in that protons in the plane of the azoxy bond are not as deshielded as those in the plane of the azo group. Thus the equatorial proton of the *N*-oxide will be shielded with respect to that of the parent diazepine.

ii) Protons adjacent to the oxidised N atom will be deshielded relative to the parent diazepine, as is confirmed by the deshielded position of the CH_2 carbon.

Thus, the combination of these two effects results in the equatorial proton being shielded and the axial proton being more deshielded with respect to the parent diazepine.

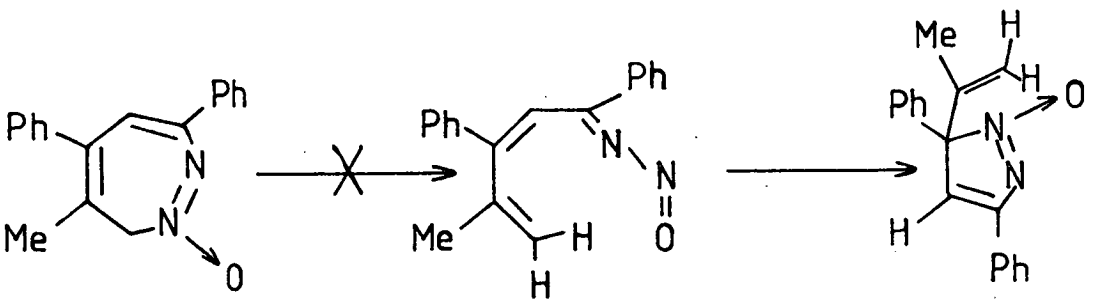
It was also notable that oxidation had much lowered the activation energy for ring inversions. Thus although the diazepines themselves had a coalescence temperature (Tc) >130°C (beyond the range of the compounds' thermal stability). The *N*-oxides (153) and (154) showed Tc of 31°C and 54°C respectively. This increased flexibility of the 3*H*-1,2-diazepine ring upon oxidation has been previously reported for 1*H*-2,3-benzodiazepines.[188]

The monocyclic 3*H*-1,2-diazepine *N*-oxide (151), prepared by previous workers, was reported to rearrange readily at room temperature to the 3*H*-pyrazole *N*-oxide (152). However, the analogous compound (154) did not show any indication of undergoing a similar rearrangement even on heating for a short period (20 min) at 120°C. In view of this result we re-examined the diazepine *N*-oxide synthesised by Argo (151) and found that it did indeed rearrange to (152) as reported.



(151) (155) (152)

The mechanism proposed for the rearrangement of the diazepine *N*-oxide involves electrocyclic ring opening to the *N*-nitrosimine (155). Thus in the case of (154) if a similar rearrangement was to occur it would involve cleavage of the CH_2-N bond to give the *N*-nitrosimine (156).



(154) (156) (157)

There are no obvious destabilising features of the *N*-nitrosamine (156) to rationalise the failure of (154) to undergo ring opening in this way. The reason why this diazepine *N*-oxide is less susceptible to rearrangement is not understood at present. However, one possible explanation may be that the rearranged product (157) has a phenyl ring out of conjugation. This factor would result in a much reduced stability, with respect to (152), perhaps sufficient to bias any (154)⇌(157) equilibrium well to the left.

SECTION 2

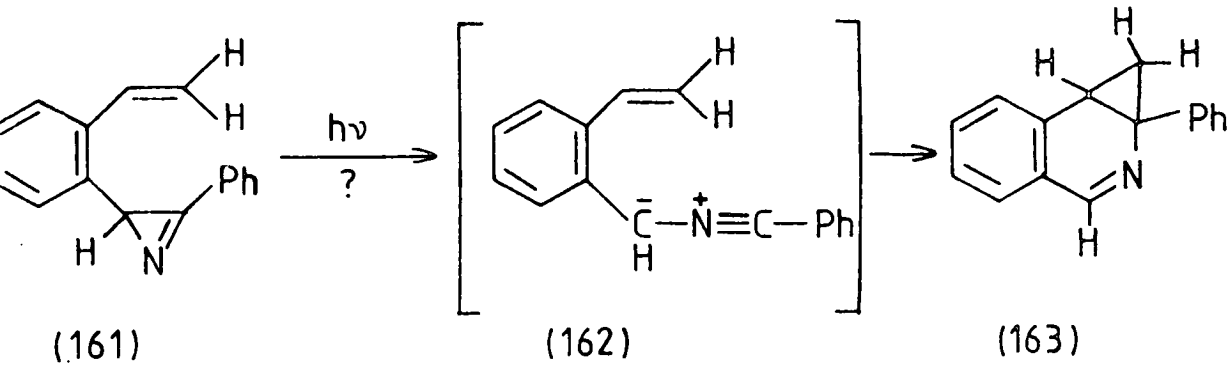
INTRAMOLECULAR REACTIONS OF α,β:γ,δ-UNSATURATED NITRILE YLIDES

2.1) Introduction

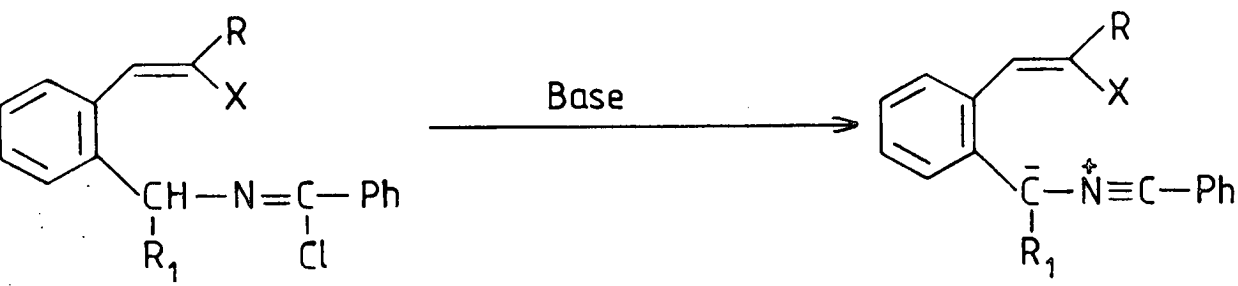
The results discussed above and earlier work have demonstrated that the 1,7-ring closure of α,β:γ,δ-unsaturated diazo-compounds provides an efficient route to 3*H*-1,2-diazepines and analogous annelated systems. Direct routes to fully unsaturated seven-membered heterocyclic systems are rare and it was thought to be of interest to extend this study of 1,3-dipolar intermediates having 4π electron extended conjugation. It was of particular interest to determine the periselectivity of other 1,3-dipoles in the competition between 1,5-and 1,7-electrocyclisation and to determine whether Z substituents at the site of cyclisation had a similar blocking effect on 1,7-closure as observed in the diazo systems.

The system chosen for investigation was the nitrile ylide (158) with an α,β-'aromatic' double bond and a γ,δ-'olefinic' bond. This system was selected for two main reasons: (i) nitrile ylides are 1,3-dipoles of the same type as diazo compounds i.e. both containing an orthogonal double bond, and (ii) the variation of the group X would provide a direct comparison with Munro's work[80-83] on the analogous diazo systems (159) (see Introduction p.40) and the work of Garanti and Zecchi[32,35] on nitrile imines (160) (see Introduction p.13).

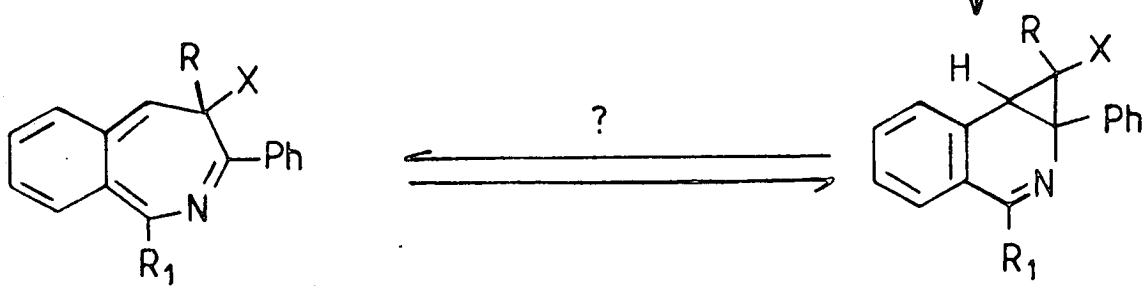
The only previous work on this type of system (158) is an isolated report by Padwa[113] that the 2*H*-azirine (161)



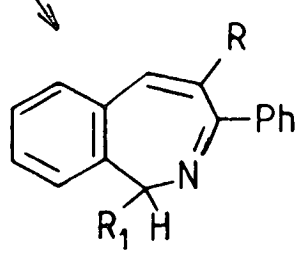
(161) (162) (163)



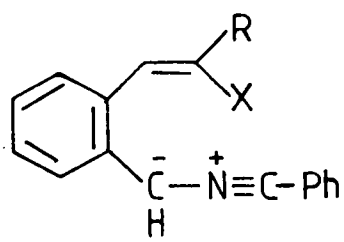
(164) (165)



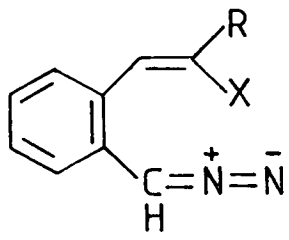
(167) (166)



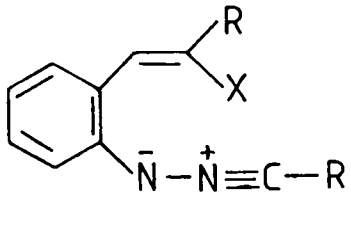
(168)



(158)



(159)

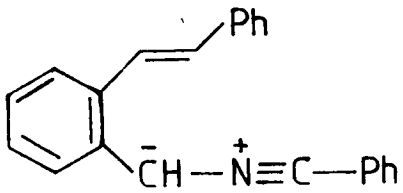


(160)

undergoes a photochemically induced conversion into the cyclopropa[c]isoquinoline (163), which was believed to proceed *via* the nitrile ylide (162). We hoped to investigate whether 'thermally' generated nitrile ylides (165) would similarly undergo 1,1-cycloaddition to give (166) or give 2-benzazepines (168) directly and whether either or both these processes were subject to similar steric inhibition by X groups other than hydrogen as observed in the diazo cyclisations.

We also wished to explore the possible isomerisation of the cyclopropa[c]isoquinoline system (166) into the 2-benzazepine system (168). As well as being of interest theoretically it was hoped that this study would lead to a viable synthetic route to the 2-benzazepine system which has great potential CNS activity.

It was decided to attempt to generate the nitrile ylides (165) *via* 1,3-dehydrochlorination of imidoyl chlorides of type (164). The first example to be studied was (175) i.e. (165; R=Ph, R_1=X=H) since it was known that the diazo analogue (159) with this substitution pattern cyclises readily to give 2,3-benzodiazepines.[80]



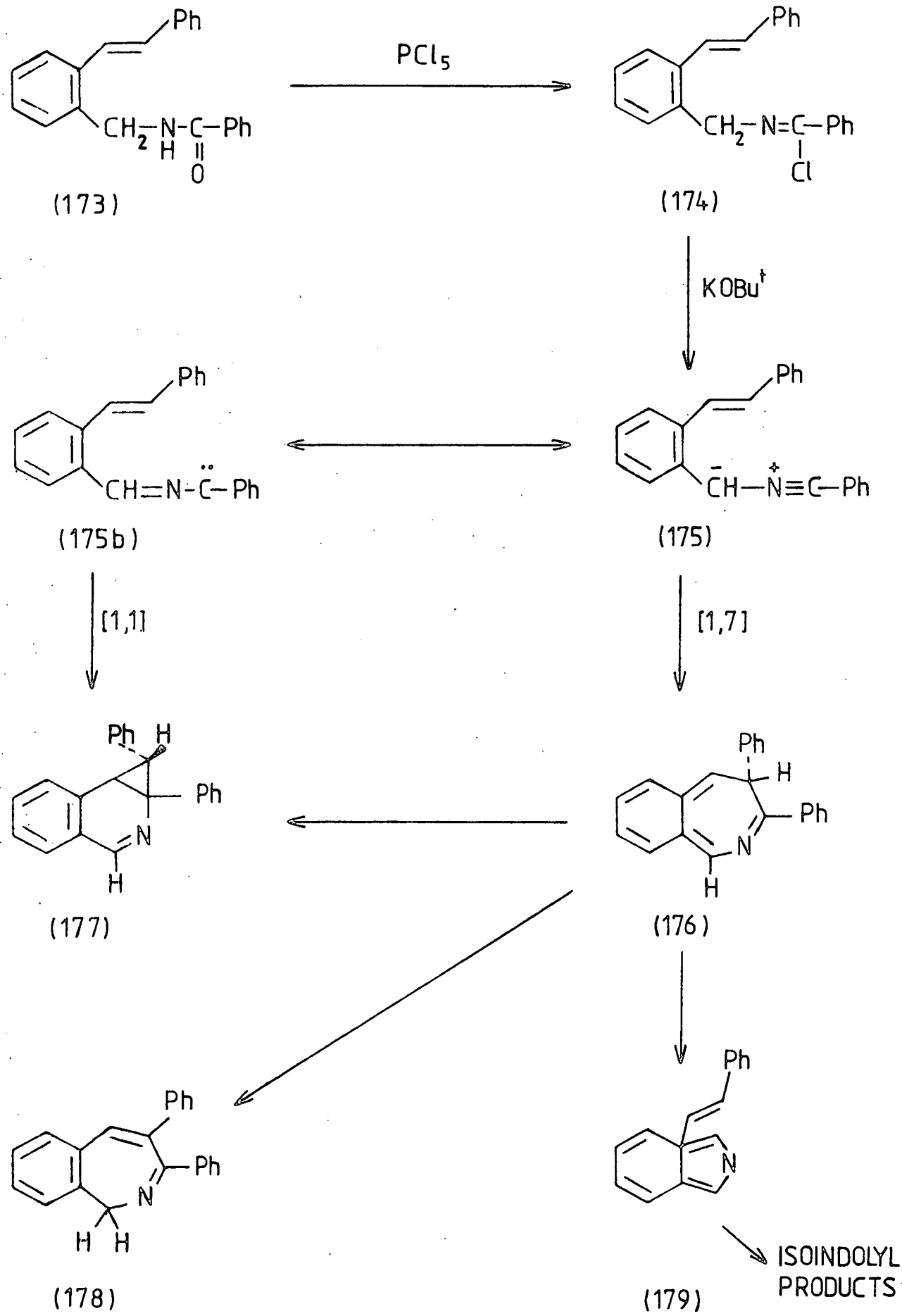
(175)

2.2) Synthesis and reaction of α,β:γ,δ-unsaturated nitrile ylides

The initial priority in this investigation was the synthesis of the *N*-benzoyl-2-alkenylbenzylamine (173) which was the precursor for the imidoyl chloride (174) and thus the nitrile ylide (175). This amide was synthesised as shown in Scheme 29.

o-Bromotoluene was brominated to give *o*-bromobenzylbromide, from which a phosphonium salt was prepared by reaction with triphenylphosphine. A Wittig reaction with benzaldehyde followed by isomerisation with iodine gave *E*-2-bromostilbene (169). A Grignard reaction with dimethylformamide gave the aldehyde (170), which was converted into the oxime (171) by reaction with hydroxylamine hydrochloride. Reduction of the oxime with lithium aluminium hydride gave the amine which was isolated as its hydrochloride salt (172). Reaction of this amine with benzoyl chloride gave the desired amide (173).

Attempts to convert this amide into the imidoyl chloride (174) by reaction with phosgene, under a variety of conditions were unsuccessful. The conversion to the imidoyl chloride was eventually achieved by reaction of the amide with one


Ph
CH2–N–C–Ph
H
O
(173)
PCl5
Ph
CH2–N=C–Ph
Cl
(174)
KOBut
Ph
CH=N–C–Ph
(175b)
Ph
CH–N≡C–Ph
(175)
[1,1]
[1,7]
Ph H
Ph
N
H
(177)
Ph
H
Ph
N
H
(176)
Ph
Ph
N
H H
(178)
Ph
N
(179)
ISOINDOLYL
PRODUCTS

Scheme 30

two equivalents of potassium *tert*-butoxide was added, under dry nitrogen, to generate the nitrile ylide (175). An initial red colour formed, presumably due to the nitrile ylide intermediate, which faded gradually to give a yellow solution. The reaction was monitored by t.l.c. until product formation appeared to be complete, but a trace of starting amide was found to be present although it was not clear if this was unreacted starting material or formed by the hydrolysis of the imidoyl chloride during the course of the reaction, or during work up.

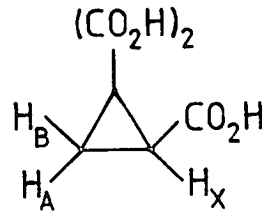
Flash chromatography gave only one product and a small amount of starting amide. This product was isolated as white crystals and mass spectrometry and elemental analysis established the molecular formula as $C_{22}H_{17}N$, confirming that the product was derived from an intramolecular reaction of the nitrile ylide (175).

From previous work it was thought that the most likely products would be (177), (178) and (179) or isomers derived from it by vinyl migration (Scheme 30). It was possible to formulate the product as (177) mainly on the basis of n.m.r. data.

The ^{1}H n.m.r. spectrum showed a deshielded proton (δ8.27), aromatic absorptions (δ7.83-6.87) and two doublets (δ1.79, J6Hz and 3.43, J6Hz). The absence of any olefinic absorptions indicated that structure (179) or products derived from its rearrangement could be discounted. The two doublets in the saturated region indicated that either (177) or (178) was the isolated product. The ^{13}C n.m.r. enabled identification of the product as being (177). A deshielded =CH (153.8 p.p.m.)

corresponding to C-1, and two saturated C-H signals and a quaternary carbon signal corresponding to the cyclopropane carbons were observed.

The final piece of structural information required for full characterisation of this compound was the assignment of the C-3 phenyl as being *exo* or *endo*. If the *exo* isomer is formed then the cyclopropane protons are *E* to each other but *Z* to each other in the *endo* isomer. This assignment was made by comparing the observed vicinal coupling constant with literature values for cyclopropanes of known stereochemistry. It is reported that the magnitude of *Z* couplings is larger than *E* in cyclopropane rings. For example, the cyclopropane (180) exhibits a *Z* coupling constant of 9.3Hz compared to the *E* coupling constant of 6.5Hz.[167]

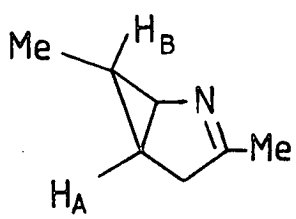


(180)

J_{BX} = 6·55Hz

J_{AX} = 9·33Hz

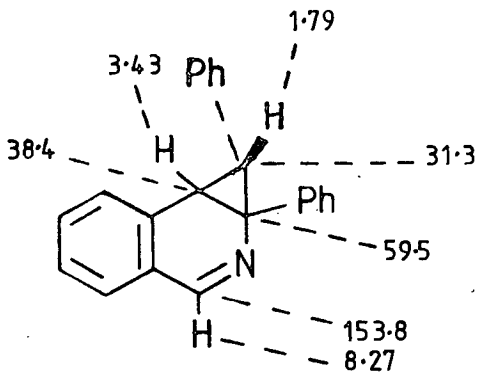
Comparison with 1,1-cycloadducts of nitrile ylides showed comparable magnitude for *E* cyclopropane protons. For example, the cyclopropane protons of the azabicyclohexene (181) had a coupling of 4.5Hz.[112]



J_{AB} = 4·5Hz

(181)

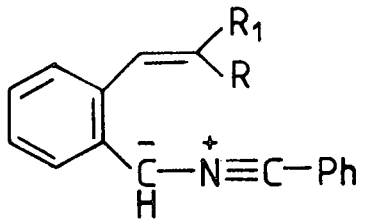
The coupling found in the product was 6Hz and thus these protons were assigned as being *E* and thus the C-3 phenyl is in the *exo* configuration. Thus the product was identified as being 2a,3,3a-trihydro-2a-phenyl-3-*exo*-phenyl-cyclopropa[c]isoquinoline (177). This product is of the same type as that obtained (163) by Padwa by the photochemical isomerisation of the 2*H*-azirine (161).



(177)

There are two distinct mechanisms which are possible to rationalise the formation of (177) from the nitrile ylide (175), depending on whether the two new bonds from the terminal carbon of the nitrile ylide are formed in a concerted or stepwise manner (Scheme 30). A stepwise reaction would proceed *via* a 1,7-electrocyclisation as the first step to give (176), followed by a rapid 1,6-electrocyclic ring closure in the azepine ring which would restore the aromatic character of the benzene ring and result in the isolated product. If this mechanism is occurring then two conditions must be satisfied, (i) the ring closure step must be very rapid and occur prior to ring flipping as otherwise the stereospecificity of the reaction would not have been observed, and (ii) the alternative reaction path from (176) to (178) *via* a [1,5]hydrogen shift is not competitive under these conditions. The second possible

mechanism is a concerted reaction occurring *via* carbene-type cycloaddition involving the γ,δ-double bond of the nitrile ylide, best visualised as occurring *via* the canonical form (175b). There is much uncertainty at present concerning the mechanism of 1,1-cycloadditions of this type in nitrilium and diazonium betaines. Early work of Padwa[112] on nitrile ylides pointed to a stepwise reaction but more recent work on nitrile imines[33,35] and diazocompounds[88] has shown that the reactions are highly stereospecific (see Introduction p.58, 13, 43). The next example to be studied was (182). The objective here was two-fold, (i) to discover if the formation of products of type (177) was prevented by the presence of a Z Me or Ph group as was the formation of 2,3-benzodiazepines in the analogous diazo systems, and (ii) to investigate the stereospecificity of the "1,1-cycloaddition" should it occur.

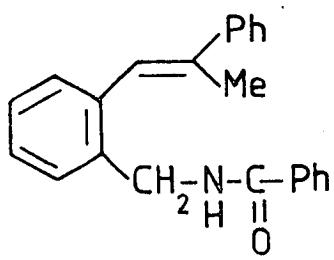


a) R=Me, R_1=Ph
b) R=Ph, R_1=Me

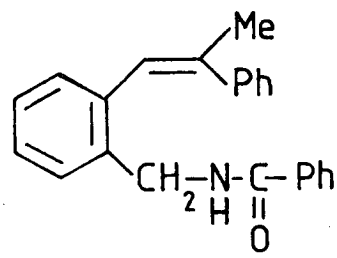
(182)

Thus it was necessary to synthesise the corresponding imidoyl chloride from the amide (183). The compounds were obtained by the route utilised to prepare (173) (Scheme 29), with the methyl group being introduced *via* the Wittig reaction with acetophenone rather than benzaldehyde. Although it would have been desirable to separately investigate both isomers of (183) it did not prove possible to separate the

E and *Z* isomers on a preparative scale at any point in the synthesis. Thus, the amide was obtained as a mixture of both isomers. However, it was possible to identify these isomers by their high-field ^1H n.m.r. spectra and establish the percentage of each one present.



(183a)



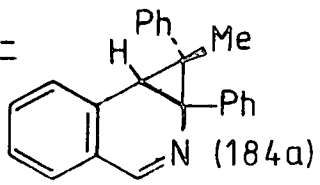
(183b)

An N.O.E. experiment showed a 2.5% enhancement between the olefinic and Me of the major isomer, and a very slight enhancement (*ca.* 0.1%) for the minor isomer. Thus, since the *Z* isomer (183b) has the Me and the olefinic closer to each other in space, with respect to the *E* isomer, it can be assumed that the *Z* isomer is the major product (63:37, *Z*:*E*) by ^1H n.m.r. integral).

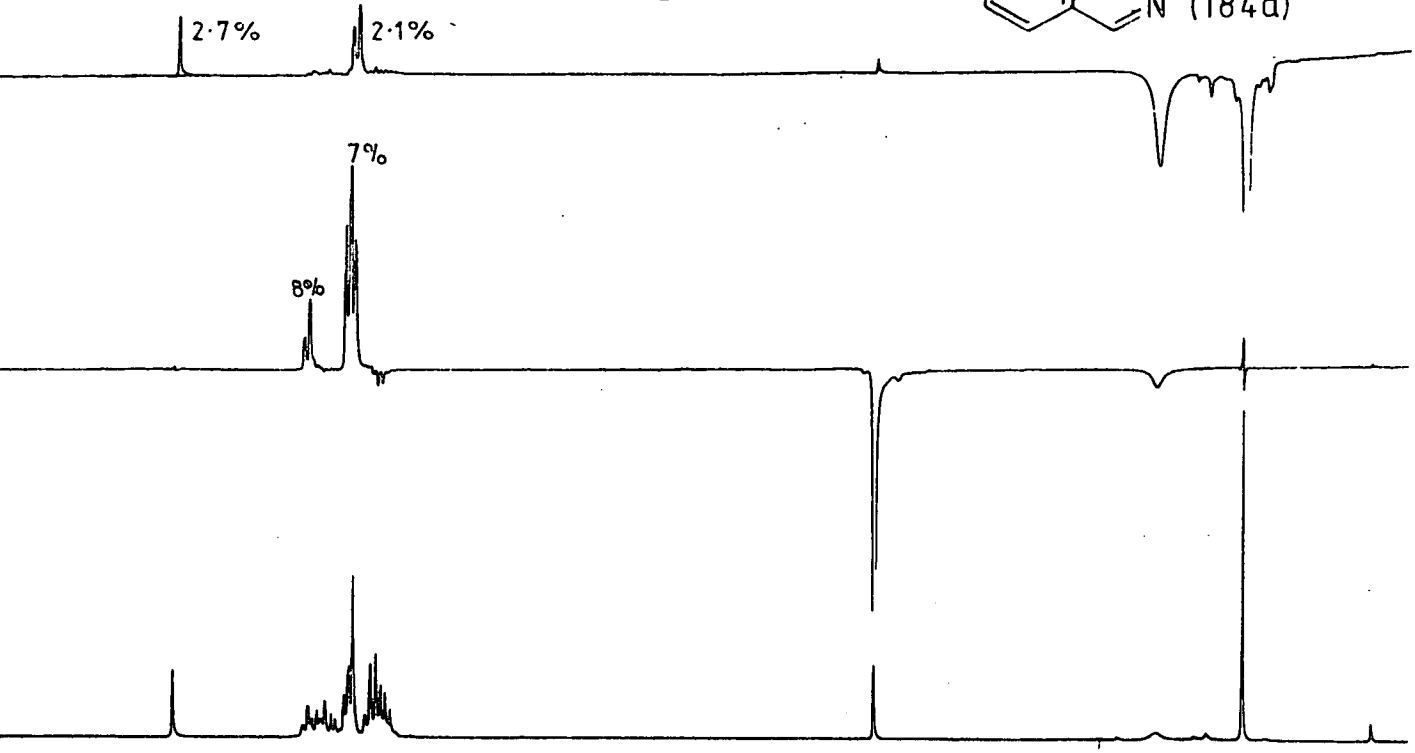
The imidoyl chloride and nitrile ylide were prepared and reacted as described previously. This reaction gave two products (184a) and (184b) which were separated by flash chromatography and characterised as being *exo* and *endo* 2a,3,3a-trihydro-3-methyl-2a-phenyl-3-phenylcyclopropa[c]isoquinoline (60:40, *endo*:*exo*). This correspondence between the product ratio and the *E*/*Z* ratio of the amide precursors indicates a highly stereospecific process.

N.O.E.Difference ^{1}H nmr spectra of cyclopropa[c]isoquinoline

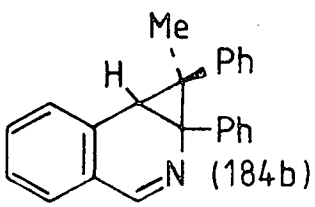
1) 2a,3,3a-Trihydro-3-methyl-2a-phenyl-3-*exo*-phenyl- cyclo- propa[c]isoquinoline



(184a)

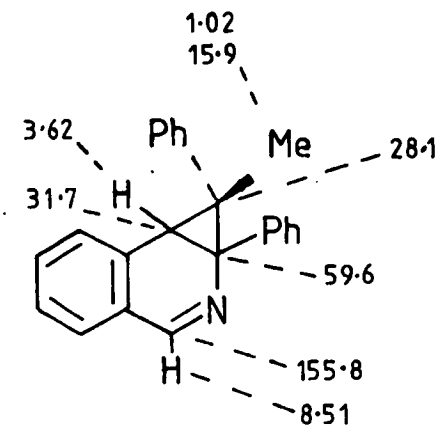


2) 2a,3,3a-Trihydro-3-methyl-2a-phenyl-3-*endo*-phenylcyclopropa[c]isoquinoline

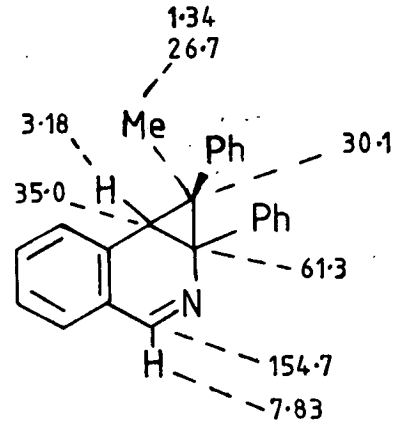


(184b)

Figure 31



(184a)



(184b)

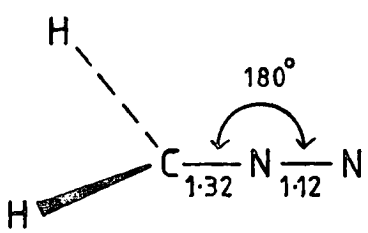
These structures were assigned on the basis of ^{1}H and ^{13}C n.m.r. spectra. A Drieding model of (184a) revealed that the Me group was lying in the shielding region of the imine bond and the shielded position of the Me, in both ^{1}H and ^{13}C n.m.r., supports the assignment of 184a as the *exo* isomer.

Further information was obtained from an N.O.E. investigation of these compounds (Figure 31). This investigation revealed enhancements of i) 2.7% between the Me protons and the C-1 imine proton for the *exo* isomer (184a), ii) 1.1% between the C-3a proton and Me protons for *endo* isomer (184b) and iii) 9.6% between the Me protons and C-3a proton for the *endo* isomer (184b). These enhancements are consistent with the values expected for the assigned structures, as the *endo* isomer (184b) would be expected to have the Me and C-3a proton Z to each other and thus closer in space than the corresponding *exo* isomer (184a).

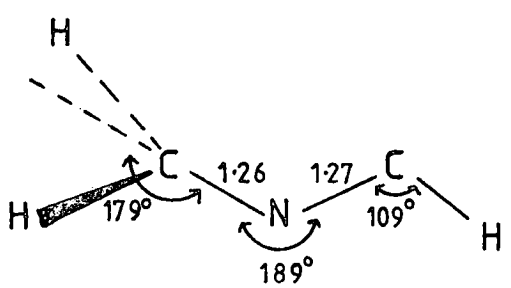
The above results show that the presence of a Z substituent does not inhibit the intramolecular cyclisation of α,β:γ,δ-unsaturated nitrile ylides. This is a major difference from

the analogous diazo system and could be taken as indicative of different primary steps in the two mechanisms , 1,7-electrocyclisation in the diazo case and concerted 1,1-cycloaddition for the nitrile ylide. However, caution should be exercised in this interpretation and it must be noted that nitrilium betaines have a different preferred geometry to diazonium betaines and this may account for the observed difference in reaction characteristics.

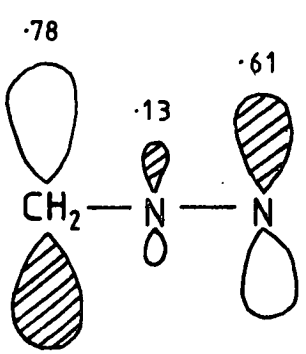
Theoretical calculations have shown that the diazo group is linear and planar[190] (185) whereas the nitrile ylide is distinctly bent with a CNC bond angle of 189° and an HCN angle of 109°[90] (186). The nitrile ylide HOMO has been shown to have the form shown in (188) which represents considerable distortion of the more usual allyl Ψ_2 type of orbital calculated for other 1,3-dipoles e.g. diazomethane (187).



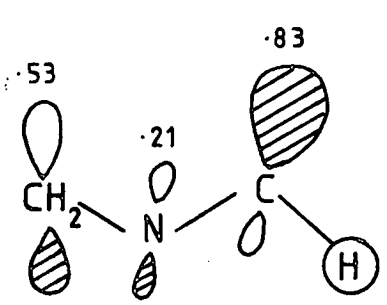
(185)



(186)

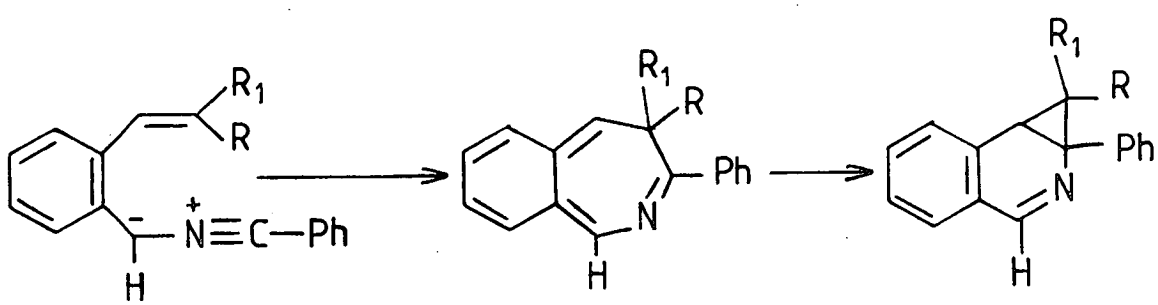


(187)

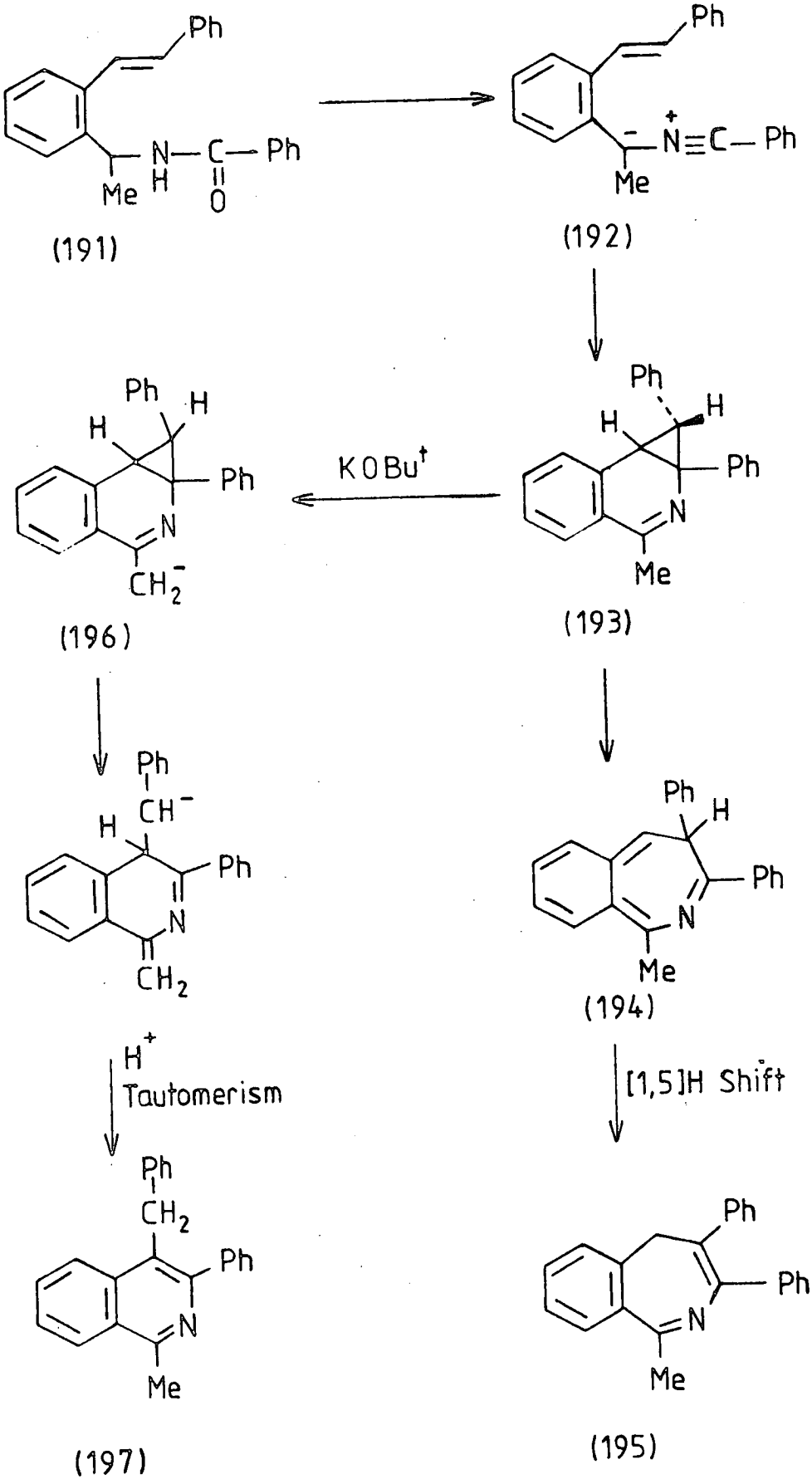


(188)

In the reactions of α,β:γ,δ-unsaturated diazocompounds it was suggested that the 1,7-ring closure occurred *via* a helical transition state (122, p.139). The inhibition of 1,7-closure when X was larger than hydrogen was attributed to a steric interaction between X and the second nitrogen (⟷ in figure 122), which inhibited overlap between the orbital lobes at the terminii of the system and so raised the activation energy for the cyclisation. If a similar transition state is involved for the 1,7-electrocyclisation of the analogous nitrile ylides then the bent geometry of this dipole will make the dipole less susceptible to steric hindrance by larger X groups because (i) the angular disposition of the orbital lobe on the terminal carbon of the dipole will allow better orbital overlap in the transition state at greater N⟷X distances and (ii) the preferred C-N-C bond angle of 189° means that the N⟷X distance will be greater at any given separation of the terminal atoms. Thus these factors indicate that it is not inconsistent that 1,7-electrocyclisation is the primary step in the formation of the cyclopropa[c]isoquinolines (177) and (184a,b). However if that is the case then the ring contraction step e.g. (189) to (190) must be rapid with respect to the rate of ring inversion or stereospecificity would not be observed.



(182) (189) (190)


Ph
N
H
C
Ph
O
Me
(191)
Ph
N≡C
Ph
Me
(192)
Ph
H
H
Ph
N
Me
(193)
KOBu^t
Ph
H
H
Ph
N
CH_2^-
(196)
Ph
CH^-
H
Ph
N
CH_2
H^+
Tautomerism
Ph
CH_2
Ph
N
Me
(197)
Ph
H
Ph
N
Me
(194)
[1,5]H Shift
Ph
Ph
N
Me
(195)

Scheme 32

As a further example it was decided to examine the reactions of the nitrile ylide (192) which has a methyl substituent on the 'anionic' carbon of the betaine. Padwa has reported that the preferred reaction paths of some nitrile ylides are sensitive to substituent effects.[102]

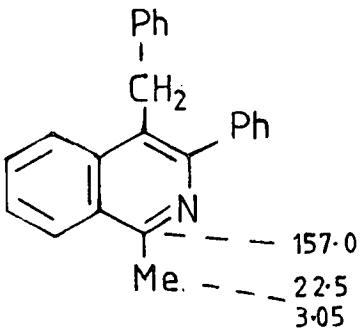
The amide (191) was synthesised by a route similar to that shown in scheme (29), the methyl group being introduced *via* a Grignard reaction of (169) with acetaldehyde followed by subsequent oxidation to the ketone. The amide (191) was converted to the nitrile ylide intermediate (192) as described previously and the product isolated by flash chromatography.

Although mass spectroscopy gave the expected formula $C_{23}H_{19}N$ the ^1H n.m.r. spectra were not as expected for compound (193) and showed a Me group (δ3.05), aromatic signals and a deshielded CH_2 (δ4.45). ^{13}C N.m.r. spectra showed a deshielded C (157.0 p.p.m.) aromatic signals, a Me (22.5 p.p.m.) and a CH_2 (34.7 p.p.m.). This data suggested two reasonable structures (195) and (197).

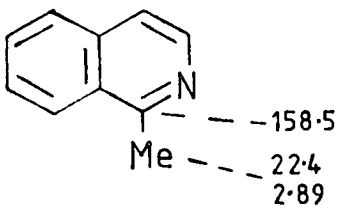
Differentiation between the 5*H*-2-benzazepine (195) and the 4-benzyl-1-methyl-3-phenylisoquinoline (197) was accomplished by variable temperature ^1H n.m.r. The CH_2 of the benzazepine structure (195) would be expected to exhibit a temperature dependent spectra, as the flexible seven-membered ring underwent temperature dependent ring inversion. However, no such effect was observed the CH_2 being a sharp singlet at 210 and 303K. The alternative structure (197) is supported by comparison of its U.V.[191] and ^1H n.m.r.[192] data with the very similar 1-methyl-3-phenylisoquinoline as shown below.

	U.V. $\lambda_{max(nm)}$, (log ε)	^{1}H n.m.r. (δ)
1-Methyl-3-phenyl isoquinoline	288, (3.15); 245 (4.69)	2.80 (Me) 7.20-7.80 (arom)
4-Benzyl-1-methyl-3-phenylisoquinoline	330, (3.65), 316, (3.66); 291, (3.91); 281, (3.94); 238, (4.52)	3.05 (Me) 4.45 (CH_2) 7.07-8.17 (arom)

Further conformation was obtained from comparison of the ^{13}C + ^1H n.m.r. spectra of 1-methylisoquinoline.[193,194]



(197)

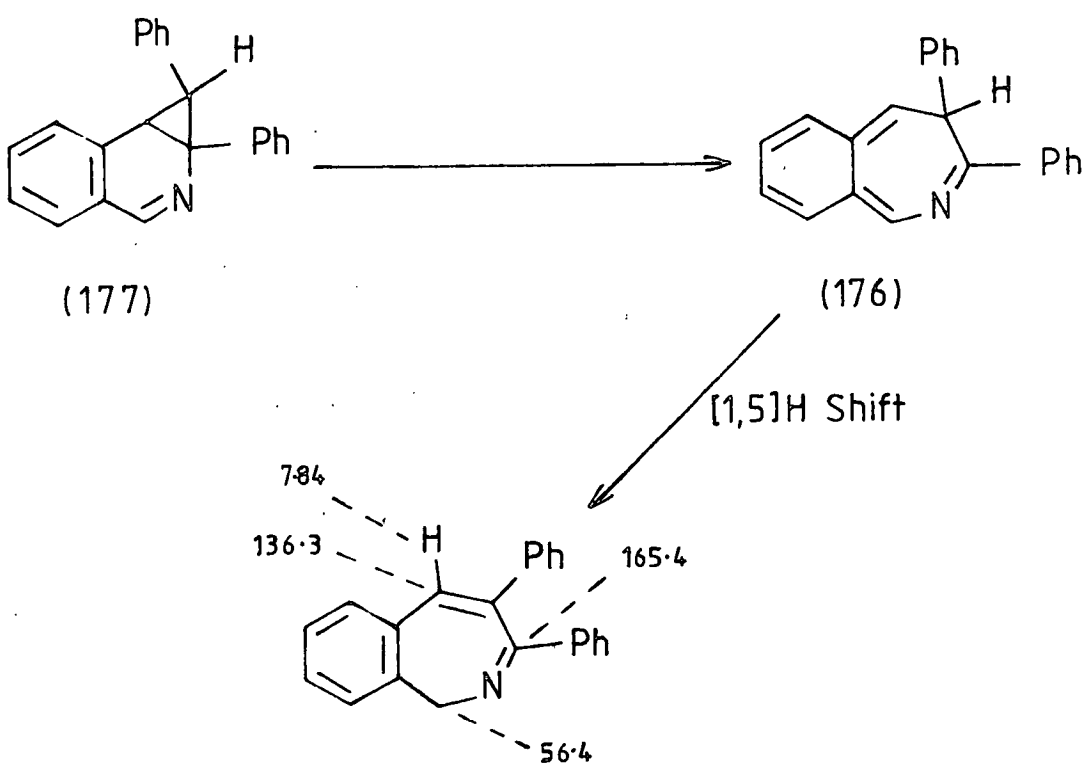


Thus this product was tentatively identified as being the substituted isoquinoline (197) which is most likely formed by a base catalysed isomerisation of the primary product, (193), as shown in scheme (32).

2.3) Rearrangement of the cyclopropa[c]isoquinolines

The high yields of the cyclopropa[c]isoquinolines discussed in the previous section were obtained in reactions carried out at room temperature. In view of the strained nature of these systems it was decided to find out whether they would undergo thermal ring expansion to give benzazepines.

On heating at 80°C for 12 h a solution of 2a,3,3a-trihydro-2a-phenyl-3-*exo*-phenylcyclopropa[c]isoquinoline (177) was converted to a single isomeric product. ^{1}H N.m.r. spectroscopy revealed aromatic signals, an olefinic proton (δ7.84) and a broad AB pattern (δ4.06 and 5.12). The AB pattern was dependent on temperature, becoming sharp (J10.1Hz) on cooling to -23°C and undergoing coalescence on heating (T_c=62°C). The ^{13}C n.m.r. spectra showed a deshielded quaternary carbon aromatic signal and a deshielded CH_2. This data is consistent with the 1*H*-2-benzazepine structure (178), having a flexible seven-membered ring. It is thought that this product was formed as shown in Scheme (33) by ring opening of the cyclopropane ring to give the non-benzoid intermediate (176) which subsequently underwent a [1,5]sigmatropic hydrogen shift to give the isolated product.

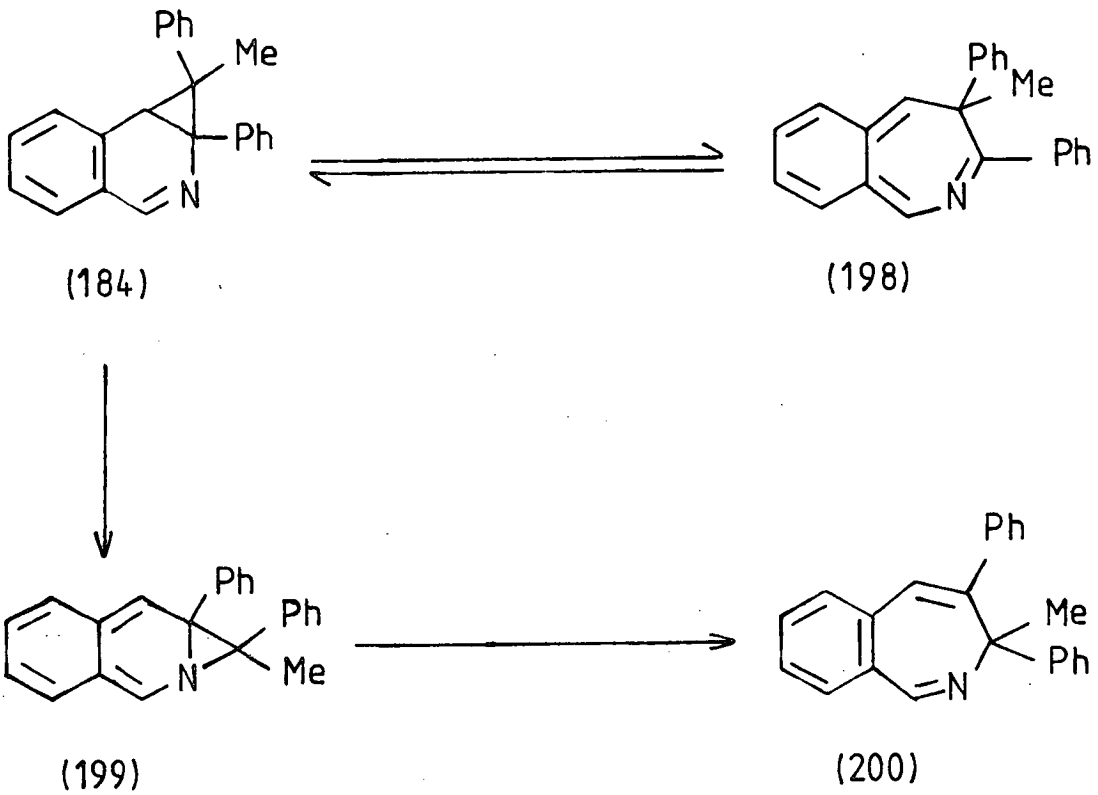


Scheme 33

It was of interest to investigate the result of heating the analogous compound (184). If this compound underwent the same ring opening reaction, as described above, it would give the non-benzoid intermediate (198). This intermediate could not readily undergo a sigmatropic rearrangement to restore the aromaticity of the benzene ring, as it is known that both Me and Ph are very much less mobile than hydrogen in sigmatropic shifts. Thus, this intermediate would be forced to undergo either a retro reaction or an alternative rearrangement to restore the benzene ring aromaticity.

Heating a mixture of the *exo* and *endo* cyclopropa[c]isoquinoline (184a,184b) at 80°C for 61h gave one product. This product was confirmed as being an isomer of the original structure by mass spectroscopy and elemental analysis. ^{1}H N.m.r. spectra showed a deshielded proton (δ8.46, d, J1.1Hz), a methyl absorption (δ1.65, s) and aromatic signals. ^{13}C N.m.r. indicated a deshielded CH (161.1 p.p.m.), a saturated quaternary (46.4 p.p.m.) and the expected Me (31.6 p.p.m.) and aromatic signals. The position of the deshielded proton and carbon suggested that an imine linkage was present. From the above spectral data the suggested structure is the 3*H*-2-benzazepine (200).

A mechanism for the formation of this structure is shown in scheme (34). Ring opening of the cyclopropa[c]isoquinoline (184) would result in the non-aromatic structure (198). This intermediate has no readily available pathway by which it can react to restore the aromaticity of the benzene ring. Thus on thermolysis an alternative pathway is adopted. A methylene walk gives the non-aromatic tricyclic intermediate (199) which readily ring opens to restore the aromaticity of the benzene



(184) (198) (199) (200)

Scheme 34

ring thereby giving the isolated 3*H*-2-benzazepine (200).

This section of work on nitrile ylides is not complete as it stands but it has laid the foundations for further work. The mechanisms of cyclopropa[c]isoquinoline formation, the formation of the isoquinoline (197) and the rearrangement giving compound (200) require further clarification. However, it is already clear that this work provides an efficient route into novel heterocyclic systems which should provide extensive scope for future workers.

Experimental

SECTION 1

DIAZEPINES AND OTHER COMPOUNDS DERIVED FROM DIAZOALKENES

SECTION 2

Page No.

AZEPINES AND OTHER COMPOUNDS DERIVED FROM NITRILE YLIDES

EXPERIMENTAL

A. Symbols and Abbreviations

b.p.	boiling point
m.p.	melting point
t.l.c.	thin-layer chromatography
g.l.c.	gas liquid chromatography
m.p.l.c.	medium pressure liquid chromatography
n.m.r.	nuclear magnetic resonance
br.	broad
s; d; t;	singlet; doublet; triplet;
q; m	quartet; multiplet
quat.	quaternary i.e. not bearing any hydrogen atoms
J	coupling constant
δ	chemical shift
i.r.	infra-red
ν	wavenumber (cm^{-1})
M^+	mass of molecular ion
m/z	mass to charge ratio
h; min;	hours; minutes;
s;	seconds
p.p.m.	parts per million
mol	moles
ml	millilitres
mmol	millimoles
N.O.E.	nuclear overhauser effect
T.H.F.	tetrahydrofuran
Hz	hertz
MHz	megahertz

Instrumentation and General Techniques

Nuclear Magnetic Resonance Spectroscopy

^{1}H N.m.r. spectra were obtained using: (i) a Varian EM360 (60MHz) spectrometer for routine samples, (ii) Varian HA100 (100MHz), Bruker WP200 (200MHz) and Bruker WH360 (360MHz) spectrometers for spectra of new compounds, decoupling studies, variable temperature studies, and high resolution spectra. All Nuclear Overhauser Effect (NOE) experiments were carried out on the Bruker F.T. instruments. ^{13}C N.m.r. spectra were obtained using a Varian CFT20 (25MHz), Bruker WP200 (50.3MHz) or Bruker WH360 (90.5MHz) spectrometers. Carbon multiplicity was established by single frequency off resonance decoupling (S.F.O.R.D.) or by distortionless enhancement by polarisation transfer (D.E.P.T.).[195] Spectra are recorded as δ values for solutions in deuteriochloroform and obtained on a Varian HA100 instrument unless otherwise stated. The spectrometers were operated by Mr. J.R.A. Millar, Mr. L.H. Bell, Dr. D. Reed and Dr. I.H. Sadler.

Mass Spectrometry

Mass spectra were obtained using an Associated Electrical Industries MS902 spectrometer, operated by Mr.D.Thomas.

Infrared Spectroscopy

Liquid samples were examined as thin films and solid samples as Nujol mulls on sodium chloride plates on a Perkin-Elmer 157G grating spectrometer. Spectra were calibrated with the polystyrene peak at 1603 cm^{-1}.

Elemental Analysis

Microanalyses for carbon, hydrogen and nitrogen were carried out on a Perkin-Elmer model 240 analyser operated by Mr.J.Grunbaum.

Melting Points

Routine melting points were determined using an Electro-thermal melting point apparatus while melting points of new compounds were determined using a Reichert hot-stage microscope.

Gas Liquid Chromatography

A Pye Series 104 Chromatograph using a flame ionisation detector and nitrogen carrier gas gave analytical chromatograms. The column used had internal diameter of 4 mm and length 5' and was packed with a silicone oil stationary phase (OV 1) supported on 80-100 mesh celite.

Medium Pressure Liquid Chromatography[196]

Preparative separations were carried out using Merck silica gel 60 (40-60 um), tap-fill packed in glass columns, (250 x 15 mm, 1000 x 15 mm, 1000 x 25 mm (Quickfit Ltd.)) fitted with solvent resistant connectors and tubing (Jobling Corning) and safety valve (50 p.s.i.: Nupro Guage Co. Ltd.). The samples were preadsorbed onto silica and packed into small 250 x 15 mm 'pre-columns'. The eluting solvent systems were based on petroleum ether 40/60 with varying amounts of ether. This was delivered at a flow rate of 5-20 ml min^{-1} from a diaphragm pump, (Metering Pumps Ltd.) depending on column size. The eluant was collected in an automatic fraction collector (Central Ignition Company Ltd.) and the fractions examined by thin layer chromatography.

Thin Layer Chromatography

This was carried out on a 0.3 mm layer of alumina (Merck, neutral aluminium oxide 60G, Type E) or silica (Merck, Kiselgel 60G) containing 0.5% Woelm fluorescent green indicator. Components in the developed chromatogram were detected by their quenching of fluorescence under ultra-violet light, and their staining by iodine.

Preparative Thin Layer Chromatography

This was carried out using 2.0 mm layers of the above supports. After locating the components by detection methods above, the separate bands were scraped off and the products removed by extraction with dichloromethane and methanol.

Gravity Column Chromatography

This was carried out on alumina (Laporte Industries, Grade H 100/200 mesh) prepared to 6% deactivation.

Flash Chromatography [197]

This was carried out using silica gel 60 (40-63 μm), tap-filled 18" glass columns (10, 20 or 30 mm) fitted with a Teflon stopcock and topped with a 24/40 glass quickfit joint, carrying a flow controller. The samples were applied as a 20% solution in the desired eluant (petrol 40/60 containing either ether or ethyl acetate). The column was run at a rate at which solvent head fell at 2.0 inches min^{-1}, and the solvent collected, in appropriate fraction sizes, in 20mm x 150 mm test-tubes. The fractions were examined by thin layer chromatography.

Drying

Anhydrous magnesium sulphate was used to dry all organic solutions, unless otherwise stated.

Purification of Solvents

"Super-dry" ethanol was prepared as described by Vogel[217] (method 1).

1,2-dimethoxyethane, cyclohexane, dimethylformamide and tetrahydrofuran were freshly distilled from calcium hydride as required. Toluene, diethyl ether and benzene were distilled from and stored over sodium wire. Carbon tetrachloride, chloroform, dichloromethane and acetone were distilled from phosphorus pentoxide and stored over Molecular Sieve 4A. Pyridine was dried as described by Vogel[217] and stored over potassium hydroxide pellets.

Petrol refers to fraction of petroleum ether b.p.40-60^{o}C.

SECTION 1

DIAZEPINES AND OTHER COMPOUNDS DERIVED FROM DIAZOALKENES

1. PREPARATION OF STARTING MATERIALS

A. TRIPHENYLPHOSPHONIUM SALTS

1) Benzyltriphenylphosphonium bromide

A mixture of freshly distilled benzyl bromide (23 g, 0.28 mol) and triphenylphosphine (79 g, 0.30 mol) in dry benzene (200 ml) was refluxed with stirring under dry nitrogen for 2 h. After cooling, the white precipitate was filtered off and washed with ether (3 x 50 ml) to give benzyltriphenylphosphonium bromide as colourless crystals (110 g, 95%), m.p. 285-287°C (lit.,[198] 283-285°C).

2) α-Bromoethylbenzene

N-Bromosuccinimide (57.0 g, 0.283 mol) was added portionwise to ethylbenzene (30.0 g, 0.283 mol) and benzoyl peroxide (0.5 g) in dry carbon tetrachloride. The mixture was heated under reflux for 3 h, cooled, and the resulting succinimide removed by filtration. The solvent was removed under reduced pressure and the residue distilled to yield α-bromoethylbenzene (42.3 g, 81%), b.p. 108°C at 32 mmHg (lit.,[199] 87°C at 15 mmHg).

3) α-Methylbenzyltriphenylphosphonium bromide

A mixture of α-bromoethylbenzene (20.2 g, 0.11 mol) and triphenylphosphine (28.7 g, 0.11 mol) in dry benzene (100 ml) was heated under reflux under dry nitrogen for 24 h. After

cooling, the white precipitate was filtered, washed with ether (3 x 100 ml) to give α-methylbenzyltriphenylphosphonium bromide (39.2 g, 80%), which was recrystallised from ethanol m.p. 230-232°C (Found: C, 69.55; H, 5.5. $C_{26}H_{24}BrP$ requires C, 69.80; H, 5.4%); δ_H 1.70, 1.87 (3H, d of d, J 19Hz, 7Hz, CH_3), 6.53 (1H, m, C-H), 7.0-7.28 (5H, m, aromatic), 7.41-7.92 (15H, m, aromatic); δ_p (24.2MHz) 26.76; m/z 448 (<1%), 446 (<1), 262 (100), 183 (37).

4) Isopropyltriphenylphosphonium bromide

Isopropylbromide (35.2 g, 0.29 mol) and triphenylphosphine (75 g, 0.29 mol) were placed in a thick wall glass tube which was sealed and heated at 150°C for 24 h. The resulting solid was recrystallised from ethanol to give isopropyltriphenylphosphonium bromide (92.7 g, 83%), m.p.237°C (lit.,[200] 238-239°C).

5) Methyltriphenylphosphonium iodide

Methyl iodide (92.0 g, 0.50 mol) was added dropwise with cooling and mechanical stirring to triphenylphosphine (170 g, 0.65 mol) in dry benzene (500 ml). The mixture was stirred for 2 h at room temperature and heated under reflux for 4 h. The resulting precipitate was filtered, washed with ether (3x300 ml) and recrystallised from ethanol to give methyltriphenylphosphonium iodide (256 g, 97%), m.p. 187°C (lit.,[201] 188-189°C).

B. SYNTHESIS OF 1-FORMYL-2-ALKENYLCYCLOPENTENES AND THEIR TOSYLHYDRAZONES

1) Cyclopentanone trimethylsilyl enol ether

This was prepared by the method of House *et al.*[202] from the reaction of trimethylsilyl chloride, triethylamine, dimethylformamide and cyclopentanone in 67% yield, b.p. 154-155°C at 760 mmHg (lit.,[202] 158-159°C at 760 mmHg) δ_H 1.0 (9H, s, $SiMe_3$), 2.45-3.2 (6H, m, cyclopentyl), 5.42 (1H, br s, olefinic).

2) 2-Dimethoxymethylcyclopentanone

This was prepared by the method of Mukaiyama and Hayashi[203]. Titanium tetrachloride (24.2 g, 0.127 mol), trimethyl orthoformate (12.8 g, 0.120 mol), and cyclopentanone trimethylsilyl eno ether (18.8 g, 0.120 mol) were stirred in dry dichloromethane (150 ml) at -78°C for 3 h. Hydrolysis was carried out by injecting the mixture (below -40°C) into rapidly stirred sodium carbonate solution (10%, 2000ml). The aqueous layer was washed with ether (3 x 300 ml), the ether extract combined with the organic layer, dried and evaporated at reduced pressure to give a yellow oil. Distillation of this afforded 2-dimethoxymethylcyclopentanone as a pale yellow oil (11.1 g, 58%), b.p. 45-47°C at 0.2 mmHg (lit.,[203] not quoted) (Found: C, 60.9; H, 9.0. $C_8H_{14}O_3$ requires C, 60.7; H, 8.9%); ν_{max} (film) 1700 cm^{-1} (C=O); δ_H 1.9-2.8 (7H, m, cyclopentyl), 3.48 (6H, s, OMe) 4.72 (1H, d, J 6Hz, C*H* $(OMe)_2$); m/z 158 (<1%), 127 (9), 75 (100).

3) 2-Methoxymethylenecyclopentanone

This was prepared by an adaptation of Mukaiyama and Hayashi's method[203]. Titanium tetrachloride (24.3 g, 0.128 mol), trimethylorthoformate (12.7 g, 0.120 mol) and cyclopentanone trimethylsilyl enol ether (18.8 g, 0.120 mol) were stirred in dry dichloromethane (120 ml) at -78°C for 3 h. The mixture was allowed to warm to room temperature and stirred for a further 2 h. Hydrolysis was carried out by adding the mixture dropwise to a rapidly stirred solution of sodium carbonate (10%, 1000ml). The aqueous layer was extracted with ether (3 x 150 ml), the ether extracts were combined with the organic layer, dried, and the solvent was removed under reduced pressure to give a black oil. Rapid distillation under nitrogen through a short Vigreux column afforded 2-methoxymethylenecyclopentanone as a clear liquid (8.5 g, 56%), b.p. 76-78°C at 2.5 mmHg (lit.,[207] 54-56°C at 0.1 mmHg) (Found: m/z, 126.068277. $C_7H_{10}O_2$ requires m/z, 126.068075); ν_{max} (film) 1695 cm^{-1} (C=O); δ_H 1.8-2.1 (1H, m, 4-H_2), 2.15-2.35 (1H, m, 3-H_2), 2.4-2.6 (2H, m, 5-H_2), 3.8 (3H, s, OMe), 7.2 (1H, br s, olefinic); m/z 126 (100%), 97 (32), 95 (43), 75 (55), and 70 (48). The 2,4-dinitrophenylhydrazone derivative had m.p. 222-224°C (Found: C, 50.8; H, 4.7; N, 18.2. $C_{13}H_{14}N_4O_5$ requires C, 51.0; H, 4.6; N, 18.3%).

4) 1-Formyl-2-(*E*-2-propenyl)cyclopentene

This was prepared using the adapted method of Dreiding and Nickel[204]. A lithium reagent was prepared from 1-bromopropene (5.33 g, 44 mmol) and lithium (0.616 g, 88 mmol) in dry ether (50 ml). The lithium reagent was decanted and then

added dropwise to a rapidly stirred solution of 2-methoxymethylenecyclopentanone (3.70 g, 30 mmol) in dry ether (50 ml) at -50°C. After the addition was complete the reaction was allowed to warm to room temperature and stirred for a further 12 h. Hydrolysis was carried out by the careful addition of hydrochloric acid (10%, 100 ml) at 0°C, after the addition the reaction mixture was stirred for a further 8 h. The aqueous layer was washed with ether (3 x 30 ml), the ether extracts were combined with the organic layer, dried and the solvent was evaporated under reduced pressure to give a brown oil. This oil was separated by medium pressure chromatography (silica, ether:petrol 40/60, 1:4) to give 1-formyl-2-(*E*-2-propenyl)-cyclopentene as a colourless liquid (1.27 g, 31.8%), b.p. 83-84°C at 1.5 mmHg (Found: m/z, 136.087861. $C_9H_{12}O$ requires m/z, 136.088810); ν_{max} (film) 1710 cm^{-1} (C=O); δ_H 1.7-2.1 and 2.5-2.9 (9H, m, cyclopentyl including Me at 1.91, d, J 6Hz), 6.1 (1H, dq, J 16Hz, J' 6Hz, CH=C*H*Me), 7.0 (1H, d, J 16Hz, C*H*=CHMe), 10.17 (1H, s, CHO). The 2,4-dinitrophenylhydrazone derivative had m.p.187-188°C (Found: C, 57.2; H, 5.0; N, 17.8. $C_{15}H_{16}N_4O_4$ requires C, 57.0; H, 5.10; N, 17.7%).

5) <u>1-Formyl-2-(*E*-2-propenyl)cyclopentene tosylhydrazone</u>

The aldehyde (0.22 g, 1.62 mmol) and *p*-toluenesulphonyl hydrazide (0.30 g, 1.62 mmol) were stirred in ethanol (20 ml) containing concentrated hydrochloric acid (1 drop) for 2 h. The reaction mixture was neutralised by the addition of solid sodium bicarbonate and most of solvent removed at reduced pressure. Dichloromethane (50 ml) was added, and the organic

phase separated, washed with water (25 ml) and dried. The solvent was removed at reduced pressure and the resulting brown oil separated by m.p.l.c. (silica, ether:petrol 40/60, 1:4) to give 1-formyl-2-(*E*-2-propenyl)cyclopentene tosylhydrazone as a white solid (0.27 g, 54%) which was recrystallised from ethanol, m.p. 111-113°C (Found: C, 63.1; H, 6.8; N, 9.3. $C_{16}H_{20}N_2O_2S$ requires C, 63.1; H, 6.6; N, 9.2%); ν_{max} (Nujol) 3180 cm^{-1} (N-H). Spectral data see Appendix 2.

6) 1-Bromo-2-formylcyclopentene

This was prepared using the method of Arnold *et al.*[205] by the reaction between dimethylformamide (110 g, 1.50 mol), phosphorus tribromide (340 g, 1.25 mol) and cyclopentanone (42.0 g, 0.50 mol). 1-Bromo-2-formylcyclopentene was distilled from the crude material as a colourless liquid (47.2 g, 54%), b.p. 45°C at 0.8 mmHg (lit.,[205] 45-47°C at 1.5 mmHg); ν_{max} (film) 1695 cm^{-1} (C=O); δ_H 1.8-3.1 (6H, m, cyclopentyl), 9.93 (1H, s, CHO).

7) 1-Bromo-2-(2-phenylethenyl)cyclopentene

A solution of sodium ethoxide, prepared from sodium (0.950 g, 41.4 mmol) in "super-dry" ethanol (50 ml) was added dropwise to a stirred suspension of benzyltriphenylphosphonium bromide (17.9 g, 41.4 mmol) in dry ethanol (200 ml). This mixture was stirred for 1 h at room temperature and then 1-bromo-2-formylcyclopentene (7.24 g, 41.4 mmol) was added dropwise to the mixture at 0°C. The reaction mixture was stirred at room temperature for 12 h and then heated under reflux for 5 min. The precipitate of sodium bromide was

removed by filtration and the solvent removed under reduced pressure to leave a brown oil. Triphenylphosphine oxide was removed by gravity chromatography on alumina eluting with petrol 40/60 to give 1-bromo-2-(2-phenylethenyl)cyclopentene (8.48 g) as a mixture of *E*/*Z* isomers (2:1). The two isomers were separated by m.p.l.c. (silica, petrol 40/60) to give:
(1) 1-bromo-2-(*E*-2-phenylethenyl)cyclopentene (5.5 g, 53%) as white crystals, recrystallised from petrol 40/60, m.p. 61-62°C (Found: C, 62.5; H, 5.42. $C_{13}H_{13}Br$ requires C, 62.7; H, 5.3%); δ_H 1.6-2.75 (6H, m, cyclopentyl), 6.41 and 7.09 (2H, AB, J 16Hz, olefinic), 7.15-7.65 (5H, m, phenyl); m/z 250 (79%), 248 (79), 169 (76), 141 (100), 91 (37).
(2) 1-bromo-2-(*Z*-2-phenylethenyl)cyclopentene (2.6 g, 25%) as white crystals recrystallised from petrol 40/60, m.p. 35-40°C (Found: C, 62.85; H, 5.3. $C_{13}H_{13}Br$ requires C, 62.7; H, 5.3%); δ_H 1.6-2.3 and 2.5-2.75 (6H, m, cyclopentyl), 6.34 and 6.64 (2H, AB, J 12Hz, olefinic), 7.05-7.4 (5H, m, phenyl). m/z 250 (63%), 248 (63), 169 (67), 141 (100), 91 (52).

8) 1-Formyl-2-(*E*-2-phenylethenyl)cyclopentene

A Grignard reagent was prepared by the addition of a solution of 1-bromo-2-(*E*-2-phenylethenyl)cyclopentene (1.4 g, 5.6 mmol) in dry T.H.F. (60 ml) to a stirred suspension of magnesium (0.13 g, 5.62 mmol) in refluxing T.H.F. over 2 h, and then stirred for a further 4 h. This was cooled to 0°C in an ice bath and dry dimethylformamide (0.62 g, 8.4 mmol) in dry T.H.F. (20 ml) was added dropwise. The reaction mixture was stirred overnight at room temperature, heated under reflux for 1 h,

and cooled before the addition of a solution of ammonium chloride (25% w/v, 50 ml). Most of the solvent was removed at reduced pressure, ether (100 ml) was added and the organic phase separated, the aqueous layer was extracted with ether (3 x 100 ml). The combined organic layers were washed with water (2 x 100 ml) and dried. Removal of solvent at reduced pressure gave a dark orange solid (0.76 g). Recrystallisation from ethanol yielded yellow crystals of 1-formyl-2-(*E*-2-phenylethenyl)cyclopentene (0.69 g, 62%) m.p.103-104°C (Found: C, 84.6; H, 7.25. $C_{14}H_{14}O$ requires C, 84.8; H, 7.1%); ν_{max} (Nujol) 1640 cm^{-1} (C=O); δ_H 1.75-2.1 and 2.55-2.95 (6H, m, cyclopentyl), 6.80 and 7.62 (2H, AB, J 16Hz, olefinics), 7.2-7.6 (5H, m, phenyl), 10.30 (1H, s, CHO).

9) 1-Formyl-2-(*E*-2-phenylethenyl)cyclopentene tosylhydrazone

1-Formyl-2-(*E*-2-phenylethenyl)cyclopentene (2.25 g, 11.4 mmol) and *p*-toluenesulphonylhydrazide (2.12 g, 11.4 mmol) were dissolved separately in ethanol (20 ml) and warmed to 35°C. The two solutions were then mixed and concentrated hydrochloric acid (1 drop) was added , stirred for 1 h and the deposited white solid was recrystallised from ethanol to yield 1-formyl-2-(*E*-2-phenylethenyl)cyclopentene tosylhydrazone as white needles (2.43 g, 58%), m.p. 147°C (Found: C, 68.6; H, 6.20; N, 7.50. $C_{21}H_{22}N_2O_2S$ requires C, 68.8, H, 6.05; N, 7.6%); ν_{max} (Nujol) 3210 cm^{-1} (N-H).

Spectral data see Appendices 2 and 3.

C. SYNTHESIS OF 1-FORMYL-2-ALKENYLCYCLOHEXENES AND THEIR TOSYLHYDRAZONES

1) 1-Bromo-2-formylcyclohexene

This was prepared using the method of Arnold *et al.*[205] by the reaction between dimethylformamide (110 g, 1.50 mol), phosphorus tribromide (340 g, 1.25 mol) and cyclohexanone (49.0 g, 0.50 mol). 1-Bromo-2-formylcyclohexene was distilled from the crude material as a colourless liquid (26 g, 27%), b.p. 60-62°C at 0.8 mmHg (lit.,[205] 51°C at 0.7 mmHg); ν_{max} (film) 1695 cm^{-1} (C=O), δ_H 1.45-2.85 (8H, m, cyclohexyl), 10.1 (1H, s, CHO).

2) 1-Bromo-2-(2-phenylethenyl)cyclohexene

A solution of sodium ethoxide, prepared from sodium (3.17 g, 0.138 mol) in "super-dry" ethanol (100 ml) was added dropwise to a stirred suspension of benzyltriphenylphosphonium bromide (59.8 g, 0.138 mol) in dry ethanol (200 ml). This mixture was stirred for 1 h at room temperature and 1-bromo-2-formylcyclohexene (26.0 g, 0.138 mol) was added dropwise to the mixture at 0°C. The reaction mixture was stirred at room temperature for 12 h and then heated under reflux for 30 min. The precipitate of sodium bromide was filtered off and the solvent removed under reduced pressure to give a brown oil. Triphenylphosphine oxide was removed by gravity chromatography on alumina eluting with petrol 40/60 and 1-bromo-2-(2-phenethenyl)cyclohexene was isolated as a clear oil (30.6 g, 84%), (Found: m/z, 262.036093. $C_{14}H_{15}{}^{79}Br$ requires m/z, 262.035760); δ_H showed the presence of *E* and *Z* isomers,

in the ratio *ca.* 2:1, *E* isomer; 1.5-1.85 and 2.1-2.7 (8H, m, cyclohexyl), 6.51 (1H, d, J 16Hz, olefinic), 7.05-7.5 (6H, m, aromatic plus one olefinic); *Z* isomer, 1.4-1.85 and 2.2-2.75 (8H, m, cyclohexyl), 6.16 and 6.43 (2H, AB, J 12Hz, olefinic), 7.1-7.5 (5H, m, phenyl); m/z 264 (31%), 262 (33), 183 (23), 141 (100), 91 (28).

3) 1-Formyl-2-(2-phenylethenyl)cyclohexene*

A Grignard reagent was prepared from 1-bromo-2-(2-phenylethenyl)cyclohexene (28.5 g, 0.108 mol) and magnesium (2.62 g, 0.108 mol) in dry T.H.F. (100 ml). This was cooled to 0°C in ice and dry dimethylformamide (11.8 g, 0.162 mol) in T.H.F. (50 ml) was added dropwise. The mixture was then allowed to stir at room temperature for 12 h. The Grignard complex was decomposed by the careful addition of saturated ammonium chloride (100 ml) at 0°C. The aqueous layer was washed with ether (3 x 50 ml) and the ether extract combined with the organic layer, dried and the solvent evaporated under reduced pressure to give a dark yellow oil. Purification of this oil by m.p.l.c. (silica, ether:petrol 40/60, 1:3) gave 1-formyl-2-(2-phenylethenyl)cyclohexene as a yellow solid (14.0 g, 61%) which recrystallized from ethanol m.p.82-83°C (Found: m/z, 212.120366. $C_{15}H_{16}O$ requires m/z, 212.120109); ν_{max} (Nujol) 1645 cm^{-1} (C=O); δ_H showed the presence of *E* and *Z* isomers in the ratio *ca.* 9:1, *E* isomer; 1.5-1.85 and 2.25-2.65 (8H, m, cyclohexyl), 6.81 and 7.72 (2H, AB, J 16Hz, olefinic), 7.2-7.55 (5H, m, aromatic), 10.38 (1H, s, CHO). The 2,4-dinitrophenylhydrazone derivative had m.p. 215-218°C (Found: C, 64.1; H, 5.05; N, 14.0. $C_{21}H_{20}N_4O_4$ requires

C, 64.3; H, 5.1; N, 14.3%).

4) 1-Formyl-2-(*E*-2-phenylethenyl)cyclohexene tosylhydrazone*

1-Formyl-2-(2-phenylethenyl)cyclohexene (10.0 g, 47.2 mmol) and *p*-toluenesulphonylhydrazide (8.78 g, 47.2 mmol) were dissolved separately in ethanol (100 ml) and warmed to 35°C. The two solutions were then mixed and concentrated hydrochloric acid (1 drop) was added. On cooling a white precipitate was deposited (9.89 g) and concentration of the mother liquors followed by purification by m.p.l.c. (silica, petrol 40/60 : dichloromethane:ether, 2:2:1) yielded a further 6.81 g. Recrystallisation of this white solid from ethanol gave 1-formyl-2-(*E*-2-phenylethenyl)cyclohexene tosylhydrazone as white needles (16.4 g, 92%), m.p. 125-126°C (Found: C, 69.2; H, 6.2; N, 7.1. $C_{22}H_{24}N_2O_2S$ requires C, 69.4; H, 6.4; N, 7.4%); ν_{max} (Nujol) 3210 cm^{-1} (NH). Spectral data see Appendices 2 and 3.

5) 1-Bromo-2-(*E*-2-phenylpropenyl)cyclohexene

To a stirred suspension of α-methylbenzyltriphenylphosphonium bromide (22 g, 49.2 mmol) in dry ether (500 ml) at 0°C was added *n*-butyllithium (1.50M in hexane, 32.8 ml, 49.2 mmol). The mixture was stirred 1 h at room temperature to generate the ylide, cooled to 0°C and 1-bromo-2-formylcyclohexene (9.3 g, 49.2 mmol) in dry ether added dropwise. The resulting reaction was stirred 1 h at 0°C, 2 h at room temperature and heated under reflux for 1 h. The reaction was allowed to

---

* Made in collaboration with Mr. C.B. Argo.

cool before hydrolysis by the addition of water (200 ml). The aqueous layer was separated, extracted with ether (2 x 200 ml) and the combined organic layer dried. Evaporation of the solvent at reduced pressure gave a yellow oil. Triphenylphosphine oxide was removed by chromatography (alumina, petrol 40/60) to give 1-bromo-2-(2-phenylpropenyl)-cyclohexene as an *E*/*Z* mixture (9.9 g, 73%). M.p.l.c. (silica, petrol 40/60) of the mixture gave 1-bromo-2-(*E*-2-phenyl-propenyl)cyclohexene (9.7 g, 71%) as a clear oil, b.p. 170°C at 0.1 mmHg (Found: C, 65.1; H, 6.3. $C_{15}H_{17}Br$ requires C, 65.0; H, 6.2%); δ_H 1.62-1.82, 2.11-2.40 and 2.48-2.78 (8H, m, cyclohexyl), 2.03 (3H, d, 1Hz, Me), 6.21 (1H, m, olefinic), 7.12-7.63 (5H, m, phenyl); m/z 278 (25%), 276 (25), 197 (97), 155 (100).

6) 1-Formyl-2-(*E*-2-phenylpropenyl)cyclohexene

n-Butyllithium (1.5M in hexane, 26 ml, 39.0 mmol) was added to a solution of 1-bromo-2-(*E*-2-phenylpropenyl)cyclo-hexene (10.7 g, 38.6 mmol) in anhydrous T.H.F. (150 ml) under N_2, at -78°C. After stirring for 30 min, anhydrous dimethyl-formamide (8.5 g, 116 mmol) in dry T.H.F. (30 ml) was added dropwise with stirring. The reaction was stirred at -78°C for 4 h, hydrolysed with ammonium chloride solution (25% w/v, 50 ml) and the mixture allowed to warm to room temperature. Most of the solvent was removed at reduced pressure, ether (200 ml) was added and the aqueous layer separated, extracted with ether (2 x 100 ml) and the combined ether layer washed with water (50 ml) and dried. Evaporation of the solvent at reduced pressure gave a brown oil which was purified by

m.p.l.c. (silica, ether:petrol 40/60, 1:4) to give 1-formyl-2-(*E*-2-phenylpropenyl)cyclohexene (5.0 g, 58%) as a pale yellow oil, (Found: m/z, 226.134625. $C_{16}H_{18}O$ requires m/z, 226.135758); ν_{max} (film) 1660 cm^{-1} (C=O); δ_H 1.6-1.8 and 2.1-2.5 (8H, m, cyclohexyl), 2.00 (3H, d, J 1Hz, Me), 6.42 (1H, br q, olefinic), 7.22-7.58 (5H, m, phenyl), 9.80 (1H, s, CHO). The 2,4-dinitrophenylhydrazone derivative had m.p. 195-196°C (from ethanol) (Found: C, 64.9; H, 5.4; N, 13.8. $C_{22}H_{22}N_4O_4$ requires C, 65.0; H, 5.45; N, 13.8%).

7) 1-Formyl-2-(*E*-2-phenylpropenyl)cyclohexene tosylhydrazone

1-Formyl-2-(*E*-2-phenylpropenyl)cyclohexene (0.96 g, 4.2 mmol) and *p*-toluenesulphonylhydrazide (0.79 g, 4.2 mmol) were dissolved separately in ethanol (20 ml) and warmed to 35°C. The two solutions were mixed and concentrated hydrochloric acid (1 drop) added and stirred for 4 h. The solvent was removed at reduced pressure and the resulting solid was recrystallised from ethanol to yield 1-formyl-2-(*E*-2-phenylpropenyl)cyclohexene tosylhydrazone as white crystals (1.4 g, 84%), m.p. 135-136°C (Found: C, 69.9; H, 6.4; N, 7.0. $C_{23}H_{26}N_2O_2S$ requires C, 70.0; H, 6.6; N, 7.1%); ν_{max} (Nujol) 3175 cm^{-1} (N-H). Spectral data see Appendices 2 and 3.

8) 1-Bromo-2-(2-methylpropenyl)cyclohexene

To a stirred suspension of isopropyltriphenylphosphonium bromide (20.4 g, 53 mmol) in dry ether (500 ml) at 0°C was added *n*-butyllithium (1.5M in hexane, 35.3 ml, 53 mmol) and stirred at room temperature for 2 h to generate the red ylide. The reaction was cooled to 0°C and 1-bromo-2-formylcyclohexene (10.0 g, 53 mmol) in dry ether (50 ml) added dropwise. The

resulting mixture was stirred 2 h at room temperature and heated under reflux 2 h before cooling to 0°C. The reaction was then hydrolysed with water (250 ml), the aqueous layer was separated, extracted with ether (3 x 200 ml) and the combined organic layer dried. Evaporation of the solvent at reduced pressure gave a yellow oil which was purified by chromatography (alumina, petrol 40/60) to give 1-bromo-2-(2-methylpropenyl)cyclohexene as a light yellow oil, which was distilled to give the pure product as a clear oil (9.0 g, 79%), b.p. 80°C at 1.0 mmHg (Found: m/z, 214.033547. $C_{10}H_{15}{}^{79}Br$ requires m/z, 214.035670); δ_H 1.5-1.91, 2.0-2.31 and 2.42-2.63 (8H, m, cyclohexyl), 1.63 (3H, d, J 1Hz, Me), 1.78 (3H, d, J 1Hz, Me), 5.60 (1H, m, olefinic); m/z 216 (45%), 214 (45), 135 (100).

9) 1-Formyl-2-(2-methylpropenyl)cyclohexene

n-Butyllithium (1.2M, 24 ml, 29 mmol) was added under dry nitrogen to a solution of 1-bromo-2-(2-methylpropenyl)-cyclohexene (6.1 g, 28 mmol) in dry T.H.F. (150 ml) at -60°C and stirred for 3 h. Dry dimethylformamide (3.2 g, 44 mmol) in dry T.H.F. (30 ml) was added dropwise with vigorous stirring, and stirred a further 3 h at -60°C before hydrolysis by addition of ammonium chloride solution (20% w/v, 50 ml). The mixture was allowed to warm to room temperature then most of the solvent removed under reduced pressure. Ether (200 ml) was added and the aqueous layer separated, extracted with ether (3 x 50 ml) and the combined organic layers washed with water (100 ml) and dried. Evaporation of solvent at reduced pressure gave a yellow oil which was purified by m.p.l.c. (silica, ether:petrol, 1:5) to give: (i) recovered starting

material (3.2 g, 52%) and (ii) 1-formyl-2-(2-methylpropenyl)cyclohexene as a clear oil (1.6 g, 35% (71% based on consumed starting material)), (Found: m/z, 164.120407. $C_{11}H_{16}O$ requires m/z, 164.120109); ν_{max} (film) 1670 cm^{-1} (C=O); δ_H 1.45-1.8 and 2.05-2.5 (8H, m, cyclohexyl), 1.59 (3H, d, J 1Hz, Me), 1.83 (3H, d, J 1Hz, Me), 5.74 (1H, br m, cyclohexyl), 1.59 (3H, d, J 1Hz, Me), 1.83 (3H, d, J 1Hz, Me), 5.74 (1H, br m, olefinic), 9.65 (1H, s, CHO).

The 2,4-dinitrophenylhydrazone derivative had m.p. 157-169°C (Found: m/z, 344.147723. $C_{17}H_{20}N_4O_4$ requires m/z, 344.148445).

10) 1-Formyl-2-(2-methylpropenyl)cyclohexene tosylhydrazone

p-Toluenesulphonylhydrazide (0.77 g, 4.15 mmol) in ethanol (20 ml) was added to 1-formyl-2-(2-methylpropenyl)-cyclohexene (0.68 g, 4.15 mmol) in ethanol (20 ml) and concentrated hydrochloric acid (1 drop) added. After stirring 2 h t.l.c. indicated the reaction had gone to completion, but no crystals were deposited after 20 h. The solvent was removed at reduced pressure, dichloromethane (100 ml) added, the organic layer separated, washed with water (2 x 50 ml) and dried.

The solvent was removed at reduced pressure to give a brown oil which was purified by m.p.l.c. (silica, ether:petrol 40/60, 1:3) to give 1-formyl-2-(2-methylpropenyl)cyclohexene tosylhydrazone as unstable white crystals (obtained on concentration of m.p.l.c. fractions to a reduced volume), m.p. 103-104°C (Found: C, 64.8; H, 7.2; N, 8.3. $C_{18}H_{24}N_2O_2S$

requires C, 65.0; H, 7.3; N, 8.4%); ν_{max} (Nujol) 3180 cm^{-1} (N-H). Spectral data see Appendices 2 and 3.

11) 1-Bromo-2-vinylcyclohexene

Lithium diisopropylamide was generated at 0°C from diisopropylamine (11.8 g, 0.116 mol), *N,N,N',N'*-tetramethylethylenediamine (13.5 g, 0.116 mol) and *n*-butyllithium (1.4M in hexane, 82.8 ml, 0.116 mol) and added, under nitrogen, to methyltriphenylphosphonium iodide (51.2 g, 0.126 mol) in dry ether (600 ml) via a direct transfer needle. The resulting mixture was stirred 1 h at room temperature and then 1-bromo-2-formylcyclohexene (20.0 g, 0.106 mol) in dry ether (100 ml) was added dropwise and then stirred for 4 h. The triphenylphosphine oxide was filtered off and washed with ether (3 x 200 ml), water (400 ml) added to the ether filtrate, separated and the combined organic layer washed with water (3 x 200 ml) and dried. Removal of the solvent at reduced pressure gave a yellow oil which was purified by chromatography (alumina, petrol 40/60) to give 1-bromo-2-vinylcyclohexene as a clear oil (11.4 g, 58%), b.p. 90° at 1 mmHg (Found: m/z, 186.004563. $C_8H_{11}{}^{79}Br$ requires m/z, 186.004461); ν_{max} (liquid) 1630 cm^{-1} (C=C); δ_H 1.42-1.86 and 2.08-2.71 (8H, m, cyclohexyl), 5.0-5.42 (2H, m, $=CH_2$), 6.91 (1H, d of d, J 17,10Hz $=CH$). m/z 188 (50%) 186 (50), 107 (65), 91 (45), 79 (100).

12) 1-Formyl-2-vinylcyclohexene

n-Butyllithium (1.5M, 33 ml, 49.5 mmol) was added under dry nitrogen to a solution of 1-bromo-2-vinylcyclohexene (6.25 g, 33.4 mmol) in dry T.H.F. (100 ml) at -110°C and

stirred for 3 min. Dry dimethylformamide (7.30 g, 100 mmol) in dry T.H.F. (30 ml) was added and the reaction allowed to warm to -78°C before stirring 3 h. The reaction was hydrolysed by the addition of a solution of ammonium chloride (25% w/v, 50 ml), most of the solvent removed under reduced pressure and ether (250 ml) added. The aqueous layer was separated, extracted with ether (2 x 50 ml) and the combined organic layers dried. T.l.c. and ^{1}H n.m.r. showed mainly the desired product however purification by m.p.l.c. (silica, ether:petrol 40/60, 1:4) gave extensive decomposition to unidentified products as well as 1-formyl-2-vinylcyclohexene as a clear oil (1.38 g, 30%), (Found: m/z, 136.088254. $C_9H_{12}O$ requires m/z, 136.088810); ν_{max} (liquid) 1665 cm^{-1} (C=O); δ_H 1.5-1.9 and 2.15-2.7 (8H, cyclohexyl), 5.55 (2H, m, $=CH_2$), 7.39 (1H, d of d, J 17,11Hz, =C-H), 10.4 (1H, s, CHO). (In subsequent preparations this aldehyde was converted to the tosylhydrazone without prior purification.)

13) <u>1-Formyl-2-vinylcyclohexene tosylhydrazone</u>

p-Toluenesulphonylhydrazide (1.5 g, 8.1 mmol) in ethanol (40 ml) was added to 1-formyl-2-vinylcyclohexene (1.1 g, 8.1 mmol) in ethanol (40 ml) and reaction stirred for 2 h when t.l.c. indicated that the reaction was complete. Solvent removed under reduced pressure and the resulting solid was recrystallised from ethanol to give 1-formyl-2-vinylcyclohexene tosylhydrazone as unstable, light sensitive white crystals (1.61 g, 65%), m.p.111-113°C (Found: C, 63.3; H, 6.4; N, 9.2. $C_{16}H_{20}N_2O_2S$ requires C, 63.1; H, 6.6; N, 9.2); ν_{max} (Nujol) 3170 cm^{-1} (N-H). Spectral data see Appendices 2 and 3.

D. SYNTHESIS OF 1-CARBONYL-2-ALKENYLCYCLOPENTENES AND THEIR TOSYLHYDRAZONES

1) 1-(1-Hydroxyethyl)-2-(*E*-2-phenylethenyl)cyclopentene

A Grignard reagent was prepared by the addition of a solution of 1-bromo-2-(*E*-2-phenylethenyl)cyclopentene (14.0 g, 56.2 mmol) in dry ether (100 ml) to a stirred suspension of magnesium (1.37 g, 56.4 mmol) in refluxing dry ether (75 ml) over 1 h. The reaction was stirred at reflux for a further 1 h before cooling to 0°C and freshly distilled acetaldehyde (5.00 g, 113 mmol) in dry ether (50 ml) added dropwise. The reaction mixture was stirred 5 h at 0°C and 1 h at room temperature, cooled to 0°C before hydrolysis by the dropwise addition of a solution of ammonium chloride (25% w/v, 150 ml). The aqueous layer was separated, extracted with ether (3 x 100 ml) and the combined ether layer washed with water (2 x 50 ml) and dried. The solvent was removed at reduced pressure to give a brown oil which was purified by chromatography (alumina ether:petrol 40/60, 1:2) to give a yellow solid which was recrystallised from petrol 40/60 and ethanol to give 1-(1-hydroxyethyl)-2-(*E*-2-phenylethenyl)cyclopentene as yellow crystals (9.86 g, 82%), m.p.50-52°C (Found: C, 83.9; H, 8.4. $C_{15}H_{18}O$ requires C, 84.1; H, 8.5%); ν_{max} (melt) 3380 cm^{-1} (OH); δ_H 1.33 (3H, d, J 6Hz, Me), 1.70-2.80 (7H, m, cyclopentyl and OH), 5.00 (1H, q, J 6Hz, C*H*-Me), 6.48 (1H, d, J 16Hz, olefinic), 7.06-7.6 (6H, m, phenyl and one olefinic). m/z 214 (46%), 171 (48), 91 (100).

2) 1-Acetyl-2-(*E*-2-phenylethenyl)cyclopentene

Chromium trioxide (24.6 g, 0.246 mol) was added during

15 min with stirring and ice cooling to dry pyridine (200 ml). 1-(1-Hydroxyethyl)-2-(*E*-2-phenethenyl)cyclopentene (7.54 g, 0.035 mol) in dry pyridine (30 ml) was added with cooling, the mixture was stirred 3 h at 0°C, 18 h at room temperature, ether (1000 ml) added and the dark precipitate was filtered off and washed with ether (3 x 200 ml). Water (500 ml) was added to the combined ether layers, the aqueous layer separated and extracted with ether (2 x 200 ml). The combined ether layers were washed with a solution of 1N hydrochloric acid (3 x 300 ml), a solution of sodium bicarbonate (20% w/v, 3 x 250 ml), water (2 x 500 ml) and dried. The ether was evaporated under reduced pressure to give a brown oil, t.l.c. indicated one major product and extensive polymerisation. The product was isolated by chromatography m.p.l.c. (silica, ether:petrol 40/60, 1:3) to give a dark yellow oil which was distilled by Kugelrohr apparatus to give 1-acetyl-2-(*E*-2-phenylethenyl)cyclopentene (1.13 g, 15%), b.p. 190° at 0.6 mmHg (Found: m/z, 212.118566. $C_{15}H_{16}O$ requires m/z, 212.120109); ν_{max} (liquid) 1670 cm^{-1} (C=O); δ_H 1.90 (2H, quintet, J 7Hz, cyclopentyl), 2.25 (3H, s, Me), 2.78 (4H, t, J 7Hz, cyclopentyl), 6.77 (1H, d, J 17Hz, olefinic), 7.1-7.65 (5H, m, phenyl), 7.95 (1H, d, J 17Hz, olefinic).

3) <u>1-Acetyl-2-(*E*-2-phenylethenyl)cyclopentene tosylhydrazone</u>

1-Acetyl-2-(*E*-2-phenylethenyl)cyclopentene (0.72 g, 3.37 mmol) in ethanol (10 ml) was added to *p*-toluenesulphonylhydrazide (0.63 g, 3.37 mmol) in ethanol (20 ml) containing concentrated hydrochloric acid (1 drop) and stirred for 2 h.

The resulting solid was filtered (0.55 g) and chromatography of the mother liquors m.p.l.c. (silica, ether:petrol 40/60, 1:3) gave a further batch of product (0.16 g). Recrystallisation from ethanol gave 1-acetyl-2-(*E*-2-phenethenyl)cyclopentene tosylhydrazone as white needles (0.67 g, 52%), m.p. 142-145°C (Found: C, 69.2; H, 6.6; N, 7.2. $C_{22}H_{24}N_2O_2S$ requires C, 69.4; H, 6.4; N, 7.4%); ν_{max} (Nujol) 3240 cm^{-1} (N-H). Spectral data see Appendices 2 and 3.

4) 1-(*p*-Toluoyl)-2-(*E*-2-phenylethenyl)cyclopentene

A Grignard reagent was prepared by the dropwise addition of a solution of 1-bromo-2-(*E*-2-phenylethenyl)cyclopentene (6.5 g, 26.1 mmol) in dry T.H.F. (50 ml) to a stirred suspension of magnesium (0.63 g, 26.1 mmol) in refluxing ether (100 ml) over 1 h. After refluxing further 1 h, the reaction was cooled to 0°C and freshly distilled *p*-tolualdehyde (4.6 g, 38.0 mmol) in dry T.H.F. (50 ml) added dropwise over 30 min. The reaction mixture was stirred further 3 h at room temperature, cooled to 0°C and hydrolysed by the addition of a solution of ammonium chloride (10% w/v, 100 ml). Ether (200 ml) was added, the aqueous layer separated, extracted with ether (2 x 100 ml) and the combined ether layers washed with water (2 x 100 ml) and dried. The solvent was removed at reduced pressure to give a brown oil which was chromatographed (alumina, ether:petrol 40/60, 1:3) to give:-

(1) 1-(*p*-toluoyl)-2-(*E*-2-phenylethenyl)cyclopentene as a yellow solid which was recrystallised from petrol 40/60 and ethanol to give yellow crystals (2.74 g, 36%) m.p. 56-57°C (Found: C, 87.4; H, 7.1. $C_{21}H_{20}O$ requires C, 87.5; H, 7.0%);

ν_{max} (melt) 1640 cm^{-1} (C=O); δ_H 1.94-2.22 (2H, m, cyclopentyl), 2.43 (3H, s, Me), 2.77-3.12 (4H, m, cyclopentyl), 6.65 and 7.07 (2H, AB, J 16Hz), 7.15-7.40 (7H, m, aromatic), 7.77 (2H,, one half of AB, J 8Hz, tosyl ArH). The 2,4-dinitrophenylhydrazone derivative had m.p. 195-198°C (Found: C, 69.0; H, 5.15; N, 11.8. $C_{27}H_{24}N_4O_4$ requires C, 69.2; H, 5.2; N, 12.0%).

(2) 1-(α-hydroxy-*p*-methylbenzyl)-2-(*E*-2-phenylethenyl)cyclopentene as a yellow solid which recrystallised from pentane and ethanol to give white crystals (3.3 g, 49%), m.p.102-103°C (Found: C, 86.7; H, 7.7. $C_{21}H_{22}O$ requires C, 86.85; H, 7.6%); ν_{max} (melt) 3380 cm^{-1} (O-H); δ_H 1.42-2.0 (2H, m, cyclopentyl), 2.05-2.80 (5H, m, cyclopentyl and OH), 2.28 (3H, s, Me), 5.87 (1H, s, C*H*-OH), 6.51 (1H, one half of AB, J 16Hz, olefinic), 6.93-7.50 (10H, m, aromatic); m/z 290 (16%), 272 (30), 119 (100), 21 (32), 91 (66).

5) <u>1-(*p*-Toluoyl)-2-(*E*-2-phenylethenyl)cyclopentene tosylhydrazone</u>

1-(*p*-Toluoyl)-2-(*E*-2-phenylethenyl)cyclopentene (0.75 g, 2.6 mmol) in ethanol (20 ml) was added to *p*-toluenesulphonylhydrazide (0.48 g, 26 mmol) in ethanol (25 ml) containing concentrated hydrochloric acid (3 drops) and stirred 2 h. The reaction mixture was warmed to 50°C for 1 h and stirred 12 h at room temperature. Most of the solvent was removed at reduced pressure, dichloromethane (100 ml) and water (50 ml) added, the aqueous layer separated and extracted with dichloromethane (2 x 50 ml). The combined organic layer was washed

with water (2 x 50 ml) and dried, the solvent removed at reduced pressure to give a brown solid which was purified by m.p.l.c. (silica, ether:petrol 40/60, 1:3) to give 1-(*p*-toluoyl)-2-(*E*-2-phenylethenyl)cyclopentene tosylhydrazone as a white solid which was recrystallised from petrol and ethanol to yield white crystals (0.84 g, 71%), m.p. 178-180^{o}C (Found: C, 73.6; H, 6.3; N, 5.8. $C_{28}H_{28}N_2O_2S$ requires C, 73.65; H, 6.2; N, 6.1%); ν_{max} (Nujol) 3175 cm^{-1} (N-H). Spectral data see Appendices 2 and 3.

E. SYNTHESIS OF 1-CARBONYL-2-ALKENYLCYCLOHEXENES AND THEIR TOSYLHYDRAZONES

1) 1-(1-Hydroxyethyl)-2-(*E*-2-phenylethenyl)cyclohexene

A Grignard reagent was prepared by the addition of a solution of 1-bromo-2-(*E*-2-phenylethenyl)cyclohexene (5.8 g, 22.2 mmol) in dry T.H.F. (75 ml) to a stirred suspension of magnesium (0.54 g, 22.2 mmol) in refluxing dry T.H.F. (50 ml). The mixture was heated under reflux for 2 h, cooled to 0°C, and freshly distilled acetaldehyde (2.9 g, 66.6 mmol) in dry T.H.F. (50 ml) added dropwise and stirred 3 h at 0°C . The mixture was hydrolysed by the addition of a solution of ammonium chloride (10% w/v, 100 ml), ether (350 ml) added, the aqueous layer separated and extracted with ether (2 x 200 ml), the combined organic layer washed with water (2 x 100 ml) and dried. Removal of solvent at reduced pressure gave a brown oil which was chromatographed (alumina, ether:petrol 40/60, 1:3) to give 1-(1-hydroxyethyl)-2-(*E*-2-phenylethenyl)cyclohexene as a clear oil (3.07 g, 61%), (Found: m/z, 228.151044. $C_{16}H_{20}O$ requires m/z, 228.151407); ν_{max} (liquid) 3380 cm^{-1} (O-H); δ_H 1.23 (3H, d, J 7Hz, Me), 1.46-1.80 and 2.08-2.80 (9H, m, OH and cyclohexyl), 5.11 (1H, q, J 7Hz, C*H*-Me), 6.45 (1H, one half of AB, J 16Hz, olefinic), 7.1-7.48 (6H, m, aromatic and olefinic); m/z 228 (42%), 213 (67), 91 (100).

2) 1-Acetyl-2-(*E*-2-phenylethenyl)cyclohexene

1-(1-Hydroxyethyl)-2-(*E*-2-phenylethenyl)cyclohexene (3.9 g, 17.1 mmol) in dry dichloromethane (50 ml) was added to a stirred suspension of barium manganate (76 g, 0.297 mol) in dry dichloromethane (250 ml). The mixture was heated

under reflux with stirring for 14 days when t.l.c. indicated the reaction had gone to completion. The dark solid was filtered off through magnesium sulphate, washed with dichloromethane and the solvent removed at reduced pressure to give a brown oil which was purified by m.p.l.c. (silica, ether: petrol 40/60, 1:4) to give 1-acetyl-2-(*E*-2-phenylethenyl)-cyclohexene as a yellow solid which was recrystallised from *n*-pentane and ethanol to yield yellow crystals (1.21 g, 31%), m.p. 32-34°C (Found: C, 85.2; H, 7.8. $C_{16}H_{18}O$ requires C, 84.9; H, 8.0%); ν_{max} (melt) 1675 cm^{-1} (C=O); δ_H 1.59-1.89 (4H, m, cyclohexyl), 2.28 (3H, s, Me), 2.17-2.58 (4H, m, cyclohexyl), 6.64 (1H, one half of AB, J 16Hz, olefinic), 7.0-7.47 (6H, m, phenyl and olefinic).

Note: Oxidation using chromium trioxide in pyridine gave the desired product in 11% yield.

3) <u>1-Acetyl-2-(*E*-2-phenylethenyl)cyclohexene tosylhydrazone</u>

1-Acetyl-2-(*E*-2-phenylethenyl)cyclohexene (1.2 g, 5.25 mmol) in ethanol (25 ml) was added to *p*-toluenesulphonylhydrazide (0.98 g, 5.25 mmol) in ethanol (25 ml) containing concentrated hydrochloric acid (1 drop) and stirred 3 h. The resulting solid was filtered (0.68 g) and chromatography of the mother liquors(m.p.l.c., silica, ether:petrol 40/60, 1:3) gave a further batch of product (0.94 g). Recrystallisation from ethanol gave 1-acetyl-2-(*E*-2-phenylethenyl)-cyclohexene tosylhydrazone (1.55 g, 75%), m.p.140-142°C (Found: C, 70.2; H, 6.6; N, 7.3. $C_{23}H_{26}N_2O_2S$ requires C, 70.0; H, 6.6; N, 7.1%); ν_{max} (Nujol) 3180 cm^{-1} (N-H). Spectral data see Appendices 2 and 3.

4) (1) 1-(α-Hydroxy-*p*-methylbenzyl)-2-(*E*-2-phenethenyl)-cyclohexene

A Grignard reagent was prepared by the addition of a solution of 1-bromo-(*E*-2-phenylethenyl)cyclohexene (5.0 g, 19 mmol) in dry T.H.F. (60 ml) to a stirred suspension of magnesium (0.46 g, 19 mmol) in refluxing dry T.H.F. (50 ml), which was heated under reflux for a further 2 h. The mixture was cooled to 0°C and *p*-tolualdehyde (6.8 g, 57 mmol) in dry T.H.F. (50 ml) added dropwise, stirred 1 h, heated under reflux 30 min, cooled to 0°C and the mixture hydrolysed by the addition of a solution of ammonium chloride (10% w/v, 100 ml). Ether (300 ml) was added, the aqueous layer separated and extracted with ether (2 x 200 ml) and the combined organic phase washed with water (3 x 100 ml) and dried. Removal of solvent under reduced pressure gave a brown oil which was purified by chromatography (alumina, ether:petrol 40/60, 1:2) to give 1-(α-hydroxy-*p*-methylbenzyl)-2-(*E*-2-phenylethenyl)cyclohexene as a clear oil (3.75 g, 65%), (Found: m/z, 304.182263. $C_{22}H_{24}O$ requires m/z, 304.182706); ν_{max} (liquid) 3300 cm^{-1} (O-H); δ_H 1.37-1.78 (4H, m, cyclohexyl), 2.25 (3H, s, Me), 2.0-2.59 (5H, m, cyclohexyl and OH), 6.08 (1H, s, C*H*-OH), 6.58 (1H, one half of AB, J 16Hz, olefinic), 6.90-7.59 (11H, m, aromatic and olefinic); m/z 304 (29%), 213 (71), 119 (100), 105 (36), 91 (52).

(2) 1-(*p*-Toluoyl)-2-(*E*-2-phenylethenyl)cyclohexene

The Grignard reagent of 1-bromo-(*E*-2-phenylethenyl)-cyclohexene was prepared and reacted with 1 equivalent of *p*-tolualdehyde as above except that dry acetone (4.8 equivalents) was added and stirred 2 h at room temperature, then heated

under reflux for 1 h; before cooling to 0°C and hydrolysis and work up as above, to give a brown oil. Chromatography of this oil m.p.l.c. (silica, ether:petrol 40/60, 1:4) gave (1) 1-(*p*-toluoyl)-2-(*E*-2-phenylethenyl)cyclohexene (22%), spectral and physical characteristics identical to product obtained from the oxidation of 1-(α-hydroxy-*p*-methylbenzyl)-2-(*E*-2-phenylethenyl)cyclohexene, see Section 1E5.
(2) 1-(α-hydroxy-*p*-methylbenzyl)-2-(*E*-2-phenylethenyl)-cyclohexene (42%).

5) 1-(*p*-Toluoyl)-2-(*E*-2-phenylethenyl)cyclohexene

Chromium trioxide (2.38 g, 23.8 mmol) was added during 10 min with stirring and ice cooling to dry pyridine (50 ml). 1-(α-Hydroxy-*p*-methylbenzyl)-2-(*E*-2-phenylethenyl)cyclohexene (1.81 g, 5.95 mmol) in dry pyridine (30 ml) was added with cooling and the mixture stirred 3 h at room temperature. Ether (120 ml) was added and the dark precipitate filtered off and washed with ether (3 x 50 ml). Water (120 ml) was added to the combined ether layers, the aqueous layer was separated and extracted with ether (2 x 100 ml). The combined ether layers were washed with 1N hydrochloric acid (2 x 100 ml), a solution of sodium bicarbonate (20% w/v, 3 x 100 ml), water (2 x 200 ml) and dried. Removal of solvent at reduced pressure gave a yellow oil which was purified by chromatography m.p.l.c. (silica, ether:petrol 40/60, 1:4) to give a white solid which was recrystallised from pentene and ethanol to give 1-(*p*-toluoyl)-2-(*E*-2-phenylethenyl)cyclohexene as white crystals (0.57 g, 32%), m.p. 110-111°C (Found: C, 87.2; H, 7.4. $C_{22}H_{22}O$ requires C, 87.4; H, 7.3%); ν_{max} (Nujol)

1650 cm^{-1} (C=O); δ_H 1.62-2.0 and 2.21-2.61 (8H, m, cyclohexyl), 2.38 (3H, s, Me), 6.52 and 6.72 (2H, AB, J 16Hz, olefinic), 7.0-7.34 (7H, m, aromatic), 7.82 (2H, one half of AB, J 9Hz, tosyl ArH).

6) 1-(*p*-Toluoyl)-2-(*E*-2-phenylethenyl)cyclohexene tosylhydrazone (attempted)

1-(*p*-Toluoyl)-2-(*E*-2-phenylethenyl)cyclohexene (0.14 g, 4.6 mmol) in ethanol (20 ml) was added to *p*-toluenesulphonylhydrazide (0.86 g, 4.6 mmol) in ethanol (20 ml) containing concentrated hydrochloric acid (3 drops) and was stirred overnight at room temperature, t.l.c. and ^1H n.m.r. showed only starting material present.

1-(*p*-Toluoyl-2-(*E*-2-phenylethenyl)cyclohexene (0.69 g, 2.29 mmol) in ethanol (20 ml) was added to *p*-toluenesulphonylhydrazide (1.07 g, 5.76 mmol) in ethanol (20 ml) containing *p*-toluenesulphonic acid (50 mg). The mixture was stirred for 120 h at 50°C, t.l.c. indicated no ketone remained and only polymer present and no desired product could be isolated.

F. SYNTHESIS OF ACYCLIC α,β:γ,δ-UNSATURATED ALDEHYDES AND THEIR TOSYLHYDRAZONES

1) *Z*-3-Bromo-2-phenyl-2-butenal and *E*-3-bromo-2-phenyl-2-butenal

These two isomers were prepared by a modification of the method of Arnold *et al.*[205] Phosphorus tribromide (50.7 g, 0.186 mol) was added over 30 min with stirring and ice cooling to a solution of dimethylformamide (16.4 g, 0.220 mol) in dry chloroform (60 ml). After 30 min a white precipitate formed and benzyl methyl ketone (10.0 g, 0.075 mol) in dry chloroform (30 ml) added dropwise and stirred for 24 h at room temperature. The solvent was removed under reduced pressure, cooled in ice, and ice (2000 g) added. To the mixture was added, with cooling, solid sodium bicarbonate until neutral. The mixture was extracted with ether (3 x 500 ml), washed with saturated sodium bicarbonate solution (2 x 250 ml), water (250 ml) and dried. Removal of solvent at reduced pressure yielded a viscous black oil which was subject to gravity chromatography (silica, ether:petrol 40/60, 1:2) which gave yellow oil which was further purified by chromatography, m.p.l.c. (silica, ether:petrol 40/60, 1:4) to give: (a) *Z*-3-bromo-2-phenyl-2-butenal as a yellow oil (4.72 g, 28%), (Found: m/z, 223.983310. $C_{10}H_9{}^{79}BrO$ requires m/z, 223.983726); ν_{max} (liquid) 1675 cm^{-1} (C=O) and 1605 cm^{-1} (C=C); δ_H 2.43 (3H, s, Me), 6.98-7.47 (5H, m, phenyl), 10.25 (1H, s, CHO); m/z 226 (21%), 224 (21), 145 (12), 117 (100), 115 (96). The 2,4-dinitrophenylhydrazone derivative had m.p. 153-155°C (Found: C, 47.2; H, 3.2; N, 13.6. $C_{16}H_{13}BrN_4O_4$

requires C, 47.4; H, 3.2; N, 13.8%).

(2) *E*-3-bromo-2-phenyl-2-butenal as a yellow oil (3.36 g, 20%), (Found: m/z, 223.982653. $C_{10}H_9{}^{79}BrO$ requires m/z, 223.983726); ν_{max} (liquid) 1670 cm^{-1} (C=O) and 1615 cm^{-1} (C=C); δ_H 2.93 (3H, s, Me), 7.07-7.48 (5H, m, phenyl), 10.06 (1H, s, CHO); m/z 226 (32%), 224 (32), 145 (23), 144 (20), 117 (100), 115 (73). The 2,4-dinitrophenylhydrazone derivative had m.p.147-149°C (Found: C, 47.2; H, 3.3; N, 13.9. $C_{16}H_{13}BrN_4O_4$ requires C, 47.4; H, 3.2; N, 13.8%).

2) *E,E*-4-Bromo-1,3-diphenylpenta-1,3-diene

To a stirred suspension of benzyltriphenylphosphonium bromide (8.42 g, 19.5 mmol) in dry ether (200 ml) at 0°C was added *n*-butyllithium (1.2M in hexane, 16.2 ml, 19.5 mmol) and stirred for 1 h. at room temperature to generate the ylide. The mixture was cooled to 0°C and Z-3-bromo-2-phenyl-2-butenal (4.38 g, 19.5 mmol) in dry ether (25 ml) added dropwise, stirred 1 h at room temperature, heated under reflux 1 h, cooled to 0°C and hydrolysed by the dropwise addition of a solution of ammonium chloride (10% w/v, 100 ml). The aqueous layer was separated, extracted with ether (2 x 100 ml) and the combined organic phase washed with water (2 x 100 ml) and dried. Removal of solvent under reduced pressure gave a yellow oil which was purified by chromatography, (alumina, petrol 40/60) to give a clear oil which solidified on standing. Recrystallisation from *n*-pentane gave *E,E*-4-bromo-1,3-diphenyl-penta-1,3-diene as white crystals (4.89 g, 84%), m.p. 51-54°C (Found: C, 68.1; H, 5.3. $C_{17}H_{15}Br$ requires C, 68.2; H, 5.05%); δ_H 2.20 (3H, s, Me), 5.97 and 7.55 (2H, AB, olefinic),

7.0-7.45 (10H, m, phenyls); m/z 300 (79%), 298 (79), 219 (100), 204 (94), 141 (26), 115 (40).

3) *E,E*-3,5-Diphenyl-2-methylpenta-2,4-dienal

n-Butyllithium (1.5M in hexane, 8.3 ml, 12.5 mmol) was added under dry nitrogen, to a solution of *E,E*-4-bromo-1,3-diphenylpenta-1,3-diene (3.4 g, 11.4 mmol) in dry T.H.F. (100 ml) at -110°C. The mixture was allowed to warm to -80°C over 10 min and stirred 40 min, dry dimethylformamide (3.7 g, 50.0 mmol) in dry T.H.F. (10 ml) was added and the mixture stirred for 5 h at -80°C. The reaction was hydrolysed by the addition of a solution of ammonium chloride (10% w/v, 100 ml), ether (250 ml) added, the aqueous phase separated and extracted with ether (2 x 200 ml) and dried. The solvent was removed at reduced pressure to give a brown oil which was purified by chromatography, m.p.l.c. (silica, ether:petrol 40/60, 1:4) to yield *E,E*-3,5-diphenyl-2-methylpenta-2,4-dienal as a yellow solid which was recrystallised from pentane and ethanol to yield yellow crystals (3.9 g, 81%), m.p. 116-119°C (Found: C, 86.8; H, 6.5. $C_{18}H_{16}O$ requires C, 87.1; H, 6.5%); ν_{max} (Nujol) 1645 cm^{-1} (C=O); δ_H 1.70 (3H, s, Me), 6.32 and 7.92 (2H, AB, J 16Hz, olefinic), 7.1-7.6 (10H, m, phenyls), 10.57 (1H, s, CHO).

4) *E,E*-3,5-Diphenyl-2-methylpenta-2,4-dienal tosylhydrazone

E,E-3,5-Diphenyl-2-methylpenta-2,4-dienal (6.9 g, 27.8 mmol) in ethanol (50 ml) was added to *p*-toluenesulphonylhydrazide (5.18g, 27.8 mmol) in ethanol (50 ml) containing concentrated hydrochloric acid (1 drop) and stirred 3 h. The resulting solid was filtered and recrystallised from ethanol to give

E,E-3,5-diphenyl-2-methylpenta-2,4-dienal tosylhydrazone as pale yellow crystals (9.17 g, 79%), m.p.130-131°C (Found: C, 72.3; H, 5.9; N, 6.6. $C_{25}H_{24}N_2O_2S$ requires C, 72.1; H, 5.8; N, 6.7%); ν_{max} (Nujol) 3190 cm^{-1} (N-H). Spectral data see Appendices 2 and 3.

5) *E,E*-2-Bromo-3,5-diphenylhexa-2,4-diene

To a stirred suspension of α-methylbenzyltriphenylphosphonium bromide (17.5 g, 39.1 mmol) in dry ether (500 ml) at 0°C was added *n*-butyllithium (1.5M in hexane, 26.1 ml, 39.1 mmol). The mixture was stirred 1 h at room temperature, cooled to 0°C and *Z*-3-bromo-2-phenyl-2-butenal (8.00 g, 35.5 mmol) in dry ether (50 ml) added dropwise. The resulting mixture was stirred 2 h at room temperature and heated under reflux for 1 h, before cooling to 0°C prior to hydrolysis by the addition of water (200 ml). The aqueous layer was separated, extracted with ether (2 x 200 ml), the combined organic layers were washed with water and dried. Evaporation of the solvent under reduced pressure gave a yellow oil which was purified by chromatography (alumina, petrol 40/60) to give a clear oil which solidified on standing. Recrystallisation from pentane and ethanol gave *E,E*-2-bromo-3,5-diphenylhexa-2,4-diene as white crystals (9.95 g, 89%), m.p. 58.5-59.5°C (Found: C, 69.2; H, 5.3. $C_{18}H_{17}Br$ requires C, 69.0; H, 5.5%); δ_H 1.69 (3H, d, J 2Hz, H⟍═⟋*Me*), 2.37 (3H, d, J 1Hz, Ph⟍═⟋*Me*), 6.67 (1H, m, olefinic), 7.11-7.57 (10H, m, phenyls); m/z 314 (32%), 312 (32), 233 (100), 218 (98), 115 (45), 91 (68).

6) *E,E*-3,5-Diphenyl-2-methylhexa-2,4-dienal

n-Butyllithium (1.5M in hexane, 10.2 ml, 15.4 mmol) was added under dry nitrogen to a solution of *E,E*-2-bromo-3,5-diphenylhexa-2,4-diene (4.37 g, 14.0 mmol) in dry T.H.F. (100 ml) at -110°C, stirred for 30 seconds and dry dimethylformamide (6.11 g, 84.0 mmol) in dry T.H.F. (20 ml) added. The mixture was stirred for 4 h at -110°C and the reaction hydrolysed by the addition of a solution of ammonium chloride (10% w/v, 100 ml), warmed to room temperature and ether (250 ml) added. The aqueous layer was extracted with ether (2 x 200 ml) and the combined organic layer dried. The solvent was removed under reduced pressure to give a brown oil which was purified by chromatography, m.p.l.c. (silica, ether:petrol 40/60, 1:4) to yield *E,E*-3,5-diphenyl-2-methylhexa-2,4-dienal as a yellow oil (2.75 g, 75%), (Found: m/z, 262.135403. $C_{19}H_{18}O$ requires m/z, 262.135758); ν_{max} (liquid) 1670 cm^{-1} (C=O); δ_H 1.92 (3H, d, J 2Hz, Me), 2.03 (3H, d, J 1Hz, Me), 6.58 (1H, m, olefinic), 7.09-7.59 (10H, m, phenyls), 9.95 (1H, s, CHO). The 2,4-dinitrophenylhydrazone derivative had m.p. 172-173°C (Found: C, 67.9; H, 5.10; N, 12.7. $C_{25}H_{22}N_4O_4$ requires C, 67.9; H, 5.0; N, 12.7%).

7) *E,E*-3,5-Diphenyl-2-methylhexa-2,4-dienal tosylhydrazone

E,E-3,5-Diphenyl-2-methylhexa-2,4-dienal (4.39 g, 16.8 mmol) in ethanol (40 ml) was added to *p*-toluenesulphonylhydrazide (3.12 g, 16.8 mmol) in ethanol containing concentrated hydrochloric acid (1 drop) and stirred 1 h. The resulting white solid was filtered off and recrystallised from ethanol

to yield *E,E*-3,5-diphenyl-2-methylhexa-2,4-dienal tosylhydrazone as white crystals (5.53 g, 77%), m.p. 160-162°C (Found: C, 72.3; H, 6.0; N, 6.8. $C_{26}H_{26}N_2O_2S$ requires C, 72.5; H, 6.1; N, 6.5%); ν_{max} (Nujol) 3180 cm^{-1} (N-H). Spectral data see Appendices 2 and 3.

8) *E,Z*-4-Bromo-1,3-diphenylpenta-1,3-diene

To a stirred suspension of benzyltriphenylphosphonium bromide (18.0 g, 41.5 mmol) in dry ether (500 ml) at 0°C was added *n*-butyllithium (1.5M in hexane, 27.6 ml, 41.5 mmol) and stirred 1 h at room temperature. The mixture was cooled to 0°C and *E*-3-bromo-2-phenyl-2-butenal (8.48 g, 37.7 mmol) in dry ether (50 ml) added dropwise, stirred 3 h at room temperature and heated under reflux for 30 min, cooled to 0°C and hydrolysed by the dropwise addition of a solution of ammonium chloride (10% w/v, 200 ml). The aqueous layer was separated and extracted with ether (2 x 100 ml) and the combined ether layer washed with water (2 x 200 ml) and dried. Removal of solvent under reduced pressure gave a yellow oil which was purified by chromatography (alumina, petrol 40/60) to give *E,Z* and *Z,Z*-4-bromo-1,3-diphenylpenta-1,3-diene as a mixture of isomers (*E,Z*:*Z,Z*; 3:1) as a clear oil (10.3 g, 91%), (Found: m/z, 298.034470. $C_{17}H_{15}{}^{79}Br$ requires m/z, 298.035760); δ_H 2.12 (3H, s, *Z,Z* Me), 2.63 (3H, s, *E,Z* Me), 6.05 and 6.46 (2H, AB, J 12Hz, *Z,Z* olefinic), 6.01 (1H, one half of AB, J 16Hz, *E,Z* olefinic), 7.07-7.60 (21H, m, phenyls and *E,Z* olefinic); m/z 300 (59%), 298 (59), 219 (100), 204 (68), 141 (18), 115 (27), 91 (25).

9) Z,E-3,5-Diphenyl-2-methylpenta-2,4-dienal

n-Butyllithium (1.5M in hexane, 13.6 ml, 20.4 mmol) was added under dry nitrogen to a solution of *E,Z* and Z,Z-4-bromo-1,3-diphenylpenta-1,3-diene (*E,Z:Z,Z*, 3:1) (6.11 g, 20.4 mmol) in dry T.H.F. (150 ml) at -110°C. The mixture was allowed to warm to -78°C over 10 min and dry dimethylformamide (4.47 g, 61.3 mmol) in dry T.H.F. (20 ml) added and stirred 5 h.

The reaction was hydrolysed by the addition of a solution of ammonium chloride (10% w/v, 200 ml), allowed to warm to room temperature and ether (400 ml) added. The aqueous phase was separated, extracted with ether (2 x 300 ml), the combined ether layer washed with water (2 x 100 ml) and dried. Removal of solvent at reduced pressure gave a brown oil which was purified by chromatography, m.p.l.c. (silica, ether:petrol 40/60, 1:4) to give Z,E-3,5-diphenyl-2-methylpenta-2,4-dienal as a yellow solid which was recrystallised from pentane and ethanol to give yellow crystals (2.71 g, 53%), m.p. 62-63°C (Found: C, 86.85; H, 6.30. $C_{18}H_{16}O$ requires C, 87.1; H, 6.5%); ν_{max} (melt) 1660 cm^{-1} (C=O); δ_H 2.11 (3H, s, Me), 6.42 and 7.58 (2H, AB, J16Hz, olefinic), 7.0-7.48 (10H, m, phenyls), 9.38 (1H, s, CHO).

10) Z,E-3,5-Diphenyl-2-methylpenta-2,4-dienal tosylhydrazone

Z,E-3,5-Diphenyl-2-methylpenta-2,4-dienal (2.10 g, 8.47 mmol) in ethanol (25 ml) was added to *p*-toluenesulphonylhydrazide (1.57 g, 8.47 mmol) in ethanol (25 ml) containing concentrated hydrochloric acid (1 drop) and stirred 3 h. The resulting solid was filtered and recrystallised from ethanol

to give *Z,E*-3,5-diphenyl-2-methylpenta-2,4-dienal tosylhydrazone as white crystals (2.42 g, 69%), m.p. 162-163°C (Found: C, 72.3; H, 5.80; N, 6.9. $C_{25}H_{24}N_2O_2S$ requires C, 72.1; H, 5.8; N, 6.7%); ν_{max} (Nujol) 3140 cm^{-1} (N-H). Spectral data see Appendices 2 and 3.

11) Pent-3-en-2-one*

This was prepared by the method of Wilds and Djerassi[206] from the aldol reaction of acetaldehyde, acetone and sodium hydroxide (18%), b.p. 120-124°C at 760 mmHg (lit.,[206] 121-122.5°C at 760 mmHg).

12) Ethyl 3-hydroxy-3-methylhexa-4-enoate*

This was prepared in 71% yield using the method of Cologne and Varagnat,[208] by the Reformatsky reaction of ethyl bromoacetate, zinc and pent-3-en-2-one. The hydroxyester was distilled from the crude material as a colourless oil, b.p. 87-90°C at 10 mmHg (lit.,[208] 93°C at 15 mmHg); ν_{max} (film) 3500 cm^{-1} (O-H), 1620 cm^{-1} (C=O); δ_H 1.28 (3H, t, J 7Hz, ethyl Me), 1.3 (3H, s, 3-Me), 1.69 (3H, d, J 6Hz, =CH*Me*), 2.57 (2H, s, CH_2), 3.44 (1H, br s, OH), 4.22 (2H, q, J 7Hz, ethyl CH_2), 5.67 (2H, m, olefinic).

13) Ethyl 3-methylhexa-2,4-dienoate*

This was obtained by slow distillation from ethyl 3-hydroxy-3-methylhexa-4-enoate with anhydrous copper sulphate according to the method of Cologne and Varagnat.[208] The ester was redistilled, after drying, as a colourless liquid (73%), b.p. 83-85°C at 14 mmHg (lit.,[208] 85°C at 15 mmHg); ν_{max} (film) 1610 cm^{-1} (C=O).

14) 3-Methylhexa-2,4-dienoic acid*

This was prepared using Burton and Ingold's method[209] by stirring ethyl 3-methylhexa-2,4-dienoate with 10% methanolic potassium hydroxide solution. This gave the acid as a white solid (84%) which was recrystallized from ethanol, m.p. 118-120°C (lit.,[209] 120°C); ν_{max} (Nujol) 2700 cm^{-1} (acidic OH), 1680 cm^{-1} (C=O); δ_H (3H, d, J 5Hz, =CH*Me*), 2.27 (3H, s, 3-Me), 5.71 (1H, br s, 2-H), 6.19 (2H, m, 4-H and 5-H), 10.91 (1H, br s, acid H).

15) 3-Methylhexa-2,4-dienoic acid chloride*

This was prepared according to Burton and Ingold's method[209] by the addition of thionyl chloride to 3-methylhexa-2,4-dienoic acid in benzene. The acid chloride was distilled as a pale yellow liquid in 77% yield, b.p. 100°C at 20 mmHg (lit.,[209] 94-95°C at 15 mmHg); ν_{max} (film) 1750 cm^{-1} (C=O).

16) 2,5-Dimethylocta-4,6-dien-3-one*

This was prepared using the adapted Heilbron method.[210] A Grignard reagent was prepared from isopropyl bromide (17.1 g, 0.139 mol) and magnesium (3.38 g, 0.139 mol) in dry ether (80 ml). This was cooled to 0°C and anhydrous cadmium chloride (12.7 g, 0.070 mol) added in one batch, under nitrogen. After rapid mechanical stirring for 30 min, 3-methylhexa-2,4-dienoic acid chloride (8.0 g, 0.056 mol) in ether (30 ml) was added dropwise. The mixture was heated under reflux for 2 h, cooled to 0°C and carefully hydrolysed with ammonium chloride solution (10%, 120 ml). The reaction mixture was then extracted with ether (3 x 50 ml), the organic phase dried,

and the solvent was evaporated under reduced pressure to give a yellow oil. Short-path distillation from this gave 2,5-dimethylocta-4,6-dien-3-one as a yellow oil (2.88 g, 33%), b.p. 95-100°C at 10 mmHg (Found: m/z, 152.119333. $C_{10}H_{16}O$ requires m/z, 152.120109); ν_{max} (film) 1680 cm^{-1} (C=O); δ_H 1.08 (6H, d, J 7Hz, isopropyl Me), 1.84 (3H, d, J 5Hz, 8-Me), 1.98 and 2.22 (3H, d, J 1.5Hz, 5-Me), 2.62 (1H, heptet, J 7Hz, 2-H), 7.57 (1H, d, J 16Hz) and 5.9-6.35 (2H, m, olefinic) *E,E* to *Z,E* ratio *ca.*2:1. The 2,4-dinitrophenylhydrazone derivative had m.p. 137-138°C (Found: C, 57.6; H, 6.0; N, 16.8. $C_{16}H_{20}N_4O_4$ requires C, 57.8; H, 6.1; N, 16.9%).

17) *E,E*-2,5-Dimethylocta-4,6-dien-3-one tosylhydrazone*

The ketone (2.50 g, 16.4 mmol) was stirred in ethanol (50 ml) with *p*-toluenesulphonylhydrazide (3.05 g, 16.4 mmol) and concentrated hydrochloric acid (1 ml) for 12 h. The reaction mixture was neutralised with sodium bicarbonate and the solvent removed under reduced pressure to give a brown oil. This was then separated by medium pressure chromatography (silica, ether:petrol 40/60, 1:4) to give (1) 3,4-hydro-3,5-dimethyl-7-isopropyl-2-tosyl-1,2-diazepine (1.42 g, 27%) which was recrystallised from ethanol m.p. 86-87°C (Found: C, 63.8; H, 7.6; N, 9.0. $C_{17}H_{24}N_2O_2S$ requires C, 63.7; H, 7.6; N, 8.7%); δ_H 0.48 (3H, d, J 8Hz, 3-Me), 1.04 (3H, d, J 7Hz, isopropyl Me), 1.11 (3H, d, J 7Hz, isopropyl Me), 1.88 (3H, br s, 5-Me), 2.18 and 2.98 (2H, AB, J 18Hz, 4-H_2), 2.4 (3H, s, tosyl Me), 2.53 (1H, heptet, J 7Hz, isopropyl CH), 4.7 (1H, quintet of d, J 6Hz, J' 2Hz,

---

* Made in collaboration with Mr.C.B. Argo

3-H) 5.7 (1H, br s, 6-H), 7.24 (4H, 7.86, AB, J 8Hz, aromatic); m/z 320 (16%), 165 (100), 123 (66), 91 (40).

(2) *E,E*-2,5-Dimethylocta-4,6-dien-3-one tosylhydrazone (0.57 g, 11%) which was recrystallized from ethanol m.p. 130-131°C (Found: C, 63.4; H, 7.4; N, 8.7. $C_{17}H_{24}N_2O_2S$ requires C, 63.7; H, 7.6; N, 8.7%). Spectral data see Appendices 2 and 3.

18) 4-Methyl-6-phenylhexa-3,5-dien-2-one tosylhydrazone

Sample kindly supplied by Dr. J.T. Sharp and was synthesised by the method of Sharp *et al.*[211] as a mixture of *E,E* and *Z,E* isomers (ratio 3:2 by ^{1}H n.m.r.).

2. (A) THERMAL DECOMPOSITION OF THE SODIUM SALTS OF THE TOSYLHYDRAZONES

The sodium salts were prepared by the addition of the solid tosylhydrazone (*ca.* 5% molar excess) to a solution of sodium ethoxide in super-dry ethanol. The solution was then stirred in the dark for 0.5 h. In some cases, the sodium salt precipitated out at this stage. The ethanol was evaporated under anhydrous conditions, and with a temperature below 45°C. The sodium salt was then dried under high vacuum over phosphorus pentoxide for at least 12 h in the dark.

Freshly distilled dry solvent was added and the reaction mixture boiled under reflux, with stirring, under dry nitrogen in the dark. During the decomposition, small samples of the reaction mixture were withdrawn and shaken with water to hydrolyse any residual sodium salt, and extracted with ether. The ether layer was analysed for unreacted tosylhydrazone by t.l.c., and the reaction continued until no tosylhydrazone remained. After cooling, the by-product of sodium toluene-4-sulphinate could be removed either by

a) filtration of the reaction mixture through Celite, evaporation of the solvent giving the products;

b) pouring the reaction mixture into water, extracting with ether, drying and evaporating the ether extracts to give the products.

1) 1-Formyl-2-(*E*-2-propenyl)cyclopentene tosylhydrazone

The sodium salt was prepared from sodium (21 mg, 0.956 mmol) in super-dry ethanol (20 ml) and the tosylhydrazone

(0.31 g, 1.02 mmol). After the usual drying procedure, dry cyclohexane (50 ml) was added and the mixture heated under reflux for 1 h and the precipitate of sodium toluene-4-sulphinate was removed by filtration. The solvent was removed under reduced pressure to give a brown oil which was chromatographed (alumina, ether:petrol 40/60, 1:4) in the absence of light to give 4-methyl-1*H*-6,7,8-trihydrocyclopenta[d][1,2]diazepine as a yellow oil (98 mg, 65%), b.p. 80°C at 0.3 mmHg (Found: C, 72.9; H, 8.3; N, 18.8. $C_9H_{12}N_2$ requires C, 72.9; H, 8.2, N, 18.90%). ^{1}H N.m.r., ^{13}C n.m.r. and mass spectra: see Appendix 4.

2) 1-Formyl-2-(*E*-2-phenylethenyl)cyclopentene tosylhydrazone

The sodium salt was prepared from sodium (21 mg, 0.91 mmol) in super-dry ethanol (20 ml) and the tosylhydrazone (0.34 g, 0.93 mmol). After the usual drying procedure, dry cyclohexane (50 ml) was added and the mixture heated under reflux for 1 h. The white precipitate formed was filtered and the yellow filtrate was evaporated under reduced pressure to give a brown oil which was chromatographed (alumina, ether:petrol 40/60, 1:4) in the absence of light to give 4-phenyl-1*H*-6,7,8-trihydrocyclopenta[d][1,2]diazepine as a brown oil (123 mg, 63%), (Found: m/z, 210.116074. $C_{14}H_{14}N_2$ requires m/z, 210.115693). ^{1}H N.m.r., ^{13}C n.m.r. and mass spectra: see Appendix 4.

3) 1-Formyl-2-(*E*-2-phenylethenyl)cyclohexene tosylhydrazone

The sodium salt was prepared from sodium (0.060 g, 2.63 mmol) in super-dry ethanol (30 ml) and the tosylhydrazone

(1.05 g, 2.76 mmol). After the usual drying procedure, dry cyclohexane (100 ml) was added and the mixture heated under reflux for 1 h. The white precipitate formed was filtered and the yellow filtrate was evaporated to give 4-phenyl-1*H*-6,7,8,9-tetrahydrocyclohexa[d][1,2]diazepine as a yellow solid which was recrystallised from pentane and ethanol (0.57 g, 92%), m.p. 111-113°C (Found: C, 80.1; H, 7.30; N, 12.4. $C_{15}H_{16}N_2$ requires C, 80.3, H, 7.2; N, 12.5%). ^1H N.m.r., ^{13}C n.m.r. and mass spectra: see Appendix 4.

4) 1-Formyl-2-(*E*-2-phenylpropenyl)cyclohexene tosylhydrazone

The sodium salt was prepared from sodium (0.191 g, 8.31 mmol) in super-dry ethanol (30 ml) and the tosylhydrazone (3.37 g, 8.56 mmol). After usual drying procedure dry cyclohexane (120 ml) was added and the mixture heated under reflux. Initially the solution turned deep red and the rate disappearance of the diazoalkene intermediate was monitored by I.R. (2060 cm^{-1}) until after 2 h no diazoalkene remained. The white solid was removed by filtration and the yellow filtrate evaporated under reduced pressure to give a viscous black oil shown by t.l.c. to contain two major components, many minor products and polymeric material. Chromatography (alumina, ether:petrol 40/60, 1:4) in the absence of light yielded (1) 1-(*E*-2-phenylpropenyl)-4,5,6,7-tetrahydroindazole as a pale yellow oil (191 mg, 9.4%) (Found: m/z, 238.145712. $C_{16}H_{18}N_2$ requires m/z, 238.146991). δ_H 1.25-1.90 (4H, m, cyclohexyl), 2.34 (3H, d, J 1.5Hz) 2.45-2.65 (4H, m, cyclohexyl), 6.84 (1H, q, J 1.5Hz, olefinic) 7.20-7.54 (6H, m, aromatic); δ_C (25.2MHz), 16.55 (Me),

20.50, 21.64, 22.64, 22.94 (C-4, C-5, C-6, C-7), 116.17 (quat), 121.67, 126.19, 127.46, 128.35, 131.99 (quat), 138.08 (C-3), 141.48 (quat); m/z 238 (65%), 237 (30), 136 (25), 135 (100).

This product was identical by t.l.c., ^{1}H n.m.r. and ^{13}C n.m.r. to the product obtained from thermolysis of 7a-(*E*-2-phenylpropenyl)-4,5,6,7-tetrahydroindazole (see Appendix 5b).

(2) 7a-(*E*-2-phenylpropenyl)-4,5,6,7-tetrahydroindazole as a clear oil which solidified and was recrystallised from pentane and dichloromethane as white crystals (0.865 g, 42%), m.p.71-72°C (Found: C, 80.9; H, 7.4; N, 11.7. $C_{16}H_{18}N_2$ requires C, 80.6; H, 7.6; N, 11.75%). ^{1}H N.m.r., ^{13}C n.m.r. and mass spectra: see Appendix 5a.

5) <u>1-Formyl-2-(2-methylpropenyl)cyclohexene tosylhydrazone</u>

The sodium salt was prepared from sodium (62.4 mg, 2.72 mmol) and the tosylhydrazone (0.92 g, 2.77 mmol) in super-dry ethanol (30 ml). After drying in the usual manner, dry cyclohexane (100 ml) was added and heated under reflux for 2 h, the resulting solid was filtered through Celite and the solvent removed under reduced pressure to give a dark brown oil shown by t.l.c. (silica, ether:petrol 40/60, 1:4) to be multi-component. This oil was subjected to flash chromatography (silica, ether:petrol 40/60, 1:4) giving only one identifiable component: 7a-(2-methylpropenyl)-4,5,6,7-tetrahydroindazole as a yellow oil (54 mg, 11%), (Found: m/z, 176.131342. $C_{11}H_{16}N_2$ requires m/z, 176.130457). ^{1}H N.m.r., ^{13}C n.m.r. and mass spectra: see Appendix 5a.

6) 1-Formyl-2-vinylcyclohexene tosylhydrazone

The sodium salt was prepared from sodium (31 mg, 1.35 mmol) in super-dry ethanol (20 ml) and the tosylhydrazone (0.41 g, 1.37 mmol). After the usual drying procedure, dry cyclohexane (100 ml) was added and the mixture heated under reflux for 3 h. Initially a red colour developed, fading slowly to leave a yellow solution and a white precipitate which was removed by filtration. The yellow filtrate was evaporated under reduced pressure to give a brown oil shown by t.l.c. to contain only one component and polymer. Flash chromatography (silica, ether:petrol 40/60, 1:1) gave 1*H*-2,6,7,8-tetrahydrocyclohexa[d][1,3]diazepine as a light sensitive, unstable, clear oil (148 mg, 71%), (Found: m/z, 148.098684. $C_9H_{12}N_2$ requires m/z, 148.100043). ^1H N.m.r., ^{13}C n.m.r. and mass spectra: see Appendix 4.

7) 1-Acetyl-2-(*E*-2-phenylethenyl)cyclopentene tosylhydrazone

The sodium salt was prepared from sodium (31 mg, 1.37 mmol) in super-dry ethanol (20 ml) and the tosylhydrazone (0.53 g, 1.40 mmol). After the usual drying procedure, dry cyclohexane (100 ml) was added and the mixture heated under reflux for 1.5 h. The white precipitate was filtered and the yellow filtrate was evaporated under reduced pressure to give a brown oil which was purified by preparative t.l.c. (alumina, ether:petrol 40/60, 1:9) to give 1-methyl-4-phenyl-1*H*-6,7,8-trihydrocyclopenta[d][1,2]diazepine as a yellow oil (0.23 g, 76%), (Found: m/z, 224.130249. $C_{15}H_{16}N_2$ requires m/z, 224.131342). ^1H n.m.r., ^{13}C n.m.r. and mass spectra: see Appendix 4.

8) 1-(*p*-Toluoyl)-2-(*E*-2-phenylethenyl)cyclopentene tosylhydrazone

The sodium salt was prepared from sodium (24 mg, 1.05 mmol) in super-dry ethanol (20 ml) and the tosylhydrazone (0.50 g, 1.08 mmol). After the usual drying procedure, dry cyclohexane (100 ml) was added and the mixture heated under reflux for 1 h. The resulting solid was removed by filtration and removal of solvent under reduced pressure gave a brown oil which was chromatographed, m.p.l.c. (silica, ether:petrol 40/60, 1:9) to yield:

(1) 2-phenyl-3-*p*-tolyl-3,4,5,6-tetrahydropentalene as a clear oil (118 mg, 40%), (Found: m/z, 272.155653. $C_{21}H_{20}$ requires m/z, 272.156493); δ_H 2.12-2.82 (6H, m, cyclopentyl), 2.28 (3H, s, Me), 3.26 (1H, br s, CH), 6.68-7.50 (10H, m, aromatics and olefinic); δ_C (90MHz) 20.9 (Me), 28.2 (C-5), 29.6 (C-4), 40.2 (C-6), 64.8 (C-3), 125.8 (C-1), 127.6 (aromatic CH), 128.0 (aromatic CH), 128.4 (aromatic CH), 128.9 (aromatic CH), 134.0 (quat), 136.2 (quat), 137.9 (quat), 142.0 (quat), 147.9 (quat), 152.1 (quat); m/z, 272 (100%), 105 (20), 91 (15).

(2) 4-phenyl-1-*p*-tolyl-1*H*-6,7,8-trihydrocyclopenta[d][1,2] diazepine as a yellow oil (24 mg, 9%), (Found: m/z, 300.164265. $C_{21}H_{20}N_2$ requires m/z, 300.162641. ^1H N.m.r., ^{13}C n.m.r. and mass spectra: see Appendix 4.

9) 1-Acetyl-2-(*E*-2-phenylethenyl)cyclohexene tosylhydrazone

The sodium salt was prepared from sodium (29 mg, 1.26 mmol) in super-dry ethanol (30 ml) and the tosylhydrazone (0.50 g, 1.28 mmol). After the usual drying procedure, dry

cyclohexane (100 ml) was added and heated under reflux for 2.5 h, the resulting white solid filtered and the yellow filtrate evaporated under reduced pressure to give a brown oil. This oil was subject to gravity chromatography (alumina, ether:petrol 40/60, 1:3) in absence of light to give 1-methyl-4-phenyl-1*H*-6,7,8,9-tetrahydrocyclohexa[d] [1,2] diazepine as a yellow oil (168 mg, 56%), (Found: m/z, 238.145250. $C_{16}H_{18}N_2$ requires m/z, 238.145250). ^1H N.m.r., ^{13}C n.m.r. and mass spectra: see Appendix 4.

10) *E,E*-3,5-Diphenyl-2-methylpenta-2,4-dienal tosylhydrazone

The sodium salt was prepared from sodium (37 mg, 1.60 mmol) in super-dry ethanol (20 ml) and the tosylhydrazone (0.67 g, 1.62 mmol). After the usual drying procedure, dry cyclohexane (100 ml) was added and the mixture heated under reflux for 1 h. The resulting white solid was filtered and the yellow filtrate evaporated under reduced pressure to give a brown oil, which was chromatographed (alumina, ether:petrol 40/60, 1:4) in the absence of light to give 4-methyl-5,7-diphenyl-3*H*-[1,2]diazepine as a yellow oil (0.30 g, 71%), (Found: m/z, 260.129349. $C_{18}H_{16}N_2$ requires m/z, 260.131342). ^1H N.m.r., ^{13}C n.m.r. and mass spectral data: see Appendix 4.

11) *E,E*-3,5-Diphenyl-2-methylhexa-2,4-dienal tosylhydrazone

The sodium salt was prepared from sodium (0.180 g, 7.83 mmol) in super-dry ethanol (100 ml) and the tosylhydrazone (3.39 g, 7.88 mmol). After the usual drying procedure, dry cyclohexane (200 ml) was added and the mixture heated under reflux for 1 h. The resulting solid was filtered, the filtrate

evaporated under reduced pressure to give a brown oil which was chromatographed (alumina, ether:petrol 40/60, 1:3) to give: (1) 4-methyl-5-phenyl-1-(*E*-2-phenylpropenyl)-1*H*-pyrazole as a yellow oil (0.67 g, 32%), (Found: m/z, 274.145588. $C_{19}H_{18}N_2$ requires m/z, 274.146991). ^1H N.m.r., ^{13}C n.m.r. and mass spectral data: see Appendix 6.

Hydrogenation of 4-methyl-5-phenyl-1-(*E*-2-phenylpropenyl)-1*H*-pyrazole was carried out to confirm the structure. 10% palladium on charcoal (48 mg) and 4-methyl-5-phenyl-1-(*E*-2-phenylpropenyl)-1*H*-pyrazole (84 mg, 0.32 mmol) in methanol (25 ml) was hydrogenated at 1 atmosphere of H_2 for 20 min. The catalyst was filtered and the filtrate evaporated under reduced pressure to give a brown oil which was purified by preparative t.l.c. (silica, ether:petrol 40/60, 1:4) to give 4-methyl-5-phenyl-1-(2-phenylpropyl)-1*H*-pyrazole as a clear oil (64 mg, 76%), (Found: m/z, 276.162641. $C_{19}H_{20}N_2$ requires m/z, 276.160337). ^1H N.m.r., ^{13}C n.m.r. and mass spectral data: see Appendix 8.

(2) 4-methyl-5-phenyl-1-(*Z*-2-phenylpropenyl)-1*H*-pyrazole as a yellow oil (0.11 g, 5%), (Found: m/z, 274.145852. $C_{19}H_{18}N_2$ requires m/z, 274.146991). ^1H N.m.r., ^{13}C n.m.r. and mass spectral data: see Appendix 6.

Hydrogenation of 4-methyl-5-phenyl-1-(*Z*-2-phenylpropenyl)-1*H*-pyrazole was carried out to confirm the structure. 10% palladium on charcoal (20 mg) and 4-methyl-5-phenyl-1-(*Z*-2-phenylpropenyl)-1*H*-pyrazole (18 mg, 0.07 mmol) in methanol (20 ml) was hydrogenated at 1 atmosphere of H_2 for 20 min. The catalyst was filtered and the filtrate evaporated under reduced

pressure to give a brown oil which was purified by preparative t.l.c. (silica, ether:petrol 40/60, 1:4) to give 4-methyl-5-phenyl-1-(2-phenylpropyl)-1*H*-pyrazole as a clear oil (11 mg, 57%) which had identical spectral properties to the product obtained above.

(3) 4-methyl-3-phenyl-5-(*E*-2-phenylpropenyl)pyrazole as a white solid which was recrystallised from pentane and ethanol to give white crystals (0.62 g, 30%), m.p.145-146°C (Found: C, 83.25; H, 6.6; N, 10.3. $C_{19}H_{18}N_2$ requires C, 83.2; H, 6.6; N, 10.2%); ν_{max} (Nujol) 3260 cm^{-1} (N-H). ^1H N.m.r., ^{13}C n.m.r. and mass spectral data: see Appendix 7.

Hydrogenation of 4-methyl-3-phenyl-5-(*E*-2-phenylpropenyl)-pyrazole was carried out to confirm the structure. 10% palladium on charcoal (20 mg) and 4-methyl-3-phenyl-5-(*E*-2-phenylpropenyl)pyrazole (37 mg, 0.14 mmol) in methanol (25 ml) was hydrogenated at 1 atmosphere of H_2 for 20 min. The catalyst was filtered and solvent removed under reduced pressure to give a brown oil which was purified by preparative t.l.c. (silica, ether:petrol 40/60, 1:1) to give 4-methyl-3-phenyl-5-(2-phenylpropyl)pyrazole as a clear oil (23 mg, 62%), (Found: m/z, 276.161921. $C_{19}H_{20}N_2$ requires m/z, 276.162641); ν_{max} (Nujol) 3180 cm^{-1} (N-H). ^1H N.m.r., ^{13}C n.m.r. and mass spectral data see Appendix 8b .

12) <u>*Z,E*-3,5-Diphenyl-2-methylpenta-2,4-dienal tosylhydrazone</u>

The sodium salt was prepared from sodium (32 mg, 1.40 mmol) in super-dry ethanol (30 ml) and the tosylhydrazone (0.60 g, 1.44 mmol). After the usual drying procedure, dry cyclohexane was added and the mixture heated under reflux 1 h.

The resulting white solid was filtered and the filtrate evaporated under reduced pressure to give a brown oil which was purified by chromatography, m.p.l.c.(silica, ether:petrol 40/60, 1:3) to yield:

(1) 4-methyl-5,7-diphenyl-3*H*-[1,2]diazepine (50 mg, 13%).

(2) 4-methyl-5-phenyl-1-(*E*-2-phenylethenyl)-1*H*-pyrazole as a yellow oil (122 mg, 33%), (Found: m/z, 260.129863. $C_{18}H_{16}N_2$ requires m/z, 260.131342). ^1H N.m.r., ^{13}C n.m.r. and mass spectral data, see Appendix 6.

Hydrogenation of 4-methyl-5-phenyl-1-(*E*-2-phenylethenyl)-1*H*-pyrazole was carried out to confirm the structure. 10% palladium on charcoal (35 mg) and 4-methyl-5-phenyl-1-(*E*-2-phenylethenyl)-1*H*-pyrazole (34 mg, 0.13 mmol) in methanol (25 ml) was hydrogenated at 1 atmosphere of H_2 for 20 min. The catalyst was filtered and the filtrate concentrated under reduced pressure to give a brown oil which was purified by preparative t.l.c. (silica, ether:petrol 40/60, 1:3) to give 4-methyl-5-phenyl-1-phenethyl-1*H*-pyrazole as a clear oil (24 mg, 69%), (Found: m/z, 262.145682. $C_{18}H_{18}N_2$ requires m/z, 262.146991). ^1H N.m.r., ^{13}C n.m.r. and mass spectral data see Appendix 8. This sample had identical spectral and physical characteristics to an independently synthesised sample (see Appendix 9b).

(3) 4-methyl-3-phenyl-5-(*E*-2-phenylethenyl)pyrazole as a white solid which was recrystallised from ethanol (74 mg, 20%), m.p.193-194^oC (Found: C, 82.8; H, 5.9; N, 10.6. $C_{18}H_{16}N_2$ requires C, 83.0; H, 6.2; N, 10.8%); ν_{max} (Nujol) 3220 cm^{-1} (N-H). ^1H N.m.r., ^{13}C n.m.r. and mass spectral data

see Appendix 7.

4-Methyl-3-phenyl-5-(*E*-2-phenylethenyl)-pyrazole was hydrogenated to prove the structure. 10% palladium on charcoal (40 mg) and the pyrazole (52 mg, 0.2 mmol) in methanol (30 ml) was hydrogenated at 1 atmosphere of H_2 for 20 min. The catalyst was filtered, the solvent evaporated at reduced pressure to give a brown oil which was purified by preparative t.l.c. (silica, ether:petrol 40/60, 1:2) to give a white solid which recrystallised from ethanol to give 4-methyl-3-phenyl-5-phenethylpyrazole as white crystals (30 mg, 57%), m.p. 102-103°C (Found: C, 82.3; H, 6.90; N, 10.6. $C_{18}H_{18}N_2$ requires C, 82.4; H, 6.90; N, 10.7%); ν_{max} (Nujol) 3150 cm^{-1} (br, N-H). ^1H N.m.r., ^{13}C n.m.r. and mass spectral data see Appendix 8b. This compound had identical spectral and physical characteristics to an authentic sample prepared from the reaction of the appropriate diketone with hydrazine hydrate (see Appendix 9).

Note: The sodium salt of the tosylhydrazone was prepared as above and the thermolysis carried out in refluxing toluene for 1 h. The resulting solid was filtered, the filtrate concentrated under reduced pressure to gave a brown oil which was purified by m.p.l.c. (silica, ether:petrol 40/60, 1:2) to give:

(1) 4-methyl-5,7-diphenyl-3*H*-[1,2]-diazepine (5.9%)

(2) 4-methyl-5-phenyl-1-(*E*-2-phenylethenyl)-1*H*-pyrazole (7%)

(3) 4-methyl-3-phenyl-5-(*E*-2-phenylethenyl)-pyrazole (61%).

13) *E,E*-2,5-Dimethylocta-4,6-dien-3-one tosylhydrazone

The sodium salt was prepared from sodium (31 mg, 1.34 mmol) in super-dry ethanol (20 ml) and the tosylhydrazone (0.44 g, 1.38 mmol). After the usual drying procedure, dry cyclohexane (60 ml) was added and heated under reflux 1.5 h. The resulting solid was filtered, and the filtrate evaporated under reduced pressure to give a brown oil which was purified by chromatography (alumina, ether:petrol 40/60, 1:1) to give 3-isopropyl-5-methyl-4-propenylpyrazole as a white crystal (0.14 g, 62%), m.p. 56-59°C (Found: m/z, 164.129099. $C_{10}H_{16}N_2$ requires m/z, 164.131342); ν_{max} (Nujol) 3160 cm^{-1} (br N-H). ^1H N.m.r., ^{13}C n.m.r. and mass spectral data, see Appendix 7b .

14) 4-Methyl-6-phenylhexa-3,5-dien-2-one tosylhydrazone

The sodium salt was prepared from sodium (36 mg, 1.56 mmol) in super-dry ethanol (30 ml) and the tosylhydrazone (0.56 g, 1.58 mmol). After the usual drying procedure, dry cyclohexane (60 ml) was added and the mixture heated under reflux for 30 min. The resulting solid was filtered and the filtrate evaporated under reduced pressure to give a brown oil which was subjected to flash chromatography (silica, ether:petrol 40/60, 1:3) to give a white solid which was recrystallised from pentane and ethanol to give 3,5-dimethyl-4-(*E*-2-phenylethenyl)-pyrazole (0.17 g, 55%), m.p. 179-180°C (Found: C, 78.6; H, 6.9; N, 14.30. $C_{13}H_{14}N_2$ requires C, 78.75; H, 7.1; N, 14.1%); ν_{max} (Nujol) 3160 cm^{-1} (br, N-H). ^1H N.m.r., ^{13}C n.m.r. and mass spectral data, see Appendix 7b.

2(B) THERMAL REARRANGEMENTS OF DIAZOALKENE CYCLISATION PRODUCTS

1) Thermolysis of 7a-(*E*-2-phenylpropenyl)-4,5,6,7-tetrahydroindazole

7a-(*E*-2-Phenylpropenyl)-4,5,6,7-tetrahydroindazole (0.12 g, 0.50 mmol) in dry 1,2-dimethoxyethane (30 ml) was heated under reflux for 10 h. The solvent was removed at reduced pressure to give a brown oil which was purified by flash chromatography (silica, ether:petrol 40/60, 1:2) to give 1-(*E*-2-phenylpropenyl)-4,5,6,7-tetrahydroindazole as a clear oil (61 mg, 51%), (Found: m/z, 238.145712. $C_{16}H_{18}N_2$ requires m/z, 238.146991). ^1H N.m.r., ^{13}C n.m.r. and mass spectral data see Appendix 5b.

2) Thermolysis of 4-methyl-5-phenyl-1-(*E*-2-phenylethenyl)-1*H*-pyrazole

4-Methyl-5-phenyl-1-(*E*-2-phenylethenyl)-1*H*-pyrazole (25 mg, 0.1 mmol) in dry toluene (25 ml) was heated under reflux for 150 h. T.l.c. and ^1H n.m.r. indicated only starting material present and no other products formed.

3) Thermolysis of 4-methyl-5,7-diphenyl-3*H*- [1,2] diazepine

4-Methyl-5,7-diphenyl-3*H*- [1,2]diazepine (87 mg, 3.4 mmol) in dry toluene (25 ml) was heated under reflux 25 h, t.l.c. showed all starting material consumed. Evaporation of the solvent at reduced pressure gave a brown solid, preparative t.l.c. (silica, ether:petrol 40/60, 1:1) gave 4-methyl-3-phenyl-5-(*E*-2-phenylethenyl)pyrazole as white crystals which were recrystallised from ethanol (70 mg, 80%), m.p.

191-193°C (Found: C, 82.80; H, 6.15; N, 10.67. $C_{18}H_{16}N_2$ requires C, 83.0; H, 6.2; N, 10.8%); ν_{max} (Nujol) 3220 cm^{-1} (N-H); δ_H ($(CD_3)_2$ S=O) 2.27 (3H, s, Me), 7.07-7.78 (12H, m, aromatic) 13.03 (1H, br s, NH); δ_C (90.5MHz, $(CD_3)_2$ S=O) 9.20 (Me), 111.12 (quat), 126.32, 127.16, 127.40, 127.44, 127.63, 128.24, 128.74, 137.02 (quat); m/z 260 (100%), 259 (87), 156 (24), 130 (15), 77 (11). ^1H N.m.r., ^{13}C n.m.r. and mass spectral data was identical with 4-methyl-3-phenyl-5-(*E*-2-phenylethenyl)-pyrazole obtained from the thermal decomposition of the sodium salt of *Z*,*E*-3,5-diphenyl-2-methylpenta-2,4-dienal tosylhydrazone (see Appendix 7). Mixed m.p. = 191-192°C.

2(C) PREPARATION OF AUTHENTIC SAMPLES, MODEL COMPOUNDS AND [1,2] DIAZEPINE *N*-OXIDES

1) 1-Formylcyclohexanone

This was prepared in 51% yield by the method of Ainsworth[212] from the reaction of cyclohexanone, ethyl formate and sodium, b.p. 76-80°C at 8 mmHg (lit.,[212] 70-72°C at 5 mmHg).

2) 1-Phenethyl-4,5,6,7-tetrahydroindazole and 2-phenethyl-4,5,6,7-tetrahydroindazole

1-Formylcyclohexanone (0.61 g, 4.8 mmol) and β-phenethylhydrazine (0.65 g, 4.8 mmol) in ethanol (50 ml) containing concentrated hydrochloric acid (1 drop) was heated under reflux for 2 h. The solvent was removed under reduced pressure, dichloromethane (100 ml) and water (50 ml) added, the organic

phase separated, washed with water (2 x 50 ml) and dried. Removal of solvent under reduced pressure gave a yellow oil which was purified by flash chromatography (silica, ether: petrol 40/60, 1:3) to give:

(1) 1-phenethyl-4,5,6,7-tetrahydroindazole as a white solid which was recrystallised from pentane and ethanol as white crystals (0.55 g, 51%), m.p. 64-65°C (Found: C, 79.4; H, 8.0; N, 12.2. $C_{15}H_{18}N_2$ requires C, 79.60; H, 8.0; N, 12.4%). ^1H N.m.r., ^{13}C n.m.r. and mass spectral data see Appendix 5b.

(2) 2-phenethyl-4,5,6,7-tetrahydroindazole as a clear oil (0.24 g, 22%), (Found: m/z, 226.146450. $C_{15}H_{18}N_2$ requires m/z, 226.146991). ^1H N.m.r., ^{13}C n.m.r. and mass spectral data see Appendix 5b.

3) 3-Phenylpropionyl chloride

3-Phenylpropanoic acid (20.0 g, 0.13 mol) in thionyl chloride (30 ml) was heated under reflux for 2.5 h, the excess thionyl chloride was removed at reduced pressure and the product distilled to give 3-phenylpropionyl chloride (14.5 g, 65%), b.p. 102-110°C at 11 mmHg (lit.,[213] 105°C at 10 mmHg).

4) 1-Phenylpentan-3-one

This was prepared by an adaption of the method of Heilbron.[210] A Grignard reagent was prepared from ethyl bromide (30.9 g, 0.28 mol) and magnesium (6.82 g, 0.28 mol) in dry ether (150 ml). This was cooled to 0°C and anhydrous cadmium chloride (25.9 g, 0.14 mol) added in one batch under nitrogen. After rapid mechanical stirring for 30 min, 3-phenylpropionyl chloride (20 g, 0.12 mol) in dry ether (75 ml)

was added dropwise. The mixture was heated under reflux for 3 h, cooled to 0°C and carefully hydrolysed with ammonium chloride solution (10% w/v, 250 ml). The reaction was filtered through Celite, ether (300 ml) added, the aqueous phase separated, extracted with ether (3 x 50 ml) and the combined organic phase dried. The solvent was evaporated under reduced pressure and the product distilled to give 1-phenylpentan-3-one as a clear oil (13.7 g, 72%), b.p. 135°C at 13 mmHg (lit.,[214] 126°C at 12 mmHg).

5) 2-Methyl-3-oxo-5-phenylpentanal

1-Phenylpentan-3-one (5.0 g, 31 mmol) and ethylformate (2.29 g, 31 mmol) in dry ether (50 ml) was added dropwise to dry sodium ethoxide powder (2.1 g, 31 mmol) in dry ether (25 ml) at 0°C. After stirring for 7 h at room temperature, the mixture was cooled to 0°C, and hydrolysed by the addition of solution hydrochloric acid (2M, 25 ml). The aqueous layer was separated, extracted with ether (2 x 200 ml) and the organic layer washed with sodium bicarbonate solution (10% w/v, 2 x 50 ml), water (2 x 50 ml) and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure and the resulting brown oil distilled to give 2-methyl-3-oxo-5-phenylpentanal (3.1 g, 54%), b.p. 98-100°C at 0.4 mmHg as a clear oil which solidified and was recrystallised from pentane and ethanol as white crystals m.p. 60-62°C (Found: C, 76.00; H, 7.1. $C_{12}H_{14}O$ requires C, 75.8; H, 7.4%); ν_{max} (Nujol) 3150 cm^{-1} (O-H), 1670 and 1605 cm^{-1} (C=O); δ_H 1.70 (3H, s, Me), 2.59-3.10 (4H, m) 7.00-7.47 (5H, m, phenyl), 7.65 (1H, d, J 9Hz, =C*H*-OH), 14.60 (1H, d, J 9Hz, O-H); m/z 190 (86%), 162 (21), 105 (87), 91 (100), 85 (98).

6) 4-Methyl-5-phenethyl-1-phenyl-1*H*-pyrazole

2-Methyl-3-oxo-5-phenylpentanal (0.71 g, 3.72 mmol) and phenylhydrazine hydrochloride (0.54 g, 3.72 mmol) in methanol (30 ml) was heated at reflux for 40 min. The solvent was removed under reduced pressure, dichloromethane (100 ml) added, washed with water (2 x 30 ml) and dried. Removal of solvent under reduced pressure gave a yellow oil which was purified by m.p.l.c. (silica, ether:petrol, 1:1) to give 4-methyl-5-phenethyl-1-phenyl-1*H*-pyrazole as a clear oil (0.45 g, 46%). (Found: m/z, 262.146967. $C_{18}H_{18}N_2$ requires m/z, 262.146991). ^1H N.m.r., ^{13}C n.m.r. and mass spectral data see Appendix 9.

7) 2-Benzoylpropanal

This was prepared by the method of Aspart-Pascot and Lematre[215] from propiophenone (30 g, 0.22 mol), ethyl formate (1.7 g, 0.22 mol) and sodium ethoxide (15 g, 0.22M) in dry ether (150 ml). The mixture was stirred 4 h, stood for 12 h at 5°C, the solid filtered, dissolved in ice (150 ml) and hydrochloric acid (2M, 100 ml) added. The precipitated product was collected and distilled (26 g, 71%), b.p. 134-138°C at 12 mmHg (lit.,[215] 155°C at 25 mmHg); m.p. 118-119°C (lit.,[215] 118-119°C).

8) 4-Methyl-3-phenyl-1-phenethyl-1*H*-pyrazole and 4-methyl-5-phenyl 1-phenethyl-1*H*-pyrazole

2-Benzoylpropanal (1.0 g, 6.2 mmol) and β-phenylhydrazine (0.84 g, 6.2 mmol) in ethanol (50 ml) containing concentrated hydrochloric acid (1 drop) was heated under reflux for 8 h. The solvent was evaporated under reduced pressure, dichloromethane (100 ml) added, the organic layer separated, washed

with water (2 x 50 ml) and dried. The solvent was evaporated under reduced pressure to give a yellow oil which was purified by chromatography, m.p.l.c. (silica, ether:petrol 40/60, 1:3) to give:

(1) 4-methyl-3-phenyl-1-phenethyl-1*H*-pyrazole as a clear oil (0.27 g, 17%), (Found: m/z, 262.145168. $C_{18}H_{18}N_2$ requires m/z, 262.146991). ^1H N.m.r., ^{13}C n.m.r. and mass spectral data see Appendix 9b.

(2) 4-methyl-5-phenyl-1-phenethyl-1*H*-pyrazole as a clear oil (0.58 g, 36%), (Found: m/z, 262.146967. $C_{18}H_{18}N_2$ requires m/z, 262.146991). ^1H N.m.r., ^{13}C n.m.r. and mass spectral data see Appendix 9b. This compound has identical spectral data to the pyrazole obtained from the hydrogenation of 4-methyl-5-phenyl-1-(*E*-2-phenylethenyl)-1*H*-pyrazole (see Appendix 8).

9) Ethyl-3-phenylpropionate

3-Phenylpropionic acid (55 g, 0.37 mol) in ethanol (250 ml) containing concentrated hydrochloric acid (5 drops) was heated under reflux for 10 h. Removal of solvent at reduced pressure and distillation gave ethyl 3-phenylpropionate (57 g, 87%) b.p. 124-126°C at 15 mmHg (lit.,[213] 238-239°C at 756 mmHg).

10) 1,5-Diphenylpenta-1,3-dione

This was prepared by a modification of the method of Hauser *et al.*[216] Sodamide (0.3 mol) in dry ether (150 ml) was prepared from sodium (6.9 g, 0.3 mol) and dry ammonia by the procedure of Vogel,[217] then acetophenone (36 g, 0.3 mol)

in dry ether (100 ml) added over 5 min. The mixture was stirred 5 min and ethyl-3-phenylpropionate (1.8 g, 0.1 mol) in dry ether (50 ml) added and the mixture heated under reflux for 4 h. The mixture was cooled to 0°C and hydrolysed by the addition of hydrochloric acid (2M, 200 ml), the aqueous layer separated, extracted with ether (2 x 200 ml), and the combined ether layer dried over anhydrous sodium sulphate. The solvent was removed at reduced pressure, the residue dissolved in methanol (70 ml) and copper(II) acetate solution (10% w/v, 100 ml) added with vigorous stirring. The resulting green precipitate was filtered, washed with petrol (2 x 200 ml) and ether (1 x 100 ml). The precipitate was dissolved in hydrochloric acid (2M, 200 ml) and then extracted with ether (3 x 300 ml) and the ether layer dried over anhydrous sodium sulphate. The solvent was removed at reduced pressure to give a yellow oil which was purified by chromatography, m.p.l.c. (silica, ether:petrol 40/60, 1:3) to give 1,5-diphenylpenta-1,3-dione as a white solid which was recrystallised from ethanol to give white crystals (14 g, 56%), m.p. 52-54°C (lit.[218] 54-55°C).

11) 1,5-Diphenyl-2-methylpenta-1,3-dione

1,5-Diphenylpenta-1,3-dione (1.4 g, 5.6 mmol), dry methyl iodide (0.97 g, 6.84 mmol) and anhydrous potassium carbonate (0.76g, 5.6 mmol) in dry acetone (60 ml) was heated under reflux for 24 h. Most of the solvent was removed under reduced pressure, dichloromethane (60 ml) and water (60 ml) added, the aqueous layer was separated, extracted with dichloromethane (2 x 30 ml) and the combined organic

layers dried over anhydrous sodium sulphate. Evaporation of the solvent under reduced pressure gave a yellow oil which was purified by chromatography, m.p.l.c. (silica, ether:petrol 40/60, 1:3) to give 1,5-diphenyl-2-methylpenta-1,3-dione as a clear oil (1.20 g, 81%), (Found: m/z, 266.129778. $C_{18}H_{18}O_2$ requires m/z, 266.130672); ν_{max} (liquid) 1720 cm^{-1}, (C=O) and 1675 cm^{-1} (C=O); δ_H 1.38 (3H, d, J 7Hz, Me), 2.55-3.0 (4H, m, 2 x CH_2), 4.43 (1H, q, J 7Hz, CH), 6.95-7.95 (10H, m, phenyls); m/z 266 (37%), 186 (21), 134 (74), 105 (100), 95 (29), 91 (81), 77 (61).

12) 4-Methyl-3-phenyl-5-phenethylpyrazole

1,5-Diphenyl-2-methylpenta-1,3-dione (0.89 g, 3.35 mmol) and hydrazine hydrate (0.17 g, 3.35 mmol) in methanol (15 ml) was heated under reflux 1 h. The solvent was evaporated under reduced pressure, dichloromethane (50 ml) and water (30 ml) added, the organic phase was separated and dried. Removal of solvent under reduced pressure gave a brown oil which was purified by chromatography, m.p.l.c. (silica, ether:petrol 40/60, 1:2) to give a white solid which was recrystallised from pentane and ethanol to give 4-methyl-3-phenyl-5-phenethyl-pyrazole (0.58 g, 66%), m.p.103-104°C (Found: C, 82.3; H, 6.8; N, 10.6. $C_{18}H_{18}N_2$ requires C, 82.4; H, 6.9; N, 10.7%); ν_{max} (Nujol) 3240 cm^{-1} (N-H). ^1H N.m.r., ^{13}C n.m.r. and mass spectral data see Appendix 9. This compound has identical spectral data to the pyrazole obtained from the hydrogenation of 4-methyl-3-phenyl-5-(*E*-2-phenylethenyl)-pyrazole (see Appendix 8b). Mixed m.p.102-103°C.

13) 4-Phenyl-1*H*-6,7,8,9-tetrahydrocyclohexa[d][1,2]-diazepine *N*-2 oxide

4-Phenyl-1*H*-6,7,8,9-tetrahydrocyclohexa[d][1,2]diazepine (165 mg, 0.74 mmol) was dissolved in dry dichloromethane (20 ml) and a solution of *m*-chloro-perbenzoic acid (85%, 0.18 g, 0.88 mmol) in dichloromethane (20 ml) added dropwise, stirred for 2 h at room temperature in the absence of light. The mixture was washed with sodium bicarbonate (10% w/v, 40 ml), water (2 x 20 ml) and dried. Removal of solvent under reduced pressure gave a yellow solid which was purified by chromatography (alumina, ether:petrol 40/60, 1:2) to give 4-phenyl-1*H*-6,7,8,9-tetrahydrocyclohexa[d][1,2]diazepine *N*-2 oxide as white solid which was recrystallised from ethanol (125 mg, 71%), m.p. 100-101°C (Found: C, 74.7; H, 6.9; N, 11.4. $C_{15}H_{16}N_2O$ requires C, 75.0; H, 6.7; N, 11.7%). ^1H N.m.r. ^{13}C n.m.r. and mass spectral data see Appendix 4b.

14) 4-Methyl-5,7-diphenyl-3*H*-[1,2]diazepine *N*-2 oxide

4-Methyl-5,7-diphenyl-3*H*-[1,2]diazepine (91 mg, 0.35 mmol) was dissolved in dry dichloromethane (20 ml) and a solution of *m*-chloro-perbenzoic acid (85%, 85 mg, 0.42 mmol) in dry dichloromethane (10 ml) added dropwise, stirred 5 h at room temperature in the absence of light. The mixture was washed with sodium bicarbonate (10% w/v, 20 ml), water (2 x 20 ml) and dried. Evaporation of solvent under reduced pressure gave a brown oil which was purified by chromatography (alumina, ether:petrol 40/60, 1:2) to give 4-methyl-5,7-diphenyl-3*H*-[1,2]diazepine *N*-2 oxide as a yellow oil (74 mg, 77%), (Found: m/z, 276.124963. $C_{18}H_{16}N_2O$ requires m/z,

276.126256). ^{1}H N.m.r., ^{13}C n.m.r. and mass spectral data see Appendix 4b.

(3) PHOTOLYTIC DECOMPOSITION OF THE LITHIUM SALTS OF TOSYLHYDRAZONES

1) *E,E*-3,5-Diphenyl-2-methylpenta-2,4-dienal tosylhydrazone

Methyllithium (1.5M in ether, 0.94 ml, 1.41 mmol) was added with stirring, under dry nitrogen to a solution of *E,E*-3,5-diphenyl-2-methylpenta-2,4-dienal tosylhydrazone (534 mg, 1.28 mmol) in dry T.H.F. (70 ml) at -60°C in a pyrex photochemical reactor. The resulting solution was stirred 1 h, then irradiated under dry nitrogen at -60°C with a 100 watt medium pressure lamp for 4 h. The mixture was allowed to warm to room temperature and water (25 ml) added. Most of the T.H.F. was removed under reduced pressure, dichloromethane (100 ml) added, the aqueous layer separated, extracted with dichloromethane (2 x 25 ml), the combined organic layers were washed with water (2 x 20 ml) and dried. Evaporation of the solvent under reduced pressure gave a brown oil which was purified by flash chromatography (silica, ether:petrol, 1:9) to give

(1) 1-methyl-3-phenyl-3-(*E*-2-phenylethenyl)cyclopropene as a clear oil (121 mg, 41%), (Found: m/z, 232.123215. $C_{18}H_{16}$ requires m/z, 232.125194). ^{1}H N.m.r., ^{13}C n.m.r. and mass spectral data see Appendix 10.

(2) 4,6a-dihydro-6a-methyl-4,6-diphenyl[1,2]diazeto[1,4-a]-pyrrole as a clear oil (84 mg, 25%), (Found: m/z, 260.132386.

$C_{18}H_{16}N_2$ requires m/z, 260.131342). ^1H N.m.r., ^{13}C n.m.r. and mass spectral data, see Appendix 11.

(3) 4,6a-dihydro-5-methyl-1,6-diphenyl[1,2]diazeto[1,4-a]-pyrrole (32 mg, 10%). (This was identical by t.l.c. and ^1H n.m.r. to 4,6a-dihydro-5-methyl-1,6-diphenyl[1,2]diazeto[1,4-a]-pyrrole formed by the photolysis of 4-methyl-5,7-diphenyl-3*H*-[1,2]diazepine.) ^1H N.m.r. and mass spectral data see Appendix 11.

2) *E,E*-3,5-Diphenyl-2-methylhexa-2,4-dienal tosylhydrazone

Methyllithium (1.5M in ether, 0.46 ml, 0.69 mmol) was added with stirring, under dry nitrogen to a solution of *E,E*-3,5-diphenyl-2-methylhexa-2,4-dienal tosylhydrazone (295 mg, 0.69 mmol) in T.H.F. (70 ml) at -60°C in a pyrex photochemical reactor. The resulting solution was stirred 1 h, then irradiated under dry nitrogen at -60°C with a 100 watt medium pressure lamp for 6 h. The mixture was allowed to warm to room temperature and water (20 ml) added. Most of the T.H.F. was removed under reduced pressure, dichloromethane (100 ml) added, the aqueous layer separated, extracted with dichloromethane (2 x 25 ml) and the combined organic layer washed with water (2 x 30 ml) and dried. Removal of solvent under reduced pressure gave a brown oil which was purified by preparative t.l.c. (alumina, ether:petrol 40/60, 1:9) to give (1) 1-methyl-3-phenyl-3-(*E*-2-phenylpropenyl)cyclopropene as a clear oil (62 mg, 37%), (Found: m/z, 246.140302. $C_{19}H_{18}$ requires m/z, 246.140844). ^1H N.m.r., ^{13}C n.m.r. and mass spectral data see Appendix 10.

(2) 4,6a-dihydro-4,6a-dimethyl-4,6-diphenyl[1,2]diazeto-[1,4-a]pyrrole as a brown oil (48 mg, 25%). (Found: m/z, 274.144532. $C_{19}H_{18}N_2$ requires m/z, 274.146991). ^1H N.m.r.

^{13}C n.m.r. and mass spectral data see Appendix 11.

3) Photolysis of 4-methyl-5,7-diphenyl-3*H*-[1,2]diazepine

A solution of 4-methyl-5,7-diphenyl-3*H*-[1,2]diazepine (371 mg, 1.43 mmol) in dry T.H.F. (70 ml) was photolysed under dry nitrogen, at -70°C, through pyrex for 30 min. T.l.c. showed only one product formed and this was isolated by flash chromatography (silica, ether:petrol 40/60, 1:1) to give 4,6a-dihydro-5-methyl-1,6-diphenyl[1,2]diazeto[1,4-a]pyrrole as a white solid which was recrystallised from pentane and ethanol as white crystals (310 mg, 83%), m.p.86-87°C (Found: C, 82.85; H, 6.00; N, 11.0. $C_{18}H_{16}N_2$ requires C, 83.04; H, 6.2; N, 10.8%); δ_H (200MHz) 1.76 (3H, d, J 1.5Hz, Me), 4.11 (2H, br s, H-4), 6.16 (1H, br s, 6a-H), 7.13-7.43 (10H, m, phenyl); δ_C (20MHz) 12.96 (Me), 62.33 (C-4), 85.59 (C-6a), 124.48, 127.37, 128.05, 128.21, 128.40, 129.31, 130.20, 131.27 (quat), 134.01 (quat), 134.73 (quat), 182.74 (quat, C-1); m/z 260 (10%), 157 (100), 156 (47), 116 (16), 115 (25), 103 (22).

SECTION 2

AZEPINES AND OTHER COMPOUNDS DERIVED FROM NITRILE YLIDES

1. PREPARATION OF STARTING MATERIALS

A. SYNTHESIS OF 2-ALKENYLARYL ALDEHYDES AND 2-ALKENYLARYL KETONES

1) 2-Bromobenzylbromide

This was prepared by the method of Shoesmith and Slater[219] from 2-bromotoluene (100 g, 0.59 mol) and bromine (92 g, 0.59 mol). Distillation yielded 2-bromobenzylbromide as a pale yellow oil (119 g, 82%), b.p. 111-113°C at 3 mmHg (lit.,[219] 129°C at 19 mmHg).

2) 2-Bromobenzyltriphenylphosphonium bromide

This was prepared by the reaction of 2-bromobenzyl-bromide (119 g, 0.48 mol) and triphenylphosphine (163 g, 0.62 mol) in dry, boiling benzene. After 1 h the precipitate was filtered off and washed with benzene, giving 2-bromobenzyl-triphenylphosphonium bromide (241 g, 99%), m.p. 195-197°C (lit.,[220] 195-197°C).

3) 1-Bromo-2-(*E*-2-phenylethenyl)benzene

A solution of sodium ethoxide [(0.44 mol) from sodium (10.1 g)] in superdry ethanol (200 ml) was added over 1 h at room temperature to a stirred mixture of redistilled benz-aldehyde (46.6 g, 0.44 mol) and 2-bromobenzyltriphenylphos-phonium bromide (225 g, 0.44 mol) in superdry ethanol (500 ml).

The reaction mixture was then stirred for 24 h at room temperature, the resulting precipitate filtered off and washed with ethanol (2x200 ml). The combined ethanol fractions were evaporated under reduced pressure to give a brown oil which was subjected to chromatography (alumina, petrol 40/60) to remove triphenylphosphine oxide. The resulting clear oil, containing *E* and *Z* isomers was isomerised to the *E* isomer by refluxing in *n*-heptane (250 ml) containing iodine (0.2 g) for 60 h. Analysis by g.l.c. (2½% OVI, 165°C) showed greater than 95% of *E* isomer. The *n*-heptane was removed under reduced pressure, dichloromethane (350 ml) added and washed with a solution of sodium thiosulphate (5% w/v, 600 ml), dried and the solvent removed under reduced pressure. Distillation gave 1-bromo-2-(*E*-2-phenylethenyl)benzene as a pale yellow liquid (81 g, 71%), b.p. 148°C at 0.2 mmHg (lit.,[221] 145°C at 0.55 mmHg).

4) 1-Formyl-2-(*E*-2-phenylethenyl)benzene

This was prepared by the method of Smith and Bayliss[222] using the Grignard reaction of 1-bromo-2-(*E*-2-phenylethenyl)-benzene (25.0 g, 97 mmol) and magnesium (2.38 g, 98 mmol) in dry T.H.F. (150 ml) and dry dimethylformamide (10.6 g, 146 mmol). The crude product was purified by chromatography (alumina, ether:petrol 40/60, 1:4) to give 1-formyl-2-(*E*-2-phenylethenyl) benzene as a yellow solid (16.2 g, 81%), m.p. 79-81°C (lit.,[223] 83°C).

5) 1-(1-Hydroxyethyl)-2-(*E*-2-phenylethenyl)benzene

A Grignard reagent was prepared from 1-bromo-2-(*E*-

2-phenylethenyl)benzene (41.8 g, 0.16 mol) and magnesium (4.30 g, 0.17M) in dry T.H.F. (250 ml). After stirring 4 h with heating under reflux, to ensure complete formation of Grignard reagent , the mixture was cooled to 0°C and freshly distilled acetaldehyde (28.0 g, 0.64 mol) in dry T.H.F. (50 ml) added dropwise over 30 min. The mixture was stirred 1 h at 0°C, 6 h at room temperature before hydrolysis by the addition of a solution of ammonium chloride (10% w/v, 200 ml). Ether (500 ml) was added, the aqueous phase separated, extracted with ether (2x200 ml), the combined organic layer washed with water (2x200 ml) and dried. Evaporation of the solvent under reduced pressure gave a brown oil which was distilled to give 1-(1-hydroxyethyl)-2-(*E*-2-phenylethenyl)benzene as a yellow oil (27.1 g, 75%), b.p. 165-175°C at 0.5 mmHg. δ_H 1.55 (3H, d, J 7Hz, Me) 5.30 (1H, q, J 7Hz, CH), 7.12 (1H, one half of AB, J 16Hz, olefinic), 7.32-7.95 (11H, m, aromatics). This was used without further purification.

6. 1-Acetyl-2-(*E*-2-phenylethenyl)benzene

Chromium trioxide (34.7 g, 0.35 mol) was added during 30 min with stirring and ice cooling to dry pyridine (250 ml). 1-(1-Hydroxyethyl)-2-(*E*-2-phenylethenyl)benzene (26.4 g, 0.12 mol) in dry pyridine (25 ml) was added dropwise, and the mixture allowed to stir overnight at room temperature. Ether (1200 ml) was added and the dark precipitate was filtered off. Water (600 ml) was added to the filtrate, the ether layer separated, and the water layer extracted with ether (2x300 ml). The combined ether layers were washed with a solution of 1N

hydrochloric acid (3x500 ml), a solution of sodium bicarbonate (20% w/v, 3x500 ml), water (2x500 ml) and dried. The solvent was removed under reduced pressure to give a yellow oil which was distilled to give 1-acetyl-2-(*E*-2-phenylethenyl)benzene (20.2 g, 77%), b.p. 168-174°C at 1.8 mmHg (lit.,[80] 134-136°C at 0.05 mmHg). This compound had an identical ^{1}H n.m.r. spectra to a sample prepared by the method of Sharp.[80]

7) 1-Bromo-2-(2-phenylpropenyl)benzene as *E/Z* mixture

A solution of sodium ethoxide [(0.064 mol) from sodium (1.33 g) in superdry ethanol (250 ml)] was added over 2 h at room temperature to a stirred mixture of acetophenone (7.68 g, 0.064 mol) and 2-bromobenzyltriphenylphosphonium bromide (30.0 g, 0.058 mol) in superdry ethanol (400 ml). The mixture was then heated under reflux, with stirring for 12 h, most of the solvent removed under reduced pressure and water (200 ml) added. This was extracted with dichloromethane (3x250 ml), the organic layer washed with water and dried. Evaporation under reduced pressure gave a brown oil which was purified by chromatography (alumina, petrol 40/60) to give a clear oil. This was distilled to give 1-bromo-2-(2-phenylpropenyl)benzene as an *E/Z* mixture (12.6 g, 80%), b.p. 140°C at 0.6 mmHg (lit.,[83] 124°C at 0.5 mmHg).

8) 1-Formyl-2-(2-phenylpropenyl)benzene as an *E/Z* mixture

A Grignard reagent was prepared by the dropwise addition of a solution of 1-bromo-2-(2-phenylpropenyl)benzene (10.8 g, 0.040 mol) in dry T.H.F. (50 ml) to a stirred suspension of magnesium (1.01 g, 0.041 mol) in dry T.H.F. (75 ml) at room

temperature over 1 h, the mixture was then heated under reflux for 1 h. The mixture was cooled to 0°C, dry dimethylformamide (5.33 g, 0.073 mol) in dry T.H.F. (50 ml) was added dropwise, stirred 1 h at room temperature and heated under reflux for 2 h. The mixture was allowed to cool before hydrolysis by the addition of a solution of ammonium chloride (10% w/v, 150 ml). Ether (350 ml) was added, the organic phase separated and washed with water (2x100 ml) and dried. Removal of the solvent under reduced pressure gave a yellow oil which was purified by chromatography, m.p.l.c. (silica, ether:petrol 40/60, 1:4) to give 1-formyl-2-(2-phenylpropenyl)benzene as an *E/Z* mixture (ratio *E:Z*, 2:3) (7.71 g, 88%). This compound had identical ^{1}H n.m.r. to that reported by Munro[83] δ_H 2.05 (3H, d, 1.5Hz, *Z* Me), 2.30 (3H, d, 1.5Hz, *E* Me) 6.90-7.97 (20H, m, aromatic), 10.20 (1H, s, *E* CHO), 10.24 (1H, s, *Z* CHO).

B. SYNTHESIS OF 2-ALKENYL-*N*-BENZOYL BENZYLAMINES

1. 1-Formyl-2-(*E*-2-phenylethenyl)benzene oxime

A mixture of 1-formyl-2-(*E*-2-phenylethenyl)benzene (5.38 g, 25.8 mmol), hydroxylamine hydrochloride (5.38 g, 77.4 mmol), pyridine (5 ml) and ethanol (50 ml) was heated under reflux for 30 min. The solvent was removed under reduced pressure, water (60 ml) and dichloromethane (100 ml) added, the aqueous phase was separated, extracted with dichloromethane (2x50 ml) and combined organic layer dried. The solvent was removed under reduced pressure to leave a brown oil which was purified by flash chromatography (silica,

ether:petrol 40/60, 1:2) to give a white solid which was recrystallised from ethanol to give 1-formyl-2-(*E*-2-phenylethenyl)benzene oxime as white needles (4.48 g, 78%), m.p. 127-128°C (Found: C, 80.5; H, 5.7; N, 6.50. $C_{15}H_{13}NO$ requires C, 80.7; H, 5.9; N, 6.3%); ν_{max} (Nujol) 3200 cm^{-1} (br, OH); δ_H (200MHz) 6.97 (1H, one half AB, J 16Hz, olefinic), 7.25-7.67 (10H, m, aromatic and olefinic), 7.75 (1H, br s, OH), 8.52 (1H, s, C*H*=N); m/z 223 (39%), 206 (35), 146 (100).

2) 2-(*E*-2-Phenylethenyl)benzylamine

A solution of 1-formyl-2-(*E*-2-phenylethenyl)benzene oxime (7.30 g, 0.033 mol) in dry ether (50 ml) was added dropwise, with mechanical stirring and ice-cooling, to lithium aluminium hydride (13.2 g, 0.330 mol) in dry ether (400 ml) over 1 h. The resulting green mixture was stirred 2 h at room temperature, heated under reflux 1 h then cooled to -20°C. The reaction was carefully hydrolysed by the dropwise addition of saturated sodium sulphate solution (200 ml), with vigorous mechanical stirring, then stirred a further 1 h at room temperature. The resulting white solid was filtered through Celite and washed with ether (4x200 ml). The aqueous phase was separated, extracted with ether (3x200 ml), and the combined ether layer washed with water (2x200 ml) and dried. Most of the solvent was removed under reduced pressure and a solution of 3N hydrochloric acid (300 ml) added with vigorous stirring. The resulting precipitate was filtered, washed with water (2x100 ml), ether (2x100 ml) and dried. This hydrochloride salt (7.01 g, 86%) of the amine was converted to the benzoyl amide without further purification.

3) *N*-Benzoyl-2-(*E*-2-phenylethenyl)benzylamine*

A mixture of 2-(*E*-2-phenylethenyl)benzylamine hydrochloride (7.01 g, 0.028 mol), freshly distilled benzoyl chloride (8.47 g, 0.060 mol), dry pyridine (60 ml) and dry benzene (100 ml) was heated under reflux for 40 min. The reaction was allowed to cool, water (1000 ml) and benzene (400 ml) added, the aqueous layer separated and extracted with benzene (2x200 ml). The combined organic layer was washed with a solution of sodium carbonate (5% w/v, 100 ml) and dried. Evaporation of the solvent under reduced pressure gave a brown oil which was purified by chromatography, m.p.l.c. (silica, ethyl acetate: petrol 40/60, 1:2) to give a white solid which was recrystallised from pentane and ethanol to give *N*-benzoyl-2-(*E*-2-phenylethenyl)benzylamine as white crystals (7.11 g, 81%), m.p. 142-144°C (Found: C, 84.05; H, 6.1; N, 4.7. $C_{22}H_{19}NO$ requires C, 84.3; H, 6.1; N, 4.5%); ν_{max} (Nujol) 3325 (N-H) and 1630 cm^{-1} (C=O). ^1H n.m.r. and mass spectral data see Appendix 12.

4) 1-Acetyl-2-(*E*-2-phenylethenyl)benzene oxime

A mixture of 1-acetyl-2-(*E*-2-phenylethenyl)benzene (20 g, 0.090 mol), hydroxylamine hydrochloride (20 g, 0.287 mol), pyridine (20 ml) and ethanol (200 ml) was heated under reflux for 30 min, then allowed to cool and the solvent removed under reduced pressure to give a brown oil. Dichloromethane (500 ml) and water (300 ml) added, the aqueous phase separated and extracted with dichloromethane (2x200 ml) and the combined

---

* Made in collaboration with Miss S. McNamara

organic layer washed with water (2x200 ml) and dried. Removal of solvent under reduced pressure gave a brown oil which was purified by chromatography m.p.l.c. (ether:petrol 40/60, 1:2) to give a white solid which was recrystallised from pentane and ethanol to give 1-acetyl-2-(*E*-2-phenylethenyl)-benzene oxime (16.9 g, 79%), m.p. 109-110°C (Found: C, 81.10; H, 6.30; N, 5.75. $C_{16}H_{15}NO$ requires C, 81.0; H, 6.4; N, 5.90%); ν_{max} (Nujol) 3260 cm^{-1} (br, O-H); δ_H (80MHz) 2.22 (3H, s, Me) 7.02 (1H, one half AB, J 16Hz, olefinic), 7.19-7.65 (10H, m, aromatic), 9.00 (1H, br s, OH); m/z 237 (28%), 220 (47), 178 (21), 160 (100), 143 (16).

5) α-Methyl-2-(*E*-2-phenylethenyl)benzylamine

A solution of 1-acetyl-2-(*E*-2-phenylethenyl)benzene oxime (7.75 g, 0.033 mol) in dry ether (50 ml) was added dropwise, with stirring and ice cooling, to lithium aluminium hydride (16.0 g, 0.421 mol) a dry ether (450 ml) over 1 h. The resulting green suspension was stirred 1 h at room temperature and heated under reflux for 20 h, then cooled to -20°C. The reaction mixture was carefully hydrolysed by the dropwise addition of a solution of saturated sodium sulphate (400 ml), with vigorous stirring and cooling, then stirred a further 1 h at room temperature. The resulting white precipitate was filtered through Celite, washed with ether (4x200 ml), the combined ether layer washed with water (3x200 ml) and dried. Most of the solvent was removed under reduced pressure then a solution of 1N hydrochloric acid (200 ml) was added. The acidic aqueous layer was separated, washed with ether (2x150 ml) then rebasified by the careful addition of a solution of

sodium bicarbonate (20% w/v, 250 ml), then extracted with ether (3x750 ml) and dried. The solvent was removed under reduced pressure to give α-methyl-2-(*E*-2-phenylethenyl)-benzylamine as a yellow oil (6.73 g, 91%) which was used without further purification. (Found: m/z, 223.135835. $C_{16}H_{17}N$ requires m/z, 223.136093); ν_{max} (liquid) 3370 and 3690 cm^{-1} (N-H); δ_H (80Mz) 1.43 (3H, d, J 6.4Hz, Me), 1.70-2.5 (2H, br, NH_2) 4.60 (1H, br, C*H*-Me), 6.96 (1H, one half AB, J 16Hz, olefinic), 7.09-7.61 (10H, m, aromatics); m/z 223 (17%), 208 (100), 130 (22), 91 (42). The picrate derivative had m.p. 214-217°C (Found: C, 58.20; H, 4.6; N, 12.1. $C_{22}H_{20}N_4O_7$ requires C, 58.4; H, 4.5; N, 12.4%).

6) *N*-Benzoyl-α-methyl-2-(*E*-2-phenylethenyl)benzylamine

A mixture of α-methyl-2-(*E*-2-phenylethenyl)benzylamine (7.13 g, 0.032 mol), freshly distilled benzoyl chloride(8.64 g, 0.062 mol), dry pyridine (57 ml) and dry benzene (135 ml) was heated under reflux for 40 min. The reaction was allowed to cool, water (1000 ml) and benzene (500 ml) added, the aqueous layer separated and extracted with benzene (2x250 ml). The combined organic layer was washed with a solution of sodium carbonate (5% w/v, 150 ml), water (2x100 ml) and dried. Removal of the solvent under reduced pressure gave a brown oil which was purified by chromatography, m.p.l.c. (silica, ethyl acetate:petrol, 1:4) to give a white solid which was recrystallised from pentane and ethanol to give *N*-benzoyl-α-methyl-2-(*E*-2-phenylethenyl)benzylamine as white crystals (9.25 g, 88%), m.p. 186-187°C (Found: C, 84.1; H, 6.6; N, 4.2. $C_{23}H_{21}NO$ requires C, 84.4; H, 6.5; N, 6.3%); ν_{max} (Nujol)

3315 (N-H) and 1635 cm^{-1} (C=O). ^1H N.m.r. and mass spectral data see Appendix 12.

7) 1-Formyl-2-(2-phenylpropenyl)benzene oxime

A mixture of 1-formyl-2-(2-phenylpropenyl)benzene as an *E/Z* mixture (5.43 g, 0.024 mol), hydroxylamine hydrochloride (5.50 g, 0.079 mol), dry pyridine (6 ml) and ethanol (50 ml) was heated under reflux for 30 min. The solvent was removed under reduced pressure, water (65 ml) and dichloromethane (100 ml) added, the aqueous phase was separated, extracted with dichloromethane (2x50 ml), the combined organic layer washed with water (2x50 ml) and dried. The solvent was removed under reduced pressure to leave a brown solid which was purified by chromatography, m.p.l.c. (silica, ether:petrol 40/60, 1:2) to give a white semi-solid as a mixture of *E* and *Z* 1-formyl-2-(2-phenylpropenyl)benzene oximes (3.81 g, 66%), (Found: m/z, 237.113207. $C_{16}H_{15}NO$ requires m/z, 237.115358); ν_{max} (Nujol) 3300 cm^{-1} (br O-H); δ_H (200MHz) 2.10 (3H, d, J 1.3Hz, *Z* Me), 2.31 (3H, d, J 1.5Hz, Me), 6.68 (1H, br q, *E* olefinic), 6.96 (1H, brd, q, *Z* olefinic), 7.07-7.89 (18H, m, aromatic), 8.41 (1H, s, *Z* *H*C=N), 8.45 (1H, s, *E* *H*-C=N), 9.15 (2H, br s, O-H); m/z 237 (21%), 222 (100), 205 (30), 160 (54). Recrystallisation from petrol and ethanol gave the major *Z* isomer as white crystals, m.p. 96-97°C (Found: C, 80.70; H, 6.2; N, 5.7. $C_{16}H_{15}NO$ requires C, 81.0; H, 6.4; N, 5.90%); ν_{max} (Nujol) 3300 cm^{-1} (OH); δ_H (80MHz) 2.07 (3H, d, J 1.3Hz, Me), 6.94 (1H, br q, olefinic), 7.24-7.90 (9H, m, aromatics), 8.37 (1H, s, *H*-C=N), 8.2-8.9 (1H, br s, OH).

8) 2-(2-Phenylpropenyl)benzylamine as *E/Z* mixture

A mixture of *E* and *Z* 1-formyl-2-(2-phenylpropenyl)-benzene oximes (18.4 g, 0.078 mol) in dry ether (150 ml) was added dropwise, with mechanical stirring and ice cooling lithium aluminium hydride (20.0 g, 0.526 mol) in dry ether (1000 ml) over 1 h. The resulting green suspension was stirred 2 h at room temperature then heated under reflux 1 h, then cooled to -20°C. The reaction mixture was carefully hydrolysed by the dropwise addition of a solution of saturated sodium sulphate (1000 ml), with vigorous mechanical stirring and cooling, then stirred a further 1 h at room temperature. The resulting white precipitate was filtered through Celite, washed with ether (3x500 ml), the ether layer separated and the combined ether layer separated, washed with water (3x300 ml) and dried. Most of the solvent was removed under reduced pressure and a solution of 2N hydrochloric acid (300 ml) added. The acidic aqueous layer was separated, washed with ether (2x200 ml) then rebasified by the careful addition of a solution of sodium bicarbonate (20% w/v, 500 ml), then extracted with ether (3x1000 ml), washed with water (2x200 ml) and dried. The solvent was removed under reduced pressure to give an *E/Z* mixture of 2-(2-phenylpropenyl)benzylamine as a brown oil (12.9 g, 75%) which was used without further purification. (Found: m/z, 223.134741. $C_{16}H_{17}N$ requires m/z, 223.136093); ν_{max} (liquid) 3160 and 3090 cm^{-1} (NH_2); δ_H (80MHz) 1.95 (4H, br, 2xNH_2), 2.13 (3H, d, J 1.3Hz, *E* Me), 2.29 (3H, d, J 1.5Hz, Z Me), 3.84 (4H, brd, s, 2xCH_2), 6.64 (1H, brd, q, J 1.4Hz, olefinic), 6.86-7.53 (19H, m, aromatic); m/z

223 (53%), 222 (41), 206 (100), 191 (65), 91 (76). The picrate derivative had m.p. 196-204°C (Found: C, 58.2; H, 4.6; N, 12.6. $C_{22}H_{20}N_4O_7$ requires C, 58.4; H, 4.5; N, 12.4%).

9) *N*-Benzoyl-2-(2-phenylpropenyl)benzylamine as an *E/Z* mixture

A mixture of *E/Z* 2-(2-phenylpropenyl)benzylamine (10.7 g, 0.048 mol), distilled benzoyl chloride (12.9 g, 0.092 mol), dry pyridine (85 ml) and dry benzene (200 ml) was heated under reflux for 20 min. The mixture was allowed to cool, water (300 ml) and benzene (300 ml) added, the aqueous layer separated and extracted with benzene (2x250 ml), the combined organic layer was washed with a solution of sodium carbonate (5% w/v, 250 ml), water (2x200 ml) and dried. Removal of the solvent under reduced pressure gave a brown solid which was purified by chromatography, m.p.l.c. (silica, ethyl acetate: petrol 40/60, 1:3) to give a yellow semi-solid gum of *E/Z N*-benzoyl-2-(2-phenylpropenyl)benzylamine (10.7 g, 86%), (*E:Z* ratio, 37:63 by n.m.r. integral; *E* and *Z* isomers identified by N.O.E. of Me on olefinic proton) (Found: m/z, 327.160862. $C_{23}H_{21}NO$ requires m/z, 327.162306); ν_{max} (neat) 3150 (N-H) and 1680 cm^{-1} C=O). ^1H N.m.r. and mass spectral data see Appendix 12.

C. INTRAMOLECULAR REACTIONS OF NITRILE YLIDES DERIVED FROM *N*-(2-ALKENYLBENZYL) BENZIMIDOYL CHLORIDES

1) Generation and reaction of nitrile ylide derived from *N*-[2-(*E*-2-phenylethenyl)benzyl] benzimidoyl chloride

A mixture of *N*-benzoyl-2-(*E*-2-phenylethenyl)benzylamine (321 mg, 1.03 mmol) and phosphorus pentachloride (217 mg, 1.03 mmol) in dry ether (50 ml) was heated under reflux for 16 h. The solvent was removed under reduced pressure and the phosphorus oxychloride formed removed by drying under high vacuum. After obtaining ^{1}H n.m.r., infrared spectra and mass spectra to confirm the formation of the imidoyl chloride, the remaining *N*-[2-(*E*-2-phenylethenyl)benzyl] benzimidoyl chloride was used without further purification (Found: m/z, 331.112279. $C_{22}H_{18}N^{35}Cl$ requires m/z, 331.112771); δ_H (80MHz) 5.20 (2H, s), 6.68-8.40 (16H, m, aromatic); m/z 333 (6%), 331 (14), 230 (3), 228 (10), 193 (100).

Dry T.H.F. (30 ml) was added to *N*-[2-(*E*-2-phenylethenyl)-benzyl] benzimidoyl chloride and then dry potassium *tert*-butoxide (217 mg, 1.92 mmol) added with stirring, under dry nitrogen. Initially a red colour developed which gradually fades to leave a yellow solution, after stirring at room temperature for 2 h. Water (20 ml) was added and most of the solvent removed at reduced pressure, ether (200 ml) added, the aqueous layer separated, extracted with ether (3x100 ml), the combined ether layer washed with water (3x100 ml) and dried. Removal of the solvent under reduced pressure gave a brown oil which was purified by flash chromatography (silica, ethyl acetate:

petrol 40/60, 1:3) to give: (1) a white solid which was recrystallised from pentane and ethanol to give white crystals of 2a,3,3a-trihydro-2a-phenyl-3-*exo*-phenylcyclopropa[c]isoquinoline (257 mg, 85%), m.p. 117-119°C (Found: C, 89.2; H, 5.6; N, 4.7. $C_{22}H_{17}N$ requires C, 89.5; H, 5.80; N, 4.7%). ^{1}H N.m.r., ^{13}C n.m.r. and mass spectral data see Appendix 13.

(2) recovered *N*-benzoyl-2-(*E*-2-phenylethenyl)benzylamine (23 mg, 7%). Identical to starting material by t.l.c. and ^{1}H n.m.r.

Note: The benzimidoyl chloride was prepared as above and treated with only one molar equivalent of potassium *tert*-butoxide, and following identical work up the same products were observed:

(1) 2a,3,3a-trihydro-2a-phenyl-3-*exo*-phenyl cyclopropa[c]-isoquinoline (69%);

(2) recovered *N*-benzoyl-2-(*E*-2-phenylethenyl)benzylamine (25%).

2) Generation and reaction of nitrile ylide derived from *N*-[α-methyl-2-(*E*-2-phenylethenyl)benzyl]benzimidoyl chloride

A mixture of *N*-benzoyl-α-methyl-2-(*E*-2-phenylethenyl)-benzylamine (124 mg, 0.38 mmol) and phosphorus pentachloride (79 mg, 0.38 mmol) in dry ether (50 ml) was heated under reflux for 12 h. The solvent was removed under reduced pressure and the phosphorus oxychloride formed removed by drying under high vacuum for 3 h. Dry T.H.F. (30 ml) was added to the

N-[α-methyl-2-(*E*-2-phenylethenyl)benzyl] benzimidoyl chloride and then dry potassium *tert*-butoxide (85 mg, 0.76 mmol) added with stirring, under dry nitrogen. The mixture was stirred at room temperature for 6 h, water added (20 ml), and most of the solvent removed under reduced pressure. Dichloromethane (150 ml) added, the aqueous layer separated, extracted with dichloromethane (2x70 ml), the combined organic layer washed with water (2x80 ml) and dried. Removal of the solvent gave a brown oil which was purified by flash chromatography (silica, ethyl acetate:petrol 40/60, 1:3) to give:

(1) 4-benzyl-1-methyl-3-phenylisoquinoline as a clear oil (74 mg, 63%) (Found: m/z, 309.150114. $C_{23}H_{19}N$ requires m/z, 309.151742). ^{1}H N.m.r., ^{13}C n.m.r. and mass spectral data see Appendix 15.

(2) recovered *N*-benzoyl-α-methyl-2-(*E*-2-phenylethenyl)benzylamine (22 mg, 18%).

3) Generation and reaction of nitrile ylide derived from *N*-[2-(*E*/*Z*-2-phenylpropenyl)benzyl]benzimidoyl chloride

A mixture of *N*-benzoyl-2-(*E*/*Z*-2-phenylpropenyl)benzylamine (1.13 g, 3.46 mmol) (*E*:*Z* ratio, 37:63 by proton n.m.r. integral) was dried by dissolving in dry ether (100 ml) and stirring with anhydrous calcium sulphate for 4 h. The drying agent was followed through a pre-dried sinter funnel and to the resulting solution of amides was added phosphorus pentachloride (0.722 g, 3.46 mmol) and the resulting mixture heated under reflux for 14 h. The solvent was removed under reduced pressure and the phosphorus oxychloride formed removed by drying under high vacuum for 3 h. Dry T.H.F. (75 ml) was added to the resulting

N-[2-(*E*/*Z*-2-phenylpropenyl)benzyl]benzimidoyl chloride and then potassium *tert*-butoxide (0.78 g, 6.93 mmol) added with stirring, under dry nitrogen. The mixture was stirred at room temperature for 12 h, water (50 ml) added and most of the solvent removed under reduced pressure. Dichloromethane (200 ml) added, the aqueous layer separated, extracted with dichloromethane (2x100 ml), the combined organic layer washed with water (2x100 ml), and dried. Removal of solvent under reduced pressure gave a brown oil which was purified by flash chromatography (silica, ethyl acetate:petrol 40/60, 1:3) to give:

(1) pure 2a,3,3a-trihydro-3-methyl-2a-phenyl-3-*exo*-phenyl cyclopropa[c]isoquinoline as a clear oil (120 mg, 11.2%) which solidified and was recrystallised from pentane and ethanol to give white crystals m.p. 128-130°C (Found: C, 89.0; H, 6.4; N, 4.7. $C_{23}H_{17}N$ requires C, 89.3; H, 6.2; N, 4.5%). ^{1}H N.m.r., ^{13}C n.m.r. and mass spectral data see Appendix 13.

(2) pure 2a,3,3a-trihydro-3-methyl-2a-phenyl-3-*endo*-phenyl cyclopropa[c]isoquinoline as a clear oil (72 mg, 6.7%), (Found: m/z, 309.150409. $C_{23}H_{19}N$ requires m/z, 309.151742). ^{1}H N.m.r., ^{13}C n.m.r. and mass spectral data see Appendix 13.

(3) a mixture of *exo/endo* 2a,3,3a-trihydro-3-methyl-2a-phenyl-3-phenylcyclopropa[c]isoquinoline as a clear oil (410 mg, 38.3%). (Ratio *exo:endo*, 30:70 by proton n.m.r.) (Total *exo* isomer = 240 mg, total *endo* = 359 mg; ratio *exo:endo*, 40:60).

(4) recovered *N*-benzoyl-2-(*E*/*Z*-2-phenylpropenyl)benzylamine (224 mg, 19.8%). Identical to starting material by t.l.c. and ^{1}H n.m.r.

4) Thermolysis of 2a,3,3a-trihydro-2a-phenyl-3-*exo*-phenyl cyclopropa[c]isoquinoline

A solution of 2a,3,3a-trihydro-2a-phenyl-3-*exo*-phenyl cyclopropa[c]isoquinoline (204 mg, 0.69 mmol) in dry benzene (30 ml) was heated under reflux, in the absence of light, for 12 h. T.l.c. indicated no starting material remaining and only one product formed. Removal of the solvent under reduced pressure gave a brown oil which was purified by flash chromatography (silica, ethyl acetate:petrol 40/60, 1:9) to give 3,4-diphenyl-1*H*-2-benzazepine as a clear oil (188 mg, 92%), (Found: m/z, 295.134533. $C_{22}H_{17}N$ requires m/z, 295.136093). ^{1}H N.m.r., ^{13}C n.m.r. and mass spectral data see Appendix 14.

5) Reaction of 3,4-diphenyl-1*H*-2-benzazepine with excess base

A solution of 3,4-diphenyl-1*H*-2-benzazepine (70 mg, 0.24 mmol) a dry T.H.F. (30 ml) and potassium *tert*-butoxide (32 mg, 0.29 mmol) was stirred at room temperature for 12 h, then heated under reflux for a further 12 h. T.l.c. and ^{1}H n.m.r. indicated only starting material present and no other products formed.

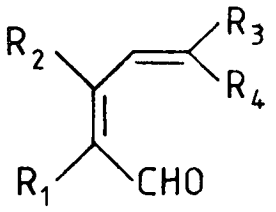
6) Thermolysis of *exo/endo* 2a,3,3a-trihydro-3-methyl-2a,3-diphenylcyclopropa[c]isoquinoline

A mixture of *exo/endo* 2a,3,3a-trihydro-3-methyl-2a,3-diphenylcyclopropa[c]isoquinoline (182 mg, 0.59 mmol) and dry benzene (50 ml) was heated under reflux for 61 h. Evaporation of the solvent under reduced pressure gave a brown oil which was purified by flash chromatography (silica, ethyl acetate: petrol 40/60, 1:9) to give a white solid which was recrystallised

from pentane and ethyl acetate to give 3-methyl-3,4-diphenyl-3*H*-2-benzazepine as white crystals (92 mg, 51%), m.p. 172-173°C (Found: C, 89.1; H, 6.1; N, 4.6. $C_{23}H_{19}N$ requires C, 89.3; H, 6.2; N, 4.5%). ^{1}H N.m.r., ^{13}C n.m.r. and mass spectral data see Appendix 14.

Appendix 1

Alkenylcyclopentenylaldehydes and Alkenylcyclohexenylaldehydes

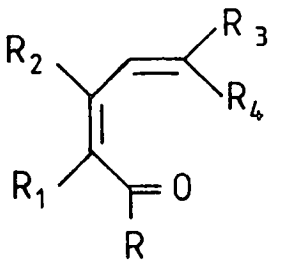


Mass spectral data m/z (% relative abundance)

R_1, R_2 = $(CH_2)_3$; R_3 = Me; R_4 = H	136 (20); 121 (100)
R_1, R_2 = $(CH_2)_3$; R_3 = Ph; R_4 = H	198 (100); 197 (44); 170 (31); 169 (33); 142 (36); 141 (57); 121 (45); 115 (24); 91 (34)
R_1, R_2 = $(CH_2)_4$; R_3 = Ph; R_4 = H	212 (100); 184 (23); 183 (30); 169 (17); 155 (21); 141 (64); 115 (32); 91 (42)
R_1, R_2 = $(CH_2)_4$; R_3 = Ph; R_4 = Me	226 (9); 211 (100)
R_1, R_2 = $(CH_2)_4$; R_3 = Me; R_4 = Me	164 (11); 149 (100); 135 (50)
R_1, R_2 = $(CH_2)_4$, R_3 = H; R_4 = H	136 (40); 135 (29); 79 (100); 77 (71)

Appendix 1 (continued)

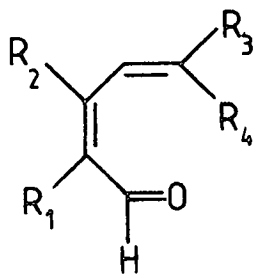
Alkenylcyclopentenylketones and Alkenylcyclohexenylketones



	Mass Spectral Data (m/z, % relative abundance)
R=Me; $R_1R_2=(CH_2)_3$; R_3=Ph; R_4=H	212 (25); 186 (27); 106 (98) 105 (100)
R=*p*-tolyl; $R_1R_2=(CH_2)_3$; R_3=Ph; R_4=H	288 (100); 211 (71); 119 (44); 105 (26); 91 (51)
R=Me; $R_1R_2=(CH_2)_4$; R_3=Ph; R_4=H	226 (100); 211 (61); 149 (89) 141 (72); 115 (64)
R=*p*-tolyl; $R_1R_2=(CH_2)_4$; R_3=Ph; R_4=H	302 (100); 225 (48); 211 (38); 119 (55); 91 (53)

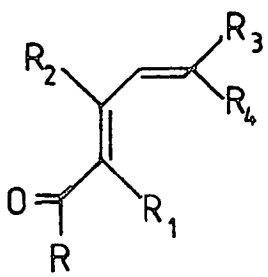
Appendix 1 (continued)

Acyclic α,β:γ,δ-Unsaturated Aldehydes and Ketones



Mass spectral data (m/z, % relative abundance)

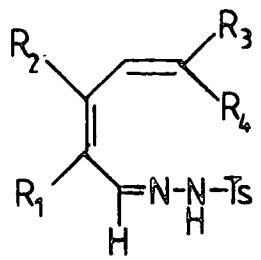
R_1=Me; R_2=Ph; R_3=Ph; R_4=H	248 (90); 205 (75); 115 (100)
R_1=Me; R_2=Ph; R_3=Ph; R_4=Me	262 (30); 247 (100); 185 (30); 115 (47); 91 (44)



R=H; R_1=Me; R_2=Ph; R_3=Ph; R_4=H	248 (100); 205 (35); 171 (32)
R=Me_2CH; R_1=H, R_2=Me R_3=Me, R_4=H	152 (27); 137 (16); 109 (100); 81 (36); 71 (29)

Appendix 2

Tosylhydrazones of Alkenylcyclopentenylaldehydes and Alkenylcyclohexenylaldehydes

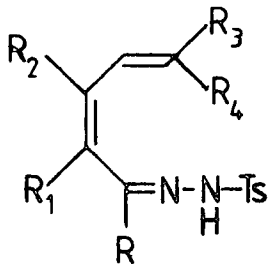


Mass spectral data (m/z, % relative abundance)

$R_1R_2=(CH_2)_3$; R_3=Me; R_4=H	304 (12); 278 (9); 156 (11); 149 (88); 139 (35); 132 (33); 121 (38); 105 (20); 91 (100); 79 (38); 77 (29); 65 (35); 55 (15)
$R_1R_2=(CH_2)_3$; R_3=Ph; R_4=H	(180°C) 338 (1); 183 (100); 141 (52); 128 (8); 115 (12); 91 (43); 77 (13); 65 (14); 51 (9); 44 (10); 39 (9)
$R_1R_2=(CH_2)_4$; R_3=Ph; R_4=H	(160°C) 352 (15); 208 (95); 197 (99); 155 (42); 141 (41); 129 (34), 115 (39); 91 (100); 77 (45); 65 (54); 51 (25); 41 (31); 39 (32)
$R_1R_2=(CH_2)_4$; R_3=Ph; R_4=Me	394 (<1); 239 (73); 225 (47); 210 (37); 156 (42)
$R_1R_2=(CH_2)_4$; R_3=Me; R_4=Me	332 (8); 177 (100); 91 (59)
$R_1R_2=(CH_2)_4$; R_3=H R_4=H	304 (5); 156 (18); 151 (64); 149 (100); 91 (70)

Appendix 2 (continued)

Tosylhydrazones of Alkenylcyclopentenylketones and Alkenylcyclohexenylketones

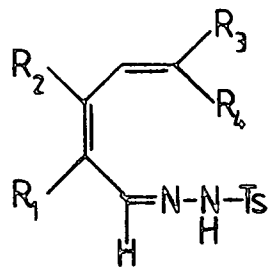


Mass spectral data (m/z, % relative abundance)

R=Me; $R_1R_2=(CH_2)_3$; R_3=Ph; R_4=H	380 (3); 352 (7); 223 (96); 91 (100)
R=*p*-tolyl; $R_1R_2=(CH_2)_3$; R_3=Ph, R_4=H	456 (3); 301 (100); 272 (29); 91 (37)
R=Me; $R_1R_2=(CH_2)_4$; R_3=Ph; R_4=H	394 (1); 239 (42); 223 (43); 91 (100); 167 (35)

Appendix 2 (continued)

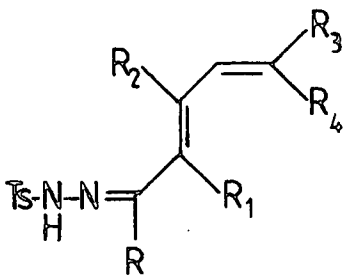
Tosylhydrazones of Acyclic-α,β:γ,δ-Unsaturated Aldehydes and Ketones



Mass spectral data (m/z, % relative abundance)

R_1=Me; R_2=Ph; R_3=Ph; R_4=H — 416 (1); 244 (77); 233 (46); 91 (100)

R_1=Me; R_2=Ph; R_3=Ph; R_4=Me — 430 (1); 275 (22); 263 (24); 247 (100); 231 (46); 91 (98)

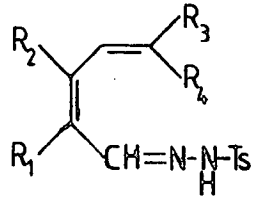


R=H; R_1=Me; R_2=Ph; R_3=Ph; R_4=H — 416 (<1); 388 (2); 233 (100); 155 (27); 91 (97)

R=Me_2CH; R_1=H, R_2=Me; R_3=Me; R_4=H — 320 (<1); 305 (18); 165 (100); 123 (85); 105 (5); 95 (12); 91 (30); 79 (20); 77 (11); 65 (9); 55 (8); 53 (6); 43 (20); 41 (28); 39 (11)

Appendix 3

Tosylhydrazones of Alkenylcyclopentenylaldehyde and Alkenylcyclohexenylaldehydes

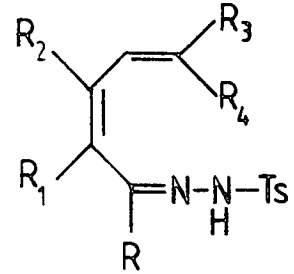


^{1}H N.m.r. spectral data ($CDCl_3$)

	NH	Methine H	Aromatic & Olefinic	Olefinic	Tosyl Me	R_3	R_4	R_1 + R_2
$R_1R_2=(CH_2)_3$; R_3=Me; R_4=H	8.20 (brd,1H)	7.90 (s,1H)	7.61 and 7.27 (AB, J8Hz,4H)	6.45 (½AB,J16Hz,1H) 5.82,5.65 (d of q, J16Hz,7Hz,1H)	2.38 (s,3H)	1.80 (d, J7Hz,3H)	-	2.72-2.30 (m,4H) 2.01-1.63 (m,2H)
$R_1R_2=(CH_2)_3$; R_3=Ph; R_4=H	8.38 (brd,1H)	8.07 (s,1H)	7.85 (½AB,J8Hz,2H) 7.48-7.08 (m,8H)	6.51 (½AB, J16Hz, 1H)	2.34 (s,3H)	-	-	2.80-2.53 (m,4H) 2.02-1.69 (m,2H)
$R_1R_2=(CH_2)_4$; R_3=Ph; R_4=H	unresolved	8.42 (s,1H)	7.79 (½AB,J8Hz,2H) 7.5-7.2 (m, 9H)	6.58 (½AB, J16Hz, 1H)	2.37 (s,3H)	-	-	2.5-2.22 (m,4H) 1.8-1.45 (m,4H)
$R_1R_2=(CH_2)_4$; R_3=Ph; R_4=Me	unresolved	7.58 (s,1H)	7.77 (½AB,J8Hz,2H) 7.48-7.15 (m, 8H)	6.12 (brd, m, 1H)	2.37 (s,3H)	-	1.79 (d,J1Hz,3H)	2.55-2.0 (m,4H) 1.77-1.48 (m,4H)
$R_1R_2=(CH_2)_4$; R_3=Me; R_4=Me	unresolved	7.59 (s,1H)	7.9-7.7 (m,3H) 7.28 (½AB,J8Hz,1H)	5.49 (brd, m, 1H)	2.38 (s,3H)	1.36 (d, J1Hz,3H)	1.70 (d,J1Hz,3H)	2.5-1.9 (m,4H) 1.7-1.48 (m,4H)
$R_1R_2=(CH_2)_4$; R_3=H; R_4=H	unresolved	8.10 (s,1H)	7.8(½AB,J8Hz,2H) 7.45-7.25 (m,3H)	6.88,6.74 (d of d,J16Hz,10Hz,2H) 5.42-5.0 (m,1H)	2.39 (s,3H)	-	-	2.52-2.15 (m,4H) 1.86-1.42 (m,4H)

Appendix 3 (continued)

Tosylhydrazones of alkenylcyclopentenylketones and alkenylcyclohexenylketones

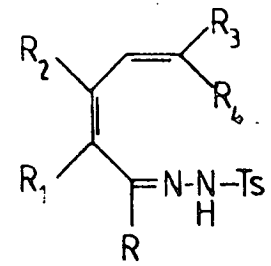


^{1}H N.m.r. spectral data ($CDCl_3$)

	NH	Aromatic and Olefinic	Olefinic	Tosyl Me	R	R_1 + R_2
R=Me; $R_1R_2=(CH_2)_3$; R_3=Ph; R_4=H	8.18 (brd,s,1H)	7.87 (½AB,J8Hz,2H) 7.42-7.05 (m,7H)	7.53, 6.52 (AB,J16Hz,2H)	2.32 (s,3H)	1.98 (s,3H)	2.80-2.50 (m,4H) 2.11-1.70 (m,2H)
R=*p*-tolyl; $R_1R_2=(CH_2)_3$; R_3=Ph; R_4=H	7.90 (brd,s,1H)	7.75 (½AB,J8Hz,2H) 7.45 (½AB,J8Hz,2H) 7.30-6.93 (m, 9H)	6.55, 6.15 (AB,J16Hz,2H)	2.31 (s,3H)	2.31 (s,3H,Me of *p*-tolyl)	1.95-2.95 (m,6H)
R=Me; $R_1R_2=(CH_2)_4$; R_3=Ph; R_4=H	7.57 (brd,s,1H)	7.68 (½AB,J8Hz,2H) 7.4-6.84 (m, 7H)	6.59, 6.13 (AB,J16Hz,2H)	2.29 (s,3H)	2.00 (s,3H)	2.43-1.54 (8H)

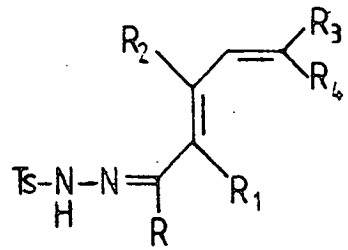
Appendix 3 (continued)

Tosylhydrazones of α,β;γ,δ-Acyclic Unsaturated Aldehydes and Ketones



^{1}H N.m.r. spectral data ($CDCl_3$)

	NH	R	Aromatic and Olefinic	Olefinic	Tosyl Me	R_1	R_2	R_3	R_4
R=H; R_1=Me; R_2=Ph; R_3=Ph; R_4=H	8.65 (brd,1H)	8.11 (s,1H)	7.88 (½AB,J8Hz,2H) 7.60-6.92 (m, 13H)	6.00 (d,16Hz,1H)	2.38 (s,3H)	1.68 (s,3H)	-	-	-
R=H; R_1=Me; R_2=Ph; R_3=Ph; R_4=Me	unresolved	7.92 (s,1H)	7.79 (½AB,J8Hz,2H) 7.50-6.95 (m, 13H)	6.38 (brd,m,1H)	2.38 (s,3H)	1.92 (d,J1Hz,3H)	-	-	1.81 (d,J2Hz,3H)

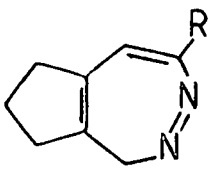


R=H; R_1=Me: R_2=Ph; R_3=Ph; R_4=H	7.50 (s,1H)	unresolved	7.75 (½AB,J8Hz,2H) 7.52-6.94 (m, 14H)	6.08 (d,J16Hz,1H)	2.38 (s,3H)	2.15 (s,3H)	-	-	-
R=Me_2CH; R_1=H; R_2=Me; R_3=Me; R_4=H	7.41 (brd,s, 1H)	2.41 (heptet J6Hz,1H) 0.9 (d,J6Hz, 6H)	7.77-7.25 (AB,J8Hz, 4H)	6.1 (d,J15Hz,1H) 5.83 (d of q, J15Hz,5Hz,1H)	2.38 (s,3H)	5.36 (brd,1H)	1.53 (t,J1.5Hz, 3H)	1.8 (d,5Hz, 3H)	-

Appendix 4

Cyclopentyl[3*H*-1,2]diazepines

^{1}H N.m.r. spectral data



	R=Me	R=Ph
cyclopentyl + quasi axial H	1.80-1.97 (m,3H)	1.75-2.39 (m,3H)
cyclopentyl	2.34-2.69 (m,4H)	2.40-3.10 (m,4H)
R	2.32 (s,3H)	7.85-7.65 (m,*o*,2H) & 7.53-7.13 (m,*m*+*p*,3H)
quasi equatorial H	5.84 (one half of doublet; 1H)	6.08 (d,J9Hz,1H)
5-H	5.86 (s,1H)	6.38 (s,1H)

^{13}C N.m.r. spectral data ($CDCl_3$)

(25.2MHz)	21.14 (Me), 24.20, 33.17, 35.38 (C-6,C-7,C-8), 66.52 (C-1), 112.45 (C-5), 126.83 (quat), 139.42 (quat), 152.79 (quat)	(20MHz) 24.03, 33.30, 35.51, (C-6,C-7,C-8), 67.37 (C-1), 110.40 (C-5), 125.58, 127.79 (quat), 127.98, 128.47, 137.30 (quat), 140.14 (quat), 154.76 (quat)

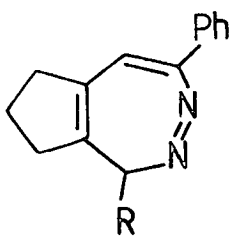
Mass spectral data

148 (7), 120 (57), 105 (100), 91 (78), 65 (14)	210 (7), 182 (100), 167 (62), 154 (69), 115 (24), 91 (25)

Appendix 4 continued

Cyclopentyl[3*H*-1,2]diazepine

^{1}H N.m.r. spectral data ($CDCl_3$)



	R=Me (360MHz)	R=*p*-tolyl (100MHz)
Cyclopentyl + quasi axial	1.93-2.12 (m, 2H) (Me superimposed) & 2.52-2.83 (m,4H)	1.81-3.08 (m,7H) (*p*-tolyl Me superimposed)
R	2.11 (s,Me + quasi axial H,4H)	2.39 (s,3H *p*-tolyl Me)
	(1*H* q and Me d on addition of $Eu(fod)_3$)	
5-H	6.39 (s,1H)	6.50 (brd, s, 1H)
m-, *p*-phenyl	7.30-7.44 (m,3H)	6.85-7.90 (m,9H)
o-phenyl	7.81-7.77 (m,2H)	

^{13}C N.m.r. spectral data ($CDCl_3$)

(20MHz)	15.98 (Me), 23.50 (C-7), 32.13, 33.48 (C-6,C-8), 72.82 (C-1), 109.96 (C-5), 125.52, 127.93, 128.44, 132.77 (quat), 137.22 (quat) 138.92 (quat), 154.44 (quat)	(90.5MHz) 21.19 (Me), 23.60, 33.52, 33.88 (C-6,C-7,C-8), 81.94 (C-1), 110.19 (C-5), 125.69, 128.18, 128.31, 129.14, 132.89 (quat), 135.63 (quat), 137.16 (quat), 137.25 (quat), 138.96 (quat), 154.29 (quat)

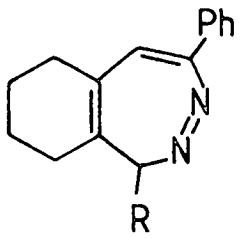
Mass spectral data

224 (<1), 196 (100), 181 (21), 168 (62)	300 (4), 272 (100), 244 (64), 229 (53), 119 (37), 115 (44)

Appendix 4 continued

Cyclohexyl[3*H*-1,2]diazepines

^{1}H N.m.r. spectral data ($CDCl_3$)



	R=H (100MHz)	R=Me (360MHz)
Cyclohexyl	1.60-1.95 (m,4H)	1.37-1.87 (m,4H), 2.32-
Cyclohexyl + quasi axial H	2.15-2.90 (m,5H)	2.54 (m,4H), 2.12 (brd, q, 1H)
1-H equatorial (R)	5.82 (d, J8Hz,1H)	2.02 (d,J6.4Hz, 3H)
5-H	6.28 (s,1H)	6.30 (s,1H)
m, *p*-phenyl	7.10-7.52 (m,3H)	7.30-7.43 (m,3H)
o-phenyl	7.62-7.90 (m,2H)	7.78-7.81 (m,2H)

^{13}C N.m.r. spectral data ($CDCl_3$)

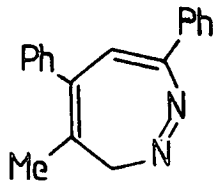
(90.56MHz)	22.42 (C-7,C-8), 29.13, 31.31 (C-6,C-9), 71.58 (C-1), 116.68 (C-5), 123.57 (quat), 125.61, 127.99, 128.50, 134.34 (quat), 137.30 (quat), 154.10 (quat)	(90.56MHz) 15.03 (Me), 22.34, 22.44, 26.30, 29.72 (C-6,C-7, C-8,C-9), 74.69 (C-1), 116.38 (C-5), 125.63, 127.34, (quat), 127.99, 128.53, 134.12 (quat), 137.24 (quat), 153.83 (quat)

Mass spectral data

224 (3), 196 (100), 168 (87), 167 (95), 91 (32)	238 (8), 210 (100), 195 (27), 181 (30), 167 (57), 91 (25)

Appendix 4 continued

4-Methyl-5,7-diphenyl-3*H*-[1,2]-diazepine



^{1}H N.m.r. ($CDCl_3$) (100MHz)

Me	2.11 (s,3H)
quasi axial H	2.35 (d of d, J8Hz, 1Hz, 1H)
quasi equatorial H	6.09 (d, J8Hz, 1H)
olefinic	6.49 (s, 1H)
aromatic	7.05-7.50 (m, 8H)
o-phenyl	7.62-7.88 (m, 2H)

^{13}C N.m.r. ($(CD_3)_2$ C=O) (90.5MHz)

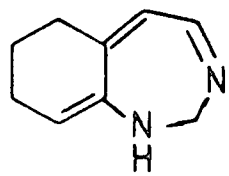
20.50 (Me), 71.92 (C-3), 114.70 (olefinic), 120.74 (quat), 124.81, 126.61, 127.47, 127.84, 128.75, 136.32 (quat), 138.29 (quat), 138.96 (quat), 153.76 (quat)

Mass spectral data

260 (1), 232 (100), 217 (56), 202 (25), 115 (25)

Appendix 4 continued

1*H*-2,6,7,8-Tetrahydro-cyclohexa[d] [1,3]-diazepine



^{1}H N.m.r. spectral data ($CDCl_3$) (360MHz)

Cyclohexyl		1.75 (brd, quintet, J6.3Hz, 2H, H-7) 2.15 (q, J5.5Hz, 2H, H-8) collapses to (t, J5Hz) on irradiation at 5.58 2.34 (t of d, J6.3Hz, 1.2Hz, H-6) collapses to (t, J6Hz) on irradiation at 5.53
CH_2	25°C	3.57 (s, 2H)
	-90°C	3.24 (d, J13.3Hz, 1H) 3.77 (brd, d of d, J12.7Hz, 4Hz, 1H) collapses to (d, J13Hz) on irradiation at 6.75 (NH)
H-5		5.53 (brd, d, J5.2Hz, 1H)
H-4		6.71 (brd, d, J5.2Hz, 1H)
H-9		5.58 (brd, t, J3.9Hz, 1H)
NH		6.37 (brd, 1H)

^{13}C N.m.r. ($CDCl_3$) (50.3MHz)

22.49, 25.42, 32.86 (C-6, C-7, C-8), 55.15 (C-2), 117.25 (olefinic), 129.19 (olefinic), 135.39 (quat), 137.60 (olefinic), 144.85 (quat)

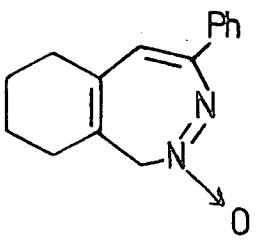
Mass spectral data

148 (100), 120 (48), 93 (34), 91 (45)

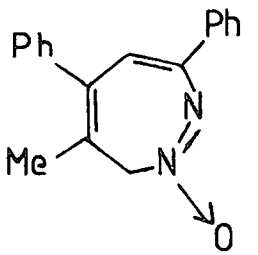
Appendix 4b

[1,2]Diazepine *N*-oxides

4-Phenyl-1*H*-6,7,8,9-tetrahydrocyclohexa[d][1,2]diazepine *N*-oxide



4-Methyl-5,7-diphenyl-3*H*-[1,2]diazepine *N*-oxide



^{1}H N.m.r. data	($(CD_3)_2C=O$)		($CDCl_3$)
Cyclohexyl	1.40-1.91 (m,4H) 2.15-2.61 (m,4H)	Me	2.10 (s,3H)
CH_2	(15°C) 3.8-5.2 (brd,1-CH_2) (-27°C) 4.09 (d,J11Hz); 5.04 (J11Hz)	CH_2	(29°C) 4.08(brd), 5.30(brd) (-15°C) 4.08(d,J9Hz), 5.33 (d, J9Hz)
5-H	6.73 (s,1H)	6-H	6.82 (s, 1H)
Aromatics	7.2-7.48 (m,3H)	Aromatics	7.01-7.5 (m,8H)
o-phenyl	7.52-7.77 (m,2H)	*o*-phenyl	7.52-7.83 (m,2H)
Tc/°C	31°C±1	Tc/°C	54°C±1

^{13}N.m.r. data

(90Mz) ($(CD_3)_2C=O$)	(20MHz) ($(CD_3)_2C=O$)
21.14, 21.39 (C-7,C-8), 27.41, 28.99 (C-6,C-9), 73.07 (C-1), 118.54 (C-5), 125.31, 125.51 (quat), 127.56, 127.63, 134.87, (quat), 136.70 (quat), 144.43 (quat)	20.46 (Me), 74.92 (C-3), 119.09 (C-6), 124.59 (quat), 126.49, 128.17, 128.63, 128.74, 129.83, 137.41 (quat), 138.75 (quat), 139.96 (quat), 146.94 (quat)

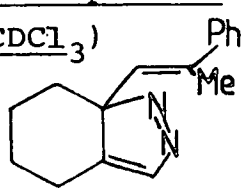
Mass spectral data

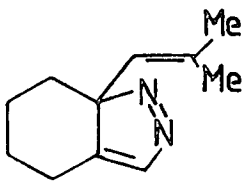
240 (13), 210 (100), 131 (16)	276 (19), 246 (100), 205 (10), 128 (33), 77 (15)

Appendix 5a

Tetrahydro-7a*H*-Indazoles

^{1}H N.m.r. spectral data ($CDCl_3$)





	(360MHz)	(80MHz)
Cyclohexyl H	0.52-0.60 (d of t, J4.2Hz, 12.9Hz, 1H)	0.40-0.60 (m, 1H)
	1.09-1.24 (m,1H)	0.80-2.03 (m,5H)
	1.61-1.76 (m,2H)	2.73-2.92 (m,2H)
	2.03-2.29 (m,2H)	
	2.88,2.92 (d of d, J13.1Hz, 3Hz, 1H)	
	2.99-3.04 (m,1H)	
Me	1.64 (d, J1.2Hz, 3H)	1.75 (d, 1.1Hz,3H)
		1.69 (d, 1.3Hz,3H)
Olefinic	5.82 (brd,d,J1.2H,1H)	5.29 (brd,1H)
3-H	7.46 (d,1.1Hz,1H)	7.34 (d, 1.5Hz,1H)
Aromatics	7.21-7.36 (m,5H)	-

^{13}C N.m.r. spectral data ($CDCl_3$)

(50MHz) 16.29 (Me), 21.56, 24.83, 28.61, 41.55 (C-4,C-5,C-7), 95.56 (quat,C-7a), 120.20 (olefinic), 125.85, 127.32, 128.05, 137.10 (C-3), 143.28 (quat), 143.49 (quat), 161.46 (quat)

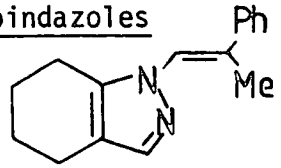
(50MHz) 17.94 (Me), 21.43, 24.77, 26.71 (Me), 28.65, 41.37, 95.56 (quat,C-7a), 117.13 (olefinic), 136.77 (C-3), 140.65 (quat), 161.49 (quat)

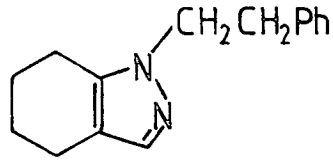
Mass spectral data

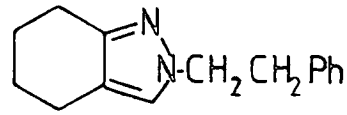
238 (70), 237 (100), 210 (37) 195 (31), 167 (61), 135 (25)

176 (66), 148 (43), 135 (90), 133 (57), 105 (100)

1-Alkyl-4,5,6,7-tetra-hydroindazoles

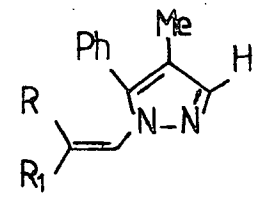






^{1}H N.m.r. spectral data ($CDCl_3$)(200MHz)				($CDCl_3$)(80MHz)	
Cyclohexyl	1.25-1.86 (m,4H) 2.50-2.60 (m,4H)	Cyclohexyl	1.67-1.85 (m,4H) 2.42-2.76 (m,4H)		1.54-1.87 (m,4H) 2.04-2.18 (m,2H) 2.38-2.53 (m,2H)
Me	2.35 (d, J1.4Hz, 3H)	CH_2	3.03-3.22 (m,2H)		3.06 (t, J7Hz, 2H)
Olefinic	6.85 (q, J1.4Hz, 1H)	CH_2	4.13-4.32 (m,2H)		4.15 (t, J7Hz, 2H)
Aromatic	7.29-7.49 (m,6H)	Aromatics	6.91-7.32 (m,6H)		6.93-7.32 (M,6H)
^{13}C N.m.r. spectral data					
(90.5MHz)	16.59 (Me), 20.54, 21.69, 22.69, 22.98 (C-4,C-5,C-6,C-7), 116.16 (quat), 121.69, 126.19, 127.44, 128.35, 132.02 (quat), 138.09 (C-3), 139.24 (quat), 141.53 (quat)	(20MHz)	20.28, 23.11, 23.32 (C-4, C-5,C-6,C-7), 37.00 (C-β), 53.02 (C-α), 115.03 (quat), 126.08, 126.21, 128,21, 128.42, 138.08 (C-3), 148.66 (quat)	(20MHz)	20.47, 20.84, 22.57, 22.84 (C-4,C-5,C-6,C-7), 36.78 (C-β), 49.93 (C-α), 115.2((quat), 126.13, 126.33, 128.24, 128.68 , 136.68 (quat), 138.39 (quat)
Mass spectral data					
	238 (60), 237 (29), 136 (22) 135 (100)		226 (38), 135 (100), 122 (62)		226 (77), 135 (86), 122 (100), 104 (48)

Appendix 6



1-Alkenyl-pyrazoles

^{1}H N.m.r. spectral data ($CDCl_3$)

	R=Me, R^1=Ph (100MHz)	R=Ph, R^1=Me (360MHz)	R=H, R^1=Ph (100MHz)
Me	2.09 (s,3H)	1.94 (s,3H)	2.06 (s,3H)
R	2.21 (d, J2Hz, 3H)	-	-
R^1	-	2.01 (d, 1.6Hz, 3H)	-
Olefinic	6.81 (brd,q, J2Hz, 1H)	6.78 (brd,q, J1.5Hz, 1H)	6.26, 6.66 (AB, J11Hz, 2H)
Aromatic	7.15-7.45 (m, 10H)	6.58-6.62,6.87-7.24 (m, 10H)	6.81-7.75 (m, 10H)
3-H	7.55 (s, 1H)	7.43 (s,1H)	7.50 (s, 1H)

^{13}C N.m.r. spectral data ($CDCl_3$)

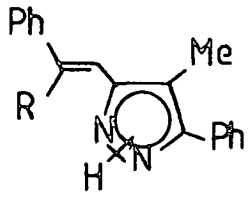
(20MHz)	8.96 (Me), 16.53 (Me), 114.44 (quat), 123.31, 126.01, 127.34, 128.02, 128.21, 128.29, 129.54, 129.98 (quat), 132.84 (quat), 140.51 (C-3), 140.99 (quat)	(90.5MHz)	8.93 (Me), 21.35 (Me), 114.44 (quat), 122.22, 126.93, 127.10, 127.18, 127.66, 127.72, 129.07, 130.03 (quat), 135.63 (quat), 138.44 (quat), 140.43 (C-3), 140.61 (quat)
(90.5MHz)	8.75 (Me), 115.00 (quat) 124.73, 125.35, 127.38, 127.68, 127.89, 128.69, 129.23, 129.55 (quat), 133.97 (quat), 140.35 (quat) 140.76 (C-3)		

Mass spectral data

	274 (27), 273 (15), 171 (100) 125 (24)		274 (45), 273 (23), 171 (100), 115 (15)
	260 (100), 259 (100), 183 (5 158 (98), 130 (55)		

Appendix 7

4-Methyl-3-phenyl-5-alkenyl pyrazoles



^{1}H N.m.r. spectral data

	R=Me ($CDCl_3$)	R=H ($(CD_3)_2S=O$)
Me	2.19 (s,3H)	2.28 (s,3H)
R	2.34 (d, J2Hz, 3H)	-
Olefinic	6.54 (brd,q, J2Hz, 1H)	Unresolved
Aromatic	7.15-7.63 (m,10H)	7.10-7.80 (m,12H)
NH	9.60 (brd, 1H)	13.96 (brd, 1H)

^{13}C N.m.r. spectral data

(20MHz) 9.23 (Me), 18.04 (Me), 112.38 (quat), 115.25 (olefinic), 125.86, 127.39, 127.51, 128.21, 128.44, 132.34 (quat), 139.68 (quat), 143.13 (quat), 143.72 (quat), 145.98 (quat)

(20MHz) ($(CD_3)_2S=O$) 9.28 (Me), 111.14 (quat), 126.33, 127.17, 127.65, 127.95, 128.53, 128.76, 136.99 (quat)

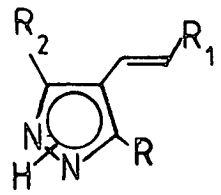
Mass spectral data

274 (100), 273 (98), 259 (12), 115 (36), 105 (35), 91 (30)

260 (100), 259 (87), 156 (14), 130 (18), 77 (19)

Appendix 7b

4-Alkenylpyrazoles



^{1}H N.m.r. spectral data ($(CD_3)_2C=O$)

	R=$(Me)_2CH$, R_1=Me, R_2=Me (80MHz)	R=Me, R_2=Me, R_1=Ph
R	1.25 (d, J7Hz, 6H) 3.07 (septet, J7Hz, 1H)	2.39 (s, 3H)
R_1	1.80 (d of d, J6.2Hz, 1.4Hz, 3H)	—
R_2	2.21 (s, 3H)	2.39 (s, 3H)
Olefinics	5.70 (d of q, J16Hz, 6.2Hz, 1H) 6.27 (d of q, J16Hz, 1.4Hz, 1H)	6.69, 6.93 AB, (J16.5Hz, 2H)
Aromatics	—	7.21-7.48 (m, 6H)
NH	8.56 (brd, 1H)	Unresolved

^{13}C N.m.r. spectral data

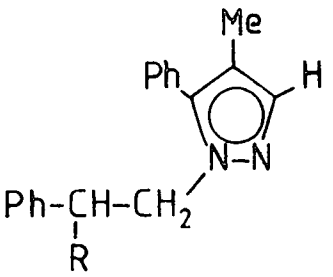
(50MHz)	10.61 (Me), 17.48 (Me), 20.77 (2xMe), 24.87 (C-H), 111.71 (quat), 121.28 (olefinic), 122.17 (olefinic), 139.89 (quat), 149.73 (quat)	(50MHz)	10.46 (Me), 113.02 (quat), 119.39, 124.86, 125.07, 125.66, 127.67, 138.05 (quat), 141.20 (quat)

Mass spectral data

164 (100), 149 (74), 135 (78)	198 (100), 183 (17), 115 (15), 91 (9)

Appendix 8

1-Alkyl-4-methyl-5-phenyl-1*H*-pyrazoles



^{1}H N.m.r. spectral data ($CDCl_3$)

	R=Me	R=H
Me	1.88 (s, 3H)	1.94 (s, 3H)
R	1.12 (d, J7Hz, 3H)	-
CH-R	3.34 (hextet, J7Hz, 1H)	3.06 (t, J8Hz, 2H)
CH_2	4.08 (d, J7Hz, 2H)	4.18 (t, J8Hz, 2H)
H-3	Unresolved	Unresolved
Aromatics	6.80-7.50 (m, 11H)	6.80-7.60 (m, 11H)

^{13}C N.m.r. spectral data

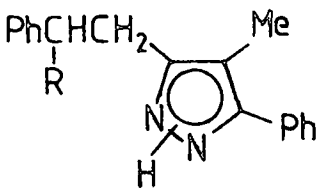
(90.5MHz)	8.67 (Me), 17.94 (Me), 40.36 (C-β), 56.36 (C-α), 114.06 (quat), 126.37, 126.99, 128.00, 128.22, 128.31, 129.76, 130.47 (quat), 139.04 (C-3), 141.26 (quat), 143.41 (quat)	(90.5MHz) 8.73 (Me), 36.73 (C-β), 50.76 (C-α), 114.26 (quat), 126.35, 128.13, 128.33, 128.38, 128.69, 129.66, 130.44 (quat), 138.31 (quat), 139.05 (C-3), 141.05 (quat)

Mass spectral data

	276 (44), 234 (62), 171 (100), 158 (68)	262 (36), 171 (74), 158 (100), 77 (37)

Appendix 8 b

5-Alkyl-4-methyl-3-phenyl-pyrazoles



^{1}H N.m.r. spectral data ($CDCl_3$)

	R=Me (360MHz)	R=H
Me	2.00 (s, 3H)	2.02 (s, 3H)
R	1.30 (d, J7Hz, 3H)	-
CH-R	3.09 (hextet, J7.1Hz, 1H)	2.86 (s, 4H)
CH_2	2.86 (m, 2H)	
NH	6.26 (brd, 1H)	Unresolved
Aromatics	7.18-7.56 (m, 10H)	7.05-7.60 (m, 11H)

^{13}C N.m.r. spectral data

(90.5MHz)	8.74 (Me), 21.16 (Me), 34.30 (C-α), 39.90 (C-β), 111.70 (quat), 126.29, 126.86, 127.31, 127.45, 128.43, 128.46, 132.76 (quat), 145.40 (quat), 146.26 (quat)	(90.5MHz) 8.55 (Me), 27.62 (C-α), 35.24 (C-β), 110.45 (quat), 126.02, 127.32, 127.54, 128.34, 128.52, 132.38 (quat), 141.32 (quat), 145.24 (quat), 146.88 (quat)

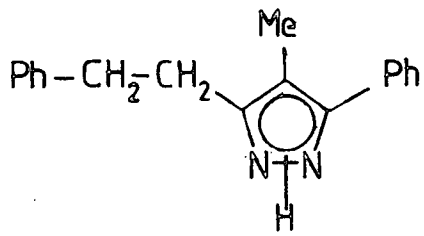
Mass spectral data

276 (100), 261 (9), 185 (8), 172 (69), 171 (61), 105 (86)	262 (75), 171 (100), 91 (19)

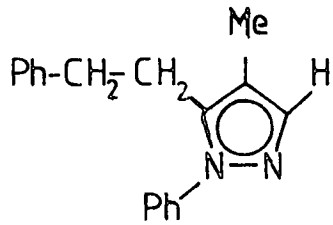
Appendix 9

Authentic Pyrazoles

4-Methyl-3-phenyl-5-phenethylpyrazole



4-Methyl-5-phenethyl-1-phenyl-1*H*-pyrazole



^{1}H N.m.r. spectral data

Me	2.02 (s, 3H)	Me	1.97 (s, 3H)
CH_2	2.87 (s, 4H)	CH_2	2.5-2.73 (m, C-α 2H)
CH_2		CH_2	2.8-3.1 (m, C-β 2H)
NH	7.65 (brd, 1H)	=N-H	Unresolved
Aromatics	7.05-7.60 (m, 10H)	Aromatics	6.80-7.05 (m, 2H) 7.10-7.50 (m, 9H)

^{13}C N.m.r. spectral data

(20MHz) 8.53 (Me), 27.33 (C-α), 35.32 (C-β), 110.09 (quat), 125.71, 127.16, 127.34, 128.07, 128.21, 132.56 (quat), 141.23 (quat), 145.48 (quat), 146.14 (quat)

(20MHz) 8.49 (Me), 26.27 (C-α), 34.72 (C-β), 114.66 (quat), 125.36, 126.01, 127.59, 128.18, 128.84, 139.00 (quat), 140.14 (quat), 140.32

Mass spectral data

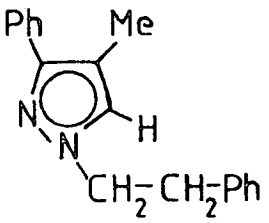
262 (93), 186 (20), 171 (100), 95 (28), 91 (27)

262 (47), 171 (100), 91 (20), 77 (15)

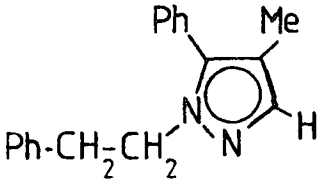
Appendix 9b

Authentic Pyrazoles

4-Methyl-3-phenyl-
1-phenethyl-1*H*-pyrazole



4-Methyl-5-phenyl-1-
phenethyl-1*H*-pyrazole



^{1}H N.m.r. spectral data	(200MHz)	(200MHz)
Me	2.22 (d, 0.8Hz, 3H)	1.97 (s, 3H)
β CH_2	3.22 (t,J7.3Hz, 2H) (2% NOE enhancement to N=C-H) (5% NOE enhancement to Ph of phenethyl)	3.08 (t, J7.5Hz, 2H) (1% NOE enhancement to N=C-H) (7% NOE enhancement to Ph of phenethyl)
α CH_2	4.33 (t, 7.4Hz, 2H) (7% NOE enhancement to N=C-H) (2% NOE enhancement to Ph of phenethyl)	4.20 (t, J7.4Hz, 2H) (0.5% NOE enhancement to N=C-H) (2.5% NOE enhancement to Ph of phenethyl)
H-C=N	7.06 (brd, q, J=0.1 Hz,1H)	7.47 (s, 1H)
Aromatics	7.14-7.50 (m, 8H)	6.92-7.39 (m, 10H)
o-ring Ph	7.73-7.78 (m, 2H)	–

^{13}C N.m.r. spectral data

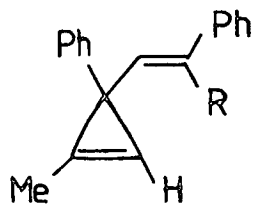
(20MHz)	9.76 (Me), 36.87 (C-β), 53.27 (C-α), 113.08 (quat), 126.37, 126.88, 127.24, 128.17, 128.33, 128.56, 129.78, 134.17 (quat), 138.12 (quat), 149.60 (quat)	(20MHz) 8.59 (Me), 36.55 (C-β), 50.58 (C-α), 114.00 (quat), 126.20, 127.97, 128.19, 128.53, 129.46, 130.18 (quat), 138.11 (quat), 138.96 (C-3), 140.86 (quat)

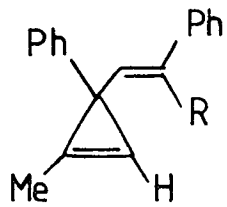
Mass spectral data

	262 (47), 171 (100), 158 (85), 77 (36)	262 (46), 171 (87), 158 (100), 77 (29)

Appendix 10

1-Methyl-3-alkenyl-3-phenyl-cyclopropenes





^{1}H N.m.r. data ($CDCl_3$)(200MHz)	R=H	R=Me
Me	2.26 (d, J1.3Hz, 3H)	2.21 (d, J0.9Hz, 3H)
R	-	2.02 (d, J0.9Hz, 3H)
Olefinic	6.27, 6.92 (AB, J16Hz, 2H)	6.23 (brd, q, J1Hz, 1H)
H-3	6.90 (brd, q, J1.2Hz, 1H)	6.82 (brd, q, J1Hz, 1H)
Aromatics	7.18-7.62 (m, 10H)	7.21-7.51 (m, 10H)

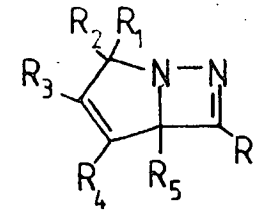
^{13}C N.m.r. ($CDCl_3$)

(50MHz)	9.25 (Me), 31.75 (C-3), 102.78, 121.40 (quat), 125.34, 125.83, 126.57, 127.10, 128.06, 128.37, 128.51, 128.68, 137.08, 137.94 (quat), 146.88 (quat)	(50MHz) 9.09 (C-1 Me), 16.69 (Me), 28.8 (C-3), 103.87, 120.10 (quat), 124.74, 125.52, 126.27, 126.47, 126.62, 127.86, 128.07, 131.22, 137.33 (quat), 143.56 (quat), 147.91 (quat)

Mass spectral data

	232 (100), 217 (38), 215 (25), 202 (25)	246 (100), 231 (36), 216 (24), 215 (29)

4,6a-Dihydro [1,2] diazeto[1,4-a]pyrroles



^{1}H N.m.r. spectral data ($CDCl_3$) 80MHz

	R=H, R_1=H, R_2=Ph, R_3=H, R_4=Ph, R_5=Me	R=H, R_1=Ph, R_2=Me, R_3=H, R_4=Ph, R_5=Me	R=Ph, R_1=H, R_2=H, R_3=Me, R_4=Ph, R_5=H
R	8.61 (s, 1H)	8.48 (s, 1H)	-
R_1	5.24 (d, J2.5Hz, 1H)	-	{ 4.11 (brd, 2H)
R_2	-	1.73 (s, 3H)	
R_3	6.04 (d, J2.5Hz, 1H)	6.26 (s, 1H)	1.76 (d, J1.2Hz, 3H)
R_4	-	-	-
R_5	1.67 (s, 3H)	1.65 (s, 3H)	6.15 (brd, 1H)
Aromatics	7.19-7.43 (m, 10H)	7.20-7.61 (m, 10H)	7.05-7.52 (m, 10H)

^{13}C N.m.r. spectral data $CDCl_3$

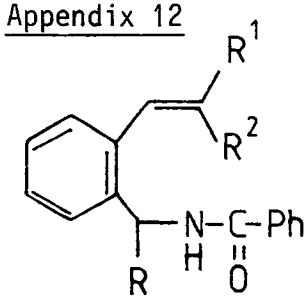
(50MHz) 18.03 (Me), 69.69 (C-4), 91.89 (quat , C-6a), 126.22, 126.71, 127.00, 127.27, 128.11, 128.58, 133.57 (quat), 141.81 (quat), 143.31 (quat), 177.15 (C-1)	17.57 (Me), 31.62 (C-4 Me), 70.52 (quat, C-4), 90.99 (quat, C-6a), 126.61, 126.70, 127.51, 127.99, 128.21, 128.65, 130.77, 133.76 (quat), 139.35 (quat), 143.25 (quat), 175.98 (C-1)	

Mass Spectral data

260 (12), 233 (100), 192 (49), 157 (48), 156 (28), 115 (45)	274 (8), 259 (100), 232 (81), 247 (47)	260 (12), 157 (100), 156 (66) 115 (34), 103 (65)

Appendix 12

2-ALKENYL-*N*-BENZOYL BENZYLAMINES



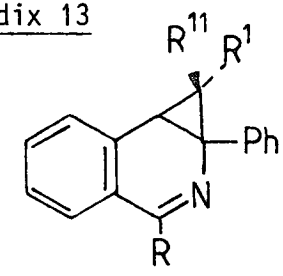
^{1}H N.m.r. spectral data ($CDCl_3$)

	R=H, R^1=Ph, R^2=H	R=Me, R^1=Ph, R^2=H	R=H, *E* isomer, R^1=Ph, R^2=Me; *Z* isomer R^1=Me, R^2=Ph
R	-	1.63 (d, J6.8Hz, 3H)	-
R^1	-	-	2.11 (d, J1.5Hz, 3H, *E* Me) 2.24 (d, J1.5Hz, 3H, *Z* Me)
R^2	-	-	
C*H*-R	4.74 (d, J5Hz, 2H)	5.78 (quintet, J6.8Hz, 1H)	4.58 (d, J5.5Hz, 2H, *Z* CH_2) 4.67 (d, J5.5Hz, 2H, *E* CH_2)
N-H	6.36 (brd, NH)	6.32 (brd, d, NH)	6.10 (brd, 1H, *Z* NH) 6.47 (brd, 1H, *E* NH)
Olefinic	6.95 (one half AB, J16Hz,1H)	6.95 (one half AB,J16.1Hz,1H)	6.63 (br, m, 1H, *Z* CH)
Aromatic	7.35-8.20 (m, 15H)	7.19-7.77 (m, 15H)	6.94-7.71 (m, 29H)

Mass Spectral Data

313 (32), 192 (100), 122 (21), 105 (81), 77 (47)	327 (23), 222 (33), 206 (100), 105 (91), 77 (44)	327 (65), 222 (43), 206 (97), 191 (55), 122 (48), 105 (100), 91 (77). 77 (98)

Appendix 13



2a,3,3a-Trihydro-2a-phenylcyclopropa-[c]isoquinolines

^{1}H N.m.r. data ($CDCl_3$)

	R=H, R^1=Ph, R^{11}=H (200Mz)	R=H, R^1=Ph, R^{11}=Me	R=H, R^1=Me, R^{11}=Ph
R	8.27 (s, 1H)	8.51 (s, 1H)	7.83 (s, 1H)
R^1	-	-	1.34 (s,3H) (9.6% NOE enhancement to H-3a)
R^{11}	1.79 (d, J6Hz, 1H)	1.02 (s,3H) (2.7% NOE enhancement to -N=C-*H*)	-
H-3a	3.43 (d, J6Hz, 1H)	3.62 (s, 1H)	3.18 (s, 1H)(1.1% NOE enhancement to Me)
Aromatics	6.87-7.83 (m, 14H)	6.95-7.70 (m, 14H)	6.92-7.69 (m, 14H)

^{13}C N.m.r. data ($CDCl_3$)

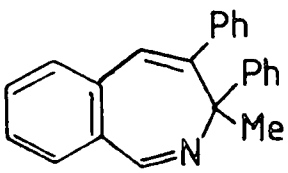
50.3MHz	31.33 (C-3), 38.40 (C-3a) 59.54 (C-2a), 123.56 (quat), 125.97, 126.55, 126.86, 127.35, 127.67, 127.90, 129.21, 129.34, 131.46, 135.85 (quat), 136.44 (quat), 139.65 (quat), 153.84 (C-1)	50.3MHz 15.92 (Me), 28.09 (C-3), 31.69 (C-3a), 59.57 (C-2a), 125.95, 126.77, 127.33, 127.50, 127.86, 128.47, 128.97, 129.20, 131.54, 133.37 (quat), 141.83 (quat), 142.40 (quat), 155.85 (C-1)	50.3MHz 26.73 (Me), 30.15 (C-3), 34.98 (C-3a), 61.26 (C-2a), 125.66, 126.05, 126.94, 127.45, 128.06, 128.32, 129.03, 131.15, 131.55, 134.42 (quat), 138.15 (quat), 142.10 (quat), 154.65 (C-1)

Mass Spectral Data

295 (52), 294 (100), 218 (8), 192 (51), 191 (37), 165 (10), 115 (7)	309 (100), 308 (98), 294 (18), 204 (47), 191 (41)	309 (20), 308 (20), 206 (13), 192 (14), 105 (100)

Appendix 14

3-Methyl-3,4-diphenyl 3*H*-2-benzazepine



^{1}H N.m.r. spectral data (C_6D_6, 200MHz)

Me	1.65 (s,3H)
H-1	8.46 (d, J1.1Hz, 1H)
H-5	5.95 (d, J1.1Hz, 1H)
Aromatics	6.92-7.34 (m, 12H)
	7.84-7.96 (m, 2H)

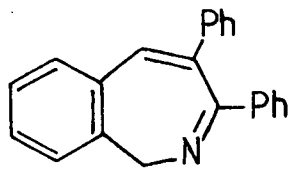
^{13}C N.m.r. spectral data ($CDCl_3$, 50.3MHz)

31.62 (Me), 46.40 (C-3), 124.25, 124.39, 126.29, 126.79, 127.05, 127.52, 128.00, 128.48, 129.69, 130.99, 132.75 (quat), 139.70 (quat), 145.97 (quat), 146.92 (quat), 148.84 (quat), 161.06 (C-1)

Mass Spectral Data

309 (88), 308 (100), 294 (15), 206 (59), 191 (47)

3,4-Diphenyl-1*H*-2-benzazepine



^{1}H N.m.r. data ($CDCl_3$, 200MHz)

CH_2	(25°C) 4.07 (brd,1H), 5.12 (brd, 1H)
	(-23°C) 4.06, 5.13, (AB, J10.1Hz)
H-5	7.84 (s, 1H)
Aromatics	7.10-7.56 (m, 14H)
T_c/°C	62°C±1

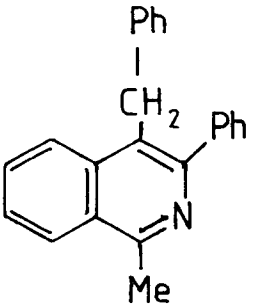
^{13}C N.m.r. data ($CDCl_3$, 50.3MHz)

56.36 (C-1), 127.06, 127.57, 128.10, 128.39, 128.65, 128.87, 135.71 (quat), 136.31 (C-5), 137.98 (quat), 139.33 (quat), 139.72 (quat), 140.06 (quat), 165.42 (quat)

295 (60), 294 (100), 192 (40), 191 (40)

Appendix 15

4-Benzyl-1-methyl-3-phenylisoquinoline



^{1}H N.m.r. data ($CDCl_3$, 80MHz)

Me	3.05 (s, 3H)
CH_2	4.45 (s, 2H)
Aromatics	7.07-8.17 (m, 14H)

^{13}C N.m.r. data ($CDCl_3$, 50.3MHz)

22.45 (Me), 34.72 (C-5), 123.86 (quat), 125.07, 125.78, 125.99, 126.20, 126.69, 127.52, 128.02, 128.38, 129.23, 129.88, 136.00 (quat), 141.05 (quat), 141.31 (quat), 152.01 (quat), 156.97 (C-1)

Mass Spectral Data

309 (100), 308 (98), 294 (7)

Ultraviolet Absorptions

$\lambda_{(max)}$ (EtOH) 330 (log ε 3.65); 316 (log ε 3.66); 291 (log ε 3.91); 281 (log ε 3.94); 238 nm (log ε 4.52)

1. R. Huisgen, R. Grashey, and J. Sauer in "The Chemistry of Alkenes" ed. S. Patai, Interscience Publishers, London/New York/Sydney, 1964.
2. R. Huisgen, Angew.Chem.Int.Ed.Engl., 1963, 2, 565, 633.
3. R. Huisgen, J.Org.Chem., 1968, 33, 2291.
4. R. Hoffman and R.B. Woodward, Acc.Chem.Res., 1968, 1, 17; Angew.Chem.,Int.Ed.Engl., 1969, 8, 781.
5. R.A. Firestone, J.Org.Chem., 1968, 33, 2285; 1972, 37, 2181.
6. R. Huisgen, J.Org.Chem., 1968, 33, 2291.
7. R.A. Firestone, J.Org.Chem., 1972, 37, 2181.
8. J.W. Linnett, J.Am.Chem.Soc., 1961, 83, 2643 and "The Electronic Structure of Molecules" Methuen, London, 1964.
9. R.E. Duke, J.K. George, K.N. Houk, J. Sims, and R.W. Strozier, J.Am.Chem.Soc., 1973, 95, 7287.
10. K.N. Houk, L.J. Luskus, J. Sims, and C.R. Watts, J.Am.Chem.Soc., 1973, 95, 7301.
11. K. Fukui, Acc.Chem.Res., 1971, 4, 57.
12. R. Huisgen, J.Org.Chem., 1976, 41, 403.
13. R.A. Firestone, Tetrahedron, 1977, 33, 3009.
14. R. Fuks and H.G. Viehe in "The Chemistry of Acetylenes" ed. H.G. Viehe, Dekker, New York, 1969.
15. G. Bianchi, C. De Micheli, and R. Gandolfi in "The Chemistry of double-bonded functional groups" Supplement A, ed. Patai, Wiley and Sons, London/New York/Sydney/ Toronto, 1977.

16. A. Padwa, Angew.Chem., Int.Ed.Engl., 1976, 15, 123.

17. W. Oppolzer, Angew.Chem., Int.Ed.Engl., 1977, 16, 10.

18. J.J. Tufariello, Acc.Chem.Res., 1979, 12, 396.

19. W. Oppolzer, Heterocycles, 1980, 14, 1624.

20. N.A. Le Bel and J.J. Whang, J.Am.Chem.Soc., 1959, 81, 6334.

21. R.B. Woodward and R. Hoffmann, J.Am.Chem.Soc., 1965, 87, 395.

22. J.C. Pommelet and J. Chuche, Can.J.Chem., 1976, 54, 1571.

23. A. Padwa and W. Eisenhardt, J.Chem.Soc., Chem.Commun., 1968, 380.

24. E. Schmitz, D. Habisch, and C. Gründemann, Chem.Ber., 1967, 100, 142.

25. H.W. Heine, L.M. Baclawski, S.M. Bonser, and G.D. Wachob, J.Org.Chem., 1976, 41, 3229.

26. R. Huisgen, Helv.Chim.Acta, 1967, 50, 2421.

27. R.M. Kellogg, Tetrahedron, 1976, 32, 2165.

28. R. Huisgen, Angew.Chem., Int.Ed.Engl., 1977, 16, 572.

29. E.C. Taylor and I.J. Turchi, Chem.Rev., 1979, 79, 181.

30. Y. Tamura, N. Tsujimoto, Y. Sumida, and M. Ikeda, Tetrahedron, 1972, 28, 21.

31. R. Huisgen, Angew.Chem., Int.Ed.Engl., 1980, 19, 947.

32. L. Garanti and G. Zecchi, J.Chem.Soc., Perkin Trans.1. 1977, 2092.

33. A. Padwa and S. Nahm, J.Org.Chem., 1981, 46, 1402; 1979, 44, 4746.

34. D. Bethell, in "Organic Reactive Intermediates" ed. S.P. McManus, Academic Press, New York, 1973, 101.

35. L. Garanti, A. Vigevari, and G. Zecchi, Tetrahedron Lett., 1976, 1527.

36. A. Steigel, J. Sauer, D.A. Kleier, and G. Binsch, J.Am.Chem.Soc., 1972, 94, 2770.

37. L. Garanti and G. Zecchi, J.Chem.Soc., Perkin Trans.1, 1980, 116.

38. L. Garanti, G. Zecchi, L. Bruché, and P. Del Buttero, J.Chem.Soc., Perkin Trans.1, 1982, 2041.

39. W. Eberbach, B. Burchardt, and U. Trostmann, Tetrahedron Lett., 1979, 4049.

40. W. Eberbach, E. Hädicke, and U. Trostmann, Tetrahedron Lett., 1981, 4953.

41. W. Eberbach, G. König, and U. Trostmann, Tetrahedron Lett., 1979, 4649.

42. T. Curtius, Chem.Ber., 1883, 16, 2230.

43. H. Boersch, Monatsh., 1935, 65, 331.

44. A.P. Cox, L.F. Thomas, and J. Sheridan, Nature, 1958, 181, 1000.

45. J. Firl, W. Runge, and W. Hartmann, Angew.Chem., Int.Ed. Engl.,1974, 13, 270.

46. E.A. Werner, J.Chem.Soc., 1919, 1093.

47. S. Hauptman, M. Fluge, K.D. Seidig, and H. Wilde, Angew. Chem., Int.Ed.Engl., 1965, 4, 688.

48. D.M. Gale, W.J. Middleton, and C.G. Krespan, J.Am.Chem. Soc., 1966, 88, 3617.

49. T. Curtius and H. Lang, J.Prakt.Chem., 1891, 44, 544.

50. W. Fischer and J.P. Anselme, Tetrahedron Lett., 1968, 877.

51. W.R. Bamford and T.S. Stevens, J.Chem.Soc., 1952, 4735.

52. A. Nickon and P.S. Zurer, J.Org.Chem., 1981, 46, 4685.

53. J. Casanova and B. Waegell, Bull.Soc.Chim.France, 1975, 922.

54. R.H. Shapiro, Org.Reactions, 1976, 23, 405.

55. W.J. Barom, M.R. Decamp, M.E. Hendrick, M. Jones, R.H. Levin, and M.B. Sohn, in "Carbenes" M. Jones, R.A. Moss; ed. Wiley, New York, 1973.

56. W. Kirmse "Carbene Chemistry" 2nd ed., Academic Press, New York, 1971.

57. J.W. Powell and M.C. Whiting, Tetrahedron, 1959, 7, 305.

58. R.H. Shapiro, J.H. Duncan, and J.C. Clopton, J.Am.Chem. Soc., 1967, 89, 1442.

59. R.H. Shapiro and M.J. Heath, J.Am.Chem.Soc., 1967, 89, 5734.

60. G. Kaufman, F. Cook, H. Schechter, J. Bayliss, and L. Friedmann, J.Am.Chem.Soc., 1967, 89, 5736.

61. R.H. Shapiro and T. Gadek, J.Org.Chem., 1974, 39, 3418.

62. H. Staudinger and J. Meyer, Helv.Chim.Acta, 1919, 2, 619.

63. H. Zollinger "Azo and Diazo Chemistry" Interscience, London, 1961.

64. G.W. Cowell and A. Ledwith, Quart.Rev., 1970, 24, 119.

65. E. Bucher, Chem.Ber., 1888, 21, 2637.

66. W. Kirmse and H. Dietrich, Chem.Ber., 1967, 100, 2710.

67. A. Padwa, New Synthetic Methods, Vol.5, Verlag Chimie, N.Y., 1979.

68. D.W. Adamson and J. Kenner, J.Chem.Soc., 1935, 286.

69. C.D. Hurd and S.C. Lui, J.Am.Chem.Soc., 1935, 57, 2656.

70. A.Ledworth and D. Parry, J.Chem.Soc.(B), 1967, 41.

71. D.Y. Curtin and S.M. Gerber, J.Am.Chem.Soc., 1952, 74, 4052.

72. G.L. Closs, L.E. Closs, and W.A. Boll, J.Am.Chem.Soc., 1963, 85, 3796.

73. G.L. Closs and W. Boll, Angew.Chem.,Int.Ed.Engl., 1963, 2, 399.

74. J.L. Brewbaker and H. Hart, J.Am.Chem.Soc., 1969, 91, 711.

75. T. Sato and S. Watanabe, Bull.Chem.Soc.Jpn., 1968, 41, 3017.

76. R.H. Findlay, J.T. Sharp, and P.B. Thorogood, J.Chem. Soc., Perkin 1, 1975, 102.

77. K.M. Stanley, J. Dingwall, J.T. Sharp, and T.W. Naisby, J.Chem.Soc., Perkin 1, 1979, 1433.

78. J. van Alphen, Recl.Trav.Chim.Pays-Bas, 1943, 62, 485.

79. R. Huttel, K. Frake, H. Martin, and J. Riedl, Chem.Ber., 1960, 93, 1425.

80. A.A. Reid, J.T. Sharp, H.R. Sood, and P.B. Thorogood, J.Chem.Soc., Perkin 1, 1973, 2543.

81. D.P. Munro and J.T. Sharp, J.Chem.Soc., Perkin 1, 1980, 1718.

82. D.P. Munro and J.T. Sharp, submitted for publication in J.Chem.Soc., Perkin 1.

83. D.P. Munro, Ph.D. Thesis, University of Edinburgh, 1981.

84. D.P. Munro and J.T. Sharp, Tetrahedron Lett., 1980, 21, 4109.

85. A. Padwa and A. Rodriguex, Tetrahedron Lett., 1981, 22, 187.

86. A. Padwa and H. Ku, Tetrahedron Lett., 1980, 21, 1009.

87. Y. Nishizawa, T. Miyashi, and T. Mukai, J.Am.Chem.Soc., 1980, 102, 1176.

88. T. Migashi, Y. Fujii, Y. Nishizawa, and T. Mukai, J.Am.Chem.Soc., 1981, 103, 725.

89. L. Salem, J.Am.Chem.Soc., 1974, 96, 3486.

90. P. Caramella and K.N. Houk, J.Am.Chem.Soc., 1976, 98, 6397.

91. A. Padwa and J. Smolanoff, J.Chem.Soc., Chem.Commun., 1973, 342.

92. A. Orahovats, H. Heimgartner, H. Schmid, and W. Heinzelman, Helv.Chim.Acta, 1975, 58, 2662.

93. R. Huisgen and R. Raab, Tetrahedron Lett., 1966, 649.

94. N. Engel and W. Steglich, Angew.Chem.Int.,Ed.Engl., 1978, 17, 676.

95. R. Huisgen, H. Stang, H.J. Sturm, R. Raab, and K. Bunge, Chem.Ber., 1972, 105, 1258.

96. K. Burger, J. Albanbauer, and F. Manz, Chem.Ber., 1974, 107, 1823.

97. K. Burger and J. Fehn, Chem.Ber., 1972, 105, 3814.

98. K. Burger, W. Thenn, E. Muller, Angew.Chem.Int., Ed. Engl., 1973, 12, 155.

99. A. Padwa and S.I. Wetmore Jnr., J.Am.Chem.Soc., 1974, 96, 2414.

100. A. Hassner and W. Fowler, J.Am.Chem.Soc., 1968, 90, 2869.

101. R.F. Parcell, Chem.Ind., 1963, 41, 1396.

102. A. Padwa and P.H.J. Carlson in "Reactive Intermediates Vol.2" ed. R.A. Abramovitch, Plenum Press, New York and London, 1982.

103. R. Huisgen, H. Stangl, J. Sturm, and H. Wagenhefer, Angew.Chem., Int.Ed.Engl., 1962, 1, 50.

104. A. Padwa, M. Dharan, J. Smolanoff, and S.I. Wetmore, Jr. J.Am.Chem.Soc., 1973, 95, 1945.

105. E.F. Ullmann and B. Singh, J.Am.Chem.Soc., 1966, 88, 1844; 1967, 89, 6911.

106. B. Singh, A. Zweig, and J.B. Gallivan, J.Am.Chem.Soc., 1972, 94, 1199.

107. A. Padwa, J. Smolanoff, and A. Tremper, J.Am.Chem.Soc., 1975, 97, 4682.

108. A. Padwa, J. Smolanoff, and A. Tremper, J.Org.Chem., 1976, 41, 543.

109. T. Mukai and H. Sukawa, Tetrahedron Lett., 1973, 1835.

110. T. Tezuka, O. Seshimoto, and T. Mukai, J.Chem.Soc., Chem.Commun., 1974, 373.

111. K. Dietiker, P. Gilgen, H. Heimgartner, and H. Schmid, Helv.Chim.Acta, 1976, 59, 2074.

112. A. Padwa and P.H.J. Carlsen, J.Am.Chem.Soc., 1975, 97, 3862; 1976, 98, 2006; 1977, 99, 1514.

113. A. Padwa and A. Ku, J.Am.Chem.Soc., 1978, 100, 2181.

114. A. Padwa, A. Ku, A. Mazzu, and S.I. Wetmore, J.Am. Chem.Soc., 1976, 98, 1048.

115. M. Nastasi, Heterocycles, 1976, 9, 1509.

116. V. Snieckus and J. Streith, Acc.Chem.Res., 1981, 14, 348.

117. J.T. Sharp, Royal Society of Chemistry, Specialist Periodical Reports, Heterocyclic Chemistry, Vol.4, in the press.

118. F.D. Popp and A.C. Noble, Adv.Heterocycl.Chem., 1967, 8, 21.

119. T. Tsuchiya, Yuki Gosei Kagaku Kyokaishi, 1981, 31, 99.

120. G.A. Archer and L.H. Sternbach, Chem.Rev., 1968, 68, 747.

121. G. Zinner and W. Deucker, Arch.Pharm., 1962, 295, 526.

122. C.D. Anderson, P.N. Anderson, and J.T. Sharp, J.Chem. Soc., Perkin Trans.1, 1979, 1640.

123. C.D. Anderson, J.T. Sharp, and R.S. Strathdee, J.Chem. Soc., Perkin Trans.1, 1979, 2209.

124. A. Steigel, J. Sauer, D.A. Kleier, and G. Binsch, J.Am.Chem.Soc., 1972, 94, 2770.

125. T. Tsuchiya, J. Kurita, and H. Igeta, J.Chem.Soc., Chem.Commun., 1974, 640.

126. T. Tsuchiya and J. Kurita, J.Chem.Soc., Chem.Commun., 1974, 936.

127. J.N. Done, J.H. Knox, R. McEwan, and J.T. Sharp, J.Chem.Soc., Chem.Commun., 1974, 532.

128. R. McEwan and J.T. Sharp, J.Chem.Soc., Chem.Commun., 1973, 85.

129. S.N. Ege and R.R. Sharp, J.Chem.Soc.(B), 1971, 2014.

130. A.A. Reid, H. Raj Sood, and J.T. Sharp, J.Chem.Soc., Perkin 1, 1976, 362.

131. C.D. Anderson, J.T. Sharp, E. Stefaniuk, and R.S. Strathdee, Tetrahedron Lett., 1976, 305.

132. C.D. Anderson, J.T. Sharp, and R.S. Strathdee, J.Chem. Soc., Perkin 1, 1979, 2730.

133. C.B. Argo and J.T. Sharp, Tetrahedron Lett., 1981, 22, 353.

134. T. Tsuchiya and J. Kurita, Chem.Pharm.Bull., 1978, 26, 1896.

135. T. Tsuchiya, J. Kurita, H. Kojima, Heterocycles, 1981, 16, 137.

136. T. Tsuchiya, M. Enkaku, and S. Okajima, J.Chem.Soc., Chem.Commun., 1980, 454.

137. T. Tsuchiya, H. Sawanishi, M. Enkaku, and T. Hirai, Chem.Pharm.Bull., 1981, 29, 1539; J.Chem.Soc., Chem. Commun., 1979, 534.

138. F.M.F. Chen and T.P. Forrest, Can.J.Chem., 1973, 51, 881.

139. G.A. Archer and L.H. Sternbach, Chem.Rev., 1968, 68, 747, p.783.

140. G. De Stevens and M. Dughi, J.Am.Chem.Soc., 1961, 83, 3087.

141. G. De.Stevens, Record.Chem.Prog., 1962, 23, 105.

142. T. Tsuchiya, S.Okajima, M. Enkaku, and J. Kurita, J.Chem.Soc., Chem.Commun., 1981, 211.

143. J. Kurita, H. Kojima, M. Enkaku, and I. Tsuchiya, Chem.Pharm.Bull., 1981, 29, 3688.

144. R.K. Smalley in "Comprehensive Organic Chemistry" ed. D. Barton and W.D. Ollis, Pergamon Press, Oxford, New York, Toronto, Sydney, Paris, Frankfurt, 1979.

145. S. Kasparek, Adv.Heterocycl.Chem., 1974, 17, 45.

146. J.A. Moore and E. Mitchell, in "Heterocyclic Compounds" ed. R.C. Elderfield, Wiley, New York, 1967, vol.9, p.224.

147. H. Plieninger and D. Wild, Chem.Ber., 1966, 99, 3070.

148. M.-S. Lin and V. Snieckus, J.Org.Chem., 1971, 36, 645.

149. M. Ikeda, K. Ohno, T. Uno, and Y. Tamura, Tetrahedron Lett., 1980, 3403; Heterocycles, 1980, 14, 123.

150. P.D. Davis and D.C. Neckers, J.Org.Chem., 1980, 45, 456, 462.

151. F. Johnson and W.A. Nasutavicus, J.Heterocyclic Chem., 1965, 2, 26.

152. D. Berney and K. Schuh, Helv.Chim.Acta, 1981, 64, 373.

153. H.W. Gschwend (Ciba-Geigy A.-G.) German Offen. 2,524,048. Chem.Abstr., 1976, 84, 121822n.

154. H.W. Gschwend (Ciba-Geigy Corp) U.S. 3,939,271. Chem.Abstr., 1976, 84, 150623d.

155. Ciba-Geigy A.G., Netherlands Appl. 7506,570, Chem.Abstr., 1976, 85, 160087s.

156. R.I. Fryer, N.W. Gilman, E.J. Trybulski, and A. Walser (Hoffmann La Roche, F., und Co. A.-G.) Eur.Pat.Appl. 14,470; Chem.Abstr., 1981, 94, 139827.

157. B. Nay, E.F.V. Scriven, H. Suschitzky, and Z.Ullah, Synthesis, 1977, 757.

158. A. Padwa and J. Smolanoff, Tetrahedron Lett., 1974, 33.

159. G. Gast, J. Schmutz, and D. Sorg, Helv.Chim.Acta, 1977, 60, 1644.

160. A. Hassner and D.J. Anderson, J.Am.Chem.Soc., 1972, 94, 8255; J.Org.Chem., 1974, 39, 3070; ibid, 1974, 39, 2031.

161. A. Lablache-Conbier and G. Surpateanu, Tetrahedron Lett., 1976, 3081.

162. T. Mukaiyma and M. Hayashi, Chem.Lett., 1974, 15.

163. F. Huet, A. Lechevallier, M. Pellet, and J.M. Coria, Synthesis, 1978, 63.

164. E.J. Corey and D. Enders, Chem.Ber., 1978, 111, 1362.

165. Z. Arnold and A. Holy, Collect.Czech.Chem.Commun., 1961, 26, 3059.

166. J.H. Short, J.Chem.Soc.(C), 1966, 313.

167. J.W. Emsley, J. Feeney, and L.H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy, Vol.2" Pergamon Press, Oxford, 1966.

168. M. Begtrup, Acta Chim.Scand., 1973, 27, 3101.

169. J. Elguero, R. Jacquier, and H.C.N. Tien Duc, Bull. Soc.Chim.Fr., 1966, 3727.

170. L. Aspart-Pascot and J. Lematre, Bull.Soc.Chim.Fr., 1971, 483.

171. J. Elguero, C. Ochoa, M. Stud, C. Esteban-Calderon, M. Martinez-Ripoll, J.P. Fayet, and M.C. Vertut, J.Org.Chem., 1982, 47, 536.

172. D.J. Field and D.W. Jones, J .Chem.Soc., Chem.Commun., 1977, 688.

173. M. Franck-Neumann and C. Dietrich-Buchecker, Tetrahedron Letts., 1976, 2069.

174. R.R. Bekmukhametov, Sovrem.Prokl.Khim., 1973, 61; (Chem.Abs., 1974, 81, 136042v).

175. H.E. Zimmerman and M.C. Havey, J.Org.Chem., 1979, 44, 2331.

176. K.N. Houk, T. Sims, R.E. Duke Jr., R.W. Strozier, and J.K. George, J.Am.Chem.Soc., 1973, 95, 7287.

177. J. Bastide and Henri-Rousseau, Tetrahedron Lett., 1972, 2979.

178. L. Garanti and G. Zecchi, J.Heterocyclic Chem., 1979, 16, 377.

179. U. Golik, J.Heterocycl.Chem., 1975, 12, 903.

180. M.G. Ahmed and P.W. Hickmott, J.Chem.Soc., Perkin II, 1977, 839.

181. N. Naulet, M.L. Filleux, G.J. Martin, and J. Pornet, Org.Magn.Reson., 1975, 326.

182. H.E. Zimmerman and W. Eberbach, J.Am.Chem.Soc., 1973, 95, 3970.

183. H. Kolbinger, G. Reissenweber, and J. Sauer, Tetrahedron Lett., 1976, 4321.

184. H.E. Zimmerman and S.M. Aasen, J.Org.Chem., 1978, 43, 1493.

185. H.E. Zimmerman and D.J. Kreil, J.Org.Chem., 1982, 47, 2060.

186. C.D. Anderson and J.T. Sharp, J.Chem.Soc., Perkin I, 1980, 1230.

187. R. Caballol, R. Carbo, and M. Martin, Chem.Phys.Lett., 1974, 28, 422.

188. C.B. Argo, Ph.D. Thesis, University of Edinburgh, 1983.

189. D.A.R. Happer and J. Vaughan in "The chemistry of the hydrazo, azo and azoxy group" ed. S. Patai, J. Wiley and Sons, London, 1975.

190. P. Caramella, R.W. Gandour, J.A. Hall, C.G. Deville and K.N. Houk, J.Am.Chem.Soc., 1977, 99, 385.

191. N.L. Dutta, M.S. Wadia and A.P. Bindra, J.Indian Chem. Soc., 1971, 48, 873.

192. A.A. Bindra, M.S. Wadia and N.L. Dutta, Tetrahedron Lett., 1968, 22, 2677.

193. J.A. Su, E. Siew, E.V. Brown and S.L. Smith, Org. Magn.Reson., 1977, 122.

194. F. Balkau and M.L. Heffernan, Aust.J.Chem., 1971, 24, 2311.

195. R. Benn and H. Günther, Angew.Chem., Int.Ed.Eng., 1983, 22, 350.

196. A.I. Meyers, J. Slade, R.K. Smith and E.D. Mihelich, J.Org.Chem., 1979, 44, 2247.

197. W.C. Still, M. Kahn and A. Mitra, J.Org.Chem., 1978, 43, 2923.

198. L.D. Bergelson, L.I. Barsukov and M.M. Shemyakin, Tetrahedron, 1967, 23, 2709.

199. "Dictionary of Organic Compounds", Eyre and Spottiswoode, London, 1965, 443.

200. U.H.M. Fagerlund and O.R. Idler, J.Am.Chem.Soc., 1957, 79, 6473.

201. G. Wittig and M. Schlossar, Tetrahedron, 1962, 18, 1023.

202. H.O. House, L.J. Czuba, M. Gall and H.D. Olmstead, J.Org.Chem., 1969, 34, 2324.

203. T. Mukaiyama and M. Hayashi, Chem.Lett., 1974, (1), 15.

204. A.S. Dreiding and S.N. Nickel, J.Am.Chem.Soc., 1954, 76, 3965.

205. Z. Arnold and A. Holy, Collect.Czech.Chem.Comm., 1961, 26, 3059.

206. A.L. Wilds and C. Djerassi, J.Am.Chem.Soc., 1946, 68, 1715.

207. L. Bardou, J. Elguero and R. Jacquier, Bull.Soc.Chim. France, 1967, 297.

208. J.Cologne and J. Varagnat, Bull.Soc.Chim.France, 1961, 234.

209. H. Burton and C.K. Ingold, J.Chem.Soc., 1929, 2022.

210. I.M. Heilborn, E.R.H. Jones and D.G. O'Sullivan, J.Chem.Soc., 1946, 866.

211. J.T. Sharp, D.C. Anderson and P.N. Anderson, J.Chem. Soc., Perkin 1, 1979, 1640.

212. C. Ainsworth, Organic Syntheses, Wiley, London, 1959, 39, 27.

213. "Dictionary of Organic Compounds" Eyre and Spottiswoode, London, 1965, 2715.

214. M.N. Maxin, Ann.Chim., 1928, 9, 55.

215. L. Aspart-Pascot and J. Lematre, Bull.Soc.Chim.France, 1971, 483.

216. C. Hauser, B.I. Ringler, F.W. Swamer and D.F. Thompson, J.Am.Chem.Soc., 1947, 69, 2649.

217. A.I. Vogel, "Practical Organic Chemistry" Longmans, London, 1979.

218. C.R. Hauser and T.M. Harris, J.Am.Chem.Soc., 1958, 80, 6360.

219. J.B. Shoesmith and R.H. Slater, J.Chem.Soc., 1926, 214.

220. E. Stefaniuk, Ph.D. Thesis, University of Edinburgh, 1976.

221. D.F. De Tar and L.A. Carpino, J.Am.Chem.Soc., 1956, 78, 475.

222. L.I. Smith and M. Bayliss, J.Org.Chem., 1941, 6, 437.

223. S. Natelson and S.P. Gottfried, J.Am.Chem.Soc., 1941, 63, 487.

A Route to 3*H*-1,2-Diazepines by the 1,7-Electrocyclisation of α,β;γ,δ-Unsaturated Diazo-compounds

Ian R. Robertson and John T. Sharp*

Department of Chemistry, University of Edinburgh, West Mains Road, Edinburgh EH9 3JJ, U.K.

In the thermal cyclisation of α,β;γ,δ-unsaturated diazo-compounds the type (**6**) with a *cis* hydrogen atom at the terminal carbon atom undergo 1,7 ring closure to give 3*H*-1,2-diazepines while those (**9**) with a methyl group at that position take an alternative reaction path to give pyrazoles *via* 1,5 cyclisation.

Reprinted from the Journal of The Chemical Society

Chemical Communications 1983

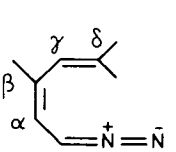
A Route to 3*H*-1,2-Diazepines by the 1,7-Electrocyclisation of α,β;γ,δ-Unsaturated Diazo-compounds

Ian R. Robertson and John T. Sharp*

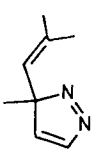
Department of Chemistry, University of Edinburgh, West Mains Road, Edinburgh EH9 3JJ, U.K.

In the thermal cyclisation of α,β;γ,δ-unsaturated diazo-compounds the type (**6**) with a *cis* hydrogen atom at the terminal carbon atom undergo 1,7 ring closure to give 3*H*-1,2-diazepines while those (**9**) with a methyl group at that position take an alternative reaction path to give pyrazoles *via* 1,5 cyclisation.

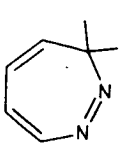
This communication is concerned with the reactions of α,β;-γ,δ-unsaturated diazo-compounds of type (**1**). This system could in principle react *via* several plausible pathways: (i) by either or both of the two competing modes (1,5 or 1,7) of electrocyclisation giving respectively (**2**) or (**3**); (ii) by a 1,1-cycloaddition[1,2] to give (**4**); (iii) *via* loss of nitrogen to give carbene-derived products. Previous work in this area has shown that compounds analogous to (**1**) but with an 'aromatic' α,β-double bond cyclise exclusively by the 1,7-mode to give 1*H*-2,3-benzodiazepines[3,4] while those with an 'aromatic' γ,δ-double bond generally favour 1,5-electrocyclisation although they can be manipulated *via* stereochemical adjustment so that the 1,7-mode becomes competitive.[5,6] In both these cases it is clear that the periselectivity of the electrocyclisation is much affected by the presence and position of an aromatic double bond in the conjugated system and so it was of interest to determine the preferred mode of cyclisation



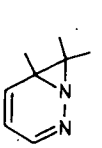
(1)



(2)

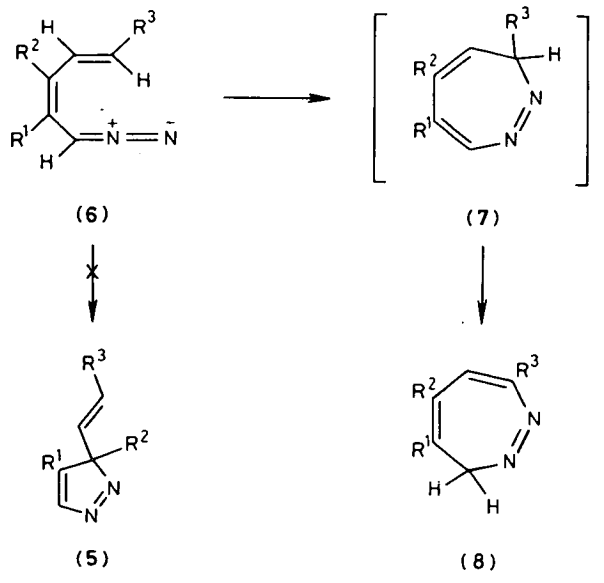


(3)



(4)

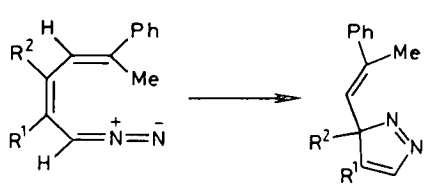
in the system (**1**) with only olefinic unsaturation. In particular it was hoped that the cyclisation of (**1**) would provide a viable route to the interesting 3*H*-1,2-diazepine system (**3**) hitherto only accessible by a base-induced elimination of toluene-*p*-sulphinic acid from 3,4-dihydro-2-tosyl-1,2-diazepines.[7]



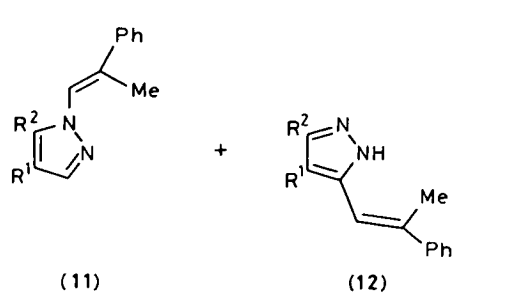
(6) (7) (5) (8)

	R^1	R^2	R^3	% Yield of (**8**)
a	$-[CH_2]_3-$		Me	65
b	$-[CH_2]_4-$		Ph	93
c	Me	Ph	Ph	71

Scheme 1



(9) (10)



(11) (12)

	R^1	R^2	% Yield (**10**)	(**11**)	(**12**)
a	$-[CH_2]_4-$		42	6	—
b	Me	Ph		37	29

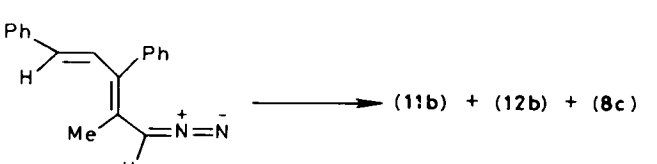
Scheme 2

As in the earlier work the diazo-compounds were generated *in situ* in aprotic solvents at *ca.* 80 °C from the sodium or lithium salts of tosylhydrazones. The results of the thermal reactions were clear-cut and are shown in Schemes 1—3. The systems shown in Scheme 1, *i.e.* those with the required *Z* stereochemistry for the α,β-double bond *and* having a *cis* hydrogen atom at the terminus of the unsaturated system, gave 3*H*-1,2-diazepines (**8**) in good to excellent yields, and in no case was any of the 3*H*-pyrazole (**5**) obtained or any other pyrazoles derived from it by rearrangement. It is notable that in all these cyclisations the primary product (**7**) was not isolated but rearranged by a 1,5 hydrogen shift to give (**8**). Such hydrogen migrations in these systems are known to be fast[7] and confer increased stability by bringing R^3 into conjugation and also in some cases by moving exocyclic double bonds to the more stable endocyclic positions.

Similar reactants (**9**) (Scheme 2) in which the terminal hydrogen atom was replaced by a methyl group did not give diazepines but cyclised by the alternative 1,5-mode to give the 3-vinyl-3*H*-pyrazoles (**10**) and/or the rearranged pyrazoles (**11**) and (**12**) as the only isolated heterocyclic products. Reactants with an *E* α,β-double bond, for example (**13**) (Scheme 3), as expected gave predominantly pyrazoles (**11b**) and (**12b**), but also a low yield of the diazepine (**8c**). The formation of the last is most likely accounted for by postulating some reversibility for the 1,5 cyclisation step; *i.e.* (**13**) cyclises to give (**5c**) which reopens to generate both (**13**) and (**6c**) thus leading to (**8c**) in low yield.

These results therefore show that 1,7 cyclisation is very strongly favoured over 1,5 in systems of type (**6**) but that the activation energy for the 1,7 process is raised so much by the presence of a *cis* methyl at the cyclisation site that the 1,5 mode is then preferred. The latter parallels a similar observation in the cyclisations of *o*-alkenylaryldiazoalkanes[8] but there the reaction path was diverted from 1,7 cyclisation to give only carbene-derived products.

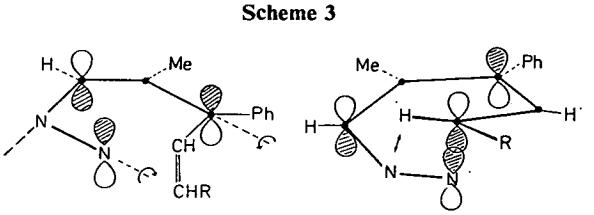
These observations can be accommodated by a transition state geometry for 1,7 cyclisation as shown in (**14**). This brings the terminal atoms into a bonding overlap and requires only the minimum angular distortion of the diazo group from its preferred linear geometry (see below). In this transition state the steric interaction [⟷ in (**14**)] between the *cis* hydrogen atom and N-2 of the diazo group is small; however



(13) (11b) + (12b) + (8c)

T/°C	% Yield (**11b**)	(**12b**)	(**8c**)
80	32	20	13
110	3	61	6

Scheme 3



(15) (14)

models show that a methyl group at that position comes into a significant steric interaction with N-2 which would either severely inhibit orbital overlap between the termini of the system or would so twist the terminal carbon atom that the conjugation required for an electrocyclisation process would be lost.

The mechanism of the 1,5-electrocyclisation of α,β-unsaturated diazo-compounds has been discussed recently by Huisgen[9] and we suggest that the lack of effective competition from this mode of cyclisation in (**6**) reflects the much greater degree of bending† required in the diazo-group, as shown in (**15**), before disrotation would result in enough orbital overlap to stabilise the transition state. This result contrasts with the cyclisation of carbonyl ylides with extended conjugation analogous to (**6**) which react by both 1,5- and 1,7-ring closure.[12]

We thank the S.E.R.C. and the University of Edinburgh for financial support (I.R.R.).

Received, 6th June 1983; Com. 724

† Calculations show a substantial energy barrier to in-plane bending of the CNN angle for diazomethane.[10,11]

References

1 A. Padwa and A. Rodriquez, *Tetrahedron Lett.*, 1981, **22**, 187.
2 T. Miyashi, Y. Fujii, Y. Nishizawa, and T. Mukai, *J. Am. Chem. Soc.*, 1981, **103**, 725.
3 A. A. Reid, J. T. Sharp, H. R. Sood, and P. B. Thorogood, *J. Chem. Soc., Perkin Trans.* 1, 1973, 2543.
4 D. P. Munro and J. T. Sharp, *J. Chem. Soc., Perkin Trans.* 1, 1980, 1718.
5 R. H. Findlay, J. T. Sharp, and P. B. Thorogood, *J. Chem. Soc., Perkin Trans.* 1, 1975, 102.
6 K. L. M. Stanley, J. Dingwall, J. T. Sharp, and T. W. Naisby, *J. Chem. Soc., Perkin Trans.* 1, 1979, 1433.
7 C. D. Anderson, J. T. Sharp, and R. S. Strathdee, *J. Chem. Soc., Perkin Trans.* 1, 1979, 2209.
8 D. P. Munro and J. T. Sharp, *Tetrahedron Lett.*, 1980, **21**, 4109.
9 R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, 1980, **19**, 947.
10 K. N. Houk, J. Sims, R. E. Duke, Jr., R. W. Strozier, and J. K. George, *J. Am. Chem. Soc.*, 1973, **95**, 7287.
11 J. Bastide and O. Henri-Rousseau, *Tetrahedron Lett.*, 1972, 2979.
12 W. Eberbach and U. Trostmann, *Chem. Ber.*, 1981, **114**, 2979.