STUDIES IN THE SYNTHESIS OF DIAZA-HETEROCYCLIC SYSTEMS BY CYCLISATION REACTIONS

PATRICK NEIL ANDERSON

Ph.D.

UNIVERSITY OF EDINBURGH

1979

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ABSTRACT.

The reaction of trans-2-formylstilbene with 1,2-dibenzylhydrazine gave the benzaldehyde benzyl(2-stilbylbenzyl)hydrazone rather than the 1H-2,3-benzodiazepine. Reaction of other aromatic aldehydes also gave the hydrazones, possibly via the azomethine imine.

The reaction of 2-ethynylbenzaldehyde with sulphonylhydrazines and benzoylhydrazide gave, via the hydrazones, the N-substituted isoquinoline N-imines rather than the 3H-2,3-benzodiazepines. Only non-cyclisable acetylenic hydrazones were obtained in the reaction of 2-ethynylbenzaldehyde with 2,4-dinitrophenylhydrazine and semicarbazide hydrochloride and in the reaction of 2-phenylethynylbenzaldehyde with p-tosylhydrazine and benzoylhydrazide.

The reaction of homophthalaldehyde with sulphonylhydrazines and benzoylhydrazide also gave N-substituted isoquinoline N-imines.

The acid catalysed reaction of varying N-substituted hydrazines with 4-methylhexa-3,5-dien-2-one gave N-substituted 3,4-dihydro-1,2-diazepines. Reaction of 4-methyl-6-phenylhexa-3,5-dien-2-one and hepta-3,5-dien-2-one with N-substituted hydrazines gave only non-cyclisable hydrazones.

The reaction of 4-methylhexa-3,5-dien-2-one with p-tosylhydrazine was carried out in deuteromethanol in the presence and absence of acid and the distribution of deuterium in the diazepine product showed that N-protonation of the tosylhydrazone is an essential primary step in the cyclisation.

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.

POST-GRADUATE COURSES

The following is a statement of post-graduate courses attended during the last three years:

Labs 10 and 29 Seminars	1975-1978
"N.m.r. Spectroscopy"	Dr. R.K. Harris
"Use of Phosphorus in Organic Chemistry"	Prof. J.I.G. Cadogan and Dr. I. Gosney
"Organic Sulphur Compounds in General Synthesis"	Dr. D. Leaver
"Stereochemistry- Basic and Advanced"	Dr. H. MacNab
"Chemistry at its most Colourful"	Staff of I.C.I. Blackley
"The History of the Chemistry Dept."	Dr. W.P. Doyle

ACKNOWLEDGEMENTS

I would like to sincerely thank Dr. J.T. Sharp for his excellent supervision of this work and also for his invaluable help during the time the work was carried out.

I am also extremely grateful to many members of the teaching and technical staff in the Department of Chemistry of the University of Edinburgh, especially Mr. T. Naisby and Mr. and Mrs. W. Macpherson.

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Studies in the Synthesis of Diaza-Heterocyclic Systems by Cyclisation Reactions

INTRODUCTION

INTRODUCTION.

A. Additions to carbon-carbon multiple bonds.

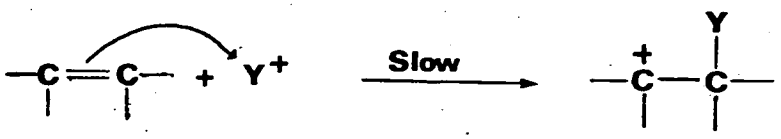
There are basically four ways in which addition to a double or triple bond may occur.[1] Three involve two-step processes, with initial attack by a nucleophile, an electrophile or a free radical. The second step is the fate of the resulting intermediate. It may combine respectively, with a positive species, a negative species or a neutral entity.

In the fourth type of mechanism the double or triple bond is attacked simultaneously at both ends.

These processes are outlined briefly in this section and nucleophilic additions most relevant to the original work in this Thesis are discussed in greater detail in Sections B and C.

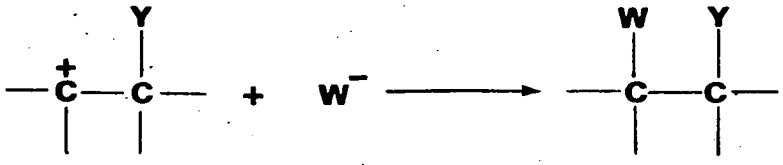
1. Electrophilic addition.

In electrophilic addition[1,2] a positive species (Y^+) approaches a double or triple bond and in the initial step a σ bond is formed by utilising a π-pair of electrons of the multiple bonds, Scheme 1.



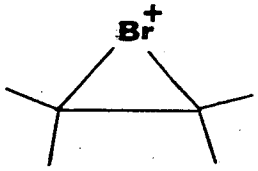
Scheme 1

This reaction leads to carbonium ions. Y in fact does not have to possess a positive charge but may be the positive end of a dipole or an induced dipole, and the negative part breaking off during the first step or shortly after. The second step is the combination of the carbonium ion with a species bearing an electron pair or usually, a negative charge (W^-), Scheme 2.



Scheme 2

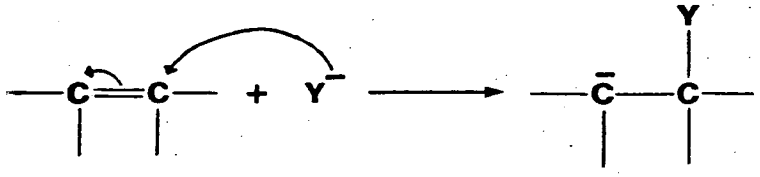
The carbonium ion may in fact not be the actual intermediate in all cases and in bromination it is recognised that the bromonium ion (1)[2] is involved.



(1)

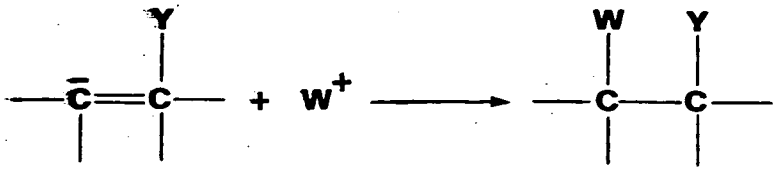
2. Nucleophilic addition.

The first step in nucleophilic addition is the attack of a nucleophile (Y^-) on one carbon atom of the double or triple bond forcing the π electrons to become centred on the other carbon, thus creating a carbanion, Scheme 3.



Scheme 3

The second step is the combination of this carbanion with a positive species (W^+), Scheme 4.

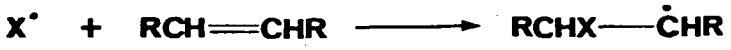


Scheme 4

It is in fact the same mechanism as the simple electrophilic addition except that the charges are reversed.

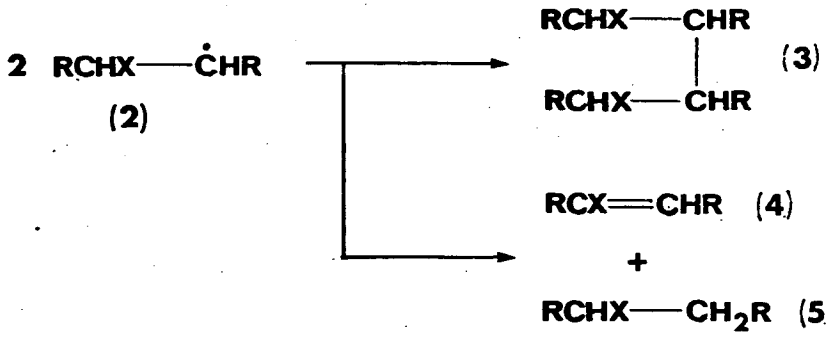
3. Free radical addition.

In free radical addition[1,3] the first step is the attack of the free radical (X·) on the double or triple bond to give new free radicals, Scheme 5.



Scheme 5

These new free radicals (2) may of course subsequently react to give the dimer (3), or by radical disproportionation to give the new olefin (4) and the addition product (5) or by radical transfer

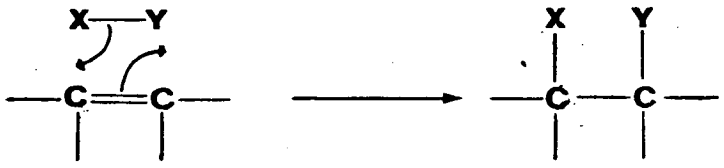


with another species (ZY) in the system to give the addition product plus propagation of the free radical mechanism, Scheme 6.

Scheme 6

4. Cyclic addition.

In some addition reactions the initial attack is not on one side of the double or triple bond but on both sides at once, Scheme 7.



Scheme 7

The transition state may be 4-, 5- or 6- membered and a most important reaction of this type is the Diels-Alder reaction.

The chemistry of the addition to carbon-carbon multiple bonds is very extensive not only as an intermolecular reaction but also as an intramolecular process where the reaction will lead to the formation of ring structures. In the formation of nitrogen containing heterocycles intramolecular nucleophilic addition of a nitrogen atom to a double or triple bond and 1,3-dipolar addition play a major role.

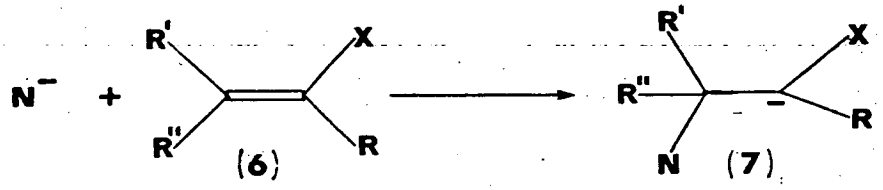
B. Nucleophilic addition to the carbon-carbon double bond.

The presence of the π-electrons in a carbon-carbon double bond makes attack by electrophilic reagents rather facile, whereas special activating factors are required for nucleophilic attack[4]. The most important of these factors is the presence of groups which

diminish the electron density in the double bond. The effect of such groups may be either inductive (-I) or resonative (-M), both effects tending to polarise the double bond with the result that a partial positive charge is developed as shown in Scheme 8.

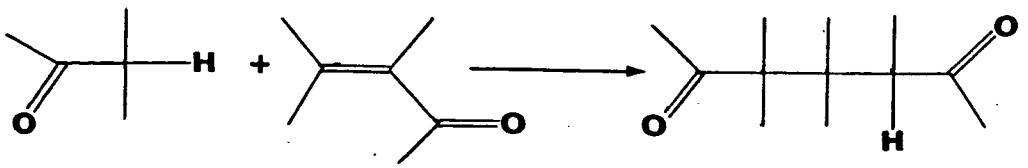
Scheme 8

Although there are a large number of substrates and nucleophilic agents[4] practically all the reactions are based on the same initial nucleophilic attack by the reagent (N^-) on the β-carbon of the double bond (6).



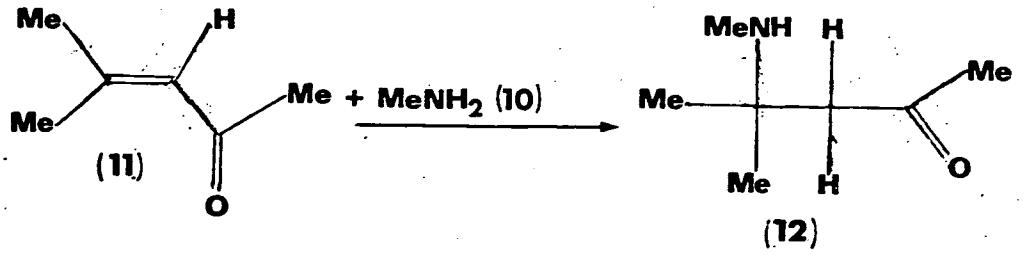
The fate of the intermediate carbanion (7) formed is determined in the later stages of the reaction by the nature of the substrate, the reagent and the medium.

The best known type of these reactions is the Michael condensation (or addition)[5]. The Michael condensation in its original scope was the addition of a donor (8) containing an α-hydrogen atom in the system O=C-CH to a carbon-carbon double bond that forms part of a conjugated system of the general formulation C=C-C=O as an acceptor (9).



(8) (9)

More recently, the Michael condensation has come to be understood to include donors and acceptors activated by groups other than carbonyl or carboxyl. Compounds containing a potential carbanion are widely used as donors in the presence of basic catalysts, i.e. malonic esters, alkylmalonic esters, cyano, nitro and carboxamide compounds as well as ketones and ketoesters. But donors are not limited only to compounds containing a potential carbanion. Nucleophiles containing oxygen, sulphur, halogens and nitrogen are well known[4] to take part in Michael condensation reactions. In the case of nitrogen only sufficiently basic nucleophiles will undergo Michael condensation type reactions. An example is given below, the addition of methylamine (10) to mesityl oxide (11)[6], the product being the amino-ketone(12).

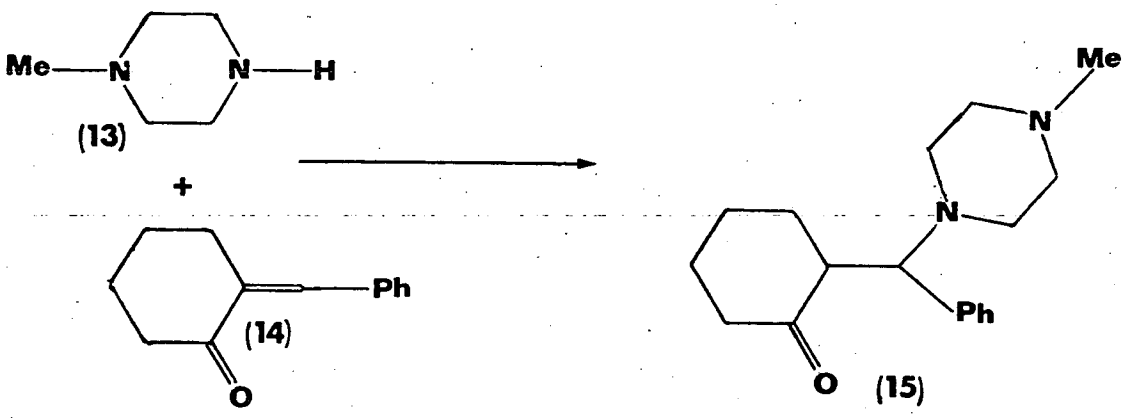


(11) (12)

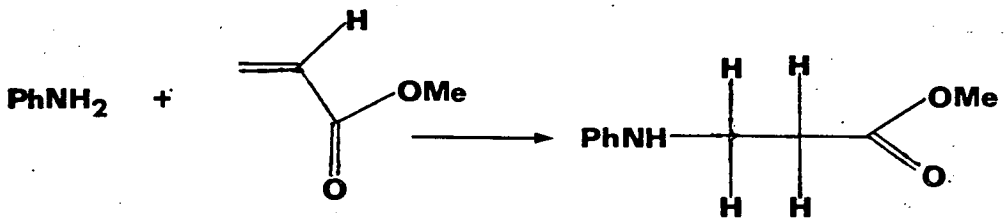
The reaction between ammonia and acrylonitrile, is interesting in that it proceeds further than the monoaddition stage[7], in fact ammonia adds twice to give the secondary amine.

Scheme 9

The facile addition of both aliphatic and aromatic amines to a wide variety of acceptors can take place[4]. One example is in the work of Baltzly et al[8] where the reaction of N-methylpiperazine (13) with benzalcyclohexanone (14) gives the adduct (15) which was used as an intermediate in the synthesis of compounds with physiological interest.



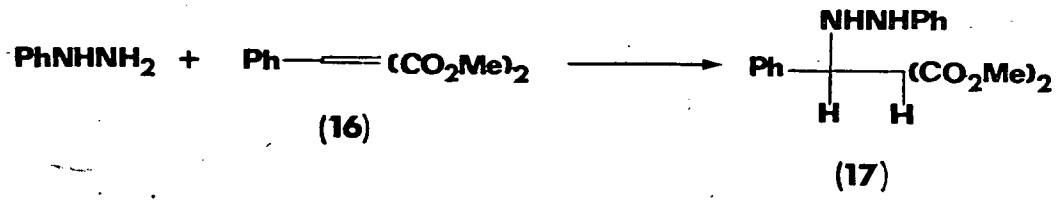
Buc et al [9,10] have shown that aniline reacts with methyl acrylate to give the Michael condensation product, Scheme 10.



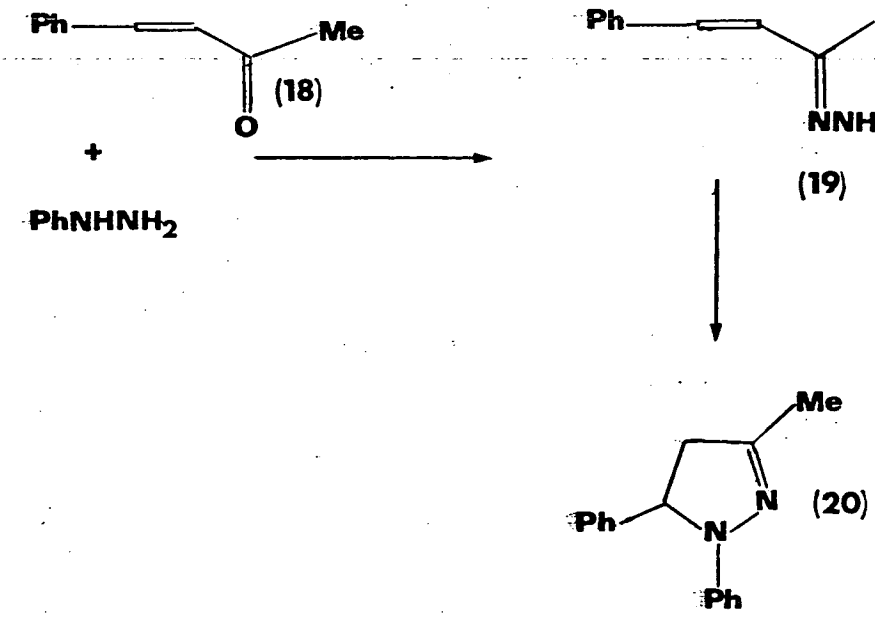
Scheme 10

The use of nitrogen containing nucleophiles is not just confined to amines. Phenylhydrazine or hydrazine may be used as donors. As early

as 1895 Blank[11] found the reaction of phenylhydrazine and benzal dimethyl malonate (16) proceeded smoothly to give the β-phenylhydrazidobenzyl dimethyl malonate (17). A similar reaction is possible with aniline.



The reaction of hydrazines with α,β-unsaturated aldehydes and ketones is a good method of synthesising pyrazolines[12]. For instance the reaction of phenylhydrazine with benzalacetone (18)[13] gives the pyrazoline (20) via the hydrazone intermediate (19).



In general, the phenylhydrazones can be isolated and these intermediates rearrange to give the corresponding pyrazolines in refluxing acetic acid. The hydrazones ring close in an intramolecular type of Michael condensation.

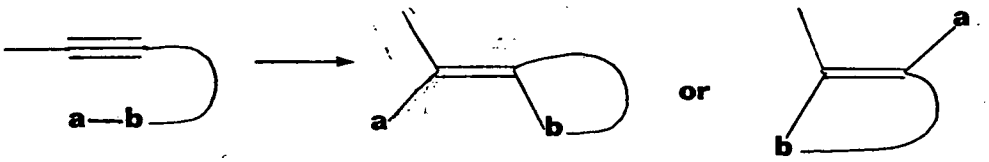
C. Nucleophilic addition to the carbon-carbon triple bond.

Additions to the carbon-carbon triple bond are among the most important reactions of acetylenic compounds[14]. Compared to the addition to olefins the acetylenes have not been studied so comprehensively. Acetylenes, like olefins will undergo electrophilic and free radical addition as well as nucleophilic addition. Whereas with olefins, nucleophiles only add to bonds which are polarised by an electronegative group, the acetylenic bond does not need this inductive polarisation. Indeed, while ionic additions to nonactivated double bonds generally proceed in an electrophilic manner, corresponding triple bonds react preferentially with nucleophilic reagents[15,16], depending on the donating force of the reaction partner and the environment of the triple bond to be attacked. This is especially true when the triple bond is conjugated to other triple or double bonds. The reason for the difference in reactivity between the triple and double is caused by the bonding pairs of electrons which in the acetylenic bond are closer to the carbon nuclei than in olefinic bonds because of the high degree of s character of the sp σ orbitals of the carbons. Thus, the acetylenic hydrogens are more acidic than ethylenic hydrogens and are more easily removed as protons. This greater affinity of the acetylenic carbons for electrons causes the rates of electrophilic additions to the triple bond to be slower than electrophilic additions to the double bond, and conversely the rates of nucleophilic addition to the triple bond are faster than those to the double bond.

The use of acetylenes in cycloadditions and cyclisations has become popular and there are many examples in the literature[16].

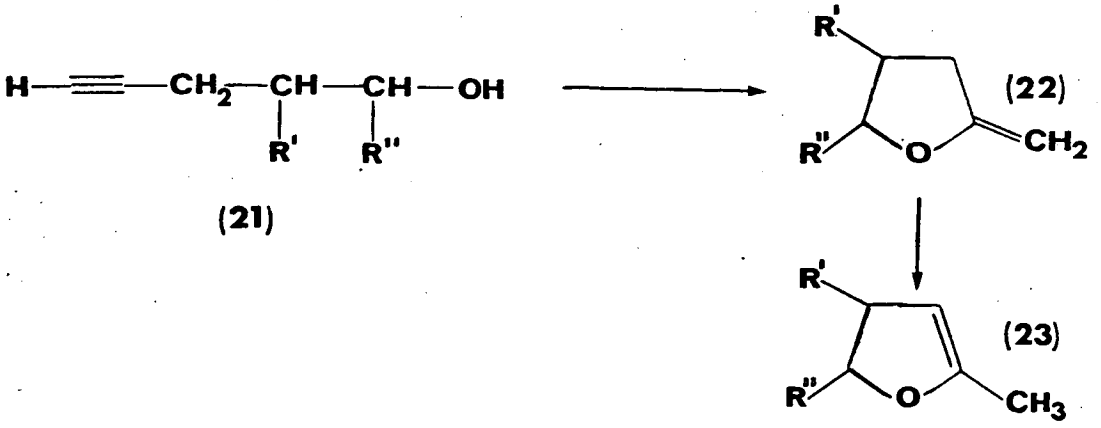
D. Cyclisation by intramolecular addition to acetylenes.

When an acetylenic molecule contains a functional group it is possible to build up various ring systems. The ring closure can be represented as:

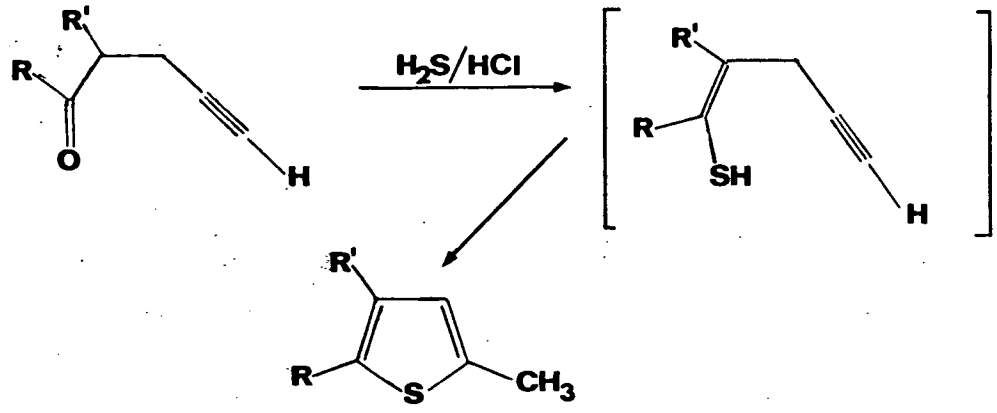


In most cases a, is hydrogen, and with b as nitrogen, oxygen or sulphur a variety of heterocyclic systems can be built up.

The intramolecular O-H addition is one of the most versatile reactions providing five or six-membered heterocycles[16]. One system that has been well studied is the reaction of γ-acetylenic alcohols. If the γ-acetylenic alcohol (21) is distilled over sodamide the product is the dihydrofuran (23) which is obtained via (22)[17,18,19,20].



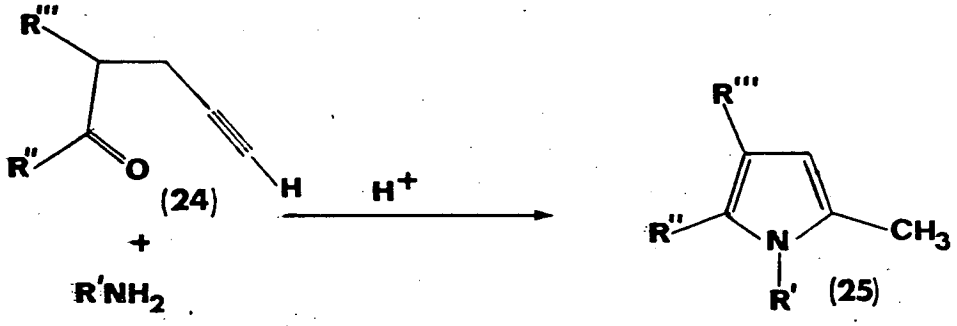
Similarly the thiophene, Scheme 11, can be produced by the treatment of the γ-acetylenic ketone with hydrogen sulphide and hydrogen chloride[21,22] presumably through enethiol intermediates.



Scheme 11

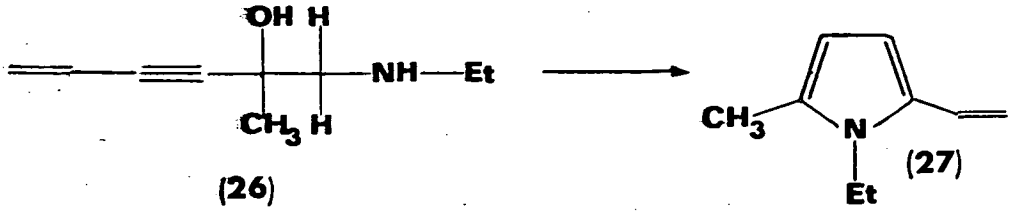
Although the literature of intramolecular N-H additions is not as large as O-H additions there are nevertheless a number of heterocycles which have been prepared in this manner[16].

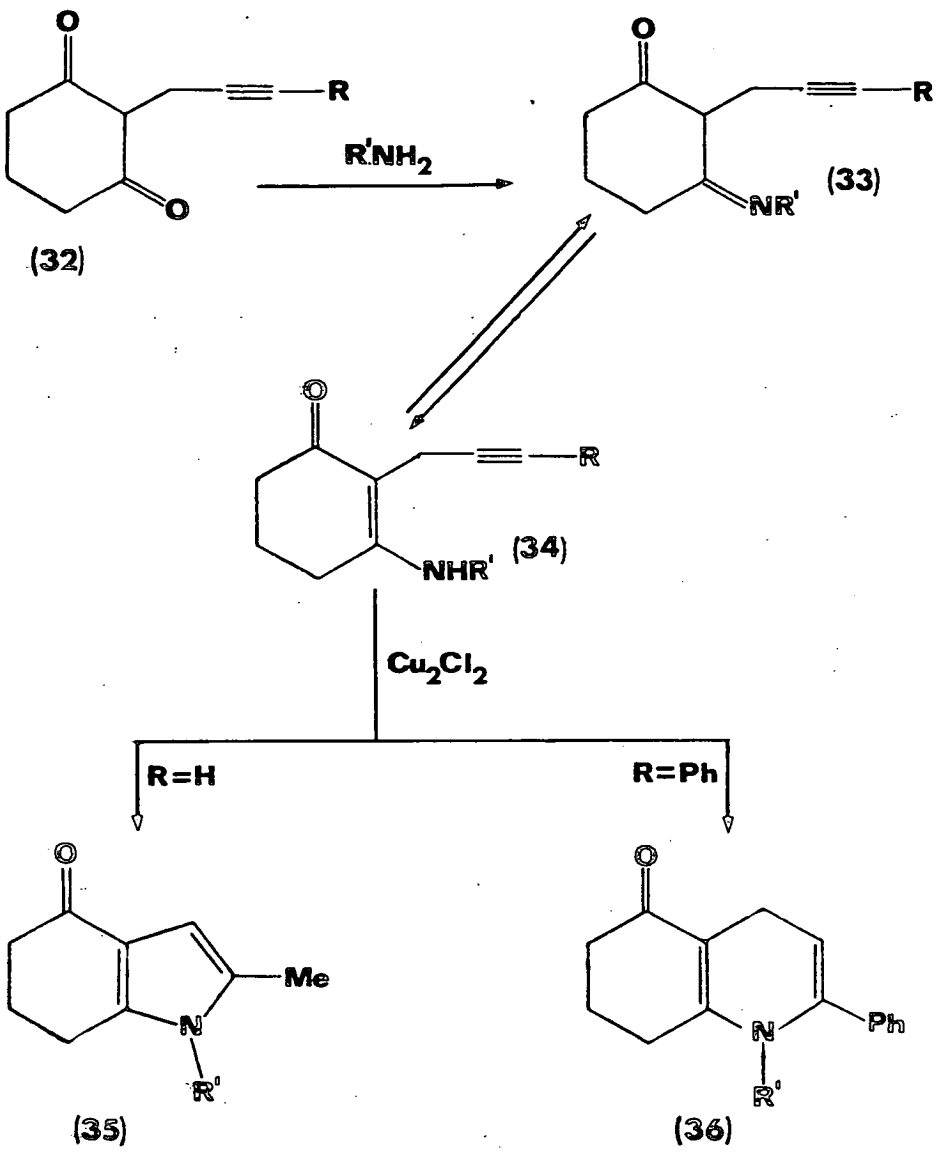
Reisch[23] has shown that γ-acetylenic ketones (24) can be used to form pyrroles (25) in good yields from their reaction with primary amines with a trace of sulphuric acid.



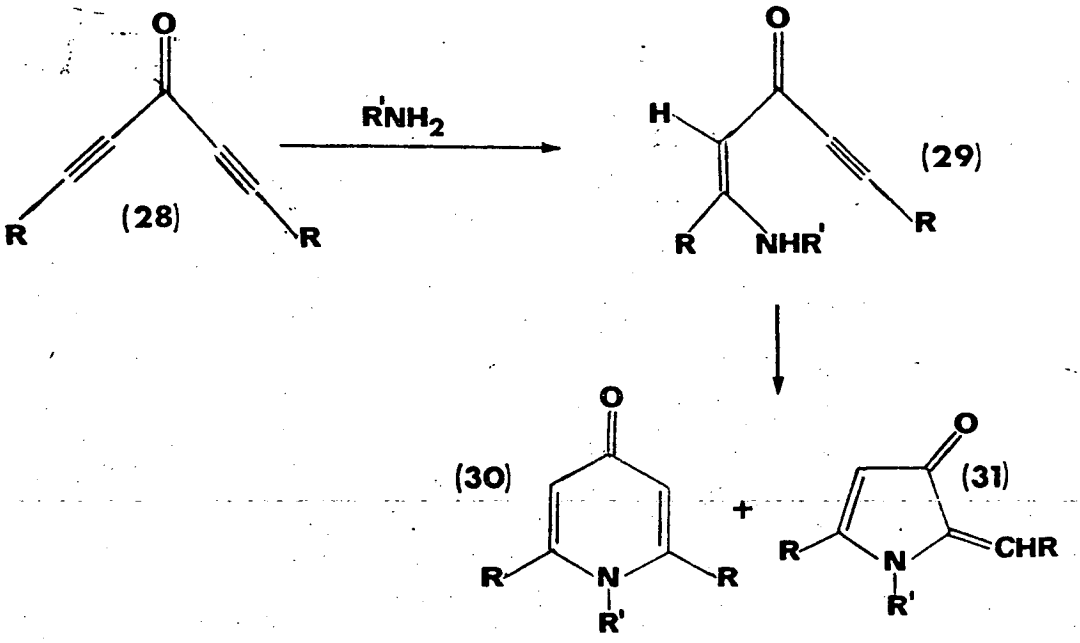
This reaction is similar to the reaction of γ-acetylenic ketones with H_2S, Scheme 11.

Ring closure of the acetylenic amine (26) by heating for 24h at 100°C in quinoline gives the pyrrole (27)[24,25].



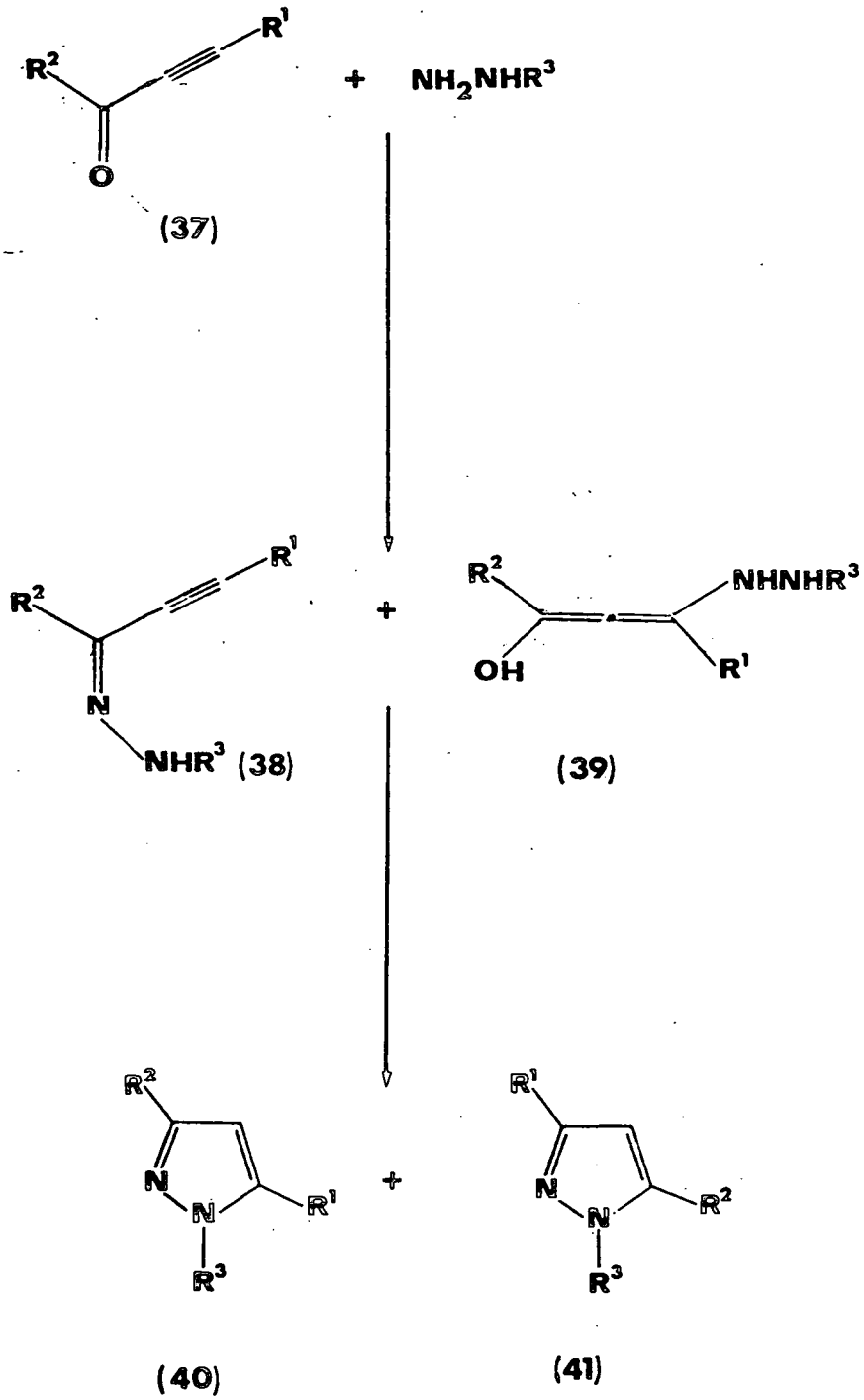

O
R
O
(32)
R'NH2
O
R
NR'
(33)
O
R
NHR'
(34)
Cu2Cl2
R=H
R=Ph
O
Me
N
R'
(35)
O
Ph
N
R'
(36)

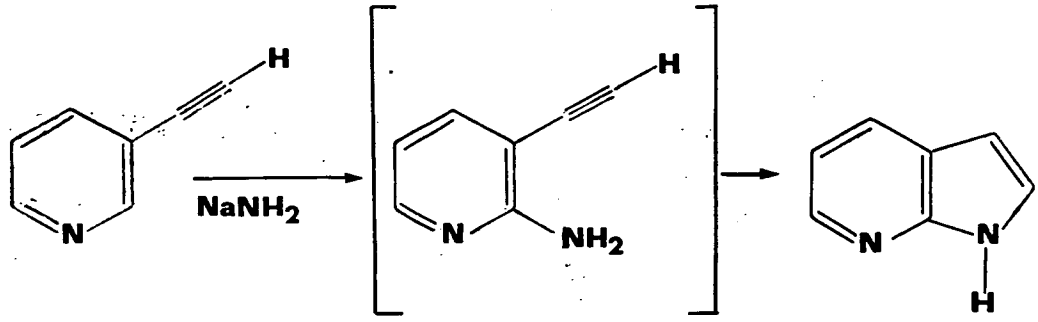
The use of acetylenic ketones is very popular and Chauvelier[26,27] has used diacetylenic ketones (28) which when reacted with amines give the α-acetylenic enaminoketones (29) which are converted in boiling xylene into 4-pyridones (30) if R is an alkyl group, or when R is an aromatic group into a mixture of pyrrolinones (31) and 4-pyridones (30)[28,29].



Some work has been done on systems already containing one ring. e.g. The reaction of 2-propargyl-1,3-cyclohexanediones (32) with primary amines. In this reaction the imine (33) is first formed which in the presence of cuprous chloride as a catalyst will cyclise through the enamine tautomer (34) to the 2-methylpyrrole derivatives (35) when R=H[30] and to the dehydropiperidine derivatives (36) when R=Ph[31].

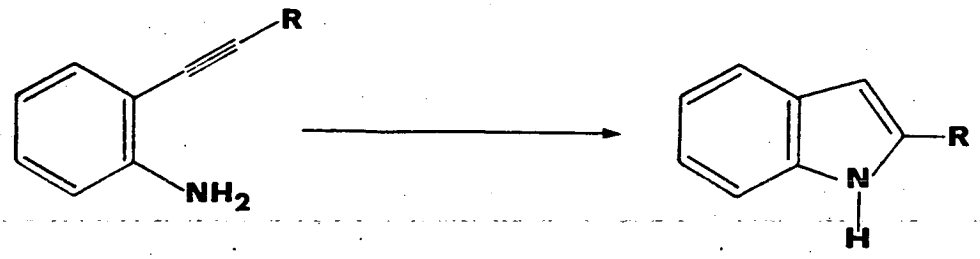
Reisch has also used acetylenes attached to aromatic rings. In his synthesis of 7-azaindole[32], Scheme 12, 3-ethynylpyridine is treated with sodamide to give the 2-amino-3-ethynylpyridine intermediate which cyclises at 170-180°C to the desired product.


R1
R2
O
+ NH2NHR3
(37)
R1
R2
N
NHR3 (38)
+
R2
NHNHR3
OH
R1
(39)
R2
N
N
R1
R3
+
R1
N
N
R2
R3
(40)
(41)



Scheme 12

In the same manner[32] but with cuprous chloride as catalyst at 170-180°C o-aminophenylacetylene (R = H) or o-aminophenylpropiolic acid (R = CO_2H) give indole and indole-2-carboxylic acid, respectively, Scheme 13.

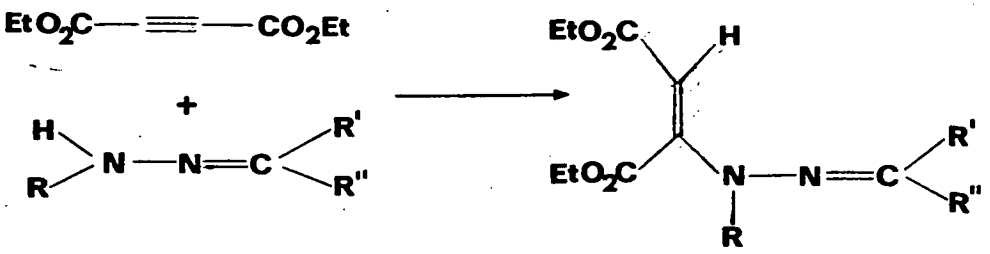


Scheme 13

There has been some work performed involving hydrazines and hydrazones with acetylenic compounds. In a reaction similar to the synthesis of pyrazolines (20) from phenylhydrazine and α,β-unsaturated ketones (e.g. benzalacetone (18)); α-acetylenic carbonyl compounds have been reacted with mono-substituted hydrazines[33,34]. The α-acetylenic ketone (37) is treated with a hydrazine with acid [33] and the product is either the hydrazone (38) by 1,2-addition or the enol (39) by 1,4-addition. Both of these can cyclise to give the pyrazoles (40) and (41).

Sucrow et al[35] have shown that hydrazones may also be added to activated acetylenic compounds, e.g. Scheme 14, aliphatic

hydrazones add to diethyl acetylenedicarboxylate to give the enehydrazones, the reaction proceeding smoothly in ethanol with acetic acid. This reaction is interesting to note as one of the sections of original work in this Thesis describes the intramolecular reaction of hydrazones with acetylenes.



Scheme 14

E. 1,3-Dipolar cycloadditions.

The field of 1,3-dipolar cycloadditions owes much to the work of Huisgen et al[36,37,38,39,40]. Huisgen was the first to recognise fully the general concept and scope of 1,3-dipolar cycloadditions.

A 1,3-dipole may be defined as a system a-b-c in which a has an electron sextet and carries a formal positive charge, and c is an anionic centre having a free electron pair. The 1,3-dipole will react with a multiple bond system, the dipolarophile, and after a cyclic shift of electrons a five membered ring is the product, Figure 1.

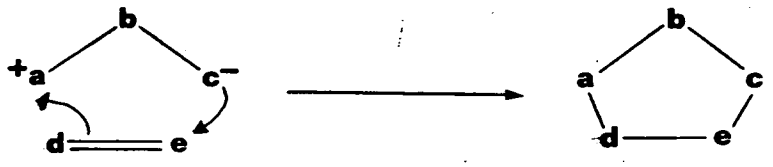
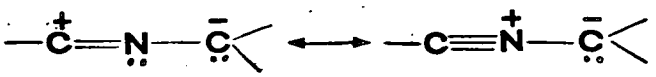


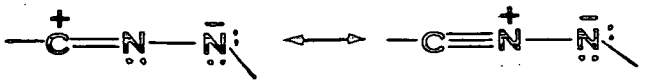
Figure 1

Octet-stabilised 1,3-dipoles 'with double bond'. (Figure 3)

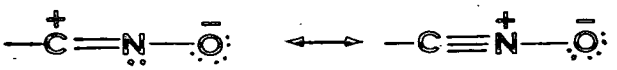
Nitrilium betaines



Nitrile ylides

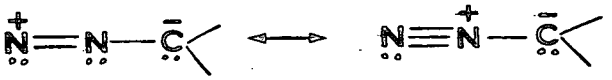


Nitrilimines



Nitrile oxides

Diazonium betaines



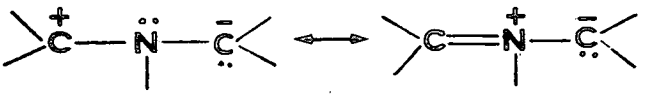
Diazoalkanes

Azides

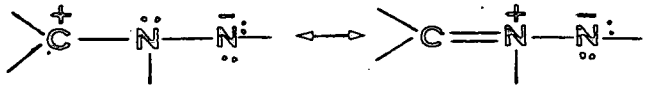
Nitrous oxide

Octet-stabilised 1,3-dipoles 'without double bond'. (Figure 4)

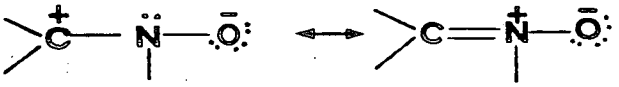
Nitrogen as central atom



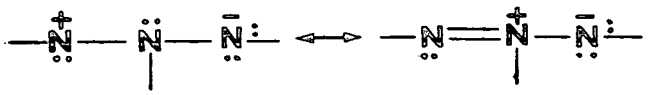
Azomethine ylides



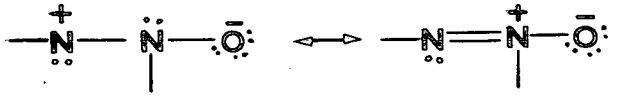
Azomethine imines



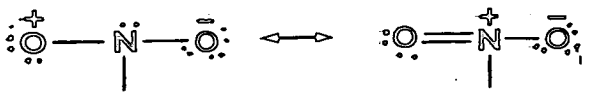
Nitrones



Azimines



Azoxy compounds



Nitro compounds

In this type of addition i.e. 3 + 2 ⟶ 5 where uncharged 5-membered rings are formed it is necessary that atom a possesses an electron sextet i.e. an incomplete valence shell combined with a positive formal charge, and that atom c, the negatively charged centre has an unshared electron pair.

Compounds in which their positive centre a is an electron-deficient carbon, nitrogen or oxygen are not stable. However stabilisation is possible if an unshared pair of electrons at atom b can relieve the electron deficiency at centre a by the formation of an electron bond, Figure 2.

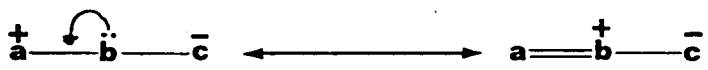


Figure 2

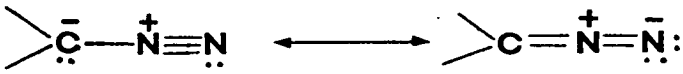
An all-octet structure is thus obtained in which b has become the seat of the formal positive charge. Betaines of this type are referred to as octet-stabilised 1,3-dipoles. By varying the atoms at a, b and c it is possible to build up a series of 1,3-dipoles.

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

A greater number of "1,3-dipoles without double bond" as in Figure 4 is possible. In addition to the six systems illustrated with nitrogen as the central atom, six others are possible with oxygen in this position.

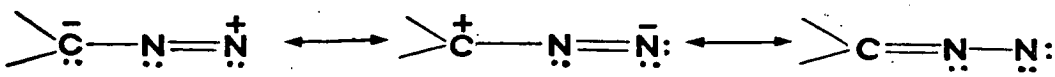
As well as the six other "1,3-dipoles without double bond" with the central atom as oxygen there are also a number of systems with no octet-stabilisation.

In the schematic representation of the 1,3-dipoles with octet-stabilisation they are shown with one sextet structure. However additional resonance structures contribute to the stability of the compounds, as may be shown for the diazoalkane. The ground state of the molecule is well represented by the two all octet structures, Scheme 15.



Scheme 15

But there is a contribution, although less significant of the sextet structures, Scheme 16.



Scheme 16

The sextet structures show that the formal charges are in fact interchangeable, thus it is not meaningful to ascribe to a certain centre electrophilic activity and to the second one nucleophilic activity.

The mechanism of 1,3-dipolar cycloaddition that has emerged from Huisgen's group is that of a single step, four centre, "no-mechanism" cycloaddition, in which two new bonds are both partially formed

in the transition state although not necessarily to the same extent[36,37,38,40].

An alternative mechanism, shown in Figure 5, that has been proposed is a two-step process involving a spin-paired diradical intermediate[41,42,43].

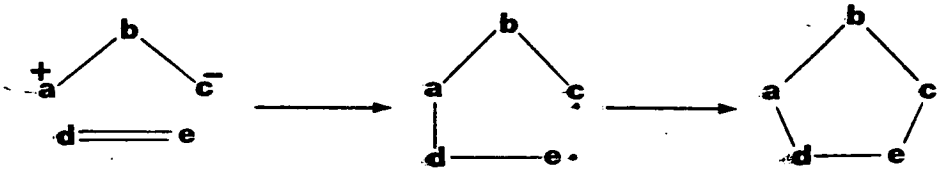


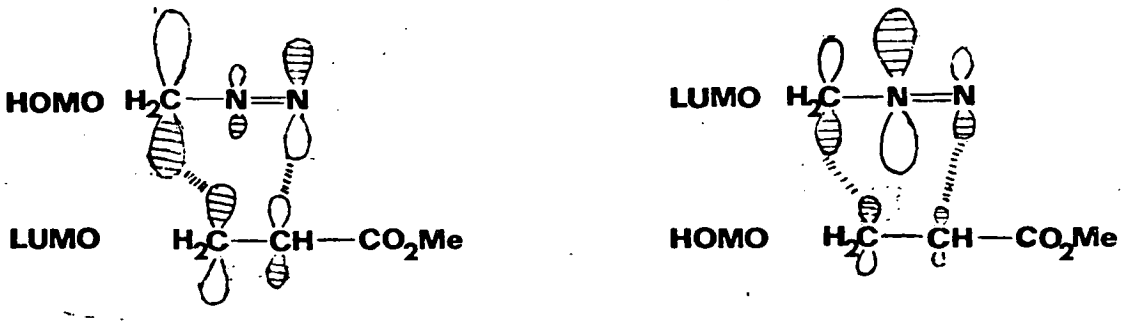
Figure 5

Houk et al[44,45,46,47] have used the frontier orbital method for rationalising the effect of substituents on rates and regioselectivity of 1,3-dipolar cycloadditions. This treatment shows that the relative reactivity of a given 1,3-dipole towards a series of dipolarophiles will be determined primarily by the extent of stabilisation obtained by the transition state by interaction of the frontier orbitals of the two reactants.

The reactions can be classified into three types, depending on whether the dominant interaction is between the highest occupied molecular orbital (HOMO) of the dipole and the lowest unoccupied molecular orbital (LUMO) of the dipolarophile, or the dipole LUMO and the dipolarophile HOMO or whether both these interactions are of equal significance. Houk calculated by CNDO/2 the orbital energies and atomic orbital coefficients of 1,3-dipoles.

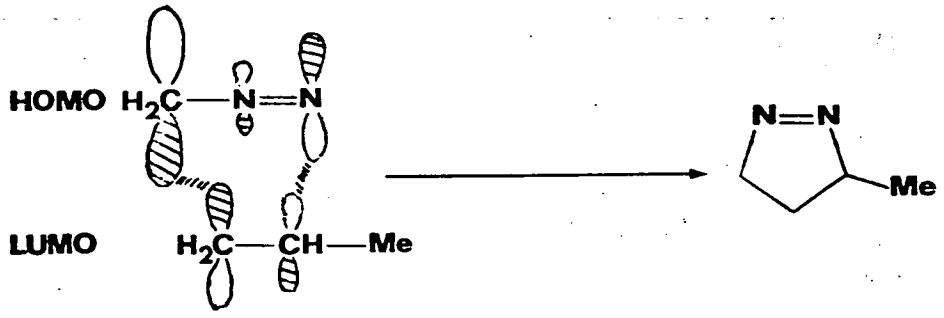
For example in the 1,3-dipolar cycloaddition of diazomethane to methyl acrylate it has been shown that the HOMO of the diazomethane interacts strongly with the LUMO of the methyl acrylate.

The reverse interaction is small, Scheme 17.



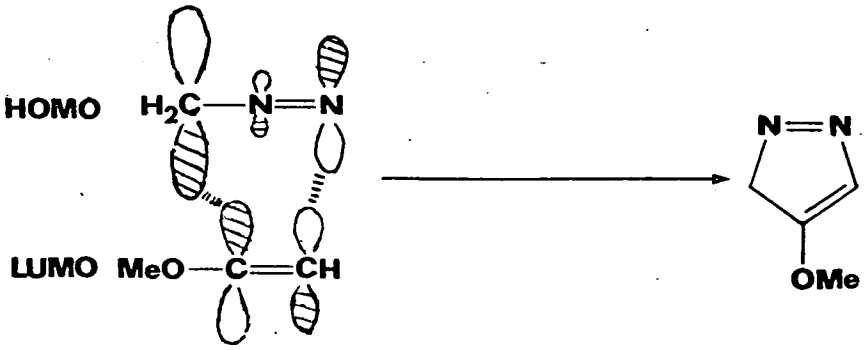
Scheme 17

The product from this reaction is a 3-substituted pyrazoline. The same applies in the reaction of diazomethane with prop-1-ene, a 3-substituted pyrazoline being formed, Scheme 18.



Scheme 18

However, the frontier orbital representation for ethoxyacetylene is different, and when the HOMO of the diazomethane interacts with the LUMO of the ethoxyacetylene the result is a 4-substituted pyrazole, Scheme 19.



Scheme 19

Huisgen[40] states that Houk's treatment of 1,3-dipolar cycloadditions supports his view of the mechanism, but the controversy remains, for recently[48] a valence bond theory has been presented to support the concerted diradical mechanism of 1,3-dipolar cycloaddition.

There is now an exceedingly large literature dealing with bimolecular 1,3-dipolar cycloadditions but only recently has much attention been shown to intramolecular cycloadditions[49,50]. 1,3-Dipoles bearing a functional group able to behave as a dipolarophile are extremely interesting substrates. In fact, the intramolecular cycloaddition of a properly functionalised 1,3-dipole represents a general scheme for the synthesis of novel fused ring heterocycles, Figure 6.

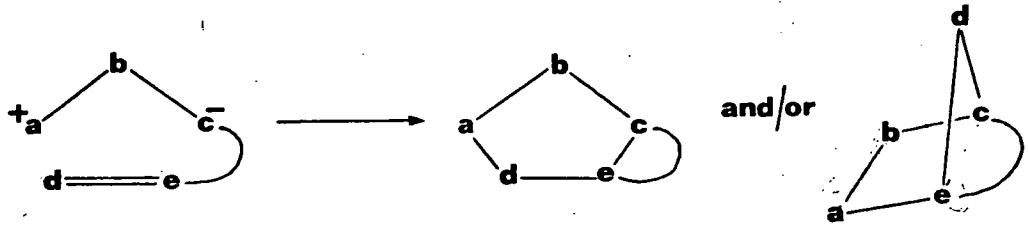
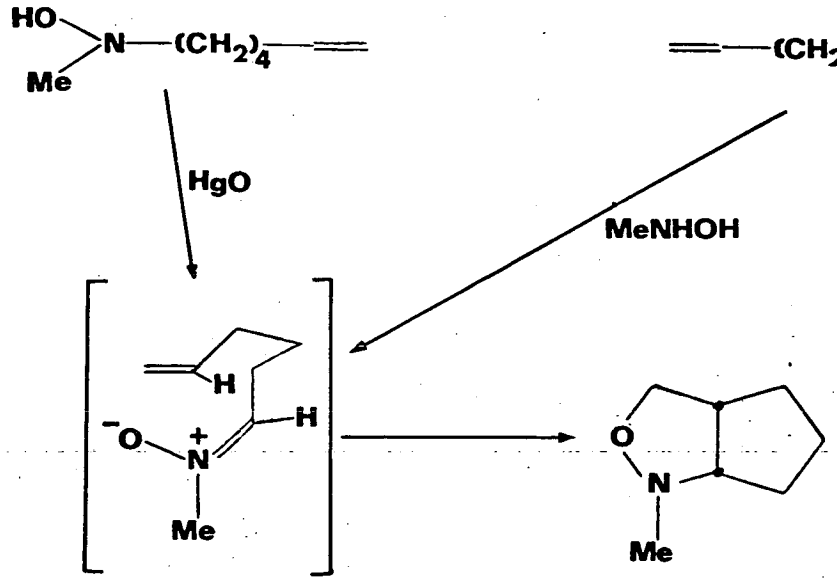


Figure 6

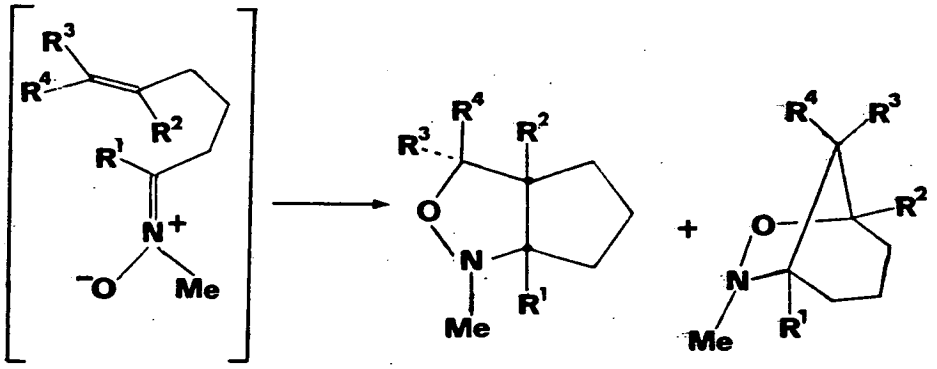
Nitrones, diazoalkanes, azides, azomethine imines, nitrile imines, nitrile ylides, carbonyl oxides and nitrile oxides have all been shown to undergo intramolecular cycloadditions[49].

For example the intramolecular cycloaddition of the nitrone (42)[51] prepared from either oxidation of a N-alkenylhydroxylamine by mercuric oxide or condensation of an unsaturated aldehyde with N-methylhydroxylamine gave a fused bicyclic isoxazolidine (43).



(42) (43)

Intramolecular cycloaddition of the homologous nitrone (44)[52] gave either the (fused) bicyclo [3.3.0] octane system (45) alone or along with the (bridged) bicyclo [3.2.1] octane system (46) depending on the nature of R^1, R^2, R^3 and R^4.



(44) (45) (46)

When only one of the substituents R^1, R^2, R^3 and R^4 is a methyl group and the others hydrogen only the fused ring product is formed but when $R^1 = R^2 = CH_3$ and $R^3 = R^4 = H$ approximately equal amounts of the fused and bridged products are formed. The presence of methyl groups in these positions (i.e. $R^1 = R^2 = CH_3$) forces them to be strongly eclipsed in the transition state that leads to the normal fused product. Thus in this case the severe steric interactions allow for the competing formation of the bridged products.

F. Baldwin's rules for ring closure.

Baldwin has put forward a set of three rules which have been found useful, on an empirical basis, to predict the relative facility of ring forming reactions[53].

As ring forming reactions are important and common processes in organic chemistry simple rules to predict the facility and selectivity of different modes of ring closure would be very useful on planning syntheses.

Modes of ring formation have been divided into two kinds, one where the breaking bond is exocyclic to the smallest so formed ring, this is called an 'Exo' process, Figure 7.

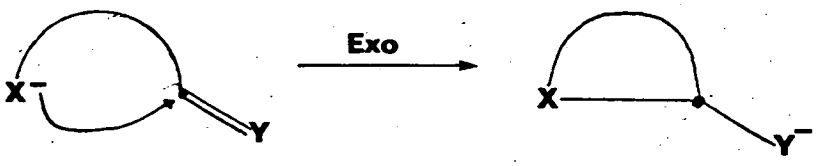
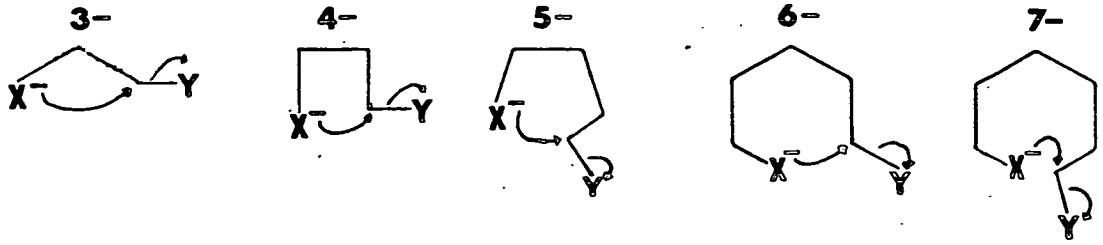


Figure 7

The other where the breaking bond is endocyclic to the smallest so formed ring is called an 'Endo' process, Figure 8.

Rule 1: Tetrahedral systems.

Exo–Tet.



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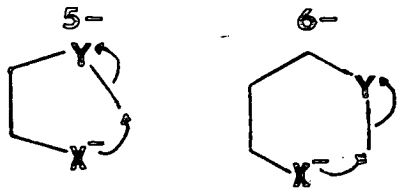
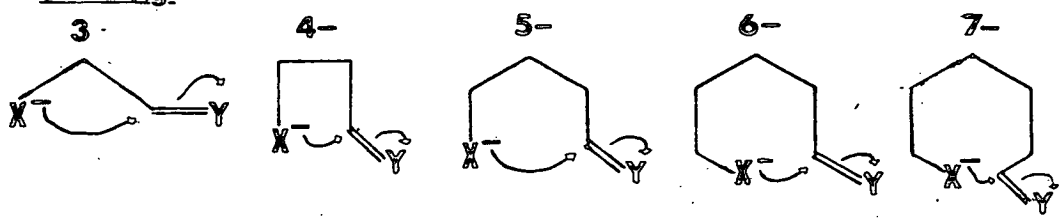
Endo–Tet.



Disfavoured.

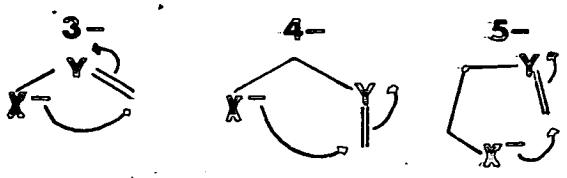
Rule 2: Trigonal systems.

Exo–Trig.

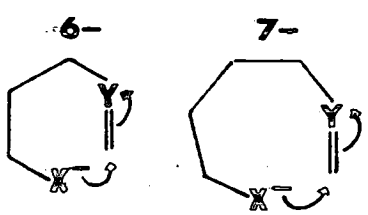


Favoured.

Endo–Trig.



Disfavoured.



Favoured.

Figure 9.

Figure 8

A numerical prefix is also used to describe the ring size, being the number of atoms constituting the skeleton of the cyclic compound. Further the suffixes Tet, Trig and Dig refer to the geometry of the carbon atom undergoing attack in the ring closure reaction; the suffixes refer to tetrahedral, trigonal and digonal carbon atoms respectively. The relative facility of ring closure is described by the terms favoured and disfavoured. This does not mean that a disfavoured ring closure is an impossible reaction, merely a process which may not compete effectively with alternative favoured ring closures or other reaction pathways.

Baldwin's Rules are as follows:-

Rule 1: Tetrahedral systems: (Figure 9)

a) 3 to 7-Exo-Tet are all favoured processes with many literature precedents[54].

b) 5 to 6-Endo-Tet are disfavoured[55].

Rule 2: Trigonal systems: (Figure 9)

a) 3 to 7-Exo-Trig are all favoured processes with many literature precedents. (e.g. lactonisations of ω-hydroxy acids or esters)

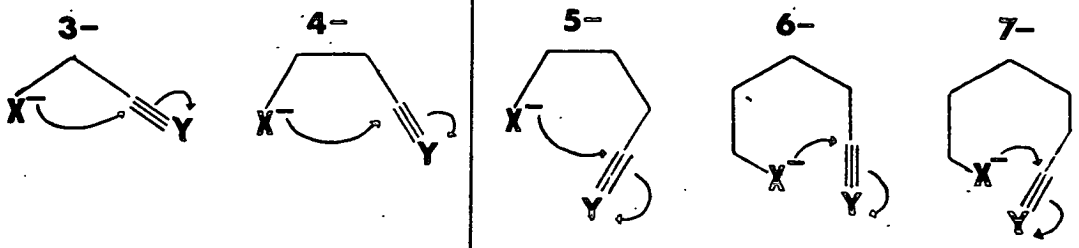
b) 3 to 5-Endo-Trig are disfavoured,[56] 6 to 7-Endo-Trig are favoured.

Rule 3: Digonal systems: (Figure 10)

a) 3 to 4-Exo-Dig are disfavoured processes, 5 to 7-Exo-Dig

Rule 3 : Digonal systems

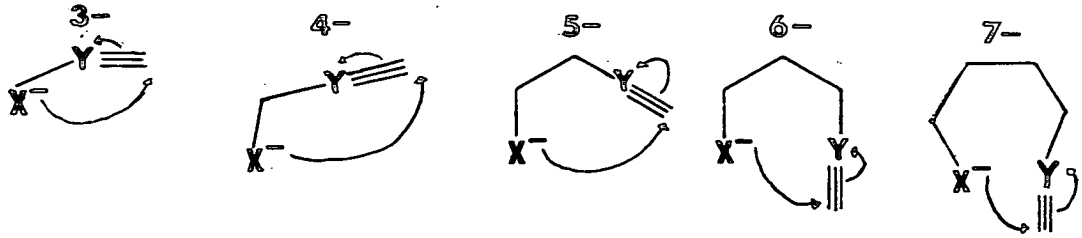
Exo–Dig



Disfavoured

Favoured

Endo–Dig



Favoured

Figure 10

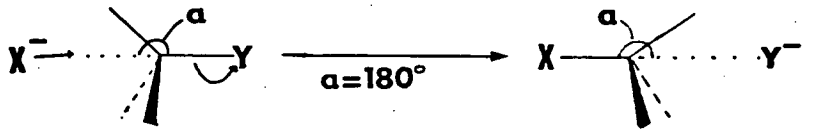
are favoured[57,58].

b) 3 to 7-Endo-Dig are favoured[57,58,59,60].

As a consequence of the larger atomic radii and bond distances in atoms of the second periodic row the geometric restraints on disfavoured ring closure may be by-passed[56]. Therefore a condition of these rules is that X must be a first row element. The physical bases of the rules lie in the stereochemical requirements of the transition states for the various tetrahedral, trigonal and digonal ring closure processes.

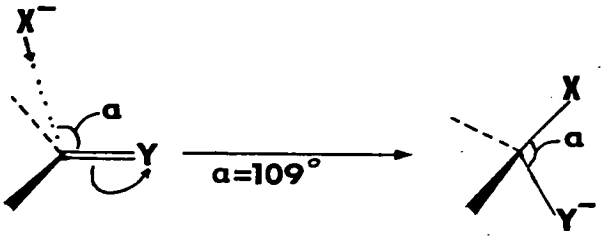
In a ring closure process, the linking chain will restrict the relative motion of the terminal groups X and Y, therefore the nature and length of this chain i.e. ring size, will determine whether X and Y can attain the required transition state geometry.

For closures to a carbon atom the favoured paths to the transition states are represented thus:-



(47) (48)

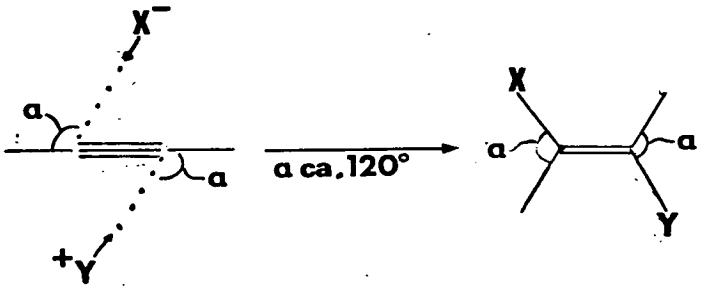
This process (47) ⟶ (48) represents the classical and well established Walden inversion of the S_N2 reaction.



(49) (50)

(49) ⟶ (50) represents the trigonal case where the approach angle is 109° and is supported by the work of Dunitz and Burgi on additions to carbonyl compounds[61].

In the digonal case (51) ⟶ (52) the angle of approach required is ca. 120° and is supported by some recent x-ray work[62,63].



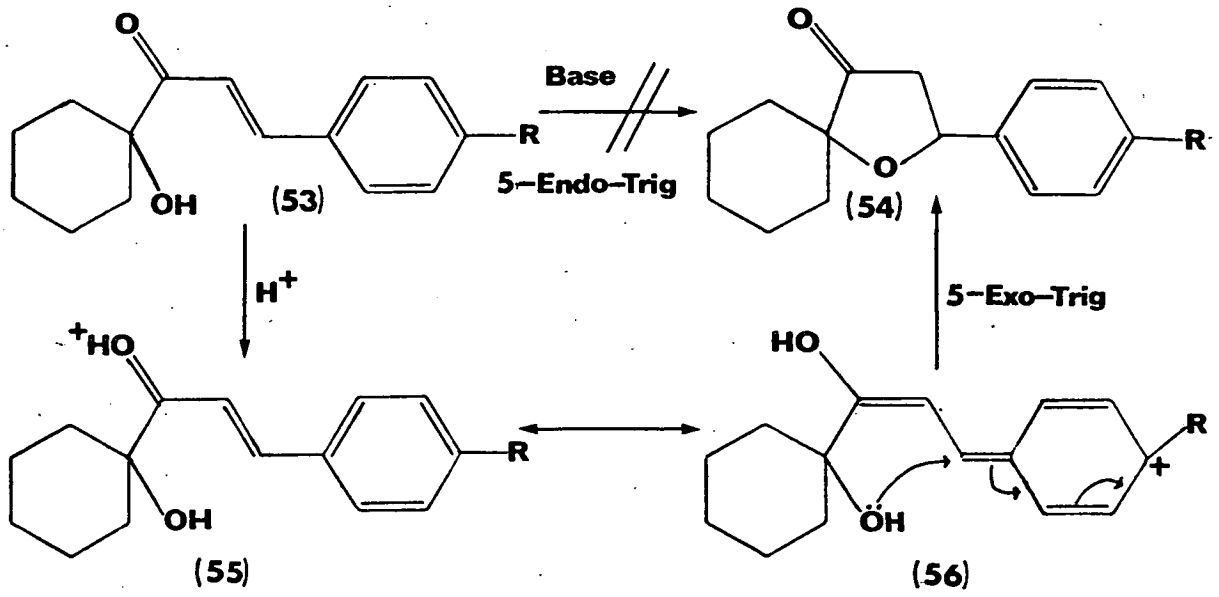
(51) (52)

In each of the three cases the subtended angle **a** between the three interacting atoms is maintained during the reaction pathway, becoming the angle between these atoms in the product. Thus when the length and nature of the linking chain allows the correct geometry to be achieved by the terminal atoms a favoured ring closure results, allowing formation of the final ring bond. Severe distortion of bond angles and distances to achieve the correct geometries lead to disfavoured processes.

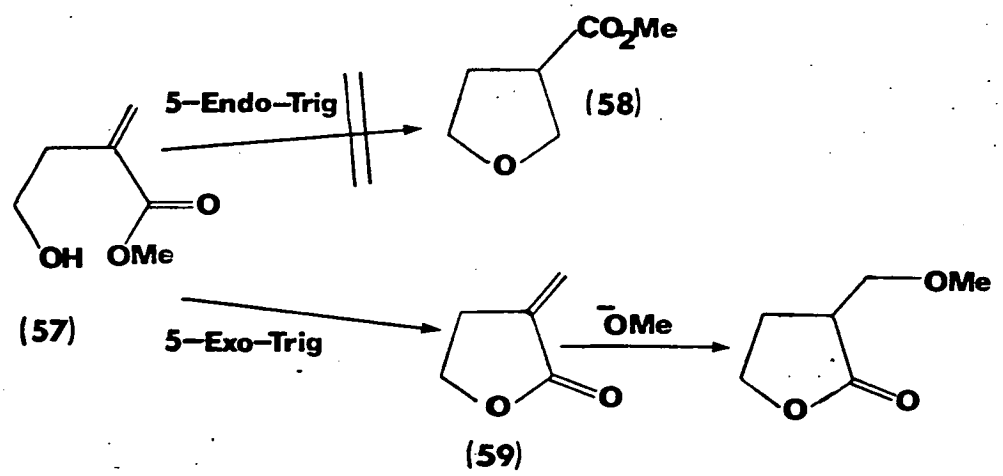
This treatment has discussed nucleophilic closures, but it also applies to homolytic and cationic processes.

An illustration of Baldwin's rules is in the 5-Endo-Trig and 5-Exo-Trig case[56]. 5-Endo-Trig is a disfavoured ring closure and 5-Exo-Trig is a favoured one. The ketols (53) will not cyclise in basic conditions to the furanones (54). This cyclisation would have to proceed through a 5-Endo-Trig process. On the other hand the ketols (53) in acidic media will cyclise *via* the protonated

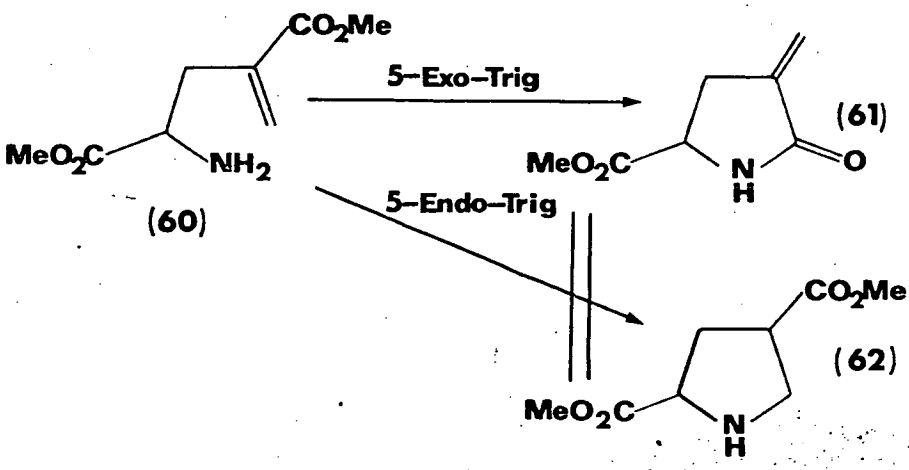
species (55) in a 5-Exo-Trig process to the furanones (56).



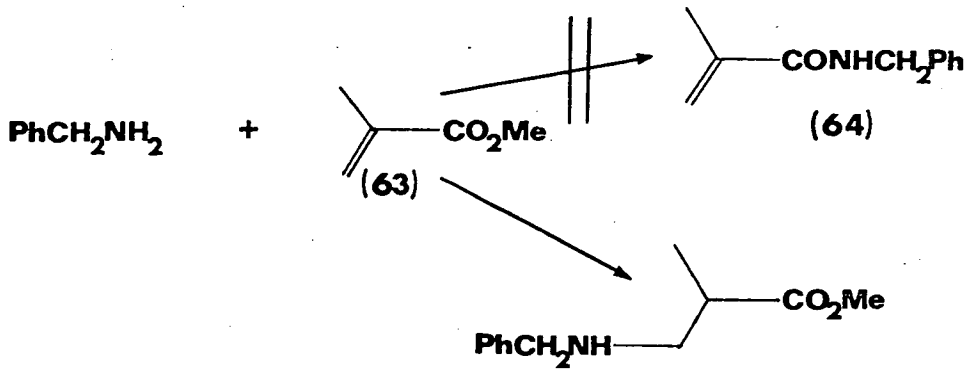
A further example is the failure of the alcohol (57) to cyclise to the cyclic ether (58). This would have involved a 5-Endo-Trig ring closure. Rather, the alcohol (57) was ring closed efficiently and clearly to the lactone (59). Indeed the lactone added smoothly methoxide showing that the double bond is susceptible to Michael addition.



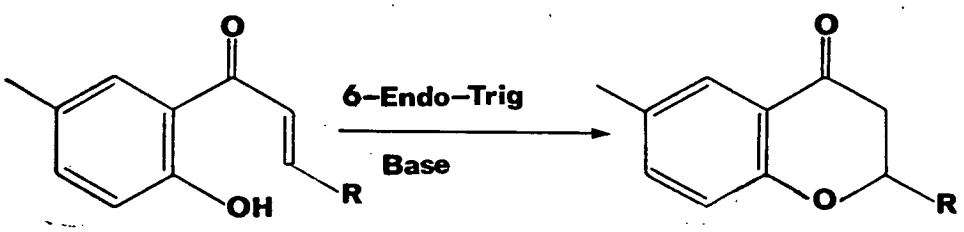
And similarly for the nitrogen analogue (60) of the alcohol (57) which cyclises *via* a 5-Exo-Trig process to the lactam (61) in 100% yield. None of the cyclic amine (62) is formed.



Normally primary amines add 1,4 to α-substituted acrylic esters (63) more rapidly than they are transacylated to α-substituted acrylamides (64)[64]. Thus the conversion of the amine (60) into the lactam (61) shows that the normally preferred 1,4-addition is disfavoured with respect to the 5-Exo-Trig transacylation.



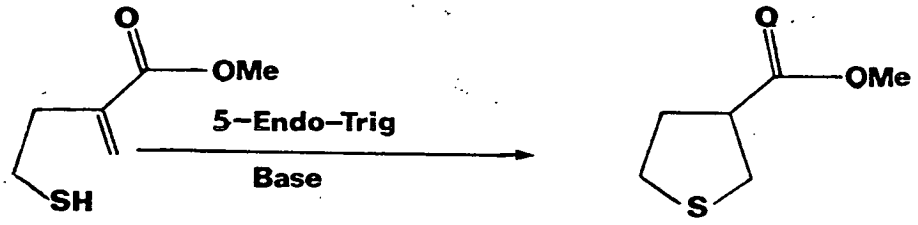
Whereas 5-Endo-Trig is a disfavoured process the 6-Endo-Trig reaction occurs readily and is illustrated by the synthesis of 4-chromanones, Scheme 20, from α,β-unsaturated ketones and base[65].



R= H, Me, Ph

Scheme 20

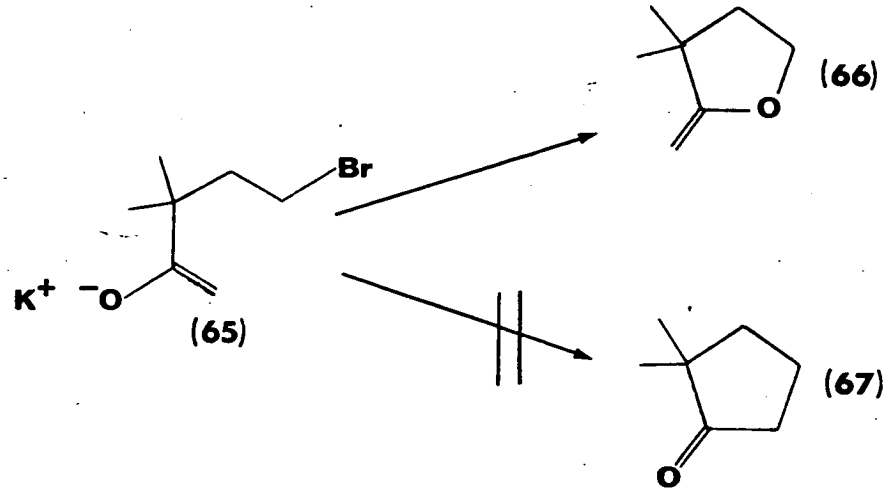
As stated before a second-row element may facilitate a normally disfavoured process. The thiol ester, shown in Scheme 21, cyclises in base <u>via</u> the 5-Endo-Trig process to give the sulphide[66].



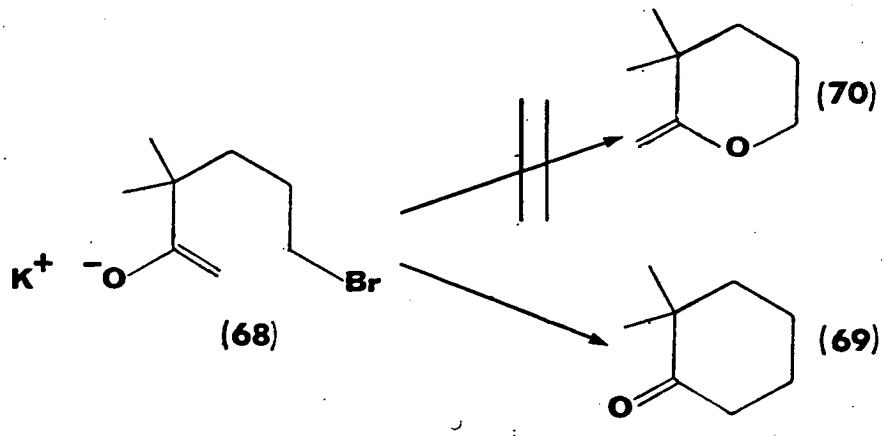
Scheme 21

Further evidence for the validity of these rules is in the endo-cyclic alkylation of ketone enolates which has been shown by Baldwin[67] to depend critically on the size of the so formed ring; six- but not five-membered cyclic ketones can be synthesised in that way. For example, the enolate of the ketobromide (65) cyclises to give the enol ether (66) only. For the formation of the cyclic ketone (67) the alkylation would have proceeded in an Endo-manner. This

Endo-alkylation to give a 5-membered ring is disfavoured from Baldwin's rules.

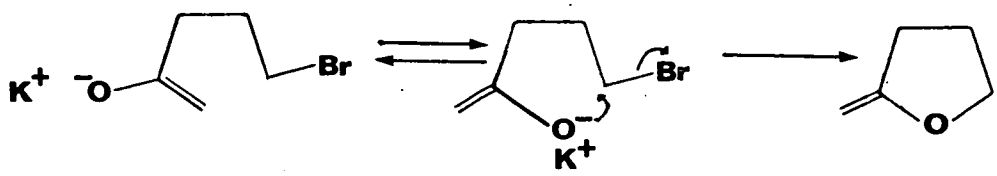


However the enolate (68) gave only the cyclic ketone (69) and none of the enol ether (70).



The Endo-alkylation to give a six-membered ring is favoured. In the case of enolate (65) it cannot take up the correct geometry for carbon alkylation, see Scheme 22, i.e. the approach of the carbon (bearing the bromine) perpendicular to the plane of the enolate. But it is possible for the correct geometry for oxygen-alkylation

to be taken up i.e. in the plane of the enolate, thus cyclising to the enol ether.



Scheme 22

However in enolate (68) the extra bond length enables a near perpendicular approach to the enolate and hence carbon-alkylation.

Although 6-Exo-Trig and 6-Endo-Trig are both favoured ring closures, Baldwin[68] has shown that when the two modes are possible the 6-Exo-Trig is the faster ring closing process. This is in agreement with earlier work[53] which showed the relative facility of the Exo mode over the Endo mode of ring closure in the trigonal system. This results from the ability to take up the correct trajectory for attack on the double bond (49) ⟶ (50). Baldwin[69] has produced a method of approximating preferred nucleophilic approach geometries to unsaturated functions, based on classical resonance structures; he has called this Approach Vector Analysis. It is possible from this analysis method to predict and explain the stereochemistry of certain reactions.

The approach of a nucleophile to a carbonyl group is at an angle of approximately 110°. This is shown below in the normal manner and in its projection in Figure 11.

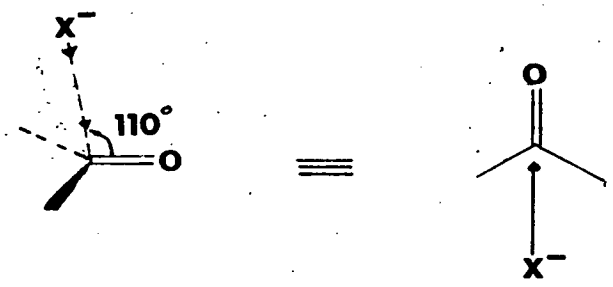
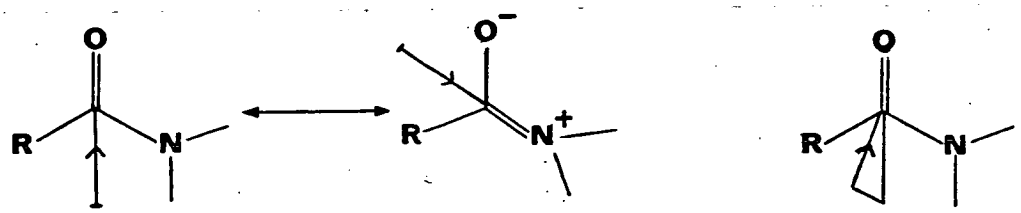


Figure 11

The electronic structure of an amide function can be represented as two resonance structures; the ketone with the approach vector as shown with a weighting C_1, and the immonium structure with the approach vector as shown with a weighting C_2. Vector summation of the two gives the resultant approach direction or approach vector, Figure 12.



Resultant

Figure 12

This analysis indicates that the approach vector for nucleophilic attack on an amide function is shifted from the symmetrical position in a ketone to a position closer to the group R. Thus the group R would interfere with the approach of a nucleophile.

It is possible to extend this treatment to other functionalities. Thus the approach of a nucleophile (e.g. H^- in a reduction) to a cyclohexenone can be represented in two forms with individual weightings C_1 and C_2 as in Figure 13.

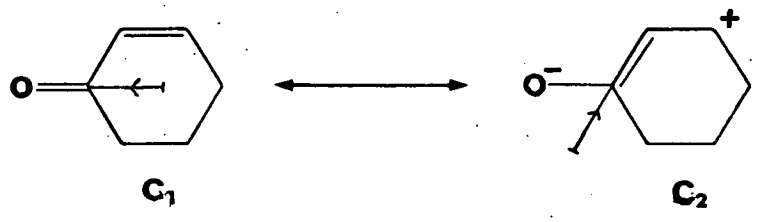


Figure 13

The vector summation, Figure 14, of the structures gives the resultant approach vector.

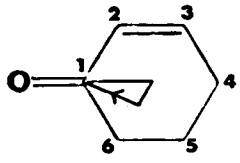


Figure 14

This projection shows that approach of a nucleophile to an enone carbonyl should be very sensitive to quasi-axial substituents at C-6 and C-5. This treatment[69] does give excellent agreement with experimental evidence, in that quasi-axial substituents at C-6 and C-5 appear totally to control the stereochemistry of the reduction, whereas those at C-4 have very little effect.

Thus, a better understanding of the processes involved in a reaction (e.g. Baldwin's rules for ring closure, and Approach Vector Analysis) will lead to a further explanation of experimental results and give the possibility of predicting reaction pathways.

G. Diazepines.

Diazepines are seven-membered monocyclic, heterocyclic compounds containing two nitrogens. There are three basic ring structures as shown in Figure 15.

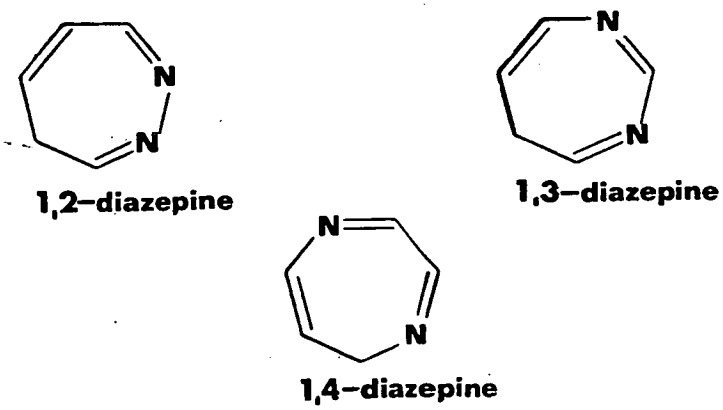


Figure 15

Diazepines have been recently reviewed by Popp and Noble[70] and by Nastasi[71] but here only 1,2-diazepines will be discussed in detail. 1,2-Diazepinones have been rather extensively studied and summaries of their reactions have appeared[70,71,72] and are not discussed here.

In this discussion the 1,2-diazepines have been divided up into their 1H-, 2H-, 3H- and 4H- groups. The fully unsaturated diazepines are treated first, their synthesis and reactions discussed, and the remaining diazepines are ordered in increasing degrees of saturation.

1. 1H-1,2-Diazepines.

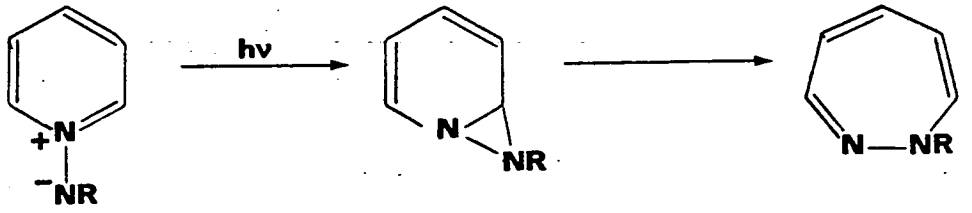
a) Synthesis of 1H-1,2-diazepines.

In the last ten years the chemistry of 1,2-diazepines has grown very rapidly due to their possible pharmaceutical value and a review by Nastasi[71] has recently been published. The large number of papers in this area is mainly due to the work of Streith, Snieckus

and Sasaki.

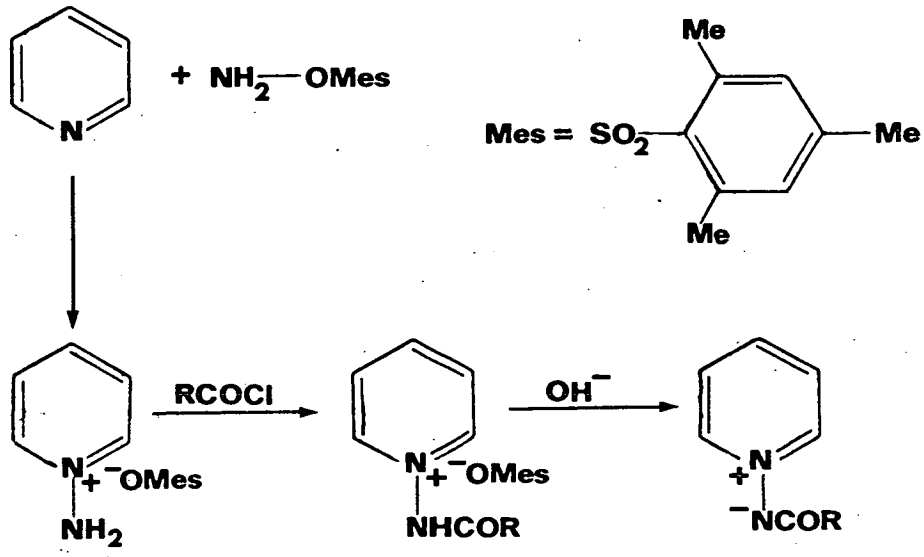
Streith and Cassal[73,74] were the first to report the synthesis of 1H-1,2-diazepines (73) from pyridine N-imines (71) and the literature now contains many examples of this reaction[71]. Heteroaromatic N-imines are photochemically reactive compounds[75] on irradiation they generally yield products of (a) N-N bond cleavage, (b) ring enlargement or (c) rearrangement.

The pyridine N-imines when photolysed give the 1-substituted-1,2-diazepines in good yields. Analagous to the photochemistry of the N-oxides[76] the formation of the seven-membered ring occurs via an intermediate diaziridine (72) which isomerises spontaneously in a thermal reaction.



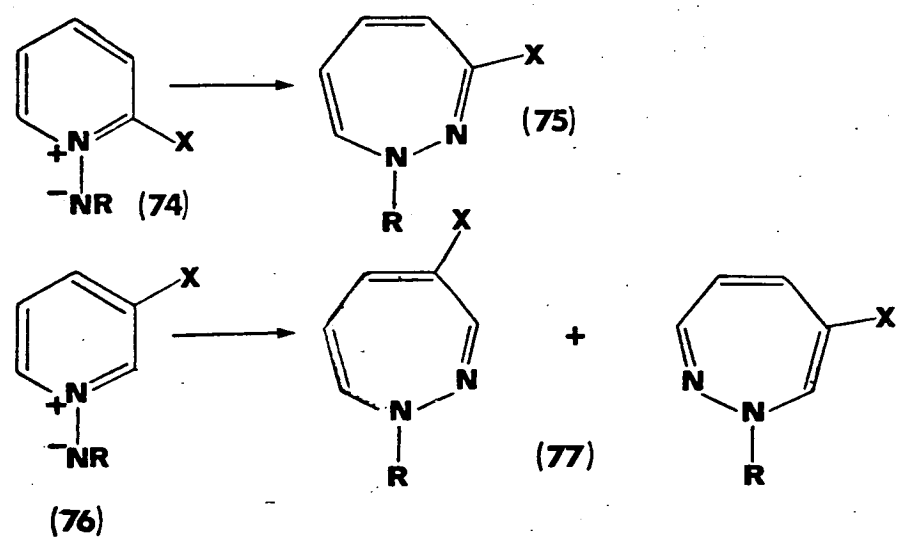
(71) (72) (73)

One of the limitations of this reaction was the difficult synthesis of the pyridine N-imines[75], but this problem has been solved by the use of O-mesitylsulphonylhydroxylamine (MSH) to effect the nitrogen-nitrogen coupling reaction to the pyridine[77,78,79], followed by treatment with an acyl chloride and deprotonation by base, Scheme 23. Thus a large number of ring substituted pyridine N-imines have been synthesised which in turn when photolysed yield 1H-1,2-diazepines.



Scheme 23

One complication with ring substituted pyridine N-imines is that it is possible to obtain two diazepines on photolysis. Pyridine N-imines (74) bearing a substituent in the 2-position cyclise exclusively to the C-6 position yielding the 3-substituted-1H-1,2-diazepines (75). However, most pyridine N-imines (76) bearing a substituent in the 3-position cyclise at both the C-2 and C-5 position to give the 6- and 4-substituted diazepines (77).



Pyridine N-imines bearing a substituent in the 2-position when photolysed can form only one diazirdine intermediate, Figure 16, thus giving one diazepine. Those pyridine N-imines bearing a substituent in the 3-position can form two different diazirdine intermediates, Figure 16, which on ring expansion give the two different diazepines.

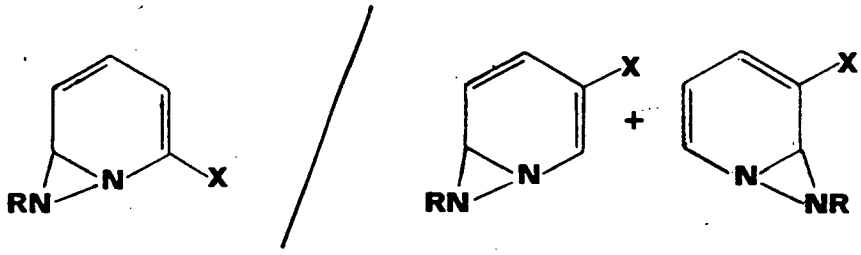
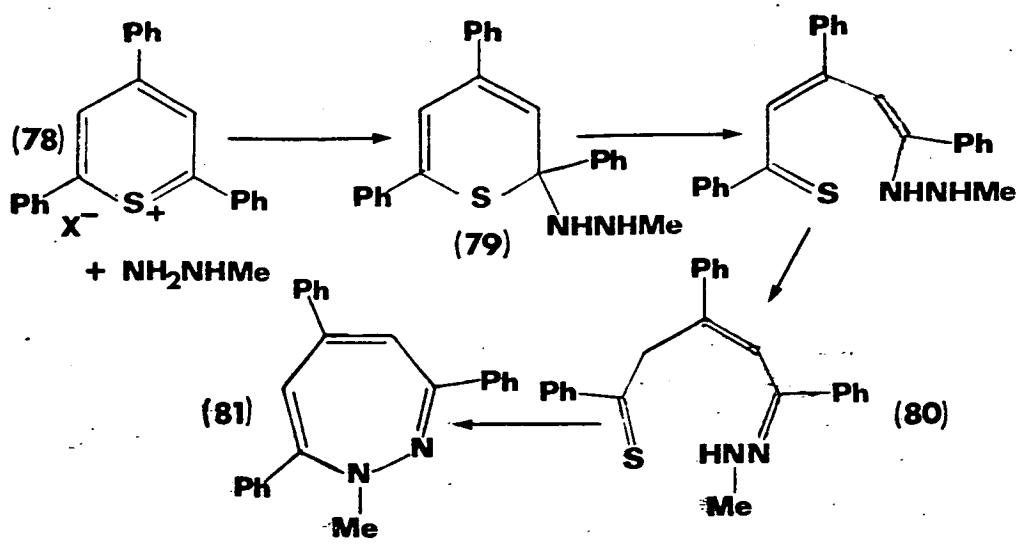


Figure 16

Ring-substituted 1H-1,2-diazepines have also been prepared by the method of Klingsberg[80] by the reaction of methylhydrazine with pyrylium and thiopyrylium salts. However, this reaction is limited in its scope as only three 1H-1,2-diazepines have been synthesised in this manner. 1-Methyl-3,5,7-triphenyl-1H-1,2-diazepine (81) is one example[81,82]. The methylhydrazine reacts with the thiopyrylium salt (78) to give the non-aromatic sulphur compound (79) which ring opens and leads to the hydrazone (80) which then ring closes to the diazepine (81).

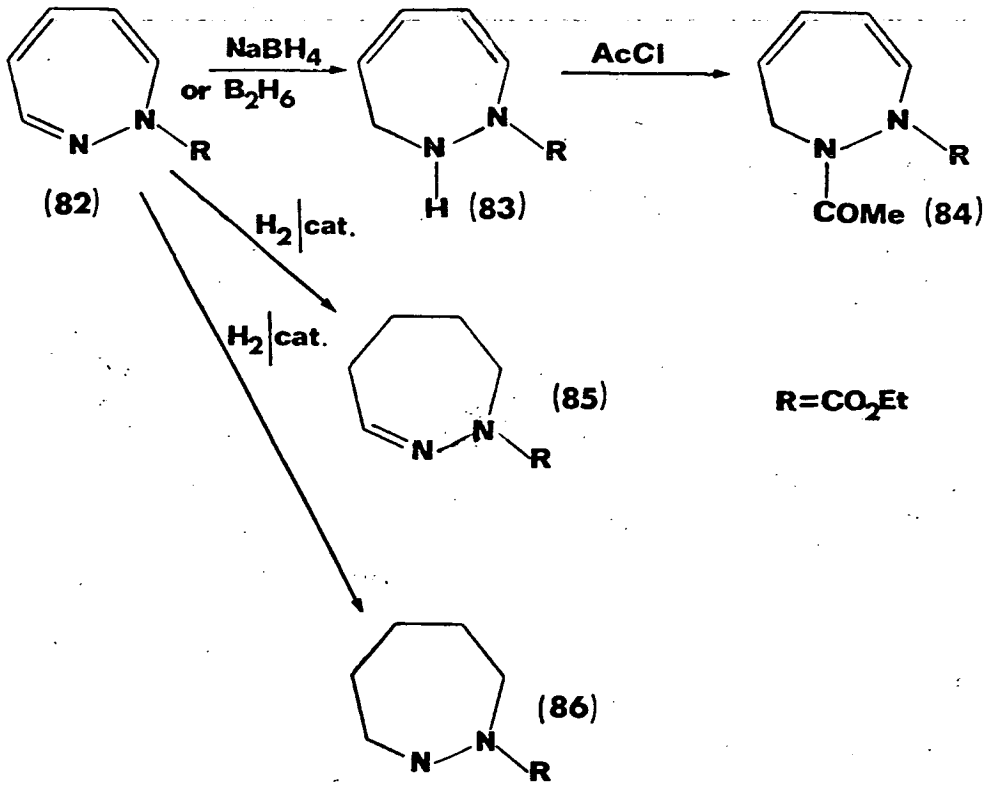


b) Reactions of 1H-1,2-diazepines.

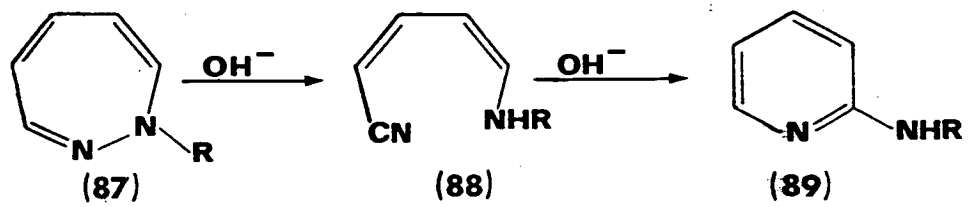
Much work has been done on the reactivity of 1H-1,2-diazepines: they will undergo reduction, base induced ring-contraction, acid-catalysed rearrangement and thermal and photochemical rearrangements. Their reactivity has been reviewed by Nastasi[71] and some examples are given here.

The 1H-1,2-diazepines (82) can be reduced to the unstable 2,3-dihydro-1H-1,2-diazepines (83) with sodium borohydride[83] or with diborane.[84] The products can be stabilised by acylation to give (84).

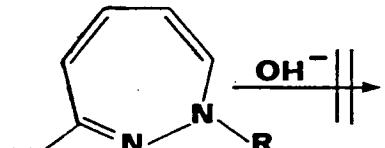
The 4,5,6,7-tetrahydro-1H-1,2-diazepines (85) and the hexahydro-1,2-diazepines (86)[74,84,85,86] can be obtained by catalytic hydrogenation.



Base induced decomposition of the 1H-1,2-diazepines (87) bearing a hydrogen atom at C-3 has been successfully carried out in a number of cases the product being the 2-aminopyridine (89). This reaction proceeds initially through a cis-cis diene(88) which then ring closes[87].



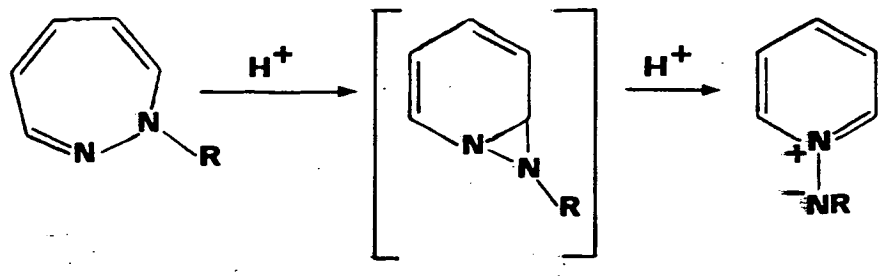
(87) (88) (89)



(90)

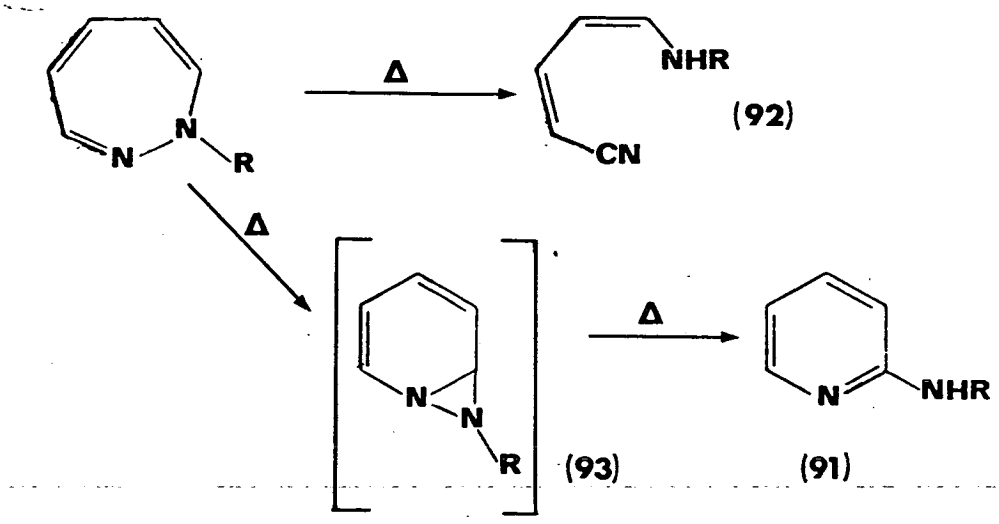
Other work[88] has shown that the 3-methyldiazepine (90) is stable towards base, thus indicating that the 3-H position is the reactive site towards a basic species.

While the 1H- 1,2-diazepines are converted to 2-aminopyridines (89) in base they rearrange back to the pyridine N-imines when treated with acid probably proceeding through the diaziridine, Scheme 24[74,88,89]. This is the reverse of the photochemical synthesis of 1H-1,2-diazepines from pyridine N-imines. The role of the acid in the rearrangement back to the pyridine N-imine is not understood.

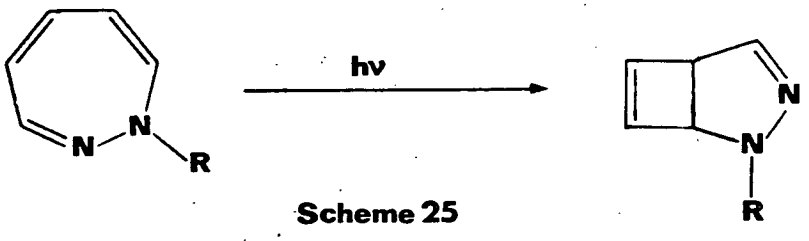


Scheme 24

The thermal reactivity of 1H-1,2-diazepines is interesting in that the products obtained are the same as for the base-induced decomposition i.e. 2-aminopyridines (91) and cis-cis dienes (92) [74,87,88,89,90]. However, the 2-aminopyridine is not produced via the cis-cis diene rather via the diaziridine (93)[87].

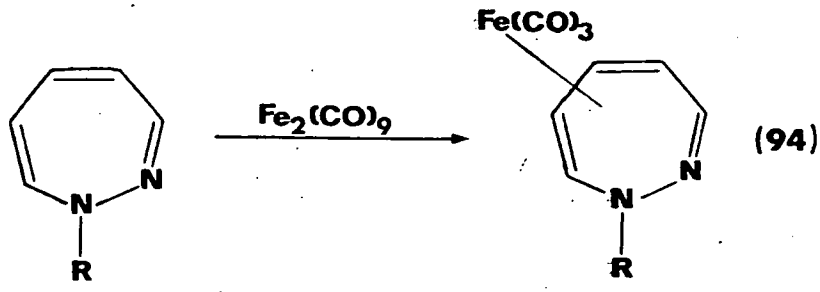


On photolysis 1H-1,2-diazepines, like many other seven-membered cyclic dienes undergo an electrocylic ring-closure of the butadiene moiety, Scheme 25, to give 2,3-diaza [3.2.0] bicyclic heptadienes[89,90,91].



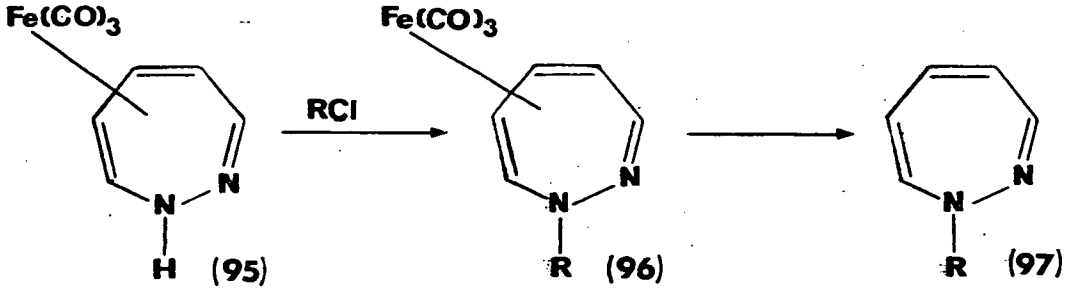
Scheme 25

For a large number of the 1H-1,2-diazepines, iron tricarbonyl complexes (94) have been formed[71] by reaction with iron nonacarbonyl. The complexation of iron tricarbonyl with dienes is well known and the diazepines are complexed as shown.



These complexes can be reduced by sodium borohydride to the 2,3-dihydro compounds. (see Section G 1.d))

An interesting use of the 1H-1,2-diazepine iron tricarbonyl complexes has been demonstrated by Harris and Snieckus[92]. 1H-1,2-diazepine iron tricarbonyl (95) when treated with an acyl chloride or benzyl bromide undergoes acylation or alkylation to the acyl or alkyl N-substituted-1H-1,2-diazepine iron tricarbonyl complex (96). The N-substituted-1H-1,2-diazepine can then be decomplexed by treatment with an amine oxide. This gives the free N-substituted-1H-1,2-diazepine (97).



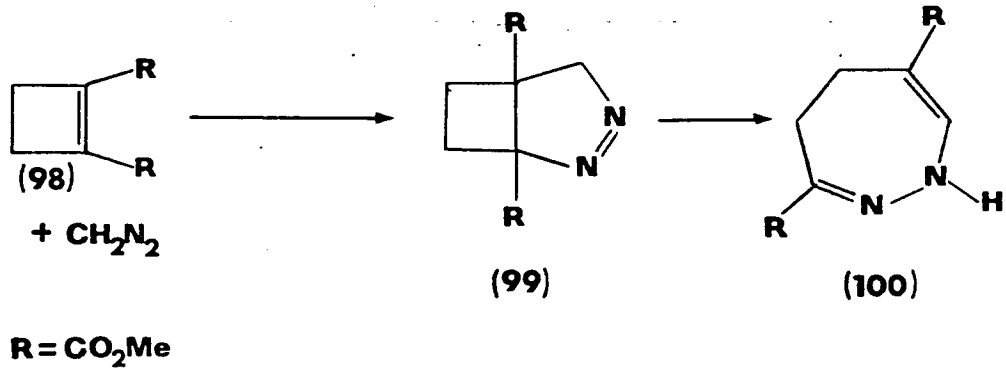
R= acyl

This reaction is useful in that it produces N-substituted-1H-1,2-diazepines not available through other syntheses.

c) Synthesis of dihydro-1H-1,2-diazepines.

The chemistry of the dihydro-, tetrahydro- and hexahydro-1H-1,2-diazepines is less extensive than for the fully unsaturated compound.

2,3-Dihydro-1H-1,2-diazepines may be synthesised from the 1H-1,2-diazepines by hydrogenation and this is discussed in Section G 1.b). The 4,5-dihydro-1H-1,2-diazepines have been prepared by the cycloaddition of diazomethane with 1,2-disubstituted cyclobutenes[93]. The initially formed 1-pyrazoline on treatment with hydrogen chloride gas in aprotic media gave the diazepine. e.g. Dimethyl-1,2-cyclobutenedicarboxylate (98) adds diazomethane to form the 1-pyrazoline (99) which gave the 4,5-dihydro-1H-1,2-diazepine-3,6-dimethylcarboxylate (100).

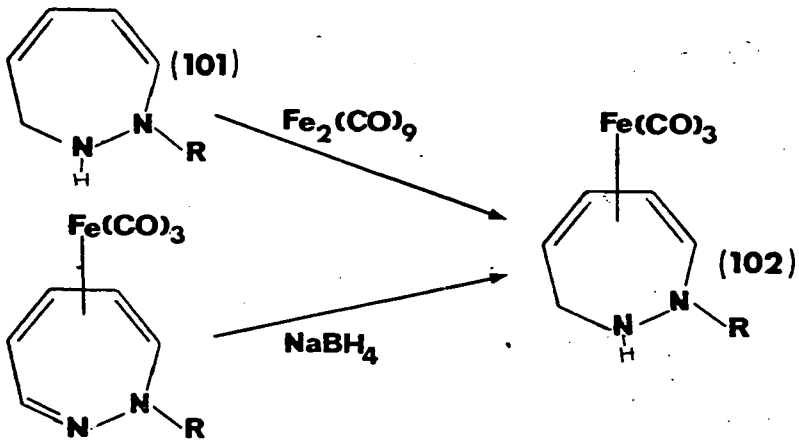


d) Reactions of dihydro-1H-1,2-diazepines.

There are two important reactions of the 2,3-dihydro-1H-diazepines. These are the conversion to 3,4-dihydro-2H-1,2-diazepines (which is discussed in further detail in Section G 2.) and their reactions with iron nonacarbonyl.

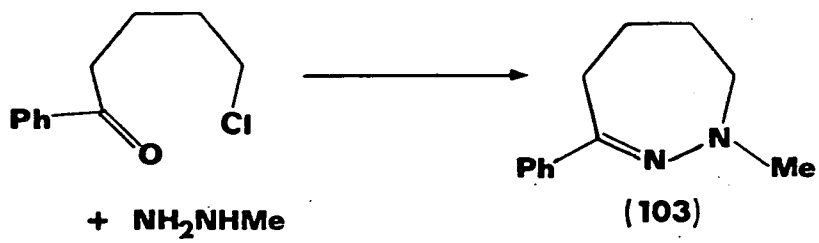
Like the 1H-1,2-diazepines the 2,3-dihydro-1H-1,2-diazepines (101) will also form complexes with iron nonacarbonyl[71]. Again the iron

tricarbonyl is complexed to the diene unit of the diazepine. The 2,3-dihydro-1H-1,2-diazepines iron tricarbonyl complexes (102) may also be prepared by reduction of the corresponding fully unsaturated diazepine iron tricarbonyl complex with sodium borohydride.



e) Synthesis of tetrahydro-1H-1,2-diazepines.

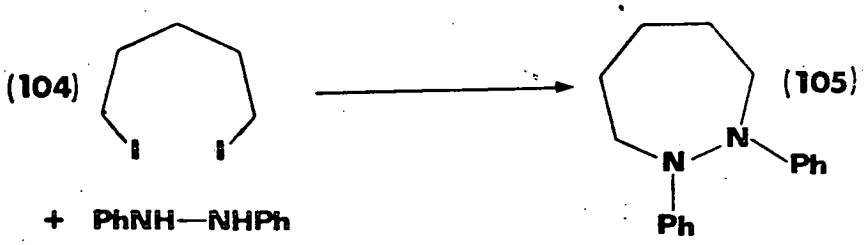
4,5,6,7-Tetrahydro-1H-1,2-diazepines can be prepared from the 1H-1,2-diazepines by hydrogenation (see Section G 1.b)). They have also been prepared by Koenig and Wermuth[94] by the reaction of substituted hydrazines with δ-chloroarylketones. For instance, as shown in Scheme 26, the reaction of methylhydrazine with the ketone gave the 3-phenyl substituted diazepine (103).

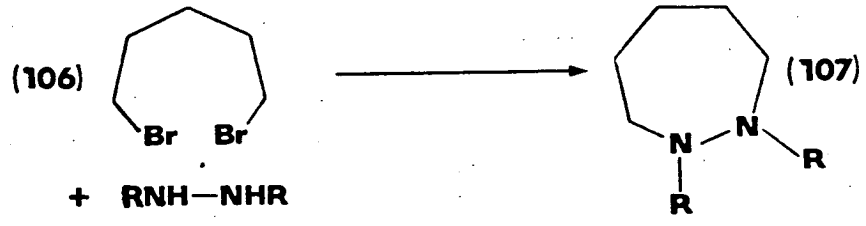


Scheme 26

f) Synthesis of hexahydrodiazepines.

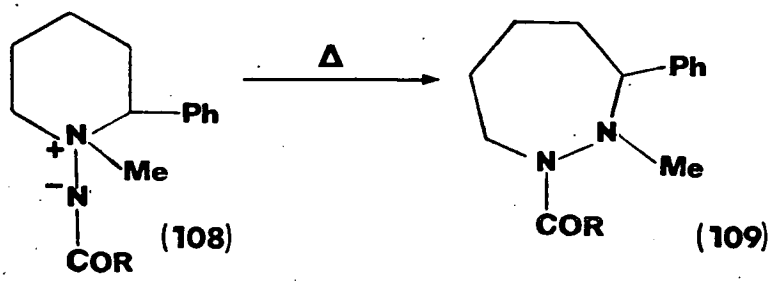
There are three different ways into this system. The first is hydrogenation of the corresponding 1H-1,2-diazepine (see Section G 1.b)). The second, which has been in the literature for many years is the reaction of 1,5-dihalogenopentanes and a substituted hydrazine. Two examples are available, one is the reaction of hydrazobenzene and 1,5-diiodopentane (104) which gives the 1,2-diphenylhexahydrodiazepine (105)[95], the other is the reaction of 1,2-dicarbethoxyhydrazine and 1,5-dibromopentane (106) in the presence of potassium which also gives a 1,2-disubstituted hexahydrodiazepine (107)[96].





$R=CO_2Et$

The third method of synthesis is the vacuum pyrolysis of 1-methyl-2-phenylpiperidine-1-acylimides (108) which ring expand to the hexahydro-1,2-diazepines(109)[97]. This reaction would appear to only give a limited range of hexahydro-1,2-diazepines.

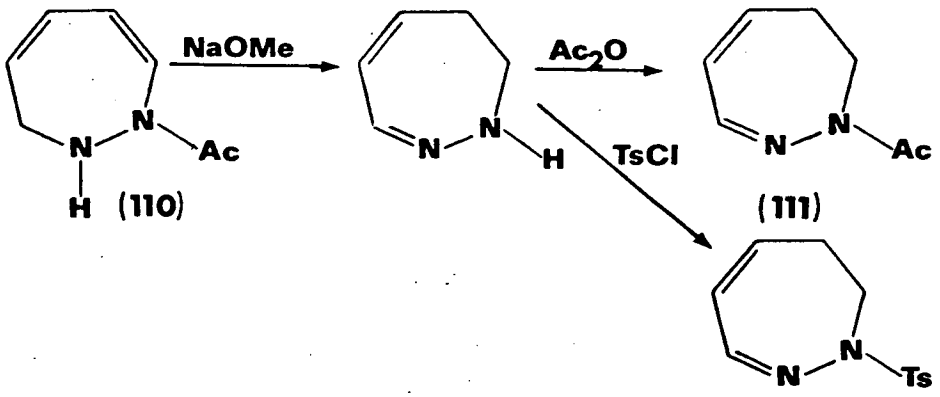


2. 3,4-Dihydro-2H-1,2-diazepines.

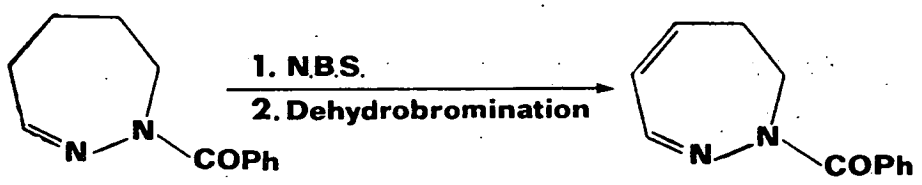
There are three methods of synthesising 3,4-dihydro-2H-1,2-diazepines all of which have been devised in recent years.

Synthesis of 3,4-dihydro-2H-1,2-diazepines.

The 3,4-dihydro-2H-diazepines (111) have been prepared by the sodium methoxide deacylation of the corresponding 1H-2,3-dihydro-1,2-diazepine (110)[83] followed by acylation or tosylation.



They may also be prepared from the bromination and dehydrobromination of the 1H-2,3,4,5-tetrahydro-1,2-diazepines, Scheme 27.[94]



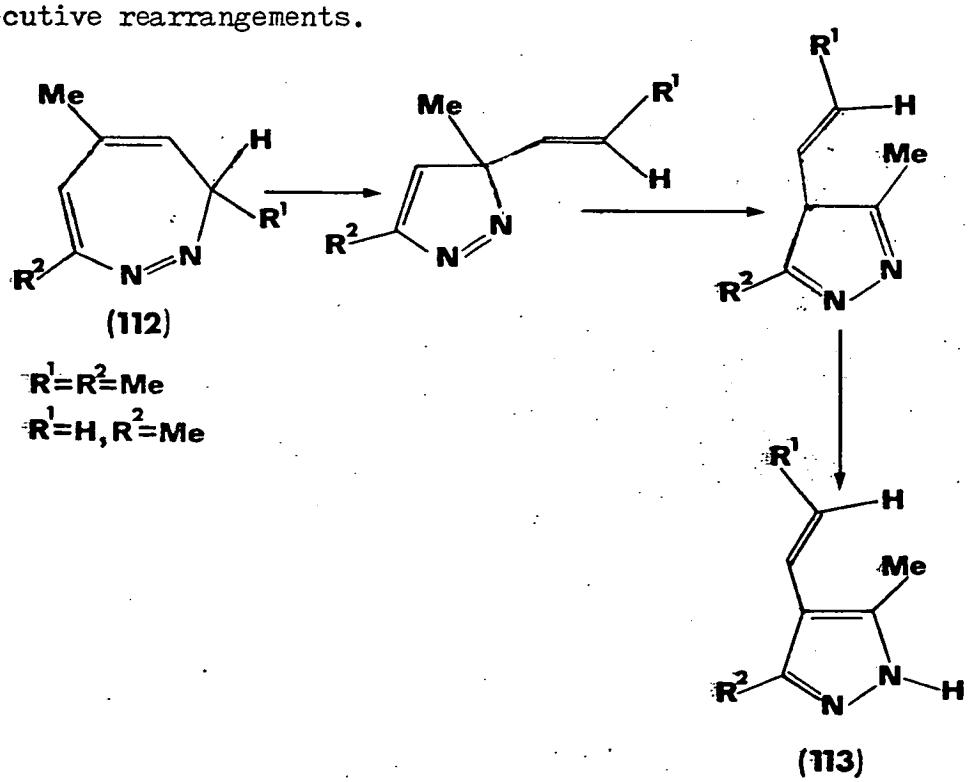
Scheme 27

The synthesis of these compounds from αβ,γδ —unsaturated ketones and p-toluenesulphonylhydrazine by Sharp and his co-workers will be dealt with in the Discussion.

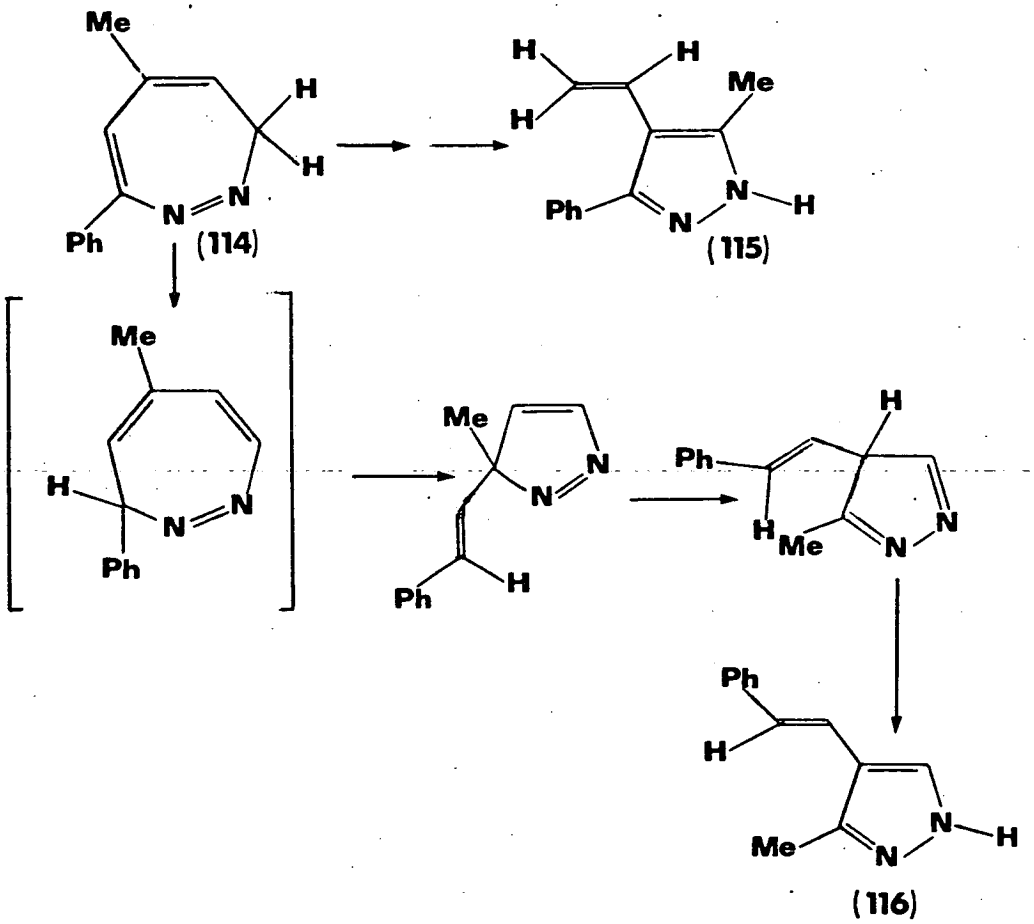
3. 3H-1,2-Diazepines.

The 3H-1,2-diazepines have been synthesised by the base induced elimination of p-toluenesulphinic acid from 3,4-dihydro-2-tosyl-1,2-diazepines. This reaction will be dealt with in the Discussion.

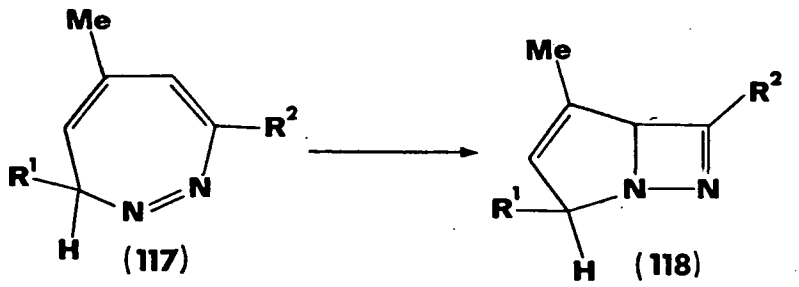
The 3H-1,2-diazepines (112)[98] have been shown to contract to 1H-pyrazoles (113) under thermal conditions apparently by three consecutive rearrangements.



The initial ring contraction is followed by a [1,5] migration of the vinyl group and then by a hydrogen shift. The thermal rearrangement in the 3H-1,2-diazepine where R^1 = H, R^2 = Ph (114) is more complicated and leads to two pyrazoles (115),(116). One pyrazole is generated in the above method, the other is derived probably from an initial [1,5] hydrogen shift in the diazepine which then undergoes the ring contraction and vinyl migration.



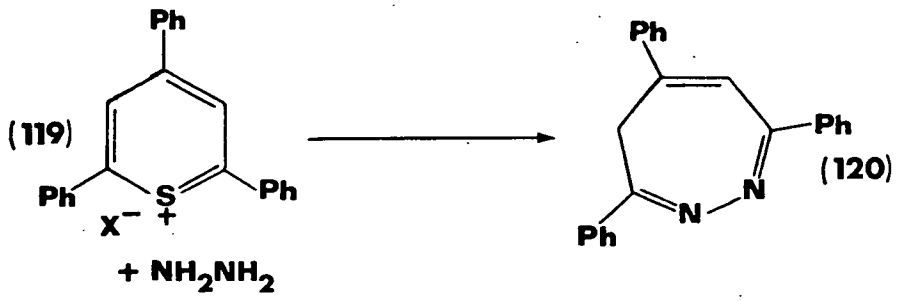
The diazepines (117) when photolysed give the [1,2] diazeto [4, 1-a] pyrroles (118) in high yield.



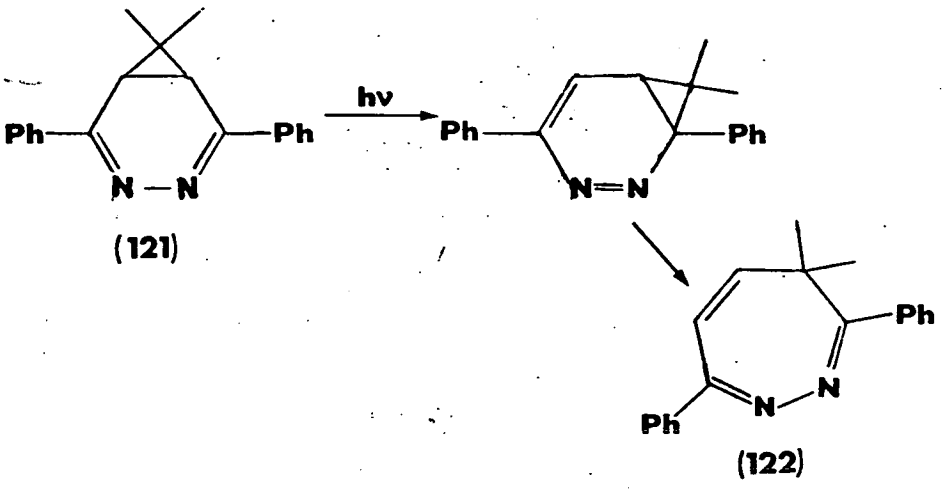
4. 4H-1,2-Diazepines.

a) Synthesis of 4H-1,2-diazepines.

4H-1,2-Diazepines have been prepared by the reaction of hydrazine with pyrylium or thiopyrylium salts. This is the method of Klingsberg[80] and the reaction is similar to the synthesis of 1H-1,2-diazepines from thiopyrylium salts and methylhydrazine (see Section G1.a)). For example 3,5,7-triphenyl-4H-1,2-diazepine (120) was synthesised from the triphenylthiopyrylium salt (119) and hydrazine [81,82]. A large number of 4H-1,2-diazepines have now been synthesised in this manner and it would appear to be a good route into the system. However its generality is limited by the need for at least two aromatic groups on the pyrylium or thiopyrylium ring.



A new method into the 4H-1,2-diazepines (122) has been reported recently by Zimmermann and Eberbach[99]. The reaction involves the photolysis of a 3,4-diazanorcaradiene (121). This photoreaction proceeds via a "photochemical walk process" involving the first $\pi\pi^*$ singlet excited state.

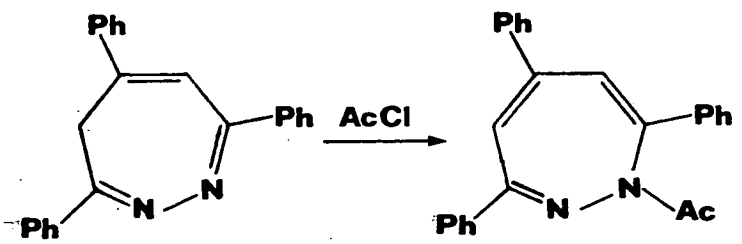


(121) (122)

Sauer et al [100,101] have extended this photochemical process and have also shown that the thermal rearrangement of 3,4-diazanorcaradienes proceeds in the same way to the 4H-1,2-diazepines.

b) Reactions of 4H-1,2-diazepines.

The reactivity of this class of diazepines has not been well studied as yet. One interesting reaction however is the acylation of 3,5,7-triphenyl-4H-1,2-diazepine with acetyl chloride which occurs at N-2 to give the corresponding acylated 1H-diazepine, Scheme 28[90].



Scheme 28

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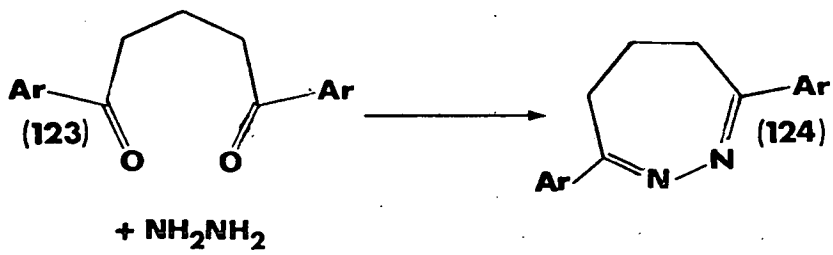
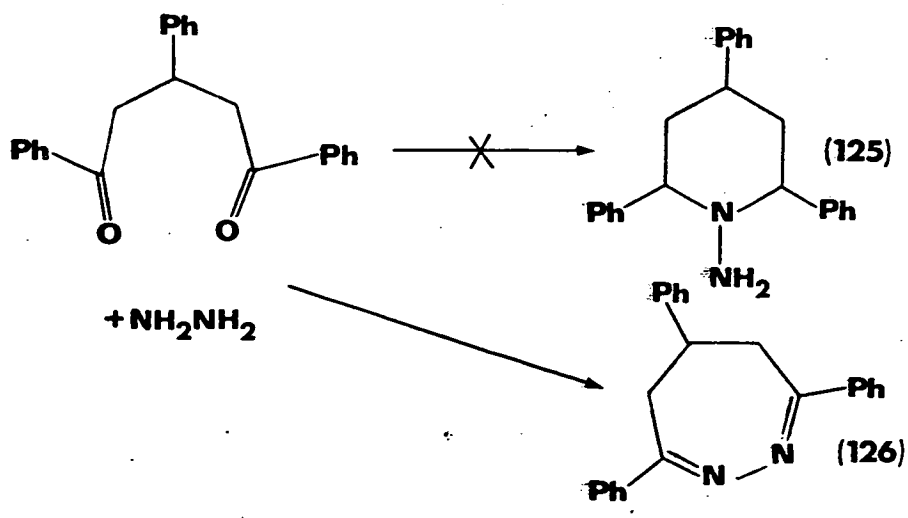
c) Synthesis of dihydro-4H-1,2-diazepines.

5,6-Dihydro-4H-1,2-diazepines have been prepared by two methods. One involves the condensation of hydrazine with diaroylpropanes, the other is the catalytic hydrogenation of the corresponding 4H-1,2-diazepine.

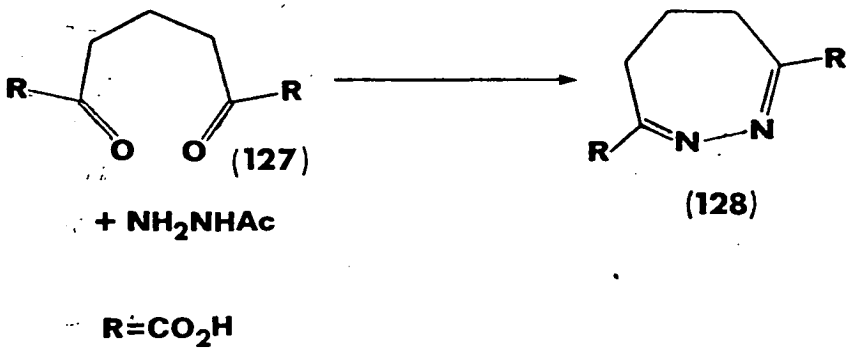
The condensation of a variety of 1,3-diaroylpropanes (123) with hydrazine gave good yields of 3,7-diaryl-5,6-dihydro-4H-1,2-diazepines (124)[102].



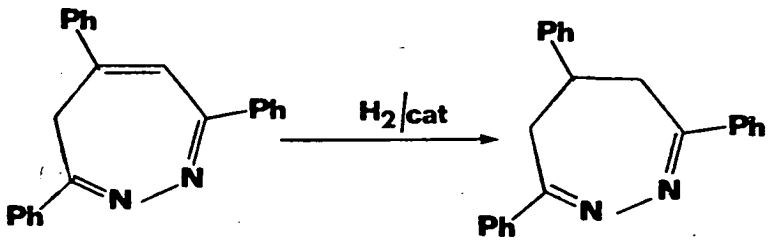
It had originally been reported by Merz and Richter[103] that the reaction of 1,3,5-triphenyl-1,5-pentanedione with hydrazine hydrate gave the 2,4,6-triphenyl-1-amino-1,4-dihydropiperidine (125) however Carpino[104] has shown that the product is the 3,5,7-triphenyl-5,6-dihydro-4H-1,2-diazepine (126).



In a very similar reaction to the previous two Blaise and Gault[105] synthesised 5,6-dihydro-4H-1,2-diazepine 3,7-dicarboxylic acid (128) from acetylhydrazide and α,α'-dioxopimelic acid (127). The diazepine precipitated almost immediately after addition of the starting materials.



The 3,5,7-triphenyl-5,6-dihydro-4H-1,2-diazepine has also been synthesised by the catalytic hydrogenation of the fully unsaturated 4H-1,2-diazepine, Scheme 29[82]. At the moment this catalytic hydrogenation is limited to only one other 4H-1,2-diazepine.

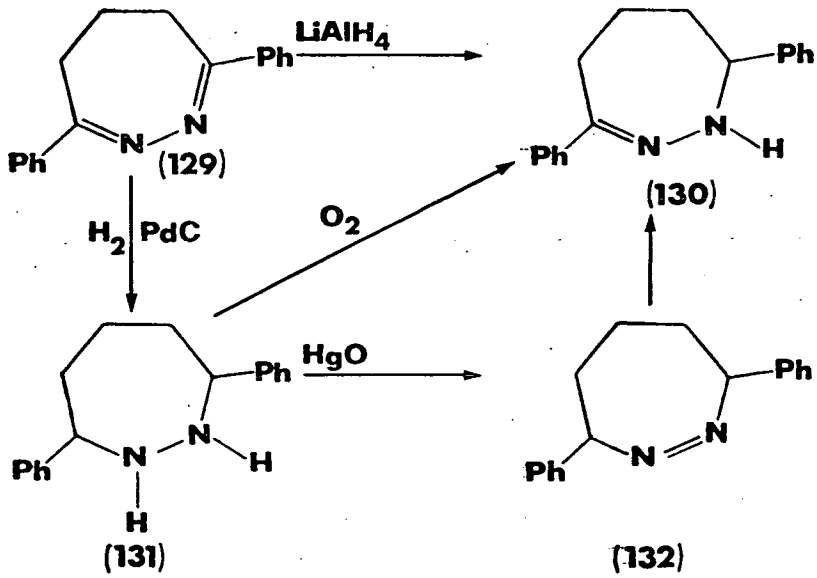


Scheme 29

d) Reactions of dihydro-4H-1,2-diazepines.

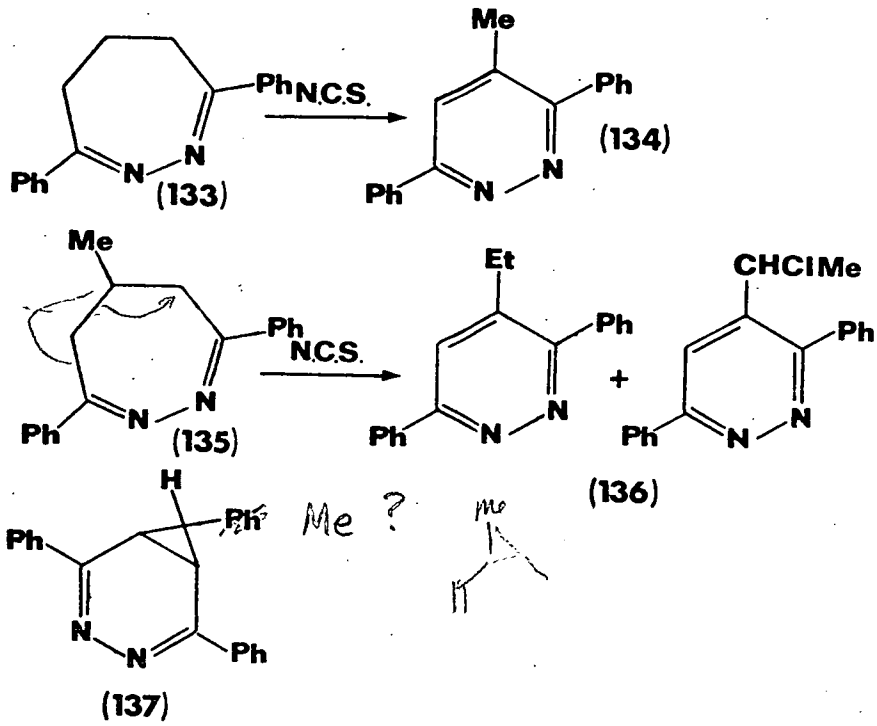
There are two reactions of 5,6-dihydro-4H-1,2-diazepines which have appeared in the literature.

In one, 3,7-diphenyl-5,6-dihydro-4H-1,2-diazepine (129) can be reduced to the tetrahydrodiazepine (130) by lithium aluminium hydride[106] and to the hexahydrodiazepine by hydrogen on palladium charcoal. However this hexahydrodiazepine (131) is readily air oxidised to the tetrahydrodiazepine (130). Treatment of the hexahydrodiazepine (131) with mercuric oxide gave a different tetrahydrodiazepine (132) which converts to the isomeric tetrahydrodiazepine (130).[107,108]



The other reaction of a 5,6-dihydro-4H-1,2-diazepine is its reaction with N-bromosuccinimide or more cleanly with N-chlorosuccinimide. When 3,7-diphenyl-5,6-dihydro-4H-1,2-diazepine (133) is reacted with N-chlorosuccinimide (N.C.S) the product is 4-methyl-3,6-diphenyl-pyridazine (134)[109]. Carbon-5 is extruded in the ring contraction, this being confirmed by treatment of the 5-methyl-substituted diazepine (135) which on treatment with N-chlorosuccinimide gave the ethyl and chloroethylpyridazines (136), and similarly with the 5-phenyl-

substituted diazepine. A bicyclic intermediate (137) can be isolated from the reaction.



H. Benzodiazepines.

Benzodiazepines are bicyclic, heterocyclic compounds which have a benzene nucleus fused to the diazepine ring. There are six basic ring structures of the benzodiazepines and are shown in Figure 17.

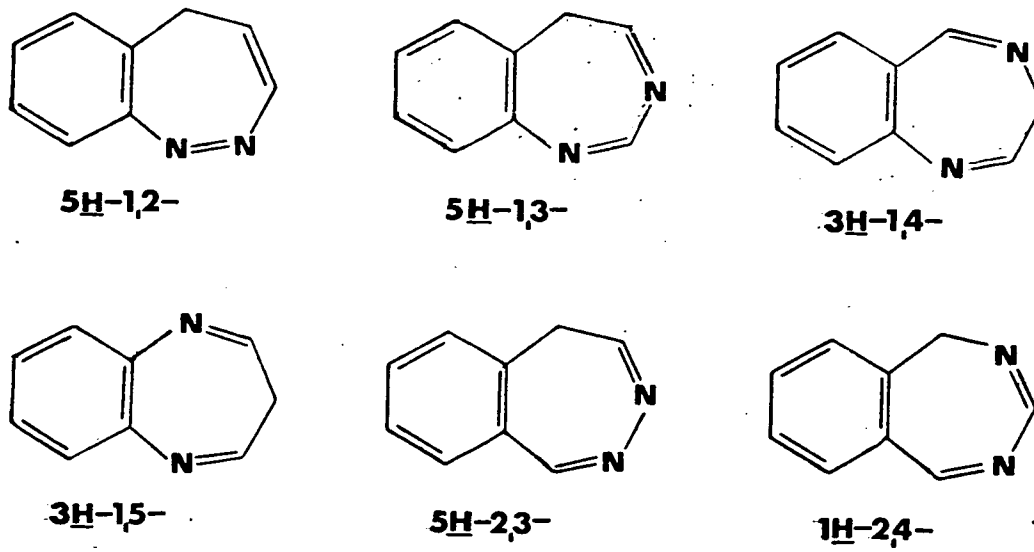
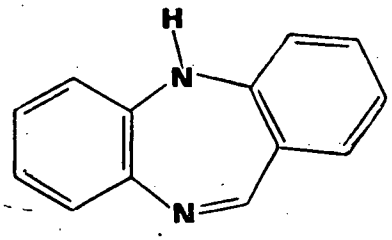
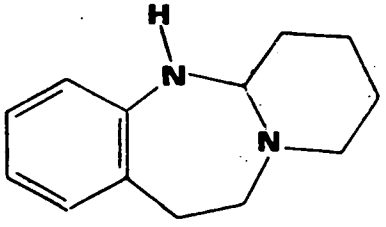


Figure 17

It is also possible to have a second ring fused to the diazepine portion of the molecule to give compounds such as dibenzodiazepines (138) and pyridobenzodiazepines (139).

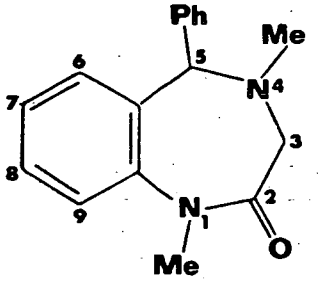


(138)

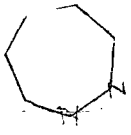


(139)

Benzodiazepines are numbered as shown in (140).

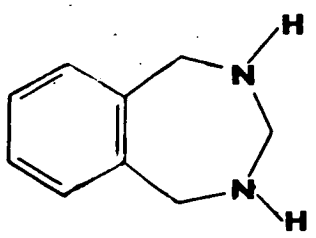


(140)



Starting at the position adjacent to the carbocyclic ring and giving the first nitrogen the lowest number possible. i.e. a 1,4-benzodiazepine rather than a 2,5-benzodiazepine.

The term benzodiazepine implies a maximum degree of unsaturation i.e. a total of three double bonds in the seven membered ring. The position of the odd hydrogen is indicated by the term 1H, 2H, etc. In dihydro- and tetrahydrodiazepines the odd hydrogen atom is given the lowest possible number. This is, however complicated by the fact that first consideration is given to the position of a functional group which is expressed as a suffix to the name of the compound e.g. (140) is a 1,3,4,5-tetrahydro-2H-1,4-benzodiazepin-2-one. However compound (141) is a 2,3,4,5-tetrahydro-1H-2,4-benzodiazepine,



(141)

the odd hydrogen given the lowest possible numerical value in the absence of a substituent named as a suffix.

The chemistry of the benzodiazepines has been reviewed by Sternbach and Archer[110]. There has been much interest in the benzodiazepines recently, especially in the 1,4-benzodiazepines which have been most extensively studied due to the discovery of[111,112] their biological activity as psychosedatives and tranquilising agents. Two drugs which have 1,4-benzodiazepines as their active ingredients are the widely used "Librium" and "Valium".

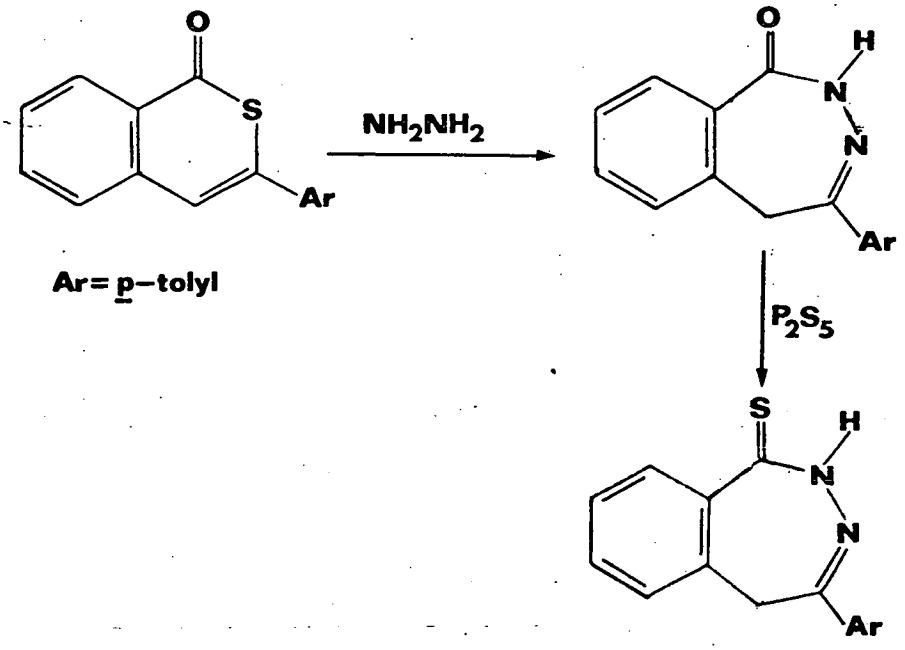
The 1,5-benzodiazepines because of their relative ease of synthesis from common starting materials have been well studied[110]. The other four types of benzodiazepines have been relatively less well studied. The 2,3-benzodiazepines, which do not have a particularly extensive literature will be discussed in detail. Their chemistry has been reviewed by Sternbach and Archer[110] and by Nastasi[71].

2,3-Benzodiazepines.

As early as 1899 Gottlieb[113] synthesised 2,5-dihydro-4-methyl-2-phenyl-1H-2,3-benzodiazepin-1-one, Scheme 30, from 3-methyl-isocoumarin and phenylhydrazine.

continued on page 59

More recently Legrand and Lozac'h[118] have treated 2-thioisocoumarins with hydrazine, the product being the benzodiazepinone and treatment of the benzodiazepinone with phosphorus pentasulphide in pyridine gave the benzodiazepin-1-thione, Scheme 31.



Ar= p-tolyl

Scheme 31

In 1961 Halford and co-workers[119] found that the intramolecular condensation of o-acetylphenylacetic acid phenylhydrazone (147) gave mixtures of 3,5-dihydro-1-methyl-3-phenyl-4H-2,3-benzodiazepin-4-one (148) and 1-methyl-2-phenylamino-3-(2H)-isoquinolone (149).

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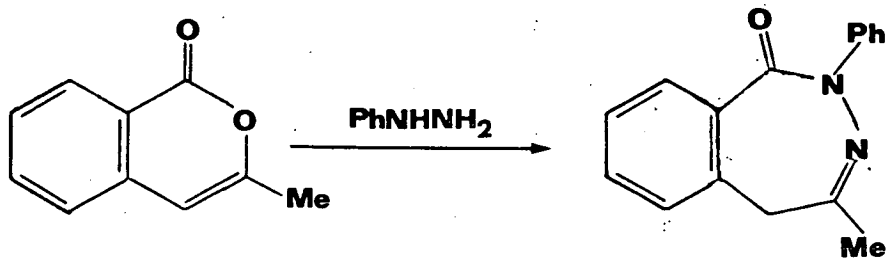
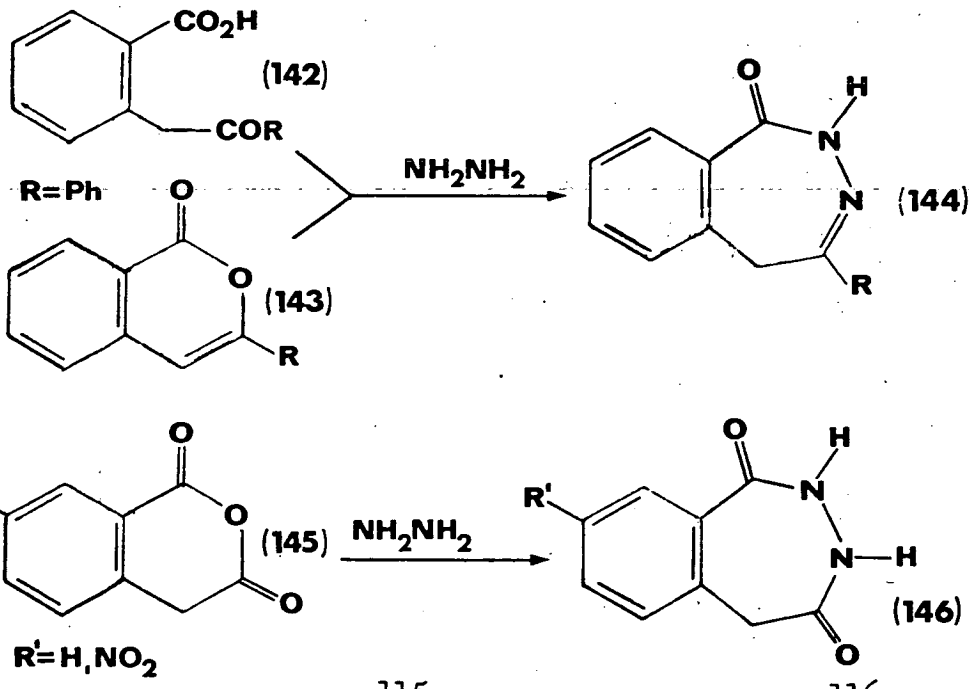


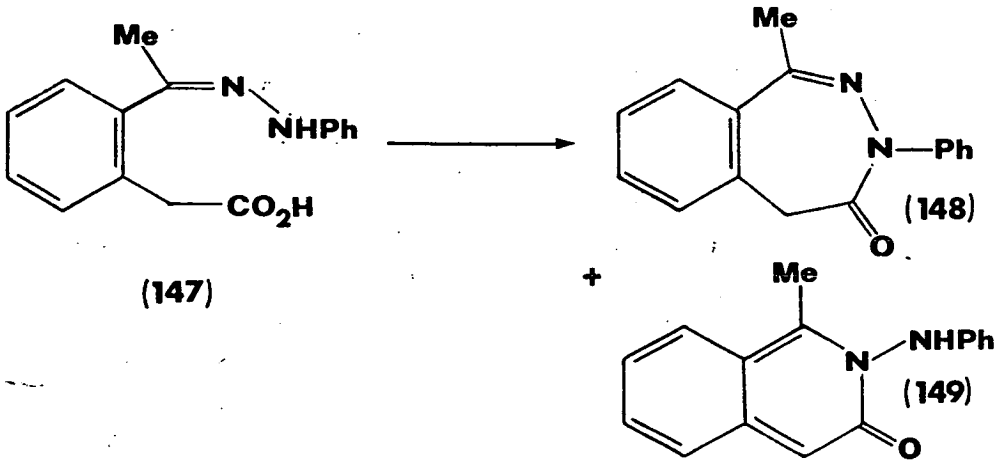
Scheme 30

Six years later, 2,5-dihydro-4-phenyl-1H-2,3-benzodiazepin-1-one (144) was prepared in a similar reaction from the reaction of β-deoxybenzoin-o-carboxylic acid (142) or of 3-phenylisocoumarin (143) with hydrazine[114].

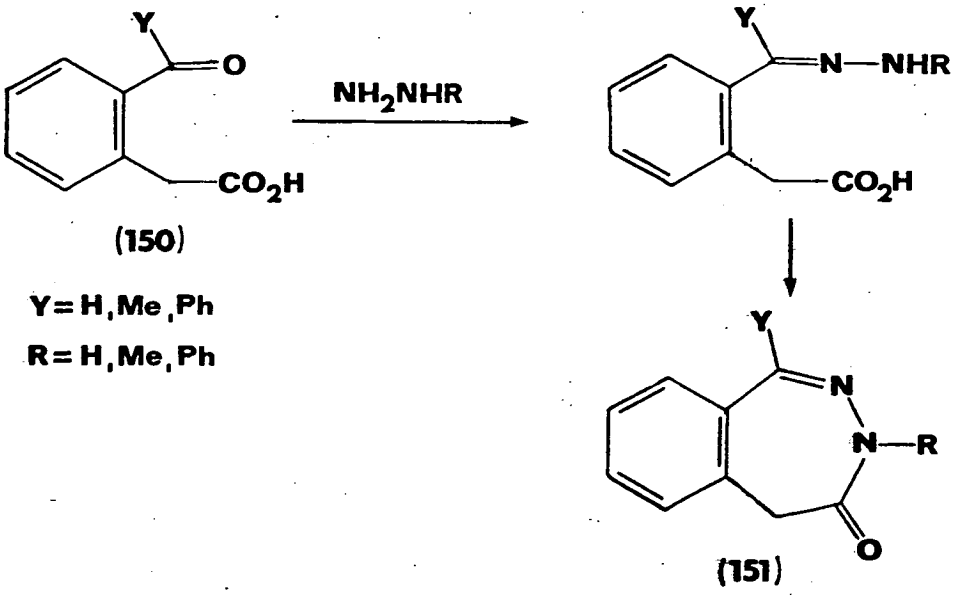


Analogues where R = m-tolyl[115] and R = p-hydroxyphenyl[116] were obtained in this way from the corresponding isocoumarins. In a similar type of reaction, Whitmore and Cooney[117] found that homophthalic anhydride (145) treated with hydrazine in boiling ethanol gave 2,3-benzodiazepin-1,4-dione (146).

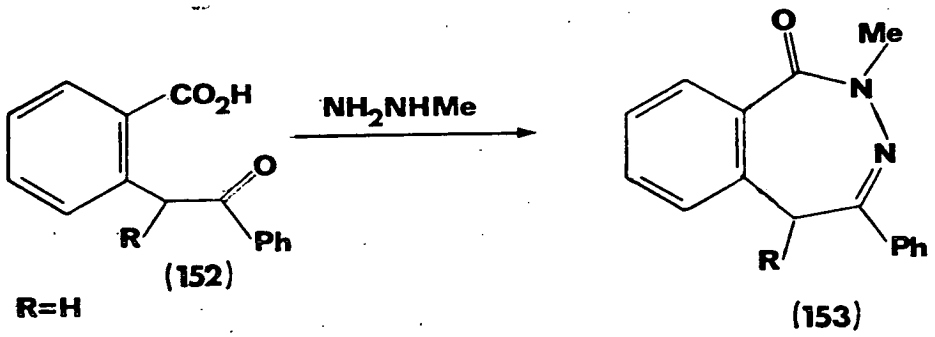
continued on page 58



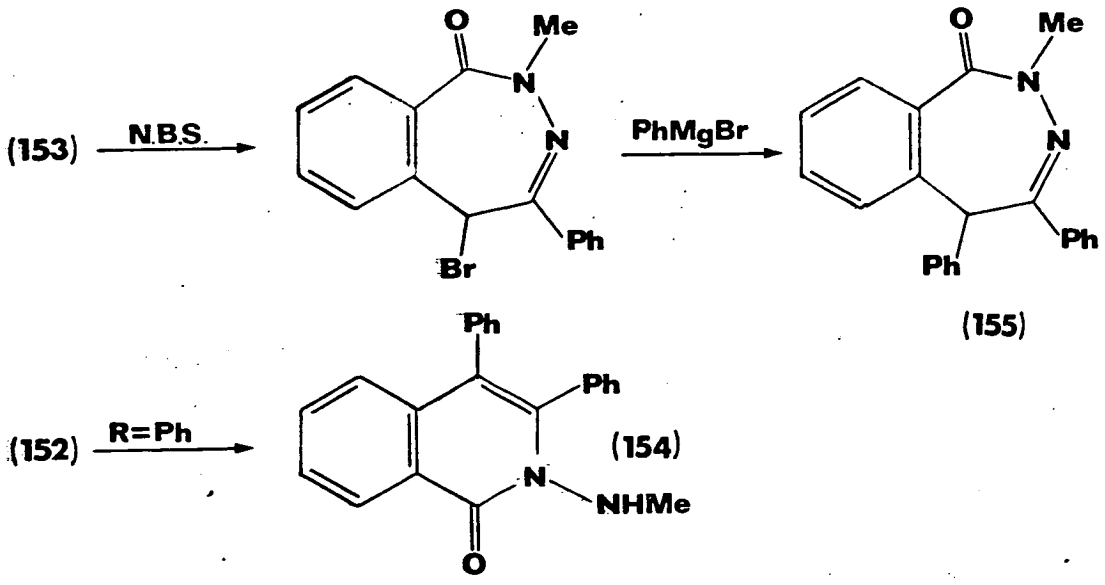
This reaction is similar to the reaction of Wolbling[114] in his synthesis of the 2,3-benzodiazepin-1-one (144). Halford found the 2,3-benzodiazepin-4-one (148) was the major product of the reaction at 190°C. The semicarbazone analogue[119] was also found to cyclise to the 2,3-benzodiazepin-4-one. Wermuth and Flammang[120] have extended the original work of Halford[119] by the use of o-aroyl-phenylacetic acids (150) which when condensed with substituted hydrazines in refluxing n-butanol give 1-aryl-3,5-dihydro-4H-2,3-benzodiazepin-4-ones (151) via the hydrazone.



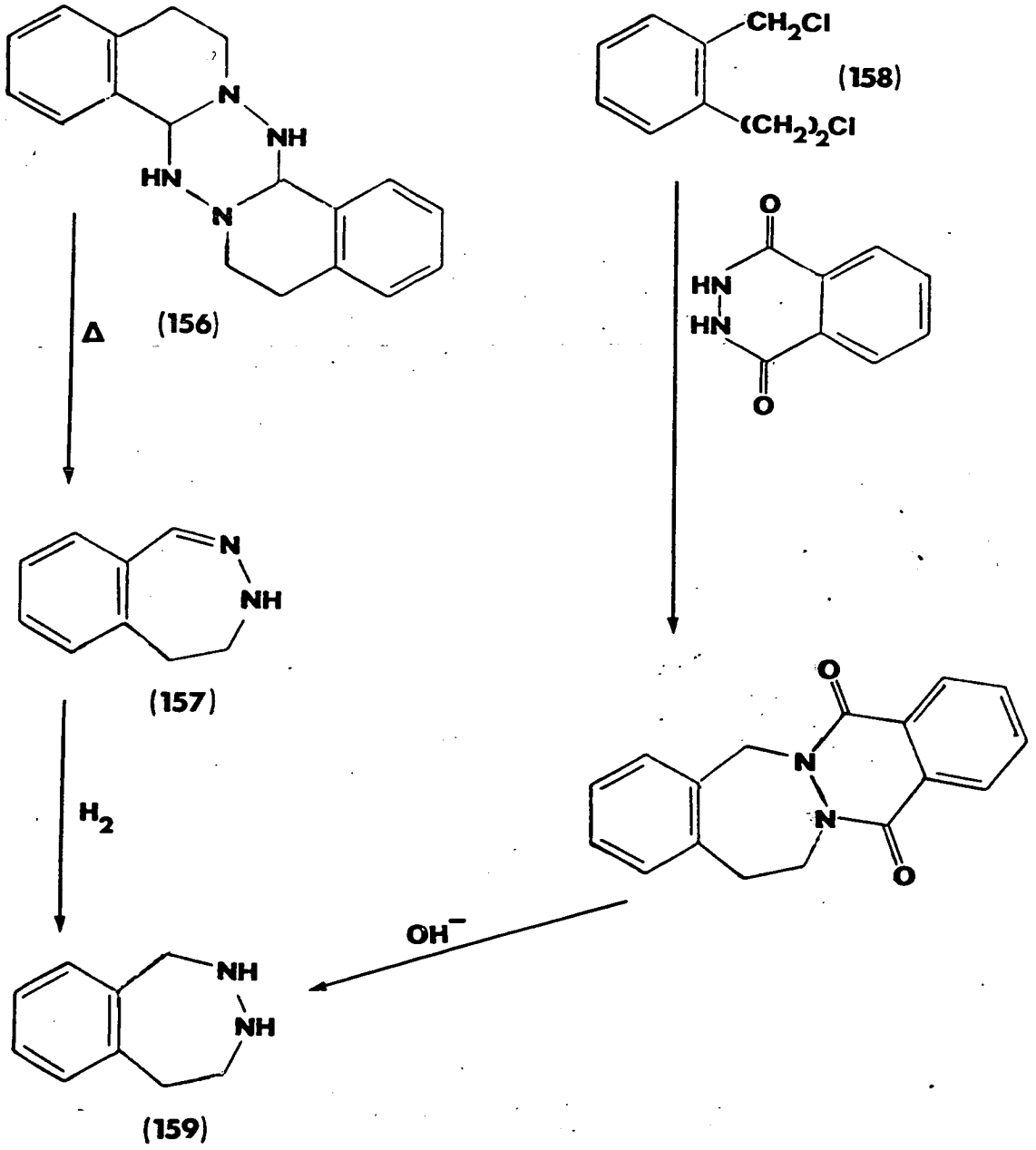
N,N-dicyclohexylcarbodiimide at room temperature has also been used to achieve this cyclisation[121]. The diazepinones (151)have a tranquilising effect in mice and consequently a large number have been synthesised[71]. In a variation of their work Flammang and Wermuth[122,123] showed that the benzoic acid derivative (152) cyclises to the 2,3-benzodiazepin-1-one (153) when treated with methylhydrazine and boiled in n-butanol.



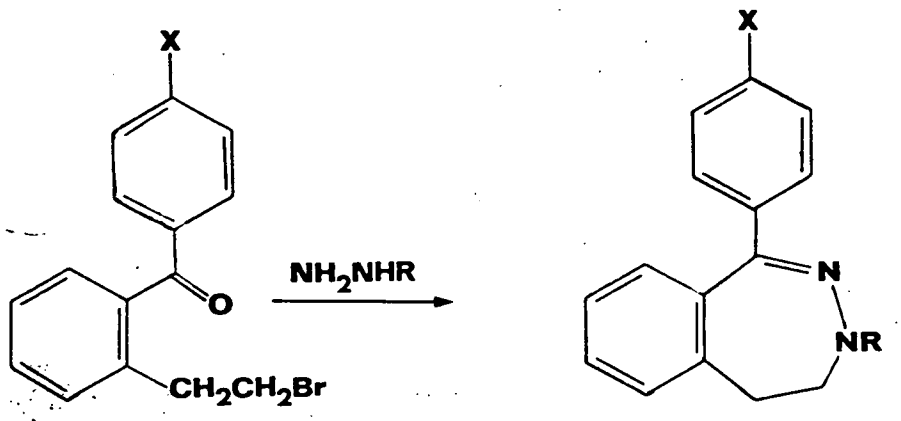
When R is phenyl only the isocoumarin (154) is formed, but the 2,3-benzodiazepin-1-one with R = Ph (155)[123] could be synthesised via bromination of the 2,3-benzodiazepin-1-one (153) with N-bromo-succinimide followed by reaction with phenylmagnesium bromide.



Schmitz and Ohme[124] in 1962 found that pyrolysis of diisoquinolinotetrazine (156) alone or in isoquinoline as solvent yielded 4,5-dihydro-3H-2,3-benzodiazepine (157) which could be reduced to 2,3,4,5-tetrahydro-1H-2,3-benzodiazepine (159) by catalytic hydrogenation. This tetrahydro compound could also be synthesised by the reaction of phthaloyl hydrazide and o-chloromethyl-2-phenylethyl chloride (158) followed by cleavage of the diazepine product.



The reaction of 2-(2-bromoethyl)benzophenone with hydrazine gives 4,5-dihydro-1-phenyl-3H-2,3-benzodiazepine, Scheme 32[125].



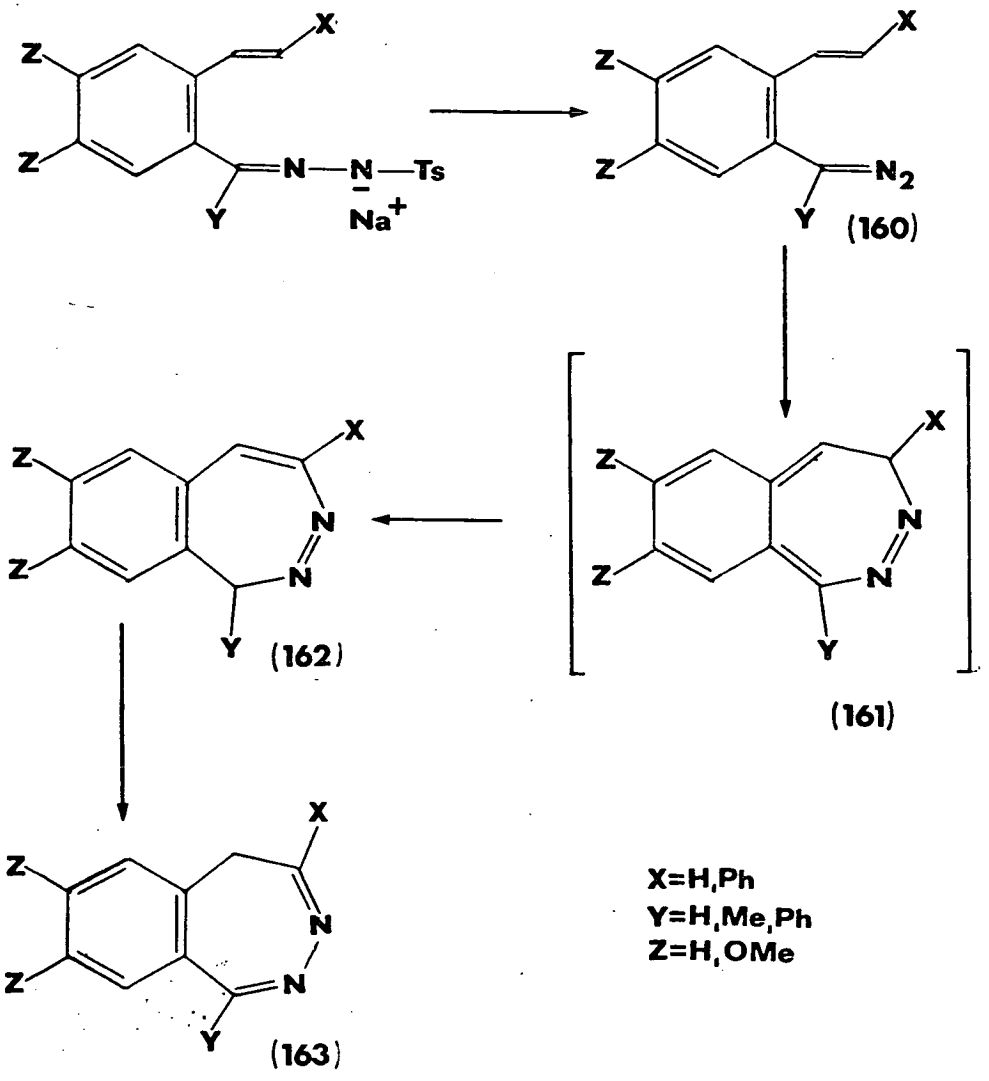
X=R=H

Scheme 32

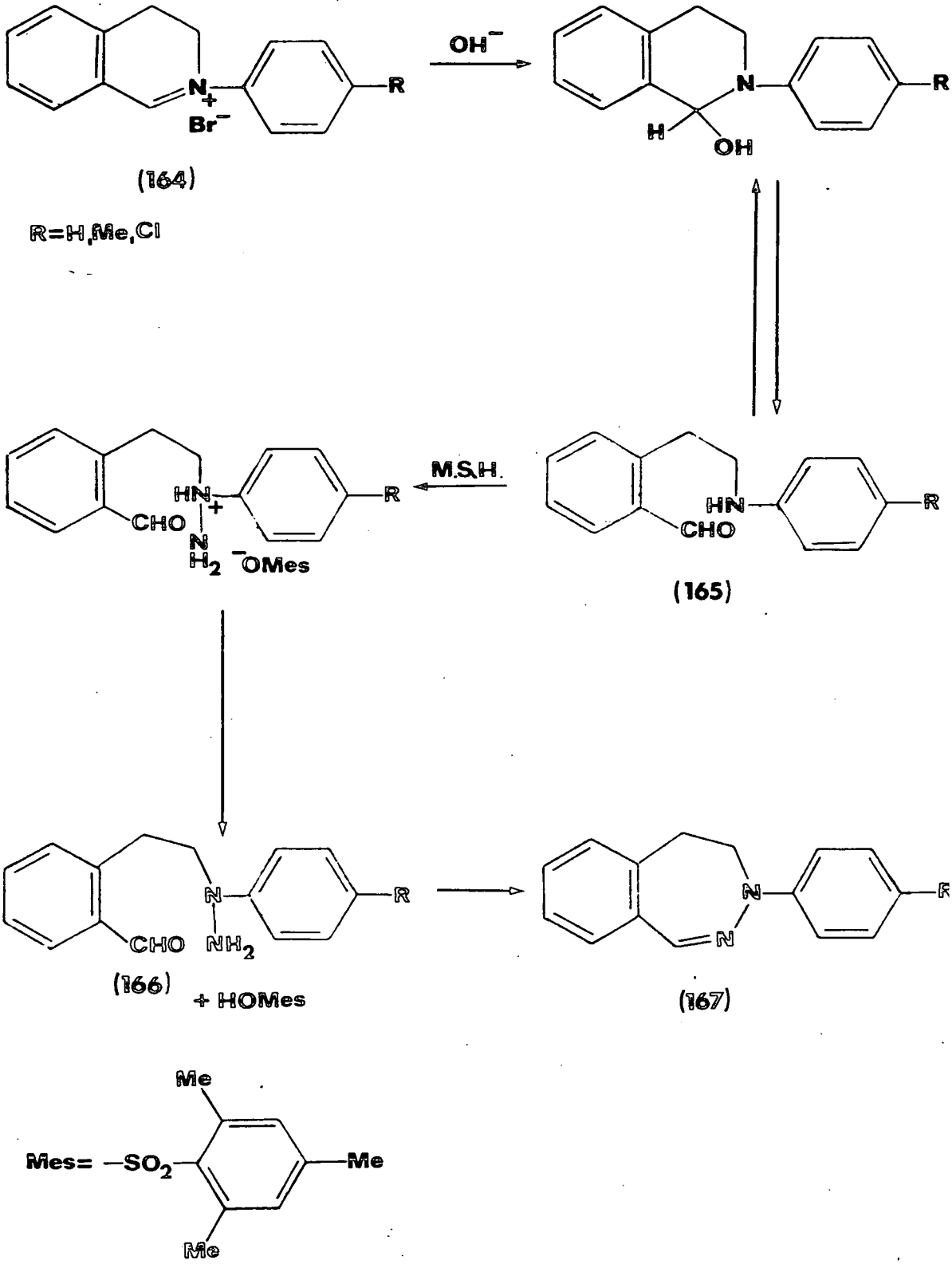
2-Hydroxyethyl analogues (R = $HOCH_2CH_2$) were prepared in a likewise manner from benzophenones (X = H and OCH_3).

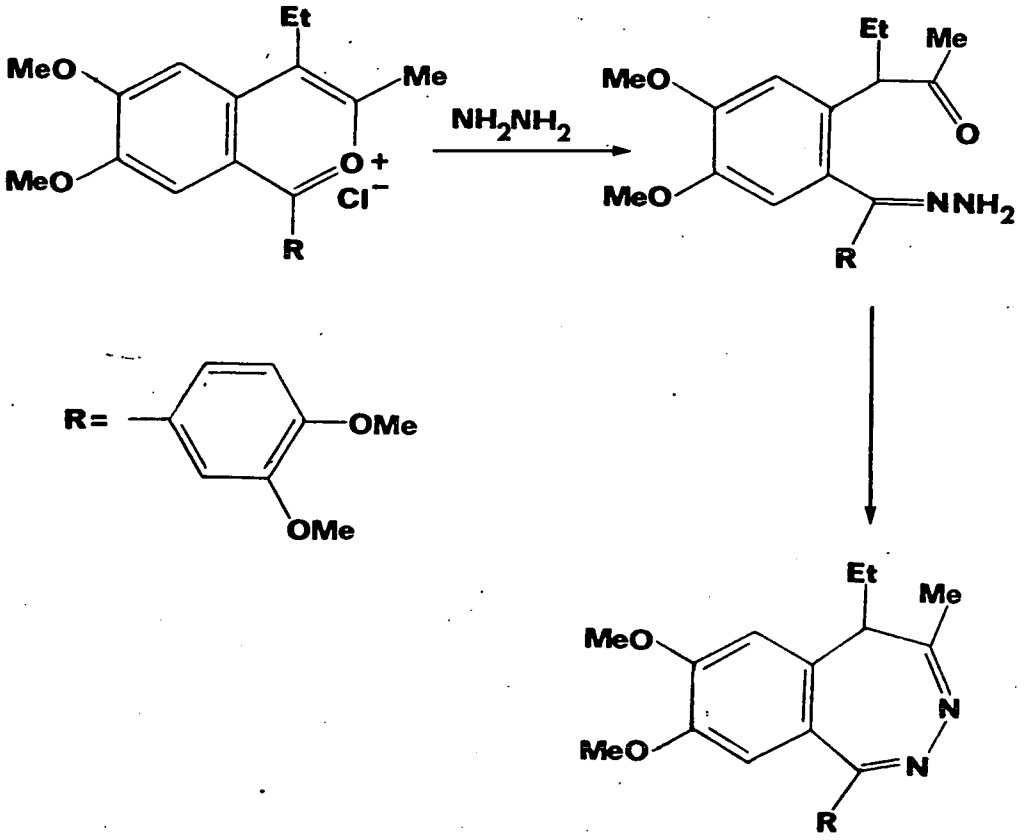
The 1H-2,3-benzodiazepines (162) were prepared by Sharp and his co-workers[126,127] by electrocylic ring closure of α-aryldiazoalkenes (160) which in turn were prepared by thermal decomposition of the corresponding tosylhydrazone sodium salt. The 4H-benzodiazepines (161) have been postulated as intermediates[128], being themselves converted into the isolated 1H-derivatives via a symmetry allowed [1,5] sigmatropic hydrogen shift. The 5H-2,3-benzodiazepines (163) were readily obtained by thermal or basic treatment of the corresponding 1H-derivative[127,128].

The reaction of α-aryldiazoalkanes will be dealt with at greater length in the Discussion.



5H-2,3-Benzodiazepines have also been prepared by the reaction of hydrazine hydrate with the benzopyrylium salt[129,130,131]. The reaction proceeds through the monohydrazone, Scheme 33.


OH⁻
R
Br⁻
(164)
R=H,Me,Cl
H
OH
(165)
M.S.H.
HN
CHO
NH₂
⁻OMes
(166)
+ HOMes
(167)
Mes= —SO₂
Me



Scheme 33

3-Aryl-4,5-dihydro-3H-2,3-benzodiazepines (167)[132] have been prepared by the treatment of dihydroisoquinolinium salts (164) with alkali followed by reaction of the resulting pseudobase (165) with O-mesitylsulphonylhydroxylamine (MSH), the intermediacy of the hydrazine derivative (166) has been postulated.

I. Isoquinoline N-imines.

In general, amine N-imines are derived formally from tertiary amines by replacing the free pair of electrons by an imino group[75]. The N-imines are members of the isoelectronic and isosteric series: N-oxides, N-imines, and N-ylides.i.e. Figure 18.

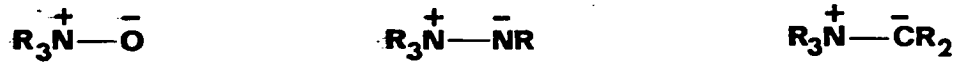


Figure 18

Aliphatic, aromatic or heteroaromatic compounds are obtained according to the nature of the amine. Heteroaromatic N-imines are derived from heterocyclic compounds with the C=N group as part of the aromatic system, thus leading to an unusually high stability for this type of compound. The number of papers published on N-imines is relatively small and efficient methods of preparation were not discovered until recently and only since 1965 has the study of N-imines been pursued to any extent.

Heteroaromatic N-imines of the following classes are known, as derivatives of pyridines, quinolines, isoquinolines, benzocinnolines, ν-triazoles, s-triazoles and thiazoles. N-imines can be classified not only by the heterocyclic nucleus but according to the substituent at the exocylic imino group. The types shown below in Figure 19 have all been synthesised. Of the heteroaromatic N-imines, the pyridine N-imines[75] have been the most widely investigated but this discussion will be mainly limited to isoquinoline N-imines since they are the subject of part of the results reported in this Thesis.

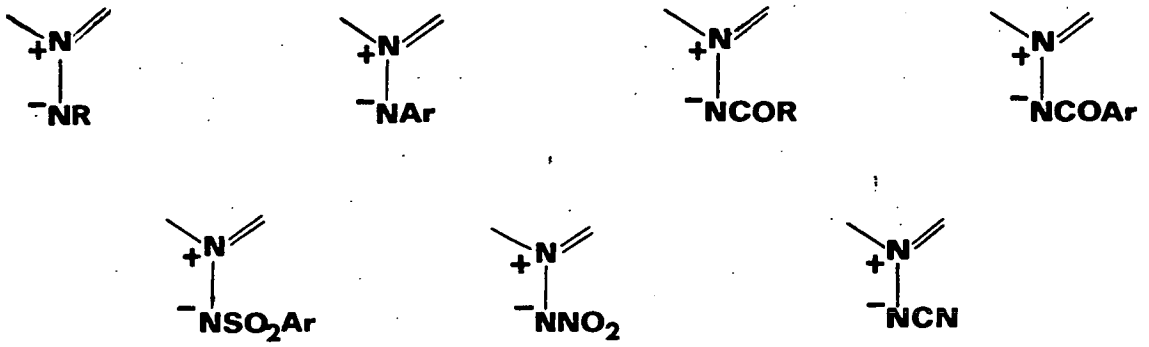
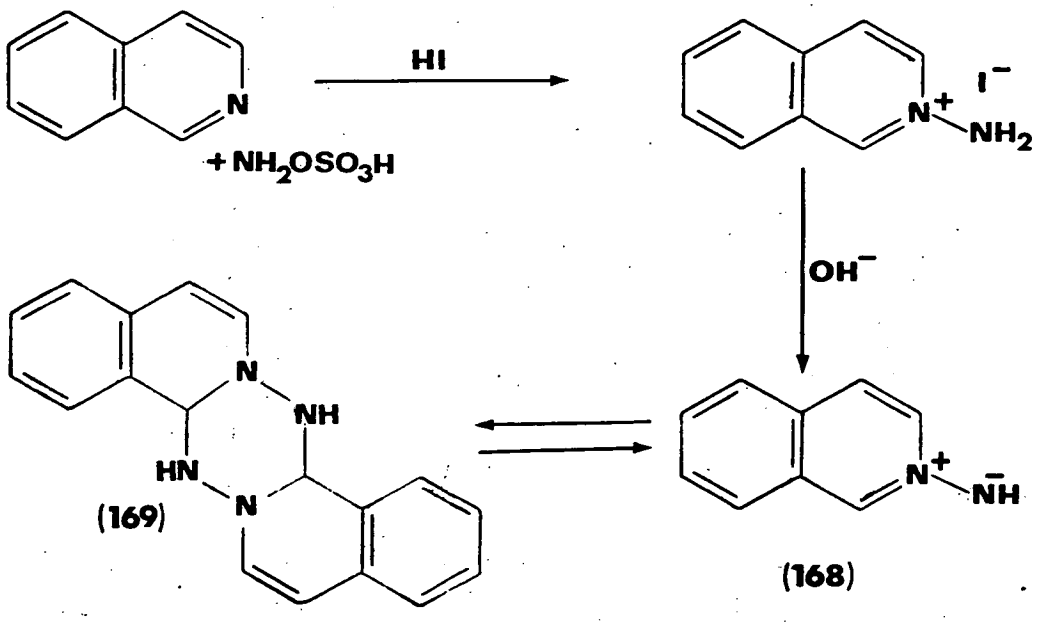


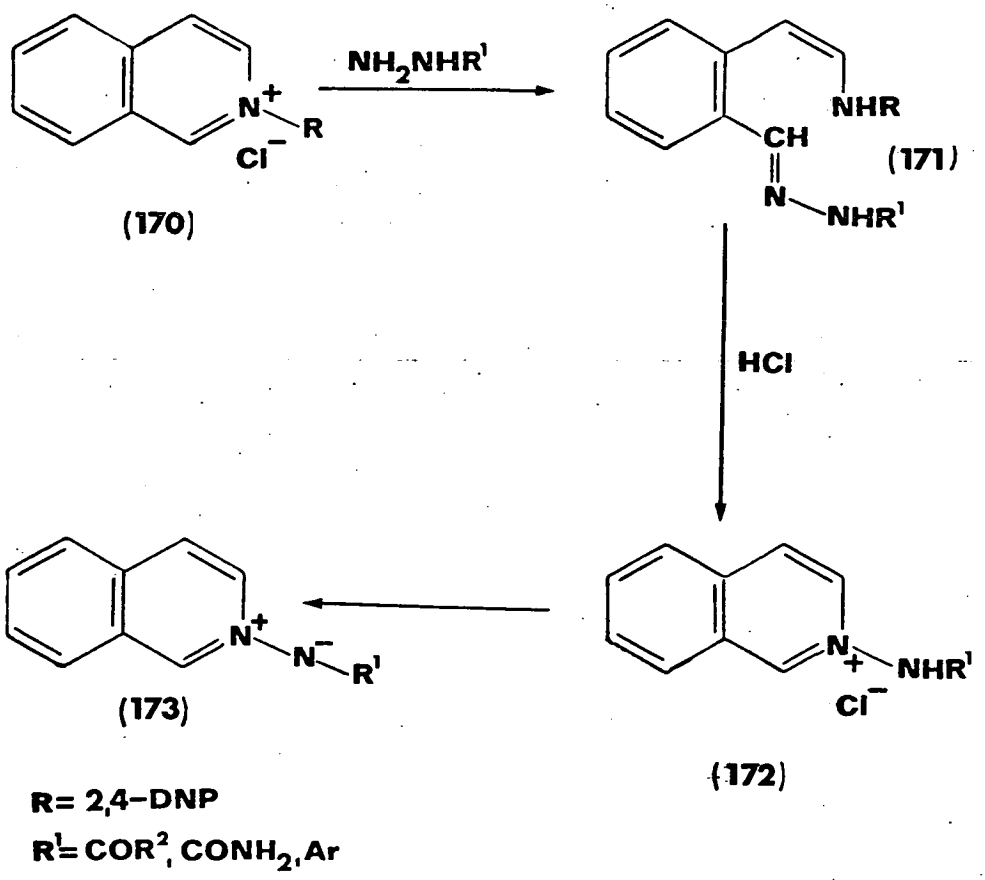
Figure 19

1. Synthesis of isoquinoline N-imines.

In 1962 Huisgen[133] reported the synthesis of isoquinoline N-imines by the amination of isoquinoline with hydroxylamine-O-sulphonic acid followed by deprotonation with hydroxide ion and this gave the unsubstituted isoquinoline N-imine (168) which dimerised to give the hexahydrotetrazine (169). This process can be reversed and the N-imine regenerated by mild heating[133,134].



Another route into the isoquinoline N-imine system is Tamura's method[134,135,136] i.e. the reaction of N-(2,4-dinitrophenyl)-isoquinolinium chloride (170)[137] with hydrazines. This gives the 2-(2,4-dinitroanilino)-o-styrylaldehyde hydrazones (171) which can by treatment with hydrochloric acid in ethanol be converted to the N-aminoisoquinolinium chloride (172) which can be deprotonated to the isoquinoline N-imine (173).



(170)

(171)

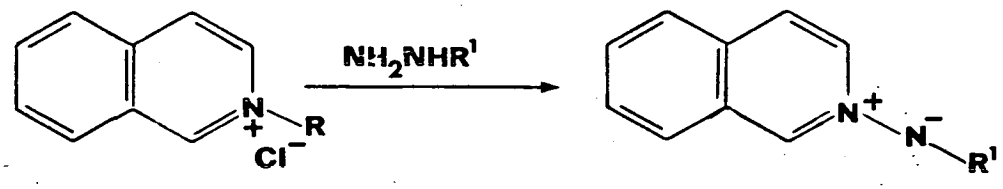
(172)

(173)

R= 2,4-DNP

R^1= COR^2, $CONH_2$, Ar

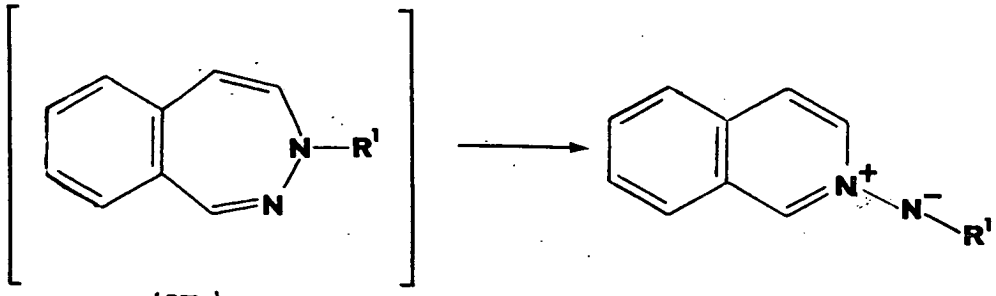
Garkusha-Bozhko and his co-workers[138,139,140] have used a method very similar to the work of Tamura in the synthesis of isoquinoline N-imines. They have also used the treatment of isoquinolinium salts with substituted hydrazines. Where Tamura only used the N-(2,4-dinitrophenyl)isoquinolinium salts; N-methyl, -tosyl,-ethyl and -H isoquinolinium salts have been used successfully to synthesise isoquinoline N-imines, Scheme 34. The isoquinolinium salt is treated with a hydrazine in aqueous sodium hydroxide and the isoquinoline N-imines are obtained in good yields.



R^1=H,COPh

Scheme 34

One very interesting point in Garkusha-Bozhko's work is that he postulates an intermediate 2,3-benzodiazepine (174) in this reaction. This 2,3-benzodiazepine was not isolated and very little detail is given about its possible existence except that it might ring contract to the isoquinoline N-imine. This is very interesting as part of the work in this Thesis was involved with the synthesis of similar 2,3-benzodiazepines which in fact were not obtained; isoquinoline N-imines being obtained instead.

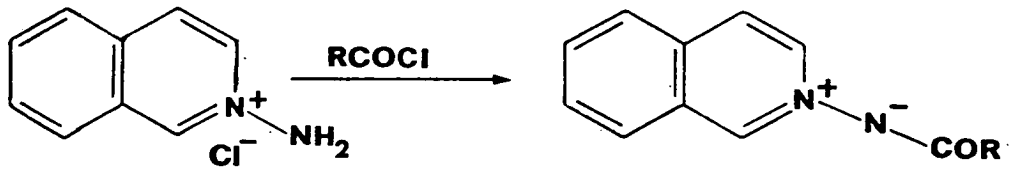


(174)

Agai and Lempert[141] have synthesised a range of isoquinoline N-imines where the N-substituent is tosyl, -COPh, $-CONHNH_2$, $-COC_6H_4$-p-NO_2, $-CO_2Et$, $-CONH_2$, -CONHPh, $-CSNH_2$, -CSNHPh and -CN. They have employed three methods for their synthesis:

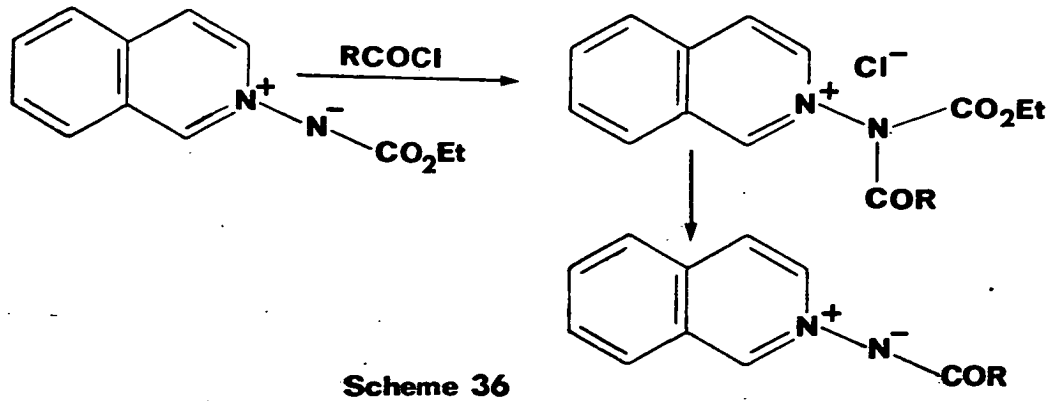
1) Tamura's method[134,135], i.e. ring closure of 2-(2,4-dinitroanilino)-o-styrylaldehyde hydrazones. (see above)

2) The acylation of N-aminoisoquinolinium chloride, Scheme 35.



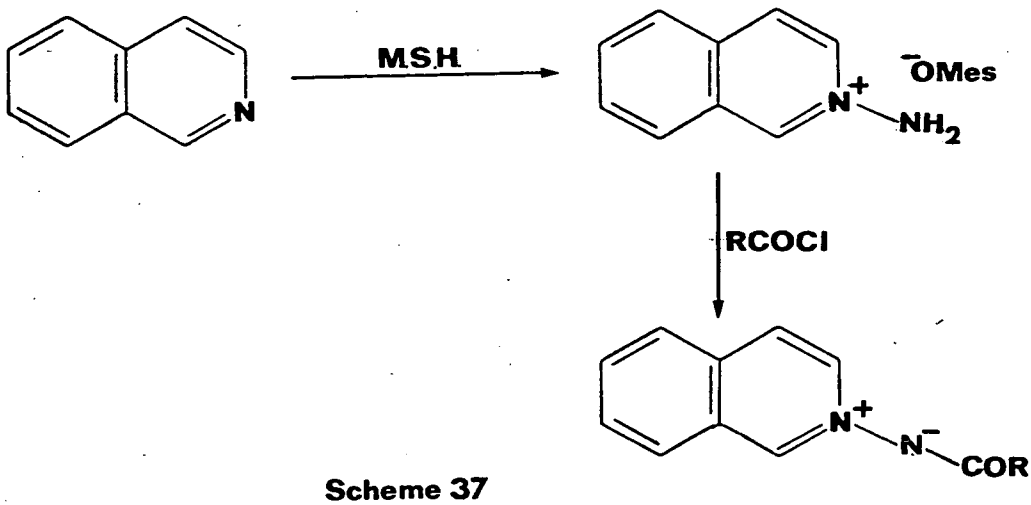
Scheme 35

3) Transacylation of N-(2-isoquinolinio)ethoxylcarbonylamidate Scheme 36.



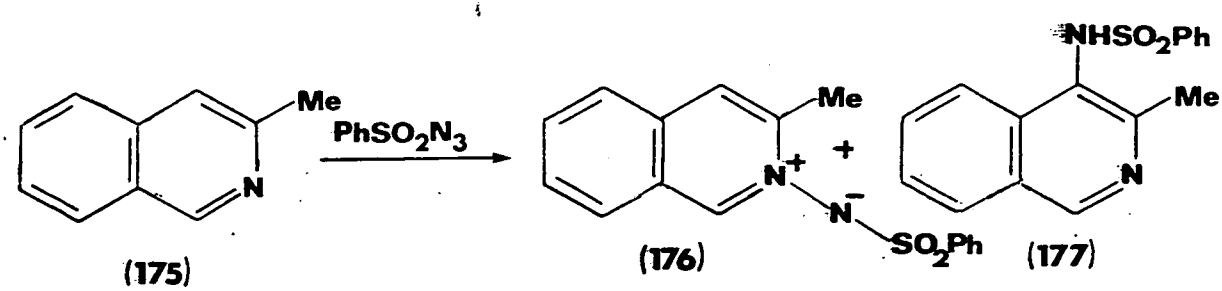
Scheme 36

Tamura[136] has also used the acylation of N-aminoisoquinolinium salts in the synthesis of isoquinoline N-imines. One innovation is the use of O-mesitylsulphonylhydroxylamine (MSH) in the amination of isoquinoline followed by acylation and deprotonation, Scheme 37.



Scheme 37

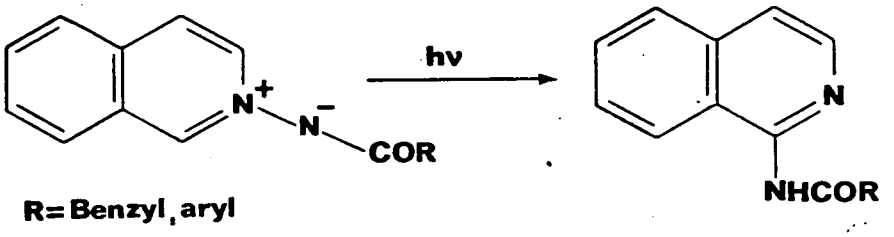
One of the classical methods of preparing pyridine N-imines is the reaction of azides with pyridines[75] although in general, the yields are quite low. Abramovitch and Takaya[142] reacted benzenesulphonyl azide with 3-methylisoquinoline (175). They obtained a 20% yield of 3-methylisoquinoline N-benzenesulphonylimine (176) and they also obtained a 12% yield of 4-benzenesulphonamido-3-methylisoquinoline (177). The reaction of isoquinoline with benzenesulphonyl azide gave no products.



(175) (176) (177)

2. Reactions of isoquinoline N-imines.

The photochemistry of the isoquinoline N-imines is different than that of the pyridine N-imines. Unlike the pyridine N-imines which on photolysis yield the N-substituted diazepines[71,75] the isoquinoline N-imines do not, rather the products obtained are the 1-acylaminoisoquinolines[143,144], Scheme 38.



Scheme 38

Heteroaromatic N-imines are in fact stable members of the group of azomethine imine 1,3-dipoles and their reactions as such are discussed in the next section.

J. Azomethine imines.

Azomethine imines are 1,3-dipoles of the structure shown below in Figure 20.

Figure 20

The azomethine imines are normally short lived intermediates with typical 1,3-dipolar reactivity i.e. they will undergo cyclo-

addition reactions characteristic of 1,3-dipoles. Most of the synthetic routes to these 1,3-dipoles have only been developed recently, however relatively stable isolable azomethine imines with the C=N bond as part of a heteroaromatic ring have been known for much longer.

Huisgen[37] was the first to recognise that there are five different types of azomethine imines:-

a) N-β-cyano(azomethine imines)

b) Azomethine imines of the 3,4-dihydroisoquinoline series.

c) Azomethine imines from 1,2-disubstituted hydrazines and aldehydes.

d) Isoquinoline N-imines.

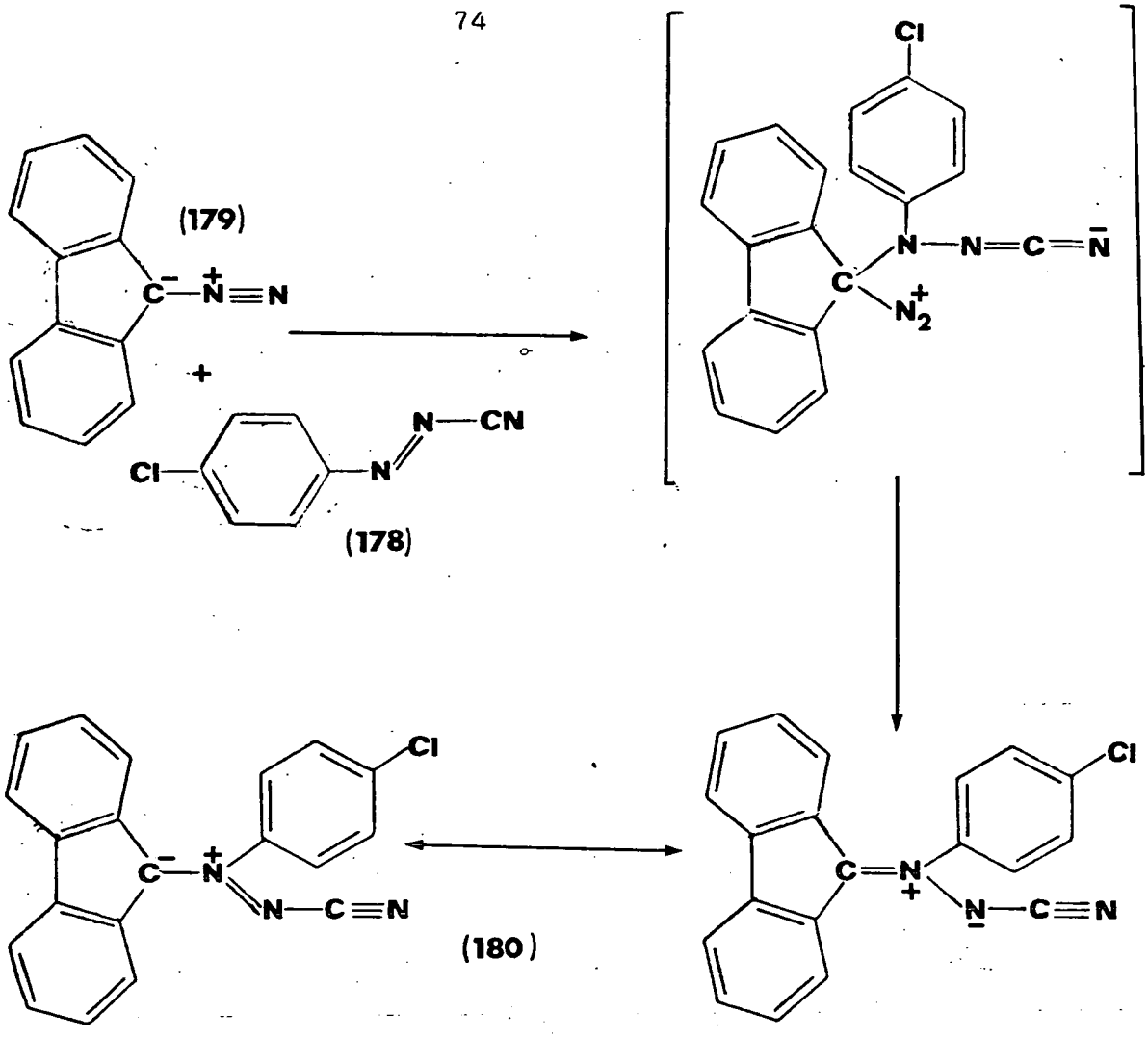
e) Sydnones.

A brief account is given here of types a, b and e; and a fuller account of types c and d i.e. azomethine imines from 1,2-disubstituted hydrazines and aldehydes; and isoquinoline N-imines.

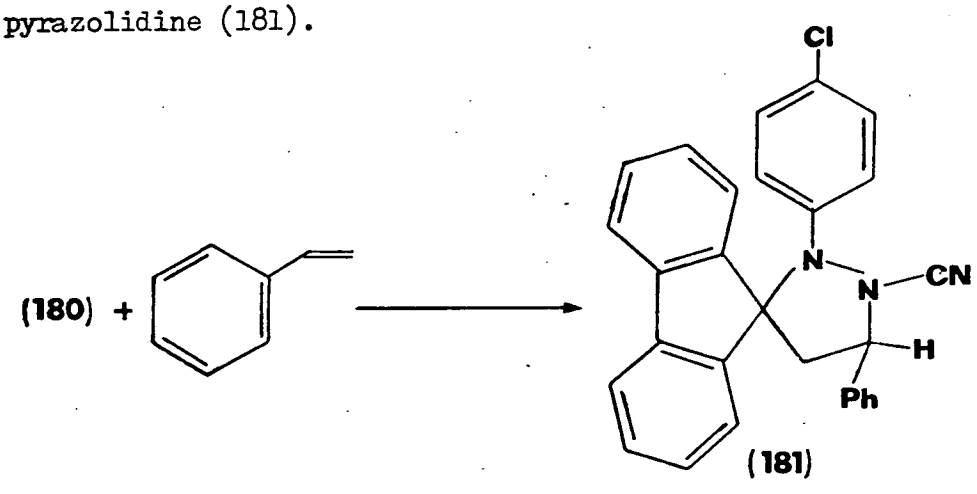
a) N-β-cyano(azomethine imines).

These are stable isolable azomethine imines which were discovered by Huisgen and his co-workers[145]. They are prepared by the reaction of diazocyanides and aliphatic diazo compounds. Thus, p-chlorophenyl-anti-diazocyanide (178) reacts with diazofluorene (179), eliminating 1 mole of nitrogen at room temperature to give the bright orange azomethine imine (180).

Analogous azomethine imines have been prepared from diphenyl-diazomethane and its nuclear substituted derivatives as well as from other diazocyanides.



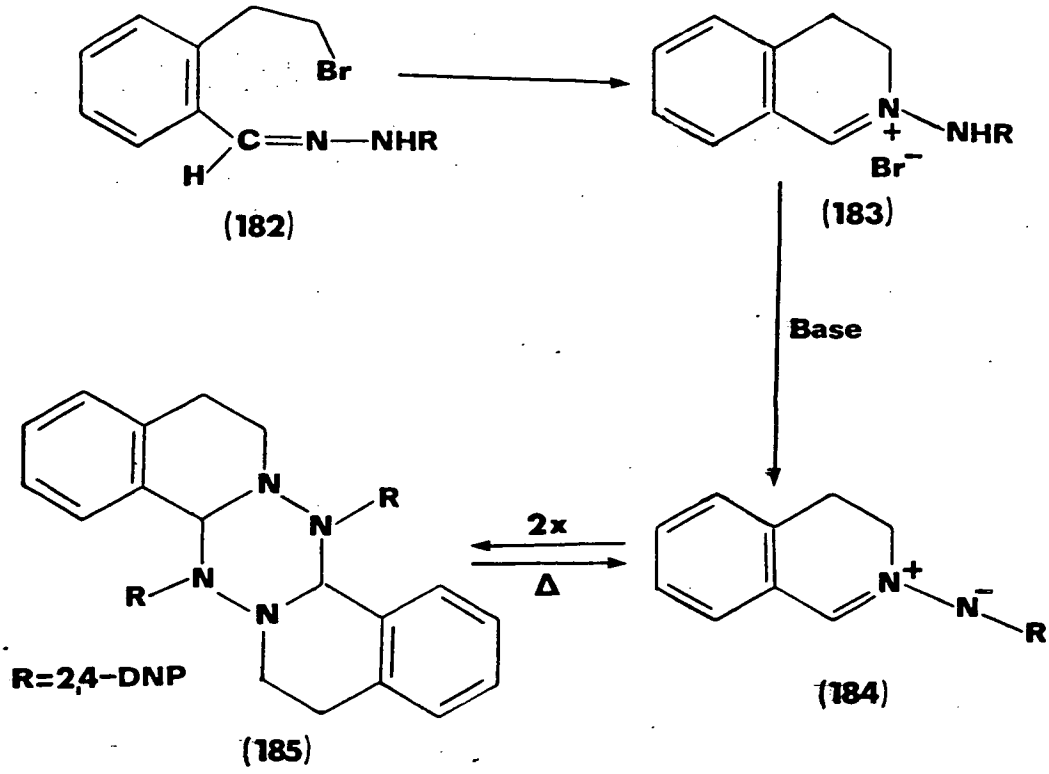
These azomethine imines undergo 1,3-dipolar cycloaddition with olefins in good yields to give pyrazolidines[146]. The azomethine imine (180) combines with styrene in 90% yield to give the pyrazolidine (181).



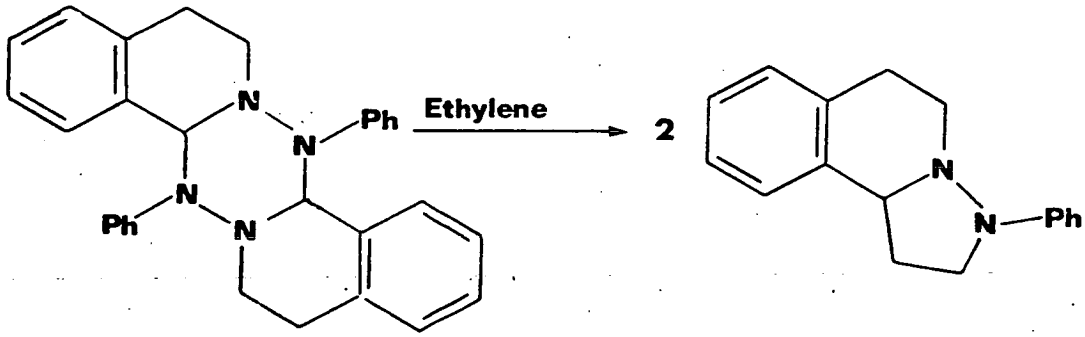
b) Azomethine imines of the 3,4-dihydroisoquinoline series.

These azomethine imines have great reactivity and as a result of this they have been the subject of intensive study in the last few years. These 1,3-dipoles are not actually isolable, but their easy preparation in situ from storable precursors make them easy to use.

In 1958 Schmitz[147] reported that o-β-(bromoethyl)benzaldehyde 2,4-dinitrophenylhydrazone (182) undergoes an intramolecular alkylation on heating to give the N-(2,4-dinitrophenylamino)-3,4-dihydroisoquinoline bromide (183). Analogous aryl- and alkyl-hydrazonium salts can be prepared[148]. Treatment of the 3,4-dihydro-isoquinoline bromide with a base abstracts the hydrazone proton and this generates the typical azomethine imine system (184). The azomethine imine which is red in colour dimerises in a head-to-tail fashion to form a derivative of hexahydro-1,2,4,5-tetrazine (185)[148].



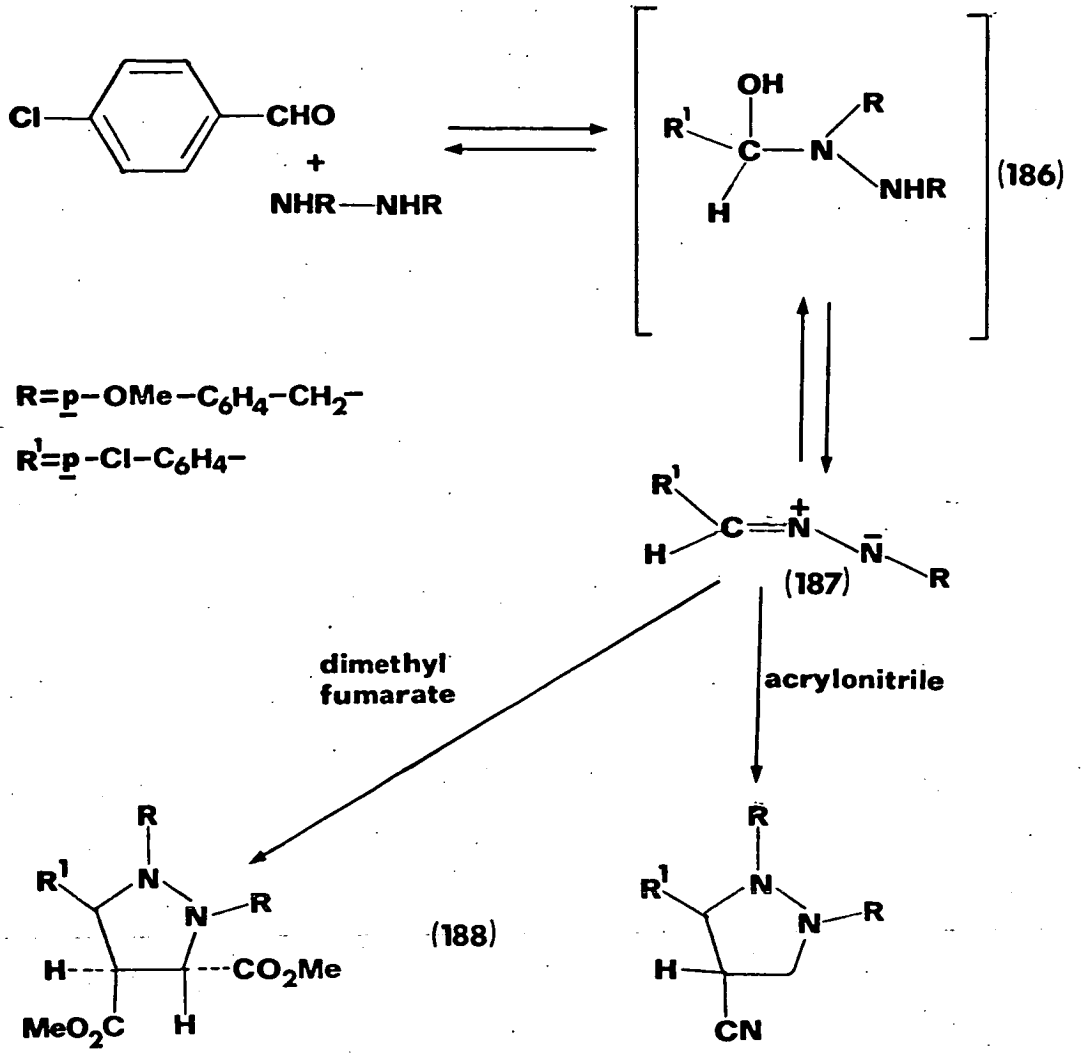
The azomethine imine can easily be recovered by gentle heating of the dimer in an inert solvent. This equililbrium which exists between the dimer and monomeric azomethine imine makes the dimer, which has an excellent shelf life, a convenient source of the 1,3-dipole. These azomethine imines enter into cycloadditions with practically all types of multiple bonds and there are many examples of their reactivity[37]. One example is the reaction of the hexahydrotetrazine, Scheme 39, which when heated with ethylene, forms the 1,3-dipole *in situ* and then combines with the olefin to give the pyrazolidine.



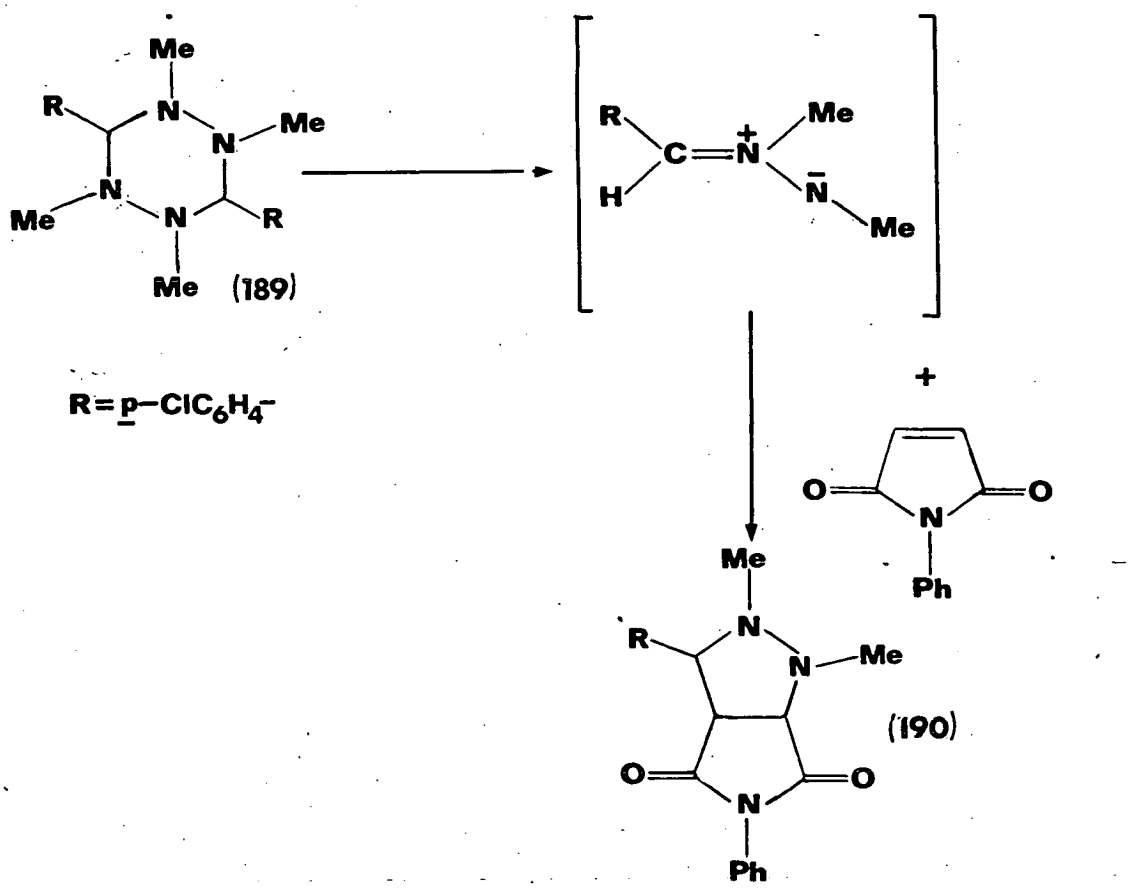
Scheme 39

c) *Azomethine imines from 1,2-disubstituted hydrazines and aldehydes.*

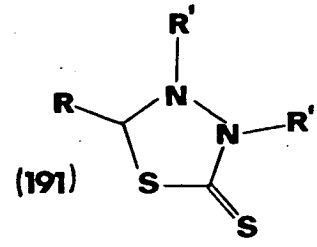
It has recently been shown by Huisgen *et al*[37,38] that the reaction of 1,2-disubstituted hydrazines with aldehydes gives azomethine imines. In the reaction of *p*-chlorobenzaldehyde and 1,2-di-*p*-methoxybenzylhydrazine the initial product is the α-hydrazinocarbinol (186) which then loses water to give the azomethine imine (187) which undergoes 1,3-dipolar cycloaddition with dimethyl fumarate and acrylonitrile to give the pyrazolidines (188).



In the absence of a trap these species also dimerise and Huisgen has described the use of hexahydrotetrazines so formed as sources of azomethine imines[37, 149], for example the hexahydrotetrazine (189) formed from p-chlorobenzaldehyde and 1,2-dimethylhydrazine reacts with N-phenylmaleimide via the intermediate azomethine imine to give the pyrazolidine addition product (190).

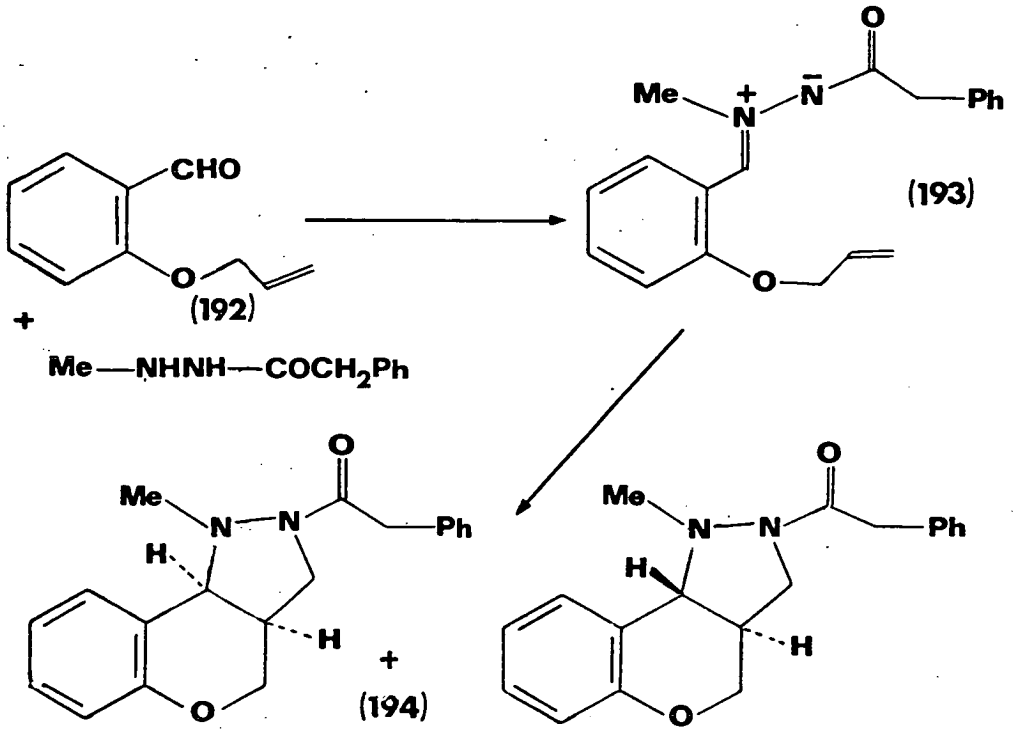


Carbon disulphide has been reported as reacting with similar azomethine imines to give the 3,4-dialkyl-1,3,4-thiadiazolidine-5-thiones (191)[149].

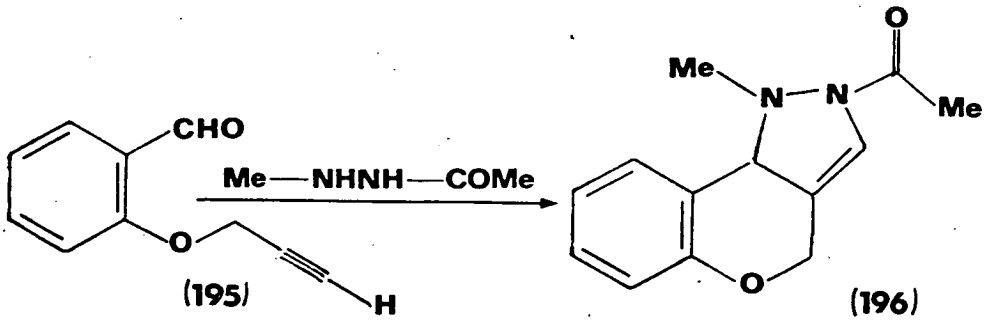


Oppolzer [150] has extended this reaction to include systems which contain the olefin and azomethine imine portions in the same molecule [151,152]. For example treatment of o-allyloxybenzaldehyde (192) with 1-methyl-2-phenylacetylhydrazine gives the two cycloaddition products

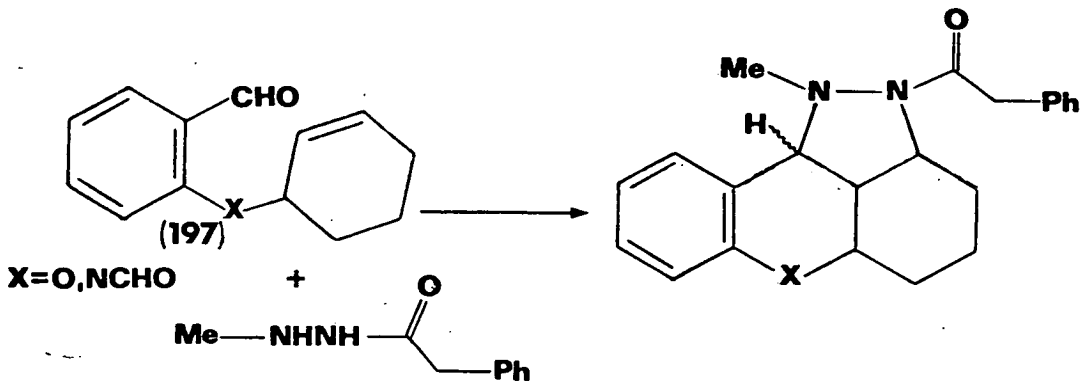
(194) via the azomethine imine (193)[152].



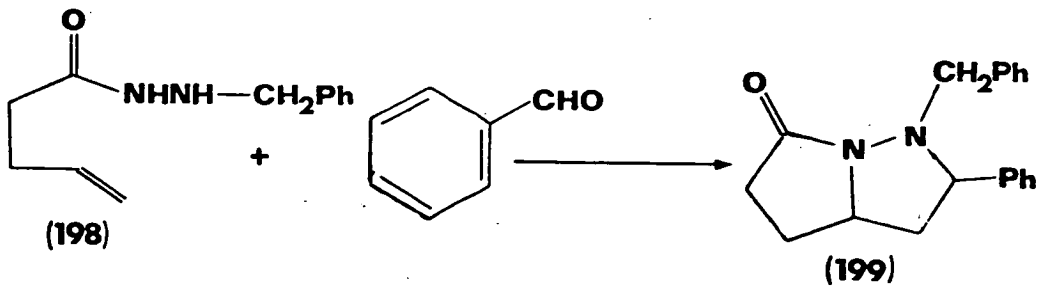
In a similar reaction the related acetylenic derivative (195) gave the cycloadduct (196) when reacted with 1-acetyl-2-methylhydrazine.

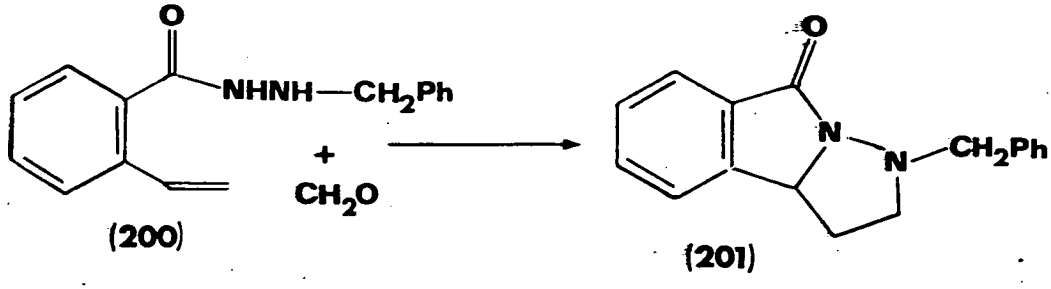


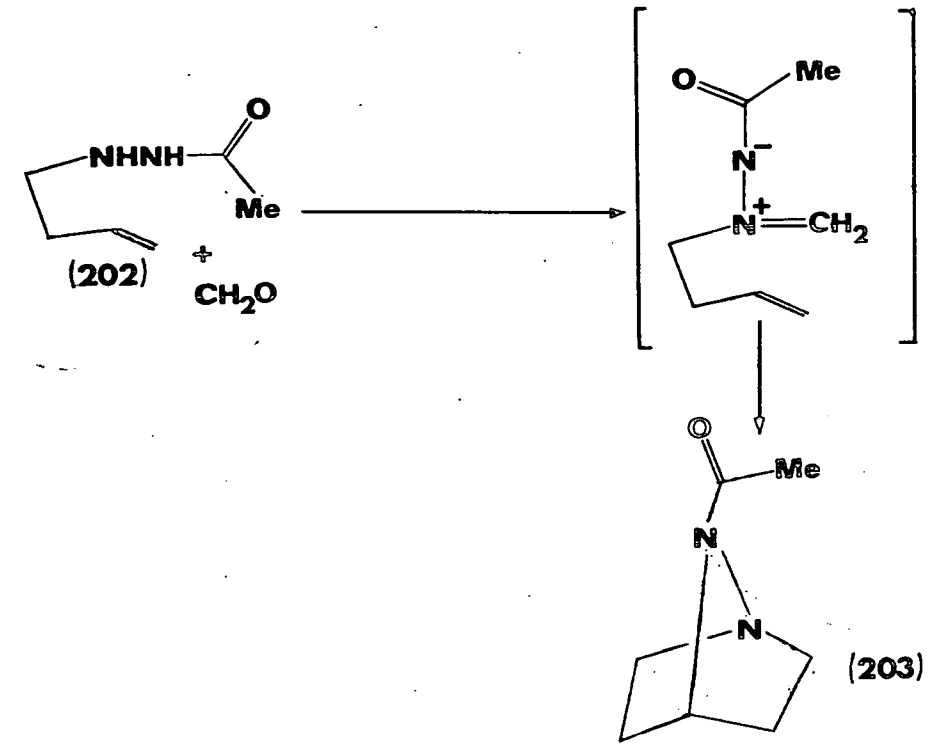
A related compound (where X = O or NCHO) (197) was found to cyclise in a similar manner[152] when treated with 1-methyl-2-phenylacetyl-hydrazine.

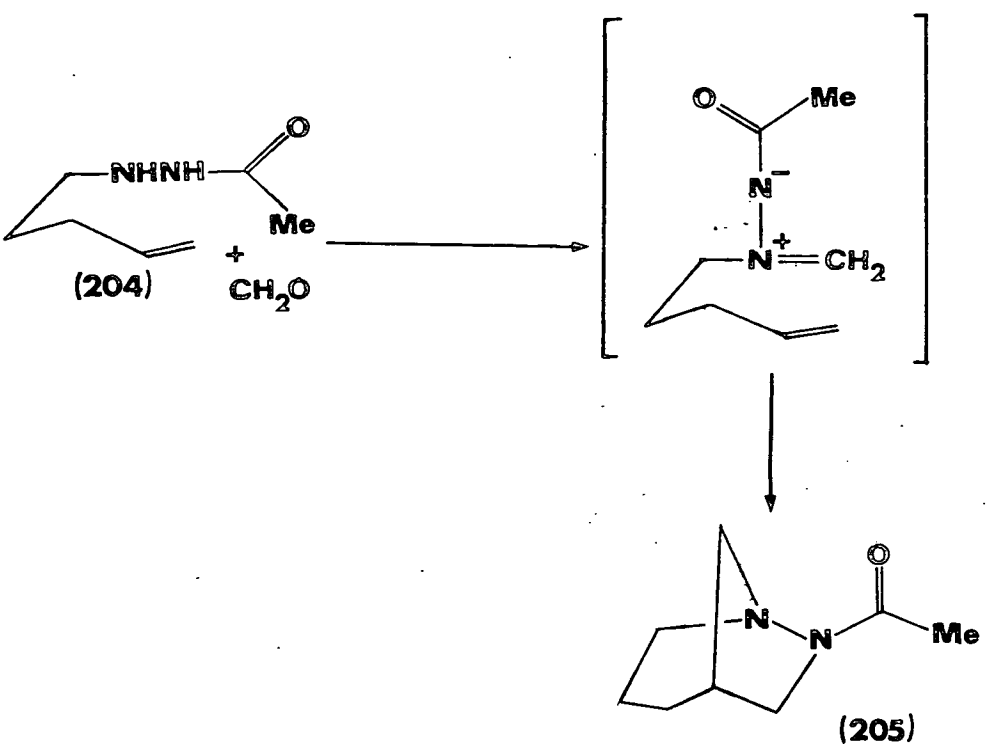


In an extension of this work to systems in which the unsaturation was originally present in the hydrazine, Oppolzer[151] found that the cycloadduct (199) was the product of the reaction of 1-benzyl-2-(4-pentenoyl)hydrazine (198) and benzaldehyde. And in a similar reaction o-vinylbenzoic acid hydrazide (200) when treated with formaldehyde cyclised to give the product (201). Oppolzer considers that both sets of reactions proceed through an intermediate azomethine imine.



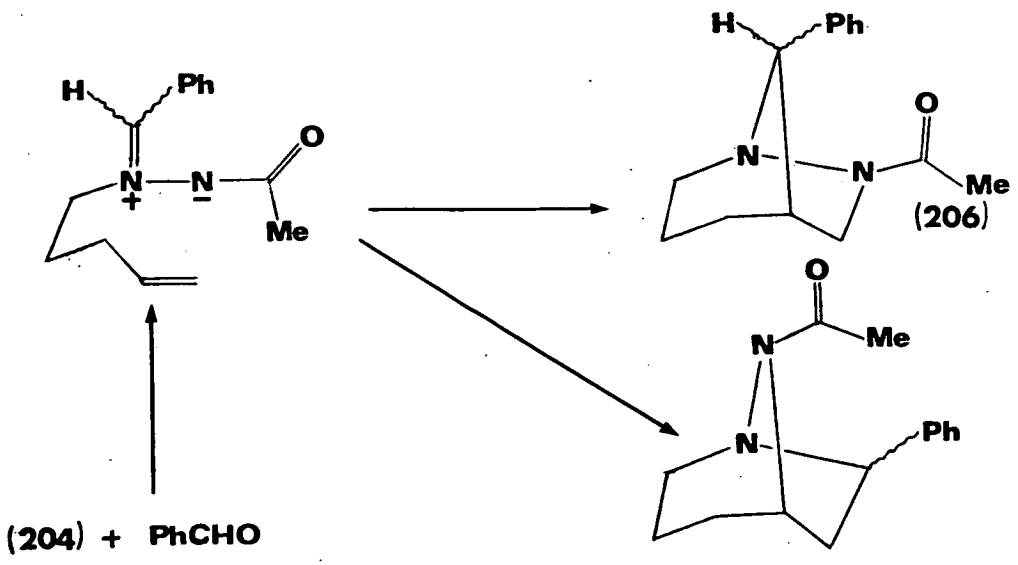



NHNH
O
Me
(202)
+
CH_2O
O
Me
N
N
CH_2
O
Me
N
N
(203)

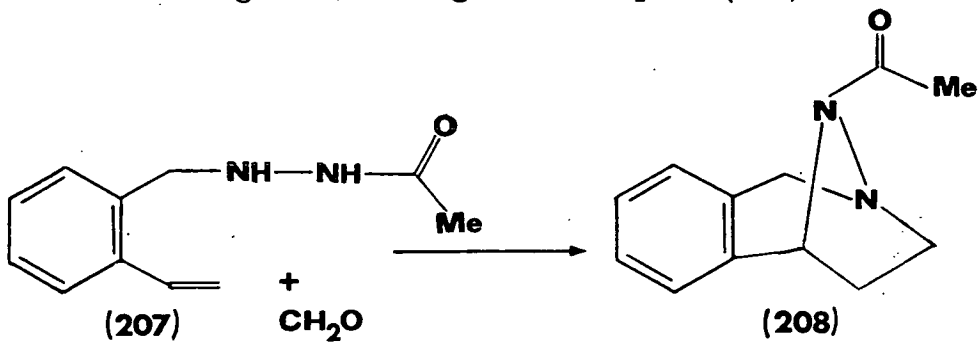

NHNH
O
Me
(204)
+
CH_2O
O
Me
N
N
CH_2
N
N
O
Me
(205)

It has been shown[50] that 1-acyl-2-alkylhydrazines react with aldehydes only on the alkyl substituted nitrogen. It is thus possible to prepare regioselective pyrazolidines with different N-substituents. The intramolecular 1,3-dipolar cycloaddition reactions of these azomethine imines represent a convenient and simple method for the synthesis of some novel diazabicyclic ring systems. Similarly the condensation of 1-acyl-2-alkenylhydrazines with aldehydes leads to azomethine imines with an alkenyl group on the central nitrogen of the dipole which also undergo intramolecular cycloadditions. For example the reaction of the alkenylhydrazine (202) with formaldehyde gave the adduct (203) in a regioselective manner. Treatment of the homologous alkenylhydrazine (204) with formaldehyde gives a different regioisomer (205), the direction of the addition being reversed with the higher homologue[50,151].

In the case of the alkenylhydrazine (204) when the condensation was carried out with benzaldehyde a mixture of the two structural cycloadducts was obtained. The major product (206) however, was the same as in the reaction with formaldehyde.



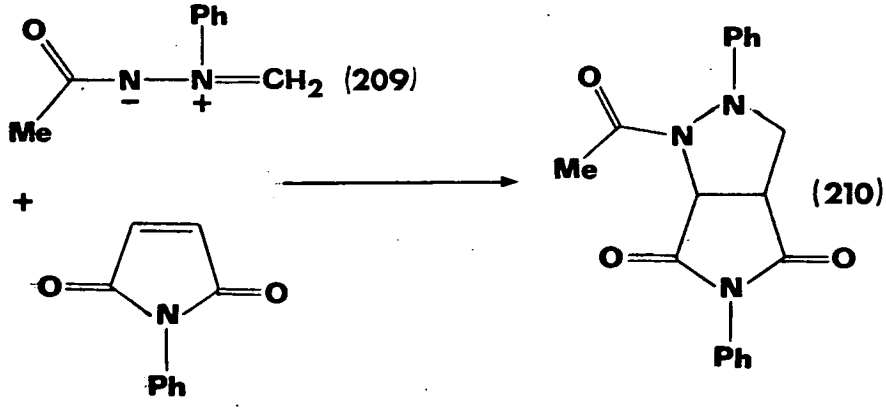
In a related reaction to that of the alkenylhydrazine (202) 1-acetyl-2-(o-vinylbenzyl)hydrazine (207) undergoes a similar intramolecular cycloaddition to give the bridged benzazepine (208)[151].



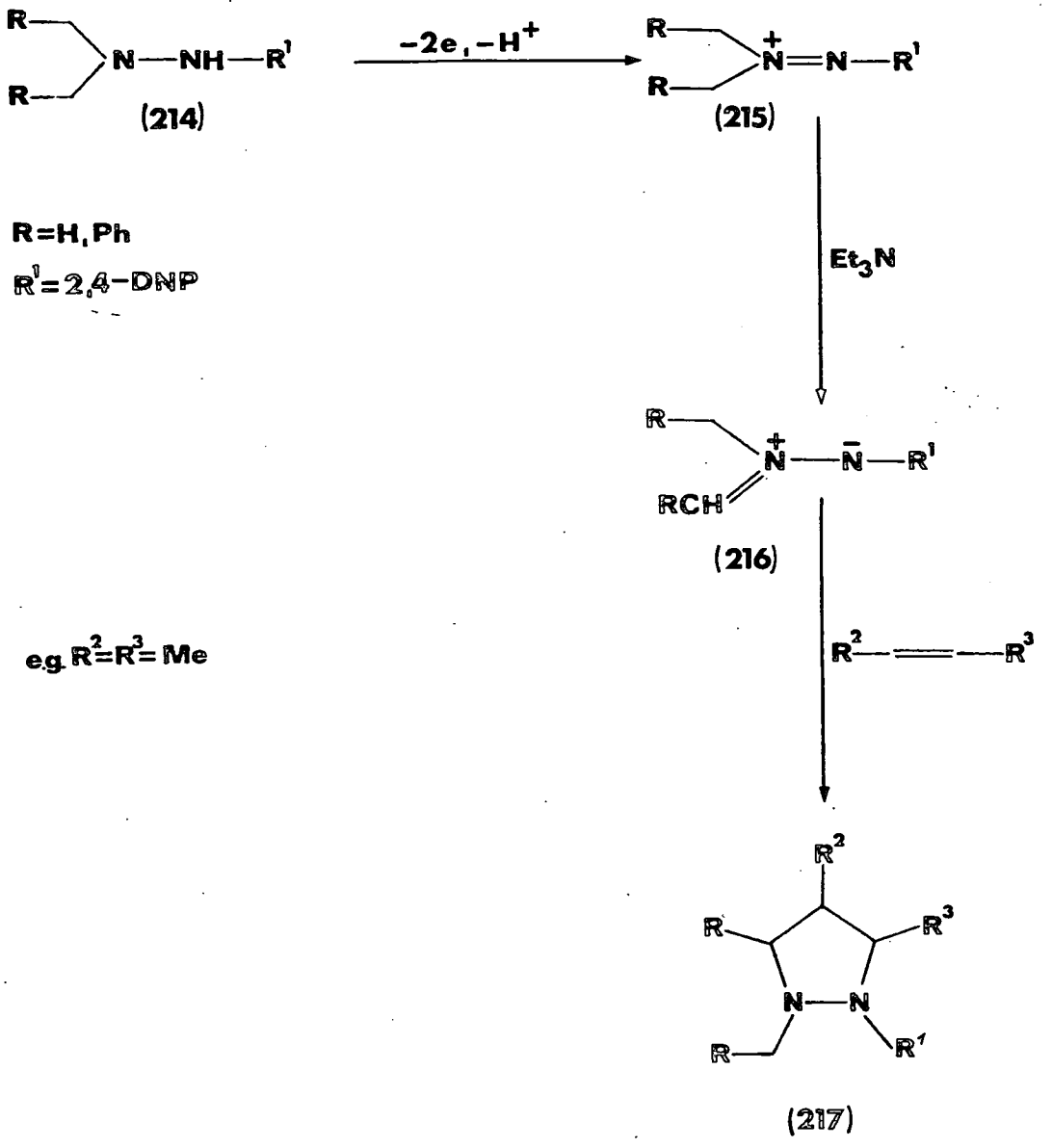
(207) (208)

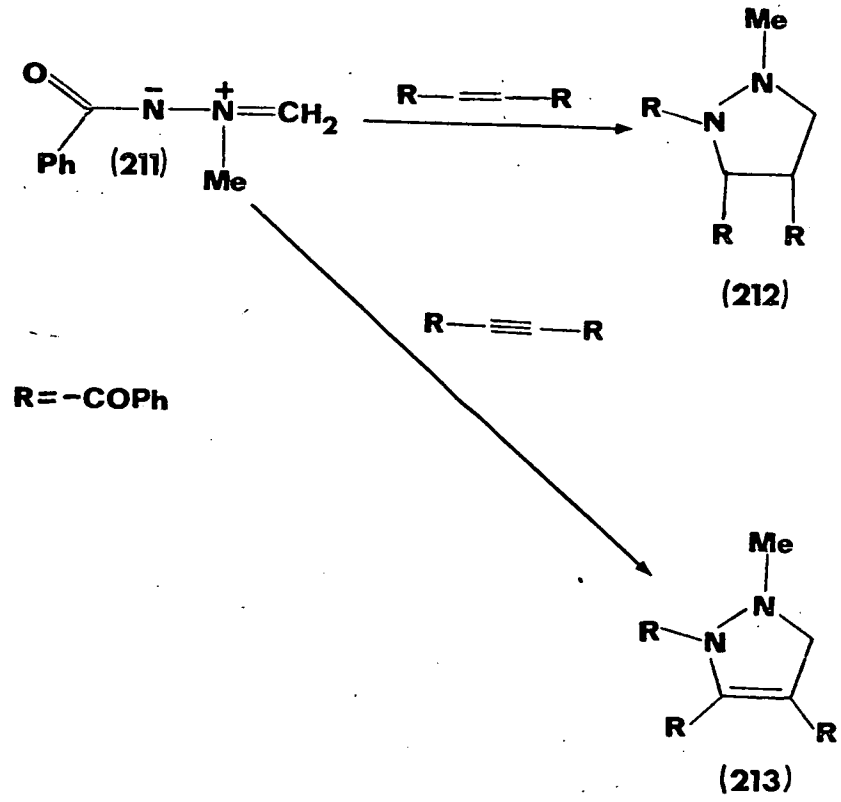
Recently Lown and Landberg[153] have investigated the use of 1-acetyl-2-phenylhydrazine and 1-benzoyl-2-methylhydrazine reacted with formaldehyde as a source of azomethine imines.

They found that the azomethine imine (209) generated from 1-acetyl-2-phenylhydrazine and formaldehyde would not react with dibenzoylethylene or dibenzoylacetylene but did react with N-phenylmaleimide to give the cycloadduct (210). Reaction of 1-benzoyl-2-methylhydrazine with formaldehyde gave the azomethine imine (211) which reacted with dibenzoylethylene to give the pyrazolidine (212) and dibenzoylacetylene to give the pyrazoline (213)



(209) (210)


R
R
N—NH—R'
(214)
-2e, -H+
R
R
N=N—R'
(215)
R=H, Ph
R'=2,4-DNP
Et3N
R
RCH
N—N—R'
(216)
eg. R2=R3= Me
R2—=—R3
R2
R
R3
N—N
R
R'
(217)

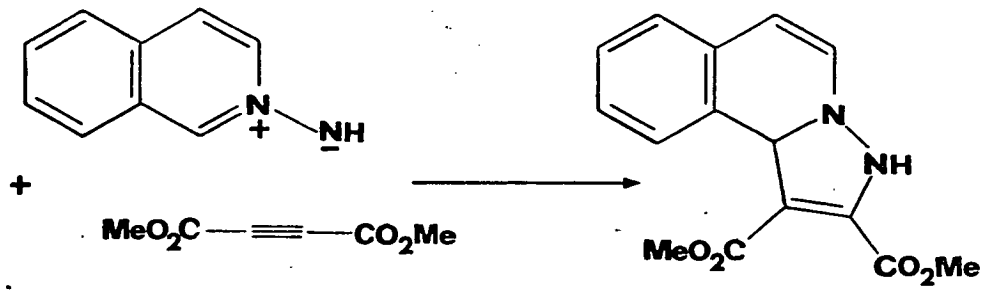


Cauquis and Chabaud[154] have produced an interesting method of preparing azomethine imines. 1,1-Disubstituted-2-(2,4-dinitrophenyl)diazenium cations (215) electrochemically prepared from the hydrazine (214), were treated with triethylamine and this generated the azomethine imine (216) by deprotonation of the alkyl group. The dipoles so produced would react with electron rich double bonds to give pyrazolidines (217) but not with electron poor double bonds.

d) Isoquinoline N-imines.

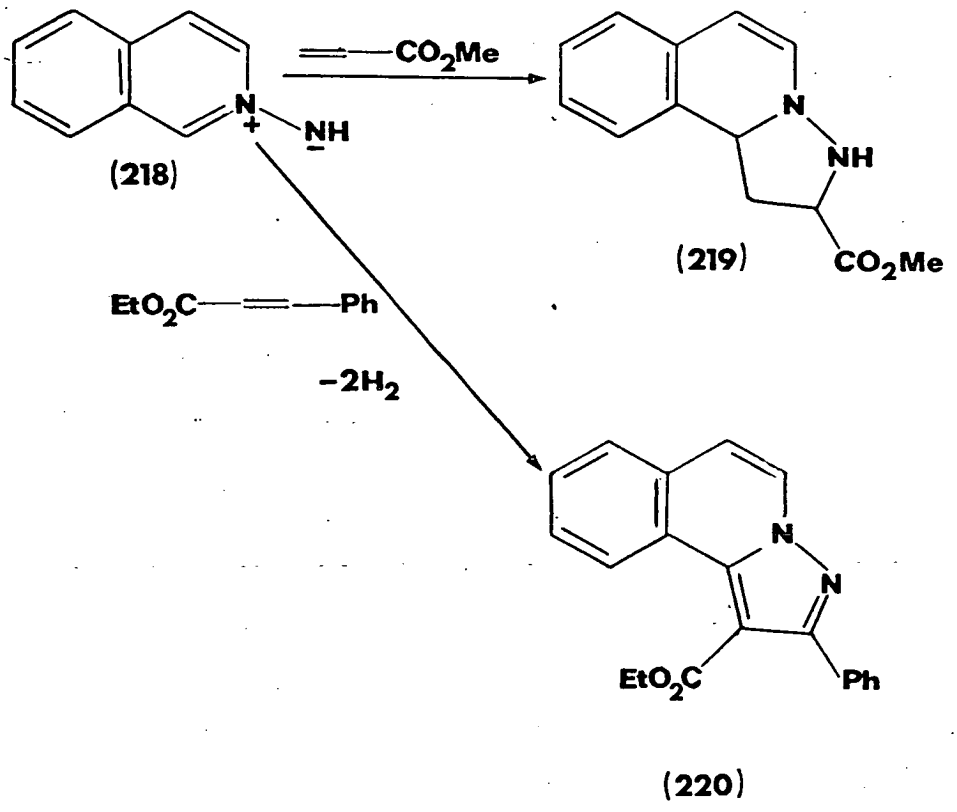
In the isoquinoline N-imines the carbon-nitrogen double bond portion of the 1,3-dipole is part of an aromatic system. Huisgen and his co-workers[36,37,133] were the first to describe the 1,3-dipolar cycloadditions of the isoquinoline N-imines. Since the pyridine ring resonance is lost in the course of the cycloaddition it is not surprising that these azomethine imines are less reactive than those of the 3,4-dihydroisoquinoline series. In general, all heteroaromatic N-imines may undergo 1,3-dipolar cycloadditions. The unsubstituted pyridine, quinoline and isoquinoline N-imines are the most reactive of all the N-imines and will add to nitriles, acetylenedicarboxylic esters, propiolic esters and carbon disulphide[75].

Unsubstituted isoquinoline N-imine, Scheme 40, reacts with diethyl acetylenedicarboxylate to give the pyrazoline, and similarly with carbon disulphide[36].



Scheme 40

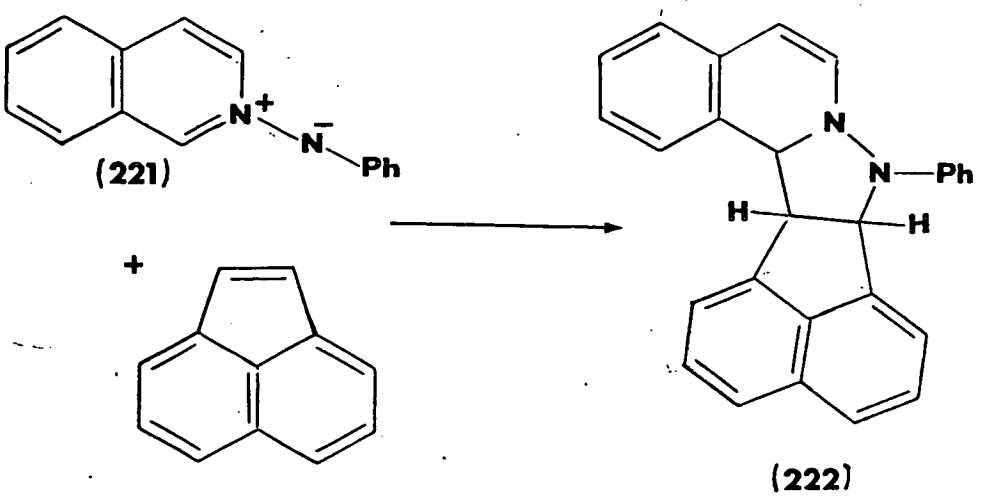
The isoquinoline N-imine (218) reacts with methyl acrylate to give the expected pyrazolidine (219) adduct but reaction with ethyl cinnamate is accompanied by loss of hydrogen to give the dihydrogenated pyrazole (220)[133].



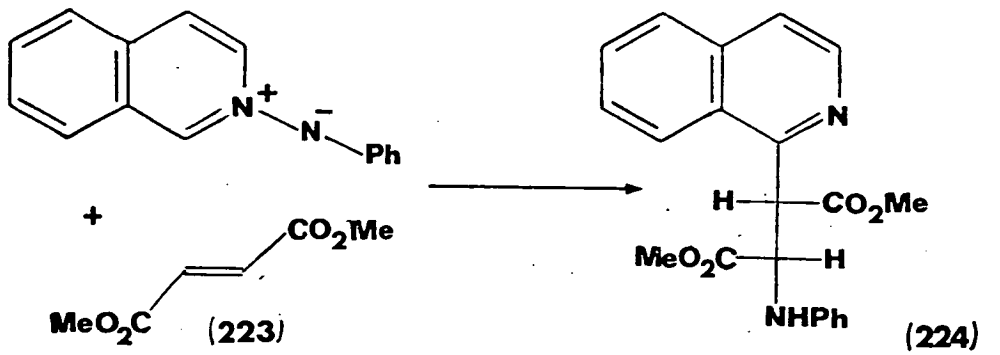
(220)

N-substituted isoquinoline N-imines will also undergo 1,3-dipolar cycloadditions with double bonds.

Isoquinoline N-phenylimine (221) reacts with acenaphthylene to give a hexacyclic pyrazolidine (222). This addition proceeds similarly with 1,4-naphthoquinone and dimethyl maleate[37,133].

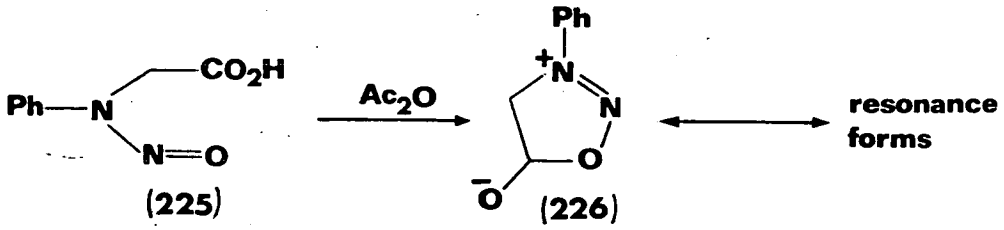


In additions of other olefins e.g. dimethyl fumarate (223), the 1,3-dipolar cycloaddition is followed by rearomatisation with ring opening to give the 1-substituted isoquinoline (224)[37]



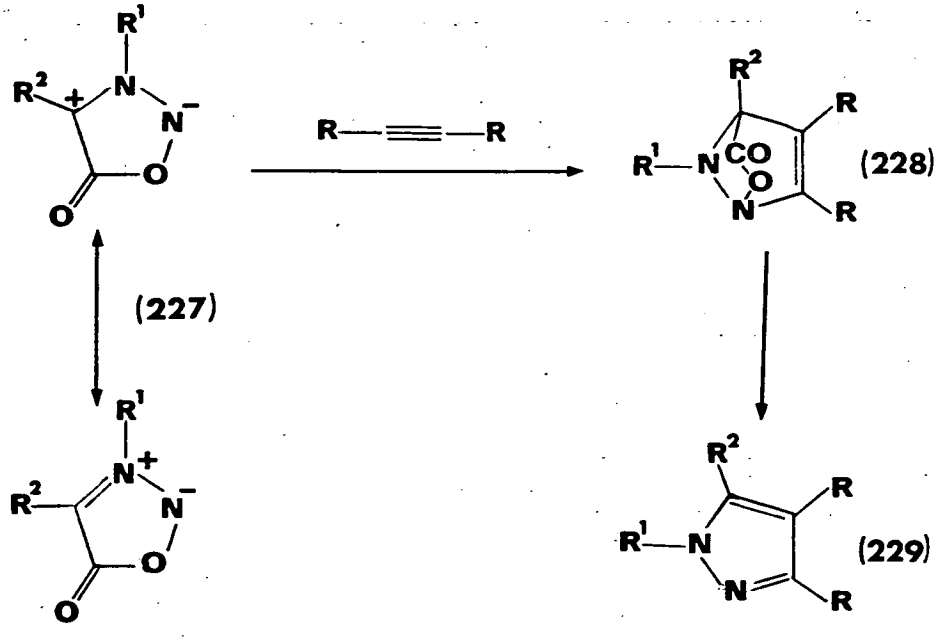
e) Sydnones.

Sydnones were first prepared by Earl and Mackney[155] from the cyclisation of N-nitroso-N-phenylglycine (225) with acetic anhydride. This has led into the general synthesis of sydnones (226)[37].



(225) (226)

The sydnones contain a mesionic aromatic system which can only be depicted with resonance structures. Two of the resonance structures possible (227) suggest a potential azomethine imine system and indeed they will add across dimethyl acetylenedicarboxylate to give the adducts (228) which lose carbon dioxide to give the pyrazoles(229)[36,37].



R = CO_2Me
R^1 = Ph
R^2 = Me

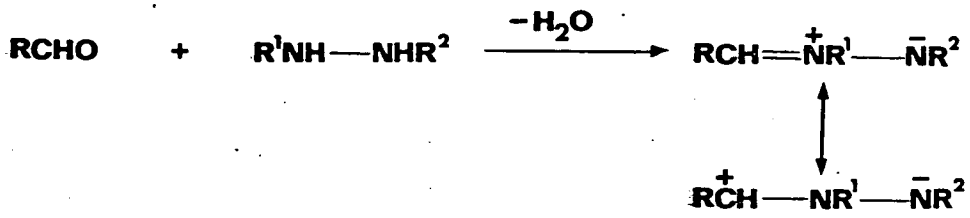
DISCUSSION

DISCUSSION

1. The reactions of aromatic aldehydes with 1,2-disubstituted hydrazines.

A. Introduction.

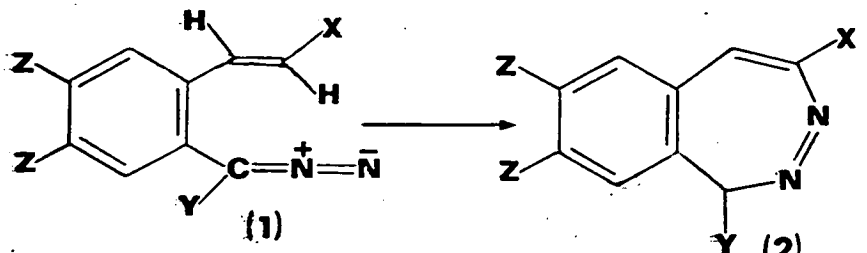
Huisgen[37,38] and Oppolzer[50] have both reported that the reaction of 1,2-disubstituted hydrazines and aldehydes gives azomethine imines, Scheme 1.



Scheme 1

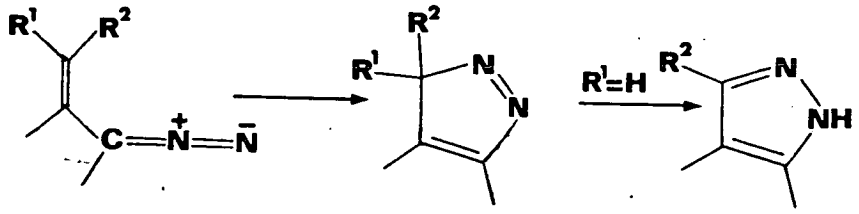
Azomethine imines are members of the 1,3-dipole class of compound. Discussions on 1,3-dipoles and azomethine imines are given in the Introduction in Sections C and J respectively.

Recently, another 1,3-dipole, i.e. the diazoalkane, has proved very useful in the synthesis of benzodiazepines. Sharp and his co-workers[126,127] have shown that electrocyclic ring closure of the α-aryldiazoalkanes (1) gives the 1H-2,3-benzodiazepines (2).



Z=H,OMe
X=H, Ph
Y=H,Me,Et,Ph

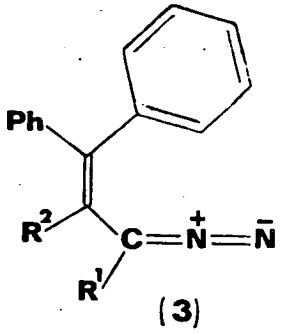
It is known that αβ-unsaturated diazoalkanes [156,157,158] react by two main pathways i) via loss of nitrogen to give carbene- or carbonium ion-derived products, depending on solvent protonicity and ii) with retention of nitrogen to give 1H- and 3H-pyrazoles, Scheme 2.



Scheme 2

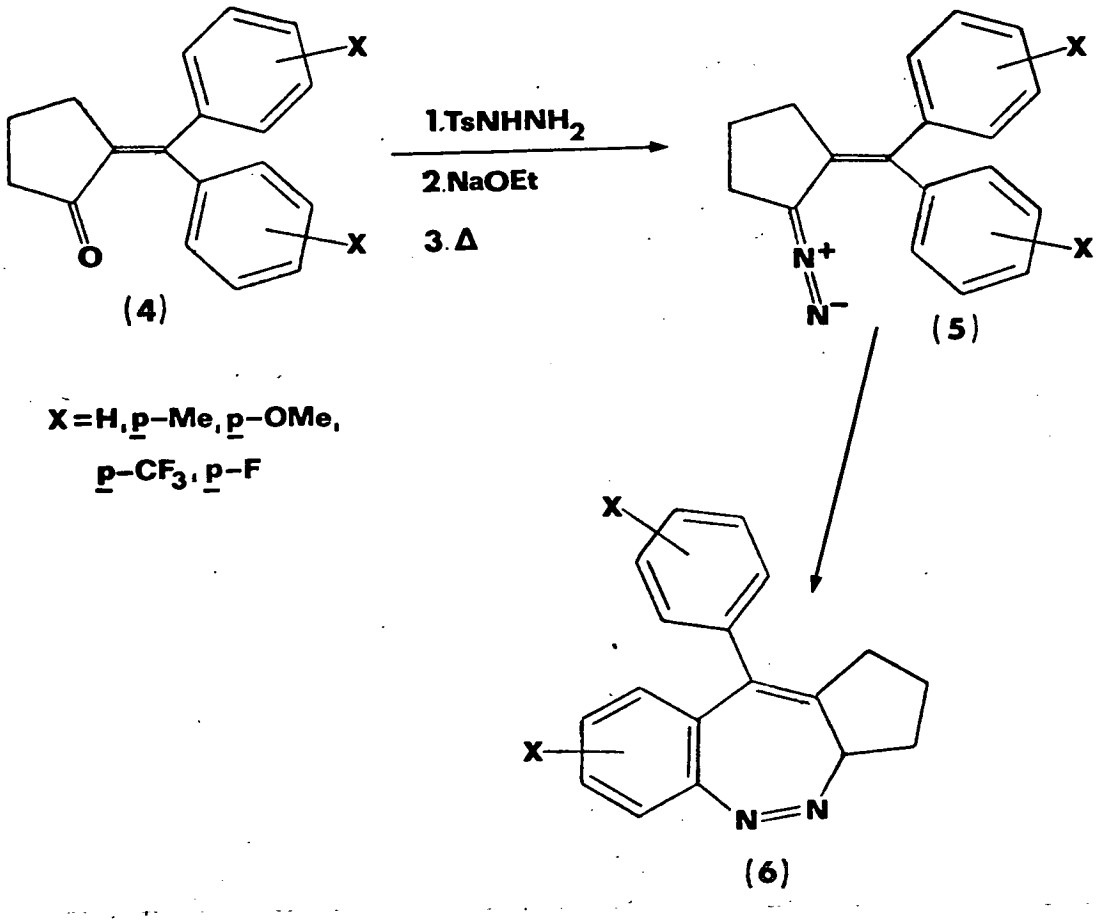
Examination of the mechanism of pyrazole formation has shown that it occurs via an intramolecular 1,3-dipolar cycloaddition[159].

In the reactions of diazoalkanes of the type with a γδ-double bond as part of an aromatic ring (3) it has been shown[158,160] that the mode of cyclisation is greatly influenced by steric factors.

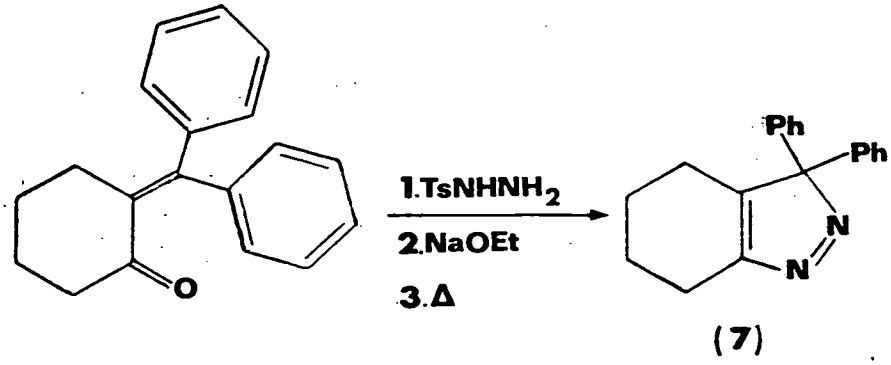


(3)

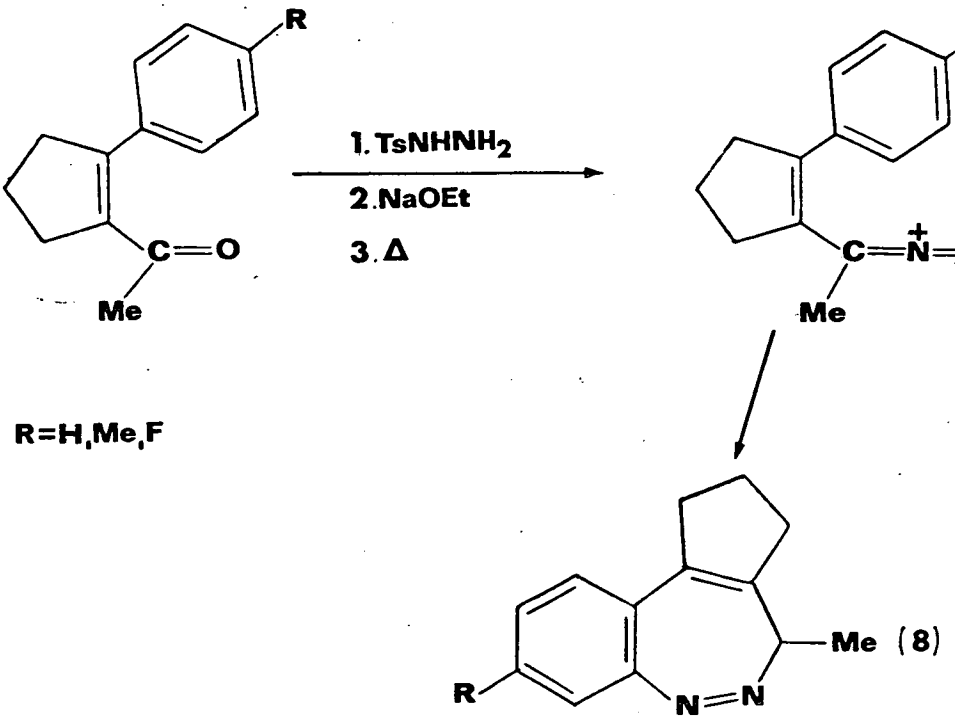
The diazoalkanes(5) produced from α-diarylmethylene cyclopentanones (4) and p-tosylhydrazine cyclise via a 1,7-electrocyclic ring closure to the 3H-1,2-benzodiazepines (6)[158,160].



When the cyclohexanone analogue of (4) is used, pyrazoles (7) are formed instead.



In a similar reaction to that of the α-diarylmethylene cyclopentanones (4) the 3H-1,2-benzodiazepines (8) have been prepared[161].



In all these cases the diazoalkane was produced from the reaction of a carbonyl group with p-tosylhydrazine and the resulting tosylhydrazone converted to its sodium salt which was then decomposed in boiling cyclohexane or dimethoxyethane.

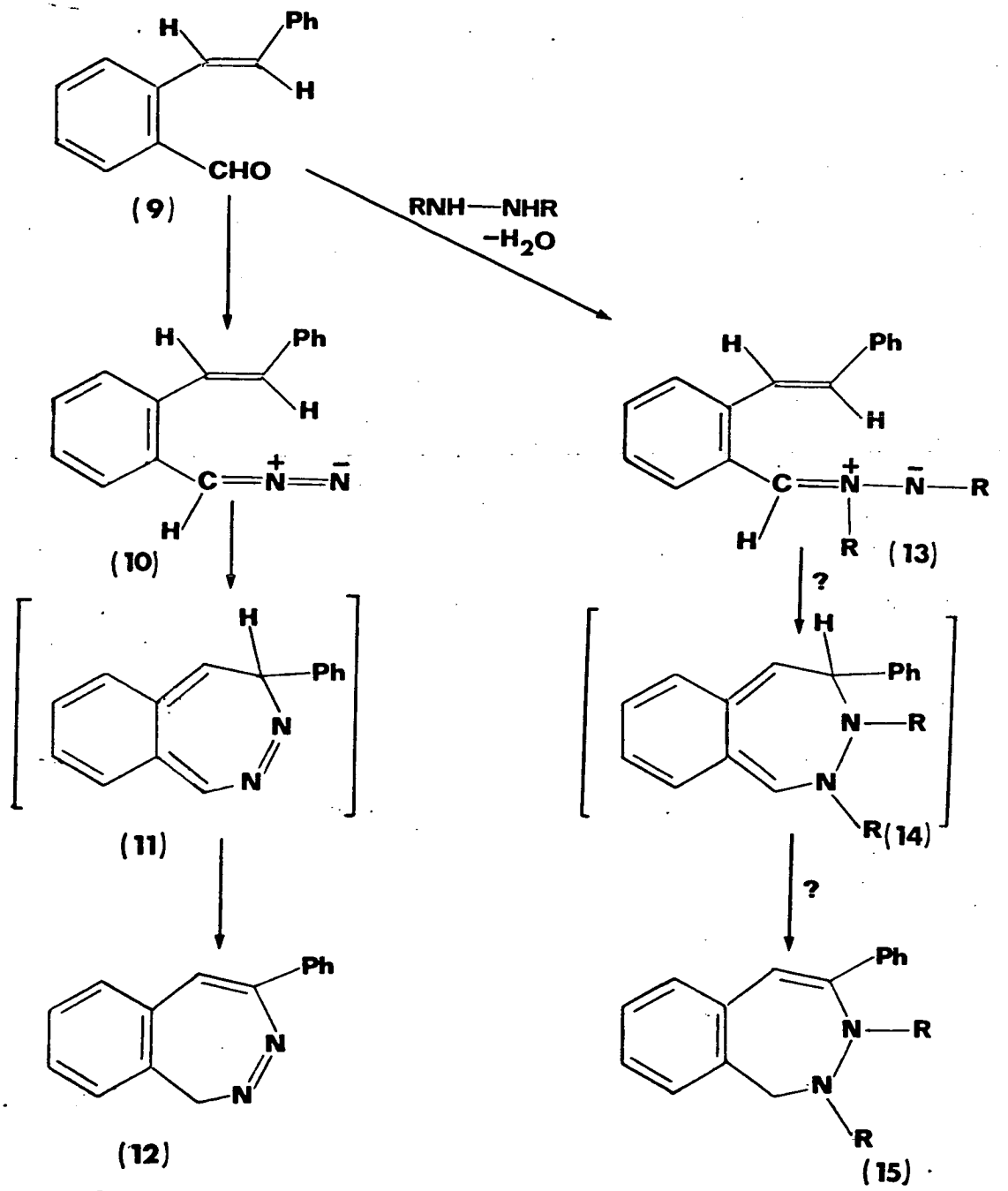
The two 1,3-dipoles i.e. diazoalkanes and azomethine imines are similar, differing in the extra double bond of the diazoalkane and the N-substitution of the azomethine imine, Scheme 3.

Diazoalkane **Azomethine imine**

Scheme 3

Thus replacing the diazoalkane with an azomethine imine could possibly lead to N-substituted benzodiazepines via a similar electrocyclic ring closure to that of the diazoalkanes. However this extension

is limited by the availability of the azomethine imines, the formation of which proceeds in the reaction of aldehydes but not of ketones with 1,2-disubstituted hydrazines. Of the electrocyclic ring closures to benzodiazepines reported, the cyclisation of α-aryldiazoalkanes offers an extension into the azomethine imine system via trans-2-formylstilbene (9).



The diazoalkane (10) is generated in the normal manner from trans-2-formylstilbene (9) and p-tosylhydrazine and the azomethine imine (13) should similarly be capable of generation from trans-2-formylstilbene (9) by reaction with a 1,2-disubstituted hydrazine. As can be seen the two 1,3-dipoles can take up similar orientations, so a similar cyclisation reaction might be expected. The diazoalkane (10) cyclises to the 4H-2,3-benzodiazepine (11), proceeding to the 1H-2,3-benzodiazepine (12) via a symmetry-allowed [1,5] sigmatropic hydrogen shift and it was hoped that the reaction of the azomethine imine would proceed in a similar manner. Thus the 4H-2,3-benzodiazepine (14) would be formed via an electrocyclic ring closure which then by a hydrogen shift would give the 1H-2,3-disubstituted 2,3-benzodiazepine (15).

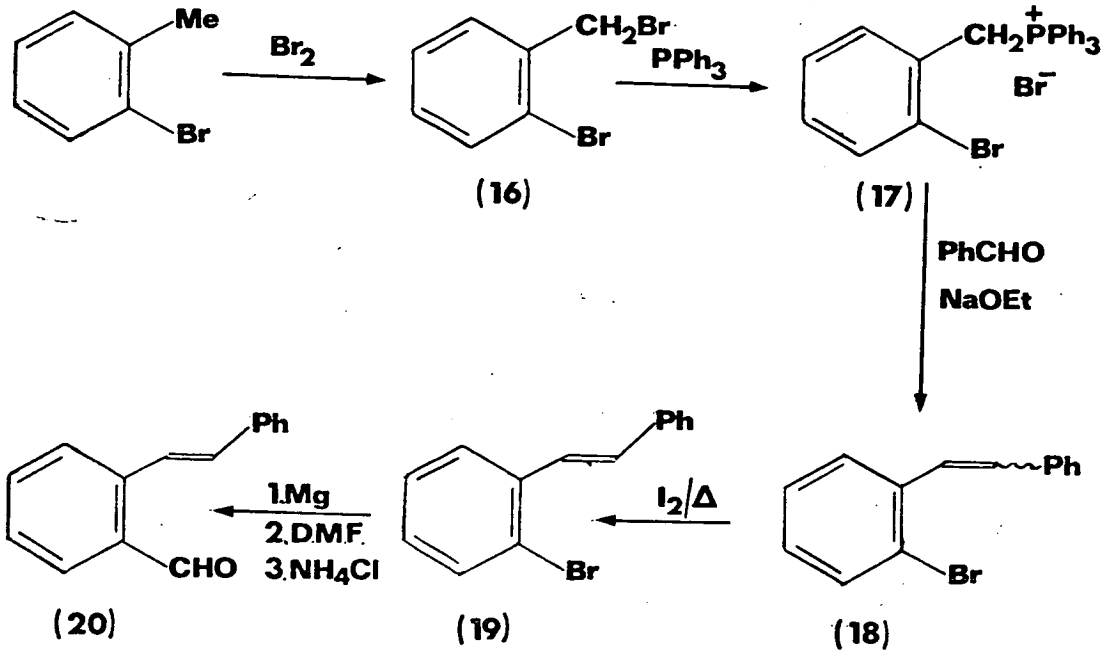
Thus this section of work was an attempt to extend the synthesis of 2,3-benzodiazepines (12) from diazoalkanes (10) into the related azomethine imine system (13).

B. The reaction of aromatic aldehydes with 1,2-dibenzylhydrazine.

1) Synthesis of starting materials.

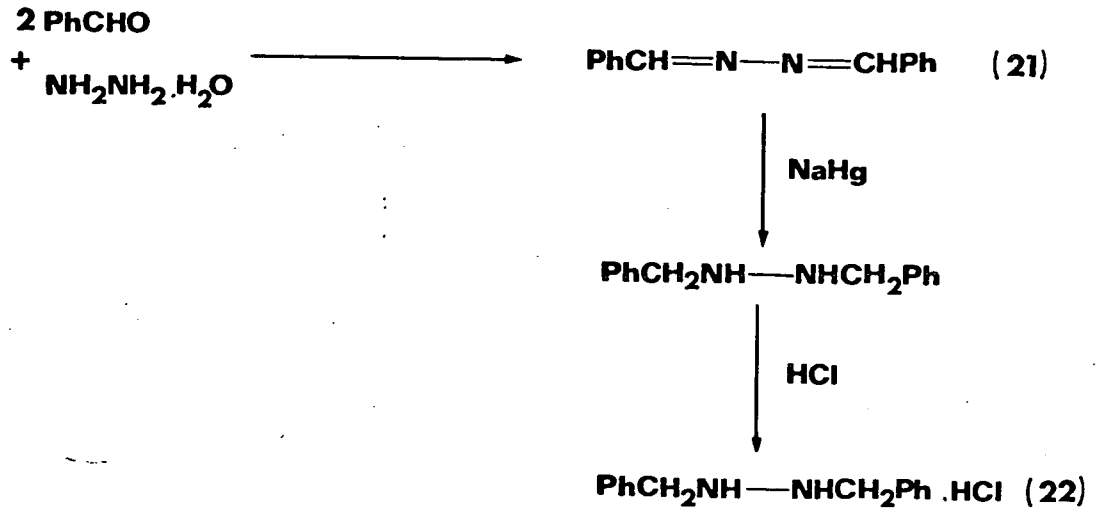
The synthesis of trans-2-formylstilbene is illustrated in Scheme 4. 2-Bromobenzyl bromide (16) was prepared by the method of Shoesmith and Slater[162] from the bromination of 2-bromotoluene. The triphenylphosphonium salt (17), prepared by reaction of (16) with triphenylphosphine, was reacted with benzaldehyde in the presence of sodium ethoxide to give a cis/trans-mixture of 2-bromostilbene (18). This was converted to the pure trans-form (19) by heating under reflux in nitrobenzene with iodine as a catalyst[163]. A Grignard reagent was prepared from trans-2-bromostilbene and reaction with dimethylform-

amide (D.M.F.) and subsequent hydrolysis gave trans-2-formylstilbene (20).



Scheme 4

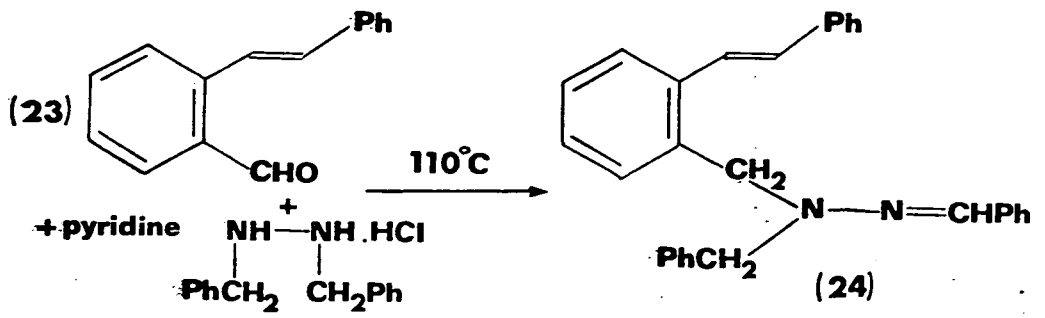
1,2-Dibenzylhydrazine hydrochloride (22) was prepared by the method of Curtius[164]. Benzalazine (21), prepared from benzaldehyde and hydrazine hydrate[165], was reduced with sodium amalgam to 1,2-dibenzylhydrazine which is very air sensitive and therefore was converted to its hydrochloride salt (22). It was convenient to use this hydrochloride salt as an in situ source of the free base, thus the majority of the reactions were carried out with the hydrochloride salt, another base e.g. pyridine or sodium carbonate and the respective aldehyde.



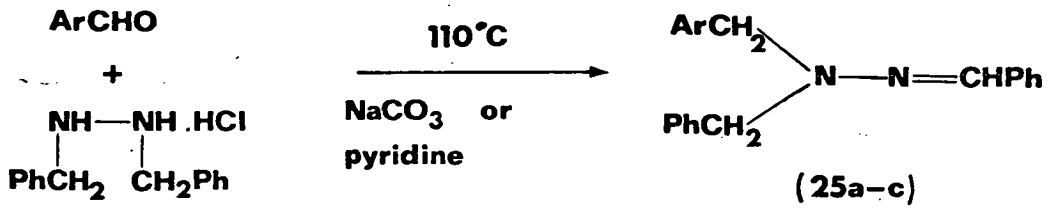
2) Reactions of aromatic aldehydes with 1,2-dibenzylhydrazine.

No reaction could be detected (by T.l.c.) when trans-2-formyl-stilbene and 1,2-dibenzylhydrazine hydrochloride (with pyridine as the supplementary base) were stirred together at the temperatures (~60°C) that Huisgen[36,37] quotes for the formation of azomethine imines from aromatic aldehydes and 1,2-dialkylhydrazines.

However under the reaction conditions used by Oppolzer[150,151,152] i.e. refluxing toluene, the trans-2-formylstilbene (23) was consumed in 2h. After work up the product obtained in 73% yield was benzaldehyde benzyl(2-styrylbenzyl)hydrazone (24).



Since this was an entirely unexpected product the reactions of several other aromatic aldehydes and 1,2-dibenzylhydrazine hydrochloride were then examined. All gave analogous products (25 a-c) in high yields. The use of sodium carbonate as the supplementary base proved as effective as pyridine.



(25a-c)

Ar = a:Ph, b:p-Cl-Ph, c:p-OMe-Ph

The structure of the hydrazone (25a) was confirmed by comparison of its spectral data with that of an authentic sample prepared from 1,1-dibenzylhydrazine and benzaldehyde[166,167]. The structures of the other hydrazones (24, 25b,c) were confirmed from their spectra by analogy.

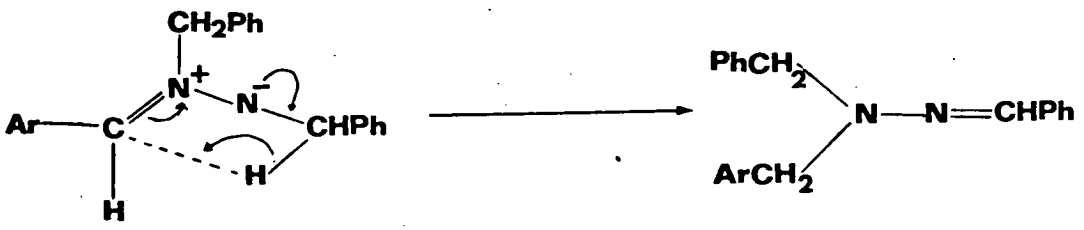
The ^{1}H n.m.r. spectra of (24) and (25b) showed two absorptions each for the differing benzyl groups and the mass spectra of (24, 25b,c) showed losses of the respective substituted benzyl groups as well as loss of the benzyl group.

The above reactions were performed with 1,2-dibenzylhydrazine hydrochloride in 50% excess over the aldehyde. An equimolar reaction of 1,2-dibenzylhydrazine hydrochloride, benzaldehyde and sodium carbonate gave the same hydrazone (25a) in 64% yield (compared to the 77% yield obtained when the hydrazine was in 50% excess). The hydrazone (25a) was again obtained in a reaction between 1,2-dibenzylhydrazine hydrochloride and benzaldehyde in the absence of a supplementary base,

the yield being lower (50%).

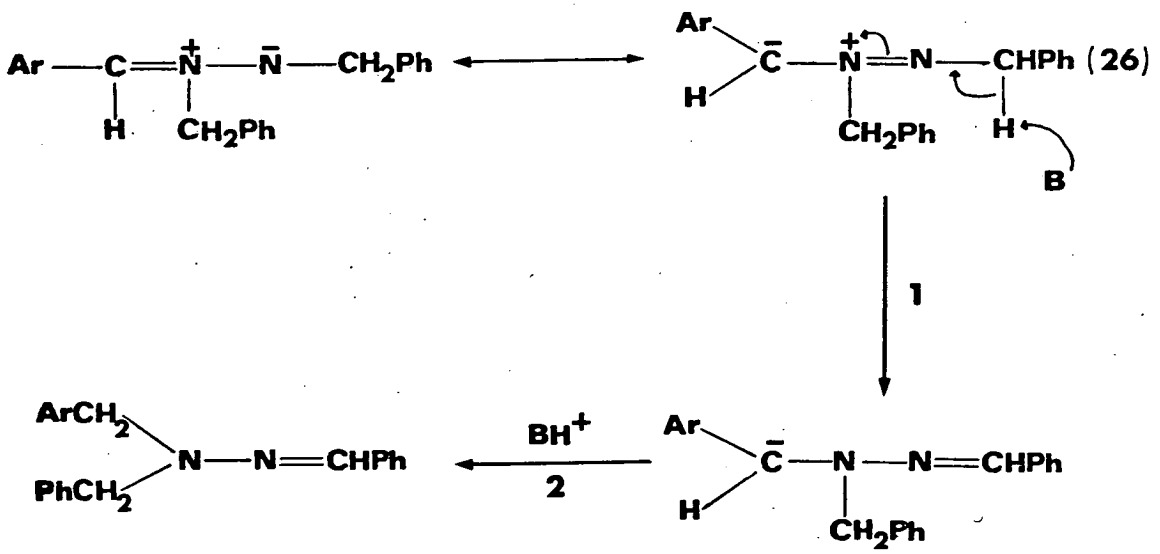
This formation of the hydrazones (24, 25a-c) would be an unprecedented reaction for azomethine imines. There are two plausible mechanisms involving an azomethine imine to yield the hydrazones (24, 25a-c).

The first involves a symmetry allowed 1,4-sigmatropic hydrogen shift, Scheme 5,



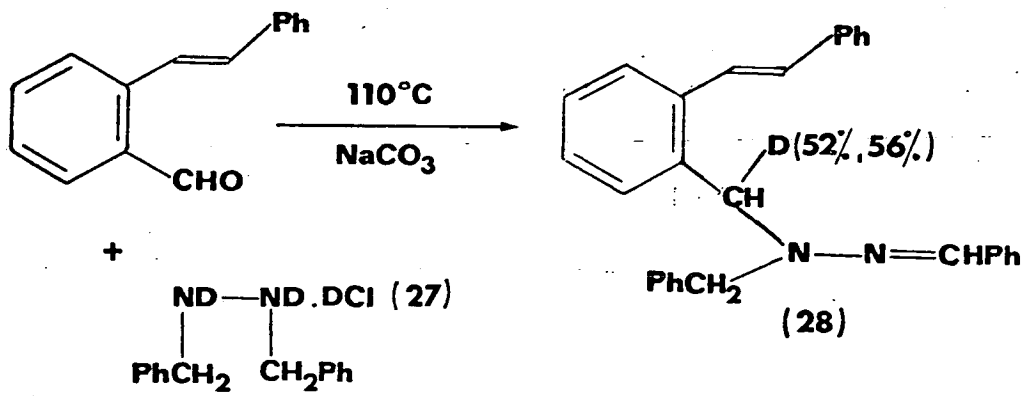
Scheme 5

and the second involves a base-catalysed deprotonation/protonation sequence, Scheme 6, <u>via</u> one of the resonance forms of the azomethine imine (26).



Scheme 6

In Scheme 6, the base B, could be the excess 1,2-dibenzylhydrazine, thus the lower yield in the equimolar reaction to give (25a). In the reaction of (23) with 1,2-dibenzylhydrazine hydrochloride these processes for the azomethine imine, Schemes 5 and 6 could be faster than the hoped-for cyclisation to give the benzodiazepine (15). In an attempt to distinguish between the two mechanisms, Schemes 5 and 6, a deuterium labelling experiment was carried out. 1,2-Dibenzylhydrazine hydrochloride (27) (deuterated on the nitrogen atoms) was reacted under the best-yielding conditions with trans-2-formylstilbene. The hydrazone (28) was obtained and was found to be deuterated on the 2-styrylbenzyl group.



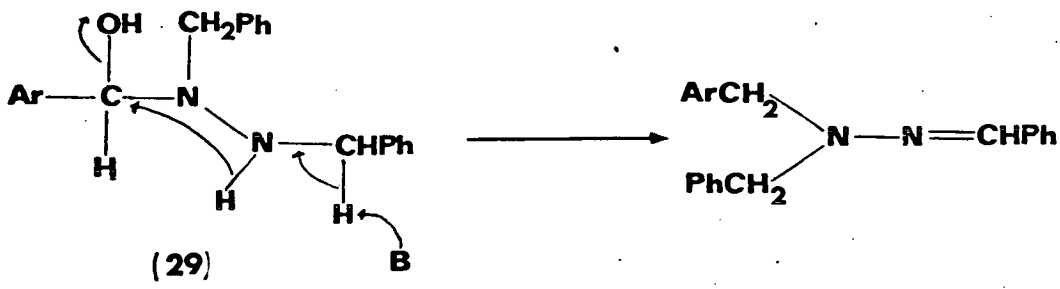
D_3=72%
D_2=18%
D_1=10%

Control reactions showed that there was no deuterium incorporation under the reaction conditions into the non-deuterated hydrazone (24) and that there was no deuterium loss in the deuterated hydrazone (28) on recrystallisation. The deuteration results exclude the symmetry

allowed 1,4-sigmatropic shift, Scheme 5, no deuterium incorporation being possible.

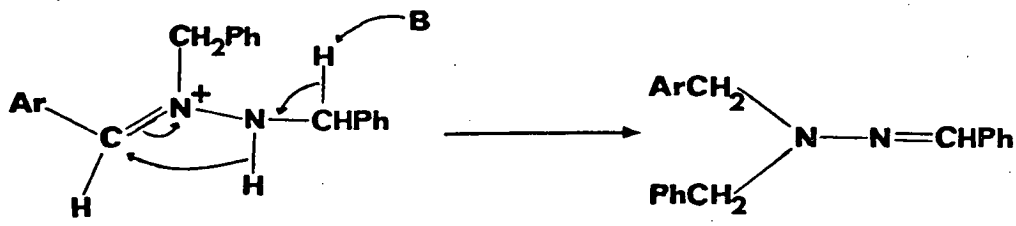
However, the base catalysed deprotonation/protonation reaction, Scheme 6, remains possible but step (1) is not reversible as there is no deuterium incorporation into the final hydrazone 'imine' proton.

It is also possible that an azomethine imine is not involved at all in the formation of the hydrazones (24, 25a-c). Two possible alternative mechanisms are 1) an intramolecular hydride transfer in the α-hydrazinocarbinol (29) (formed prior to the azomethine imine)



(29)

and 2) a hydride transfer in the hydrazonium ion (30) (formed by loss of an OH^- group from the α-hydrazinocarbinol(29)).



(30)

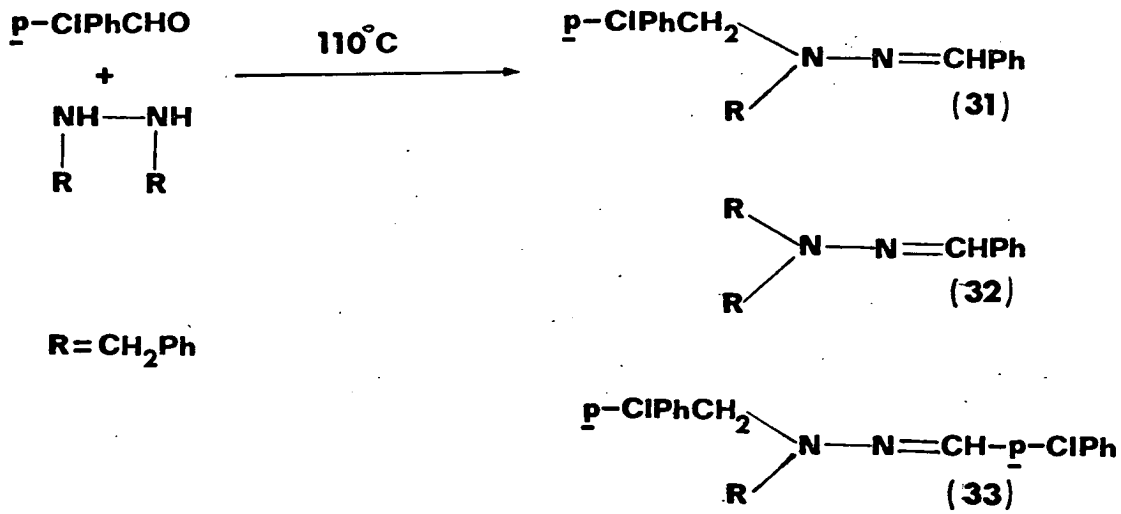
Both of these mechanisms are consistent with the results of the deuterium labelling experiment.

If an azomethine imine is involved then clearly the hydrazone forming pathway, Scheme 6, is preferred to the projected intramolecular cyclisation of the azomethine imine to the stilbyl group, i.e. (13) → (14).

However it was thought that it might be possible to intercept the azomethine imine with a reactive dipolarophile i.e. dimethyl fumarate. In a reaction of benzaldehyde, 1,2-dibenzylhydrazine hydrochloride, sodium carbonate and dimethyl fumarate under the standard reaction conditions the yield of benzaldehyde dibenzylhydrazone (25a) was not reduced and no adduct was detected. This implies that there is either a fast rearrangement of the azomethine imine or that it is never present at all.

In a reaction to clarify whether the use of the 1,2-dibenzylhydrazine as its hydrochloride salt had any effect on the reaction, the free 1,2-dibenzylhydrazine was reacted under the same conditions as before with p-chlorobenzaldehyde in the absence of a supplementary base. The main product obtained was the hydrazone (25b).

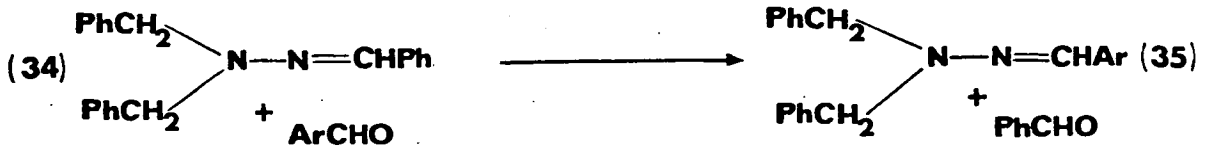
However, benzaldehyde dibenzylhydrazone (32) and p-chlorobenzaldehyde benzyl(p-chlorobenzyl)hydrazone (33) were obtained as minor products in the formation of the hydrazone (31).



After chromatography of the crude reaction product a mixture of the hydrazones (31-33) was still obtained. The percentages of the products (31-33) were calculated by H.P.L.C. (assuming equal U.V.

absorptions of the three hydrazones). The expected hydrazone (87%)(31) had a retention time of 8.5 min. which corresponded to a pure sample of the hydrazone (31). There were two other sample peaks, one (8%) with a retention time of 11 min corresponded to a pure sample of benzaldehyde dibenzylhydrazone (32), the other (5%) with a retention time of 5 min was probably p-chlorobenzaldehyde benzyl(p-chlorobenzyl)-hydrazone (33). These structural assignments are supported by the mass spectrum of the mixture. This showed the parent ion m/e 334/336 for the hydrazone (31) but also had peaks not present in the mass spectrum of the pure hydrazone, i.e. m/e 300 which corresponded to benzaldehyde dibenzylhydrazone (32)(parent ion m/e 300) and m/e 368/370/372 (characteristic of a molecule containing two chlorine atoms) which was probably the hydrazone (33)(parent ion m/e 368/370/372). The ^{1}H n.m.r. spectrum of the mixture has a small extra absorption at 4.50δ corresponding to the benzyl protons of (32), along with the absorptions of the benzyl protons of (31) at 4.41 and 4.45δ .

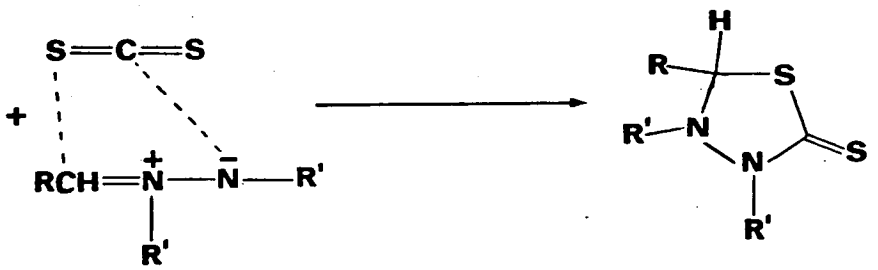
The generation of the minor products can be described in terms of aldehyde/hydrazone exchange reactions. In a control reaction where benzaldehyde dibenzylhydrazone (34) was boiled with an excess of p-chlorobenzaldehyde in toluene and after chromatography to recover the hydrazone (34) the mass spectrum showed a parent ion m/e 300 for the hydrazone (34) but also additional parent ion peaks m/e 334/336 due to p-chlorobenzaldehyde dibenzylhydrazone (35). This hydrazone (35) is derived by the exchange of p-chlorobenzaldehyde with the hydrazone (34) thus releasing benzaldehyde.



Ar=p-Cl-Ph

The hydrazone (33) is probably produced in a similar exchange reaction with the hydrazone (31) or unreacted p-chlorobenzaldehyde. The formation of the hydrazone (32) is less readily explainable, the exchange reaction occuring possibly with one of the reaction intermediates.

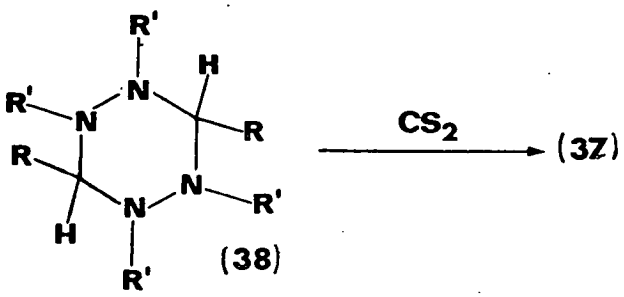
From Huisgen's early work[36,37,149] it appeared that the hydrazine/aldehyde route to azomethine imines was a general one, e.g. azomethine imines (36) formed from 1,2-dialkylhydrazines and aromatic aldehydes when reacted with carbon disulphide gave 1,3,4-thiazolidine-5-thiones (37).



(36) (37)

Huisgen[149] also described the synthesis of 1,3,4-thiazolidine-5-thiones (37) from hexahydrotetrazines (38) (which generate azomethine imines on heating) and carbon disulphide. However those hexahydro-

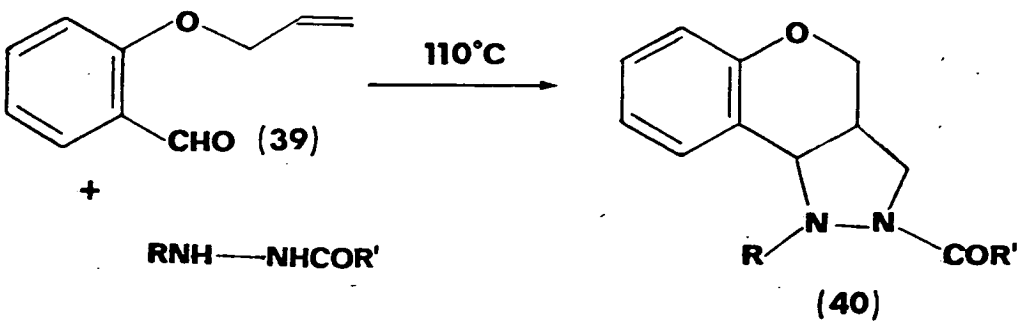
tetrazines used had only methyl or phenyl groups as substituents, no hexahydrotetrazines being obtained with benzyl substitution.



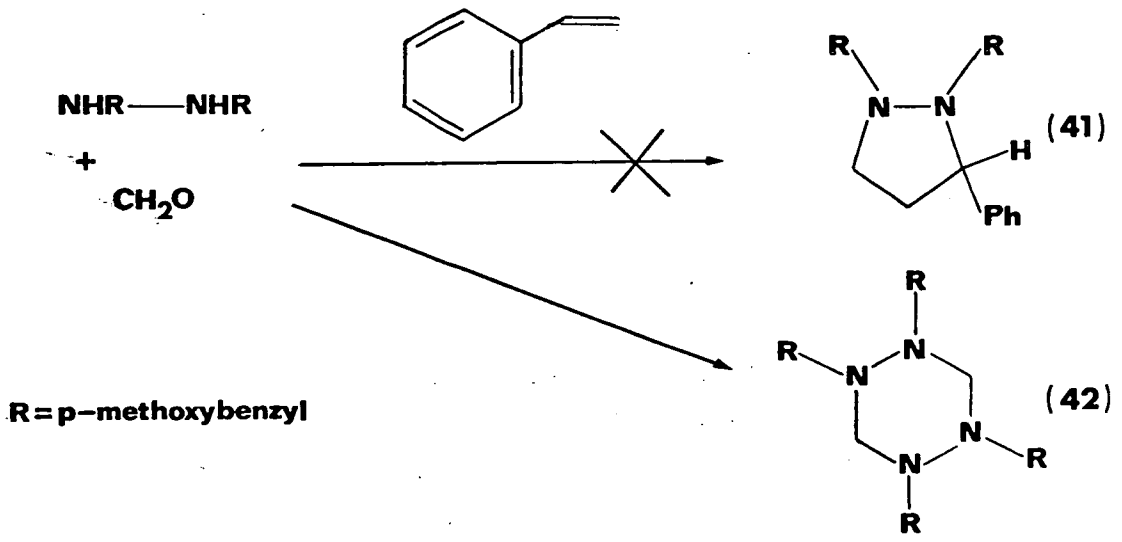
R=aryl R'=Me,Ph

The evidence from Huisgen's work for the existence of azomethine imines in reactions involving 1,2-dibenzylhydrazines and aldehydes is not conclusive. Recently there have been several other reports which throw some doubt on the generality of this reaction.

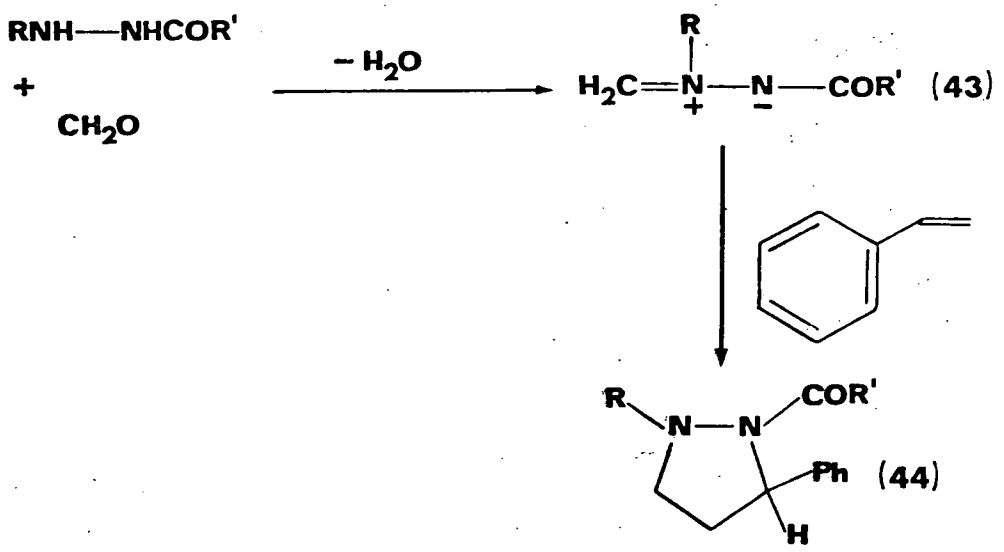
Oppolzer[50] found that although reaction of 1-acyl-2-alkylhydrazines with the olefinic aldehyde (39) gave the pyrazolidines (40), reaction of 1,2-di(p-methoxybenzyl)hydrazine did not produce an isolable pyrazolidine when reacted with the same olefinic aldehyde (39). No details on what was formed were given[50].



Oppolzer[50,150] also found that no pyrazolidine (41) was obtained in the reaction of 1,2-di(p-methoxybenzyl)hydrazine with paraformaldehyde in styrene, the hexahydrotetrazines (42) being the product instead.



This is not in agreement with the previous observation[150,152] that 1-acyl-2-alkylhydrazines when reacted with paraformaldehyde in styrene gave pyrazolidines (44) in high yields via the azomethine imines (43).



Oppolzer[50] states that his observations on the reactions of 1,2-di(p-methoxybenzyl)hydrazine and aldehydes are not in agreement with

Huisgen's postulate[36,37,149] that intermediate azomethine imines are formed in these reactions.

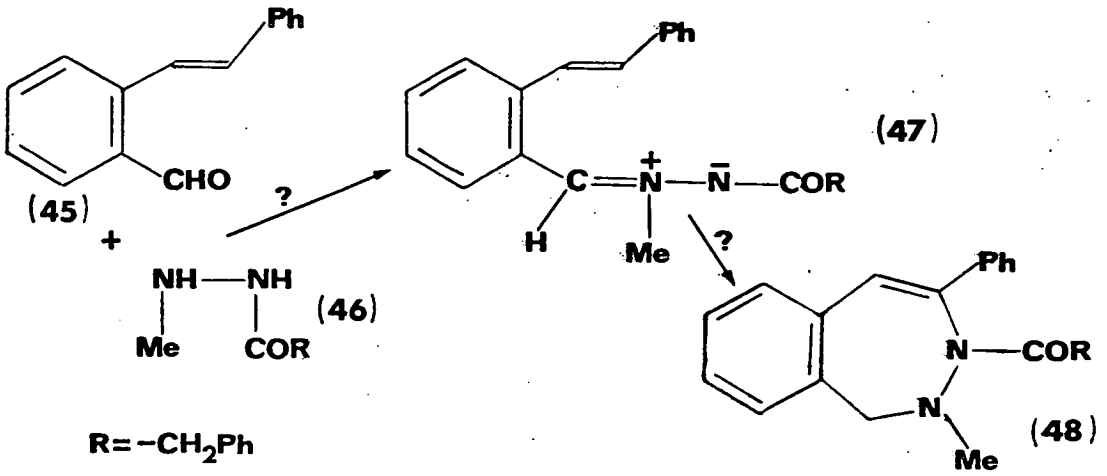
The hexahydrotetrazine (42) could be formed from two molecules of either the α-hydrazinocarbinol (29) or the hydrazonium ion (30) rather than from the dimerisation of the azomethine imine. But in this case there must be no equilibrium between the hexahydrotetrazine (42) and the azomethine imine or alternatively that styrene is not a reactive enough dipolarophile.

Therefore the case for the presence of azomethine imines in the reactions of 1,2-dibenzylhydrazines and aldehydes is not conclusive and if they are present they may undergo reactions other than 1,3-dipolar cycloadditions. Thus this uncertainty led into the investigation of the reaction of a 1-acyl-2-alkylhydrazine with trans-2-formylstilbene. The experimental evidence for the presence of azomethine imines from 1-acyl-2-alkylhydrazines and aldehydes is well documented by the work of Oppolzer[50,150,151,152].

C. The reaction of trans-2-formylstilbene and 1-methyl-2-phenylacetylhydrazine.

By analogy with the literature[49,50] trans-2-formylstilbene (45) and 1-methyl-2-phenylacetylhydrazine (46) should condense in refluxing toluene to give the azomethine imine (47) the aldehyde function reacting with the alkyl substituted nitrogen. It was thus possible that the desired 1H-2,3-benzodiazepine (48) would be formed. However when 1-methyl-2-phenylacetylhydrazine (46) (prepared from methylhydrazine and ethylphenylacetate[168]) was heated with trans-2-formylstilbene (45) in toluene under reflux no reaction could be detected by T.l.c. Only when the reaction temperature was raised to boiling

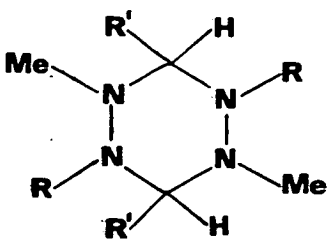
t-butylbenzene (180°C) did any reaction occur. Work-up of the reaction mixture gave a 20% yield of a white crystalline material which by T.l.c. appeared to be a single compound.



However the ^{1}H n.m.r. and ^{13}C n.m.r. spectra indicated the presence of several species. The ^{13}C n.m.r. spectrum has 30 absorptions, the 2,3-benzodiazepine (48) would have 20 absorptions. The ^{1}H n.m.r. spectrum is complicated having a larger number of absorptions than would be expected for a compound such as (48). The mass spectrum has a parent ion m/e 354 (74%) consistent with the loss of a water molecule from trans-2-formylstilbene and 1-methyl-2-phenylacetyl-hydrazine, and has a large number of high abundance fragments.

The spectral data is not consistent with the proposed structure (48) or with the possible alternative product i.e. the hexahydro-tetrazine (49). It is possible that the material obtained is polymeric or that it is a mixture of compounds which is not resolved by T.l.c.

R=-CH_2Ph
R'= 2-stilbyl



(49)

As the synthesis of 2,3-benzodiazepines from azomethine imines proved to be rather unsuccessful it was decided to move onto another reaction system i.e. the reaction of acetylenic aldehydes with N-substituted hydrazines.

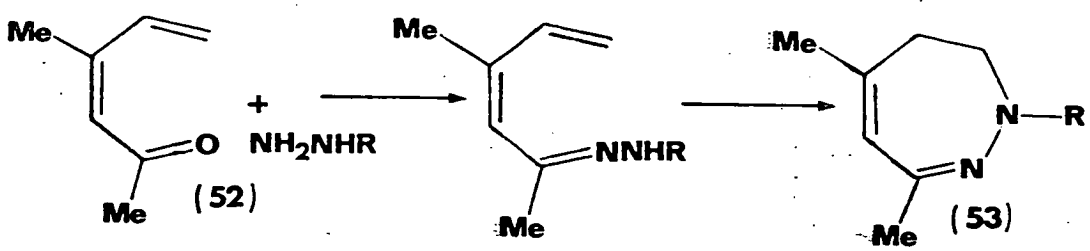
2. The reactions of acetylenic aldehydes and homopthalaldehyde with hydrazines.

A. Introduction.

Many different 1,2-disubstituted benzene molecules have been used as the starting point in the synthesis of fused heterocyclic systems. The range of substituents and reactions to give the heterocyclic systems is very varied. The basic concept is to have a molecule (50) with substituents A and B which will interact with another molecule i.e. X-Y in some way to give the fused system (51).

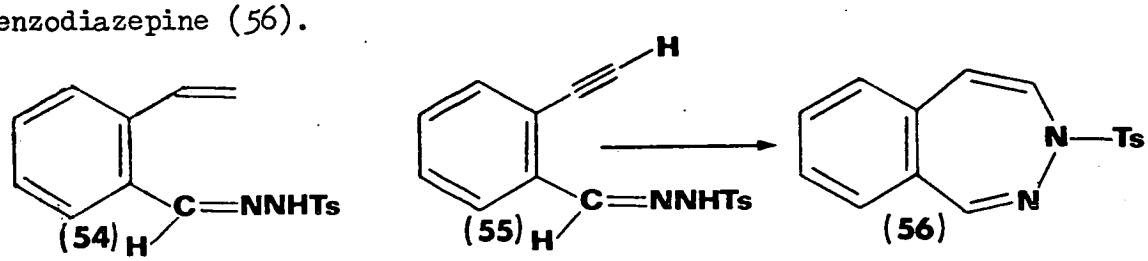
(50) (51)

It has been shown [172,173], see Section 3, that αβ,γδ-unsaturated ketones, e.g. (52) when reacted with N-substituted hydrazines give the N-substituted 1,2-diazepines (53).

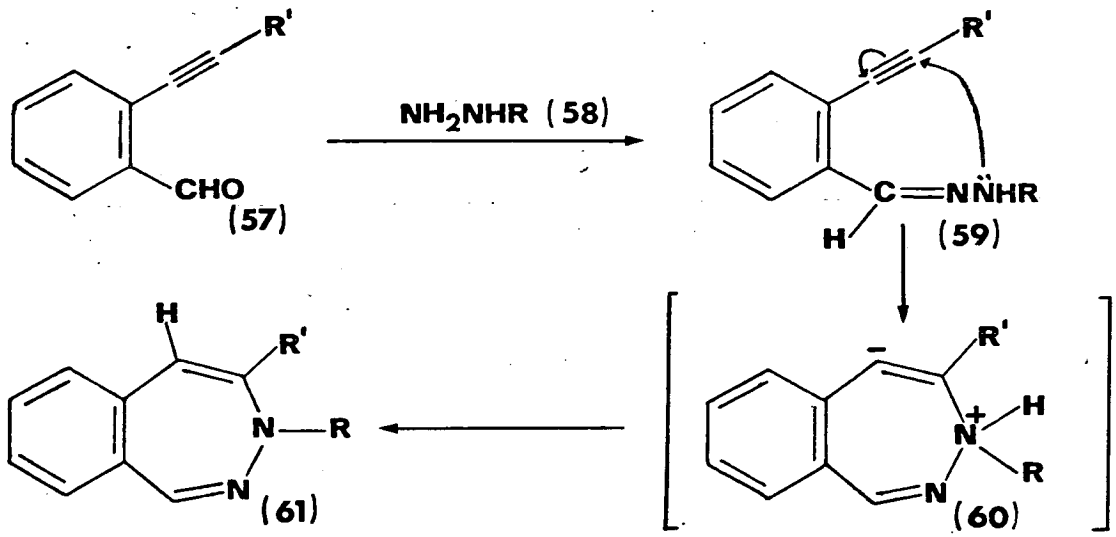


This shows that N-substituted hydrazones can in suitable molecules undergo intramolecular cyclisation to give N-substituted heterocycles. No cyclisation is obtained with 2-formylstyrene tosylhydrazone (54), however if the styrene double bond was made more reactive to nucleophilic attack e.g. 2-ethynylbenzaldehyde tosylhydrazone (55), the 3H-2,3-benzodiazepine might be obtained via an intramolecular cyclisation.

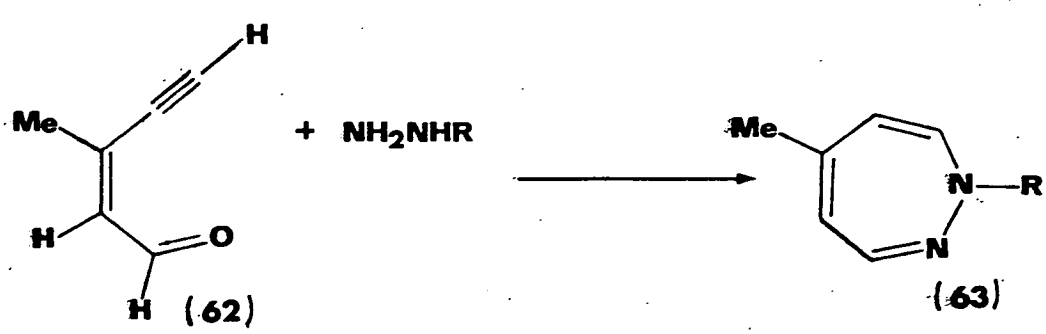
This is a potentially interesting reaction because if it were successful it would provide a route to the as yet unknown 3H-2,3-benzodiazepine (56).

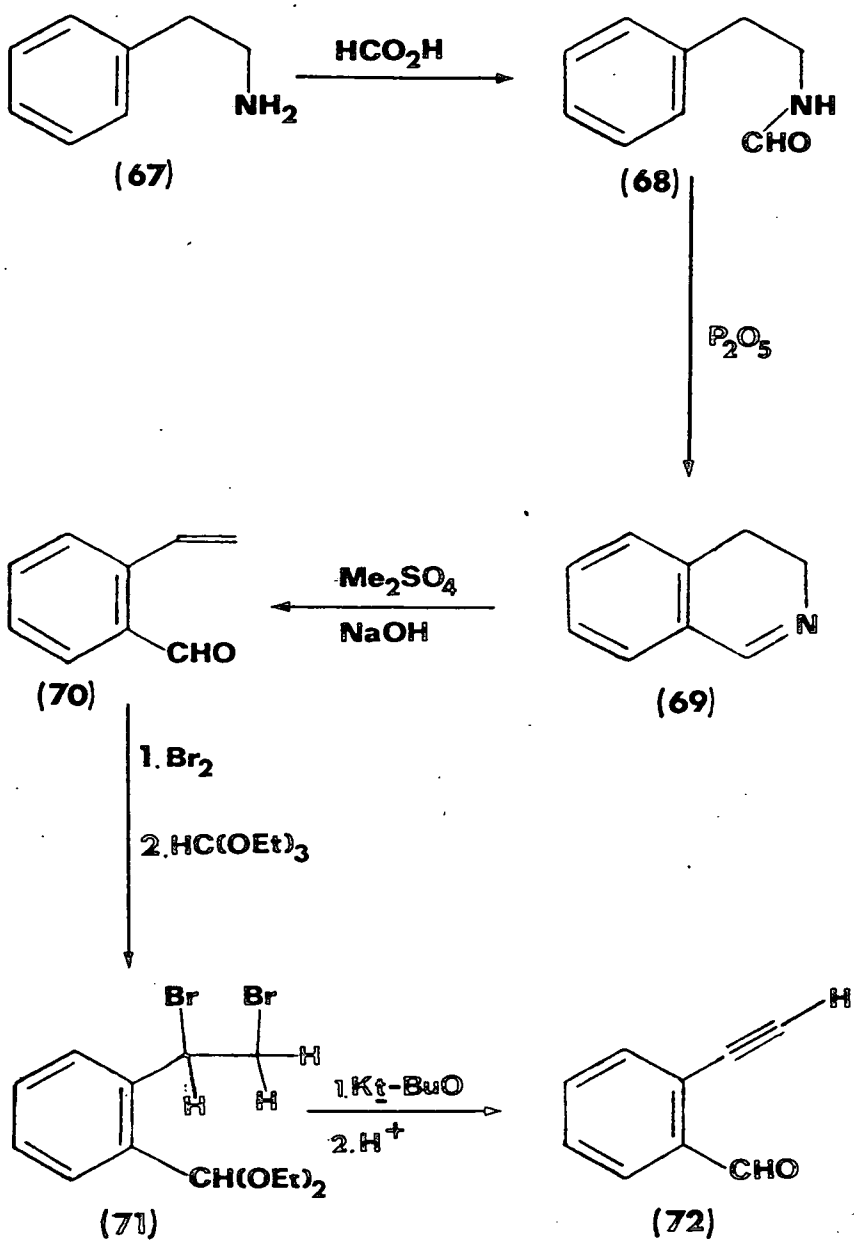


With 2-ethynylbenzaldehyde (57), R' = H, it was hoped that the N-substituted hydrazines (58) would first react to form the hydrazones (59), the free nitrogen of which could attack the triple bond by nucleophilic addition to give the intermediates (60) which by proton transfer from nitrogen would give the desired 3H-2,3-benzodiazepines (61).

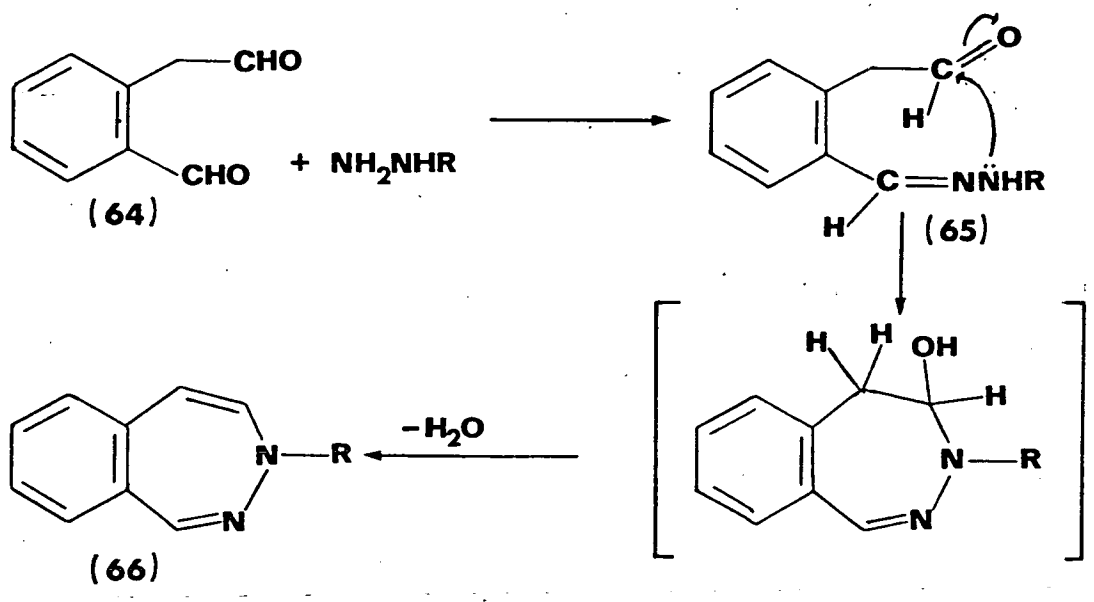


In a similar vein it was hoped that the non-benzenoid acetylenic aldehyde (62) when reacted with N-substituted hydrazines would give the known 1H-1,2-diazepines (63).




HCO2H
NH2
NH
CHO
(67)
(68)
P2O5
Me2SO4
NaOH
CHO
N
(70)
(69)
1. Br2
2. HC(OEt)3
Br
Br
H
H
H
1. Kt-BuO
2. H+
CH(OEt)2
H
CHO
(71)
(72)

Another precursor which appeared to offer a route to the same 3H-2,3-benzodiazepines (61) was homophthalaldehyde (64). It was hoped that reaction with N-substituted hydrazines would give the hydrazone (65) which by a further condensation would then give the 3H-2,3-benzodiazepine (66).



Thus it was decided to investigate the potential of both acetylenic aldehydes and homophthalaldehyde for the synthesis of 2.3-benzodiazepines and 1,2-diazepines.

B. The reaction of 2-ethynylbenzaldehyde with hydrazines.

1) Synthesis of starting materials.

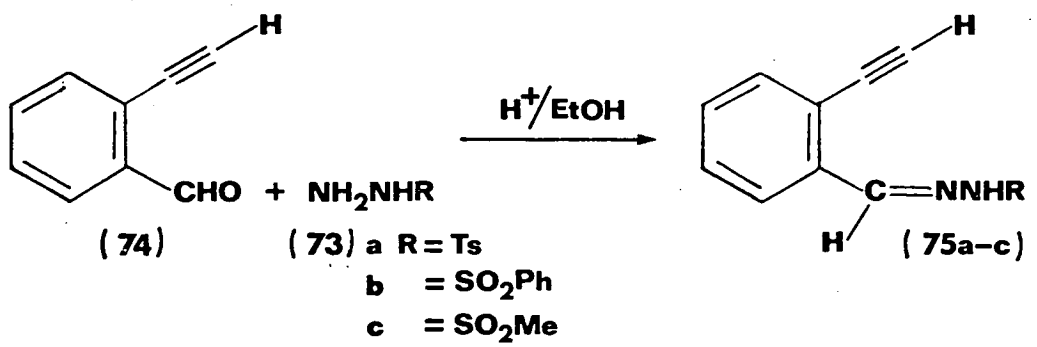
2-Ethynylbenzaldehyde (72) was prepared by an adaptation of the method of Ojima et al[174] from 2-formylstyrene (70). 2-Formylstyrene (70) was prepared in the following manner, N-β-phenylethylformamide (68)[175] was synthesised by the reaction of 2-phenylethylamine (67) with formic acid, and was cyclised in a Bischler and Napieralski reaction with polyphosphoric acid to give the 3,4-dihydroisoquinoline (69)[176].

2-Formylstyrene (70) was prepared from the 3,4-dihydroisoquinoline (69) by treatment with dimethyl sulphate and sodium hydroxide[176]. The 2-formylstyrene (70) was brominated, and the crude dibromide treated with triethyl orthoformate in benzene with a little p-toluene-sulphonic acid to give, the protected, 2-(1,2-dibromoethyl)benzaldehyde diethyl acetal (71). This compound was then dehydrobrominated with potassium t-butoxide and hydrolysed in 6M hydrochloric acid to give 2-ethynylbenzaldehyde (72) as white crystals after distillation.

p-Tosyl-, benzenesulphonyl- and methylsulphonylhydrazine were prepared by the reaction of hydrazine hydrate with the respective sulphonyl chloride[177,178,179]. Benzoylhydrazide[180] was prepared by the reaction of ethyl benzoate and hydrazine hydrate.

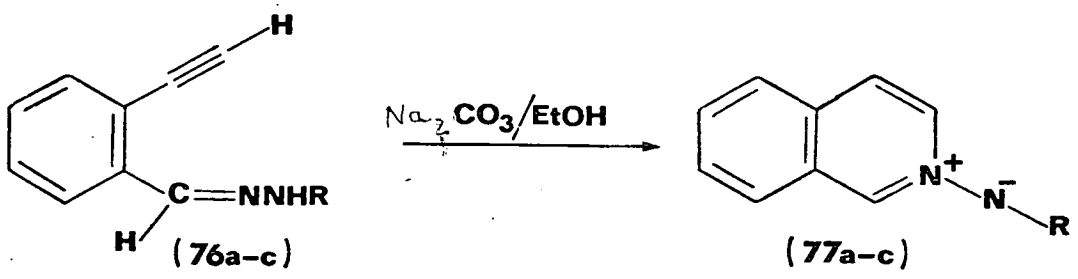
2) Reactions of 2-ethynylbenzaldehyde with hydrazines.

When p-tosyl-, benzenesulphonyl- and methanesulphonylhydrazine (73a-c) and 2-ethynylbenzaldehyde (74) were stirred in ethanol in the cold with a little acid, T.l.c. showed the consumption of the aldehyde (74) and the production of a new spot, in each case after about 1h. On evaporation of the solvent the hydrazones (75a-c) were obtained as yellow oils.



The hydrazones (75a-c), identified by the ^1H n.m.r. spectra of the crude materials, could not be isolated in their pure form, indeed they darkened considerably on handling.

In a similar reaction the same hydrazines (73a-c) were first reacted with 2-ethynylbenzaldehyde (74) in ethanol with a little acid to give the hydrazones (76a-c) and then were stirred with a large excess of sodium carbonate until T.l.c. showed the consumption of the hydrazones. After work-up the products obtained were the isoquinoline N-imines (77a-c) in 47%, 40% and 40% yields respectively.



(76a-c) (77a-c)

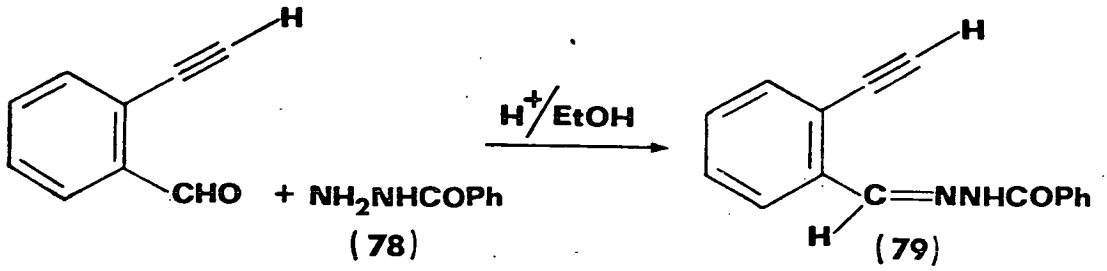
R = a=Ts, b=SO_2Ph, c=SO_2Me

A control reaction showed that the acetylenic hydrazones (76a-c) were not converted to the isoquinoline N-imines (77a-c) by stirring in ethanol alone.

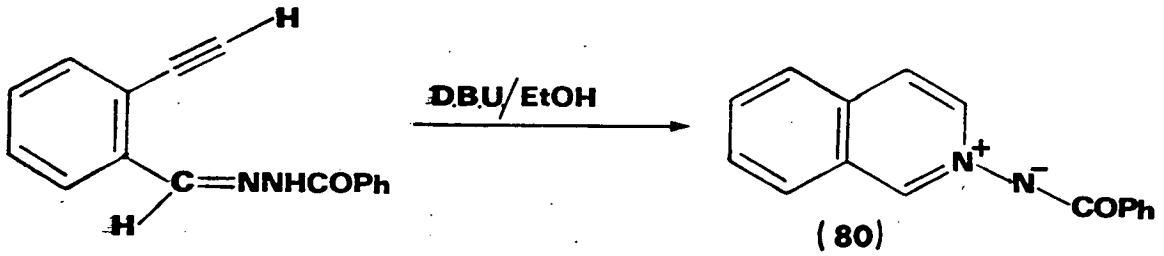
In a similar reaction the tosylhydrazone (76a) was first isolated by evaporation of the solvent and then ethanol and an excess of sodium carbonate were added and the reaction mixture stirred and after work up the isoquinoline N-tosylimine (77a) was again obtained (48% yield). The yields of the isoquinoline N-tosylimine (77a) from the hydrazone (76a), ethanol and sodium carbonate and from the in situ route, i.e. 2-ethynylbenzaldehyde, p-tosylhydrazine, ethanol and acid followed by treatment with sodium carbonate, were comparable. This shows that the intermediate involved in the cyclisation to the

isoquinoline N-imines (77a-c) is indeed the hydrazones (76a-c). The isoquinoline N-imines (77a-c) are stable, high melting crystalline solids whereas the hydrazones (76a-c) are unstable oils. The generality of this reaction was then explored using other N-substituted hydrazines.

In the reaction of benzoylhydrazide (78) with 2-ethynylbenzaldehyde in ethanol with a little acid the benzoylhydrazone (79) precipitated out of the reaction mixture within 30 min. This was filtered off and was recrystallised from ethanol (61% yield). The benzoylhydrazone (79), unlike the hydrazones (76a-c), is a stable white solid.



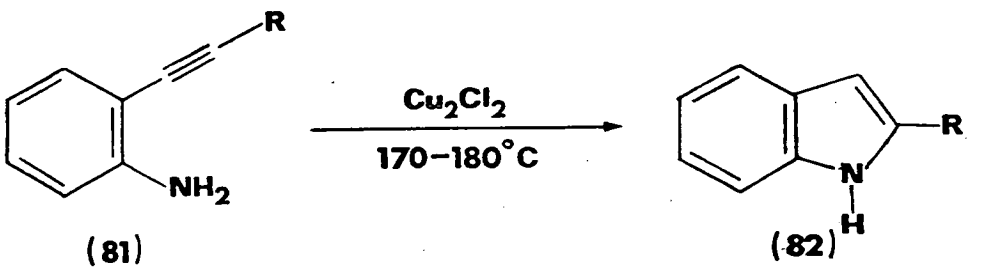
It was found however that the benzoylhydrazone (79) could not be converted to the isoquinoline N-benzoylimine by stirring it in ethanol with sodium carbonate; however the conversion was readily achieved by using a stronger base, e.g. when the benzoylhydrazone (79) was stirred in ethanol for three days with 1,5-diazabicyclo [5,4,0] - undec-5-ene (D.B.U.) the isoquinoline N-benzoylimine (80) was obtained in 77% yield.



In a similar reaction a slurry of the benzoylhydrazone (79) formed from 2-ethynylbenzaldehyde and benzoylhydrazide (78) with a little acid in ethanol was neutralised with sodium bicarbonate and was then converted to the isoquinoline N-benzoylimine (80) (50% yield) after stirring with D.B.U. From a control reaction it had previously been found that sodium bicarbonate did not induce the cyclisation of the benzoylhydrazone (79).

The tosylhydrazone (76a) could also be converted to the isoquinoline N-tosylimine (77a) by stirring in ethanol with D.B.U., the yield being slightly lower than in the cyclisation of (76a) with sodium carbonate.

Cuprous chloride has been used (see Section D of the Introduction) to facilitate ring closure of acetylenes e.g. the o-aminophenylacetylenes (81) were cyclised at 170-180°C to give the indoles (82)[32].

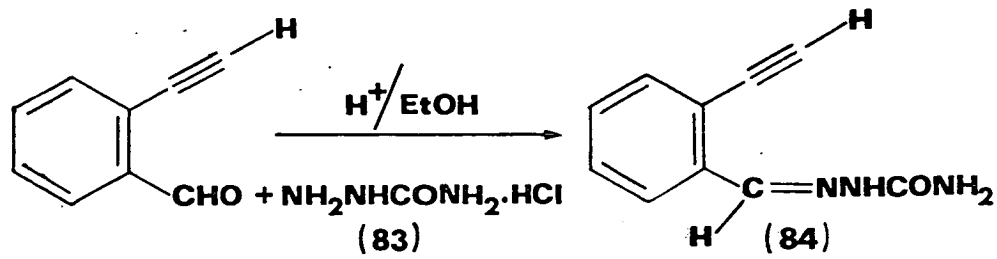


(81) (82)

When the benzoylhydrazone (79) was heated under reflux in ethanol with a catalytic amount of cuprous chloride it was converted to the isoquinoline N-benzoylimine (80) in 28% yield in 1h. The triple bond is activated towards nucleophilic attack presumably by complexation with the copper ion. A control reaction showed no cyclisation under similar conditions in the absence of cuprous chloride.

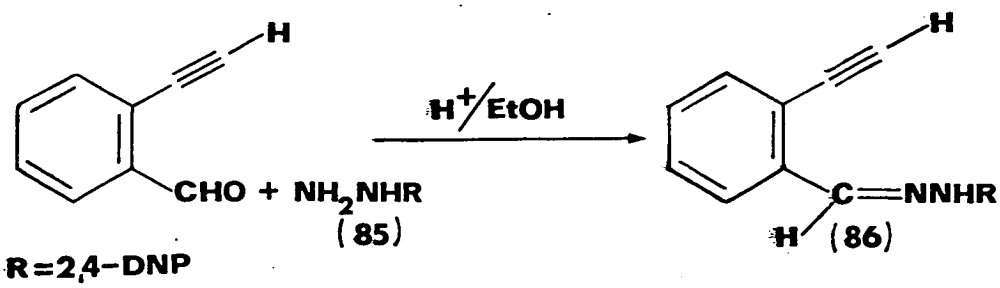
When semicarbazide hydrochloride (83) was stirred with 2-ethynylbenzaldehyde in ethanol with a little acid the semicarbazone (84)

precipitated out of the reaction mixture within 30min.



The semicarbazone (84) is a stable white crystalline solid with a fairly high melting point (188.5-190°C) and is obtained in good yield (67%). However when the semicarbazone (84) was stirred in ethanol with either sodium carbonate or D.B.U. only recovered starting material was obtained. When the semicarbazone (84) was treated with a stronger base, i.e. sodium ethoxide in ethanol, T.l.c. showed the consumption of the semicarbazone (84) but only polymeric material was obtained on work up. When the semicarbazone (84) was heated under reflux in ethanol with a catalytic amount of cuprous chloride T.l.c. showed the consumption of the semicarbazone (84) but no product spots could be detected. Chromatography of the reaction mixture did not yield any identifiable material.

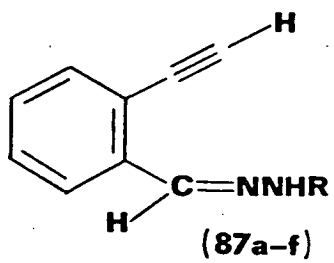
When 2,4-dinitrophenylhydrazine (85) and 2-ethynylbenzaldehyde were stirred in ethanol with a little acid the 2,4-dinitrophenylhydrazone (86) precipitated out of the reaction mixture. This was filtered off and recrystallised from ethanol in 77% yield, the 2,4-dinitrophenylhydrazone (86) was a stable, orange high melting solid.



The 2,4-dinitrophenylhydrazone (86) could not be cyclised with sodium carbonate or D.B.U., recovered starting material only being obtained. When the 2,4-dinitrophenylhydrazone (86) was heated under reflux in ethanol/sodium ethoxide T.l.c. showed the consumption of the hydrazone (86) but no products could be detected and work up only gave black polymeric material.

The spectral data of the acetylenic hydrazones (76a-c, 79, 84, 86) was consistant with the proposed structures. The structures of the isoquinoline N-imines (77a, 80) were confirmed by comparison of their spectral data to that reported[141]. The isoquinoline N-imines (77b,c) structures were confirmed by analogy.

If it is assumed that the base catalysed cyclisation of the hydrazones (87a-d) involves a primary deprotonation of nitrogen then the potential effectiveness of the cyclisation of (87a-f) can be related to the acidity of the N-H group.



(87a-f)

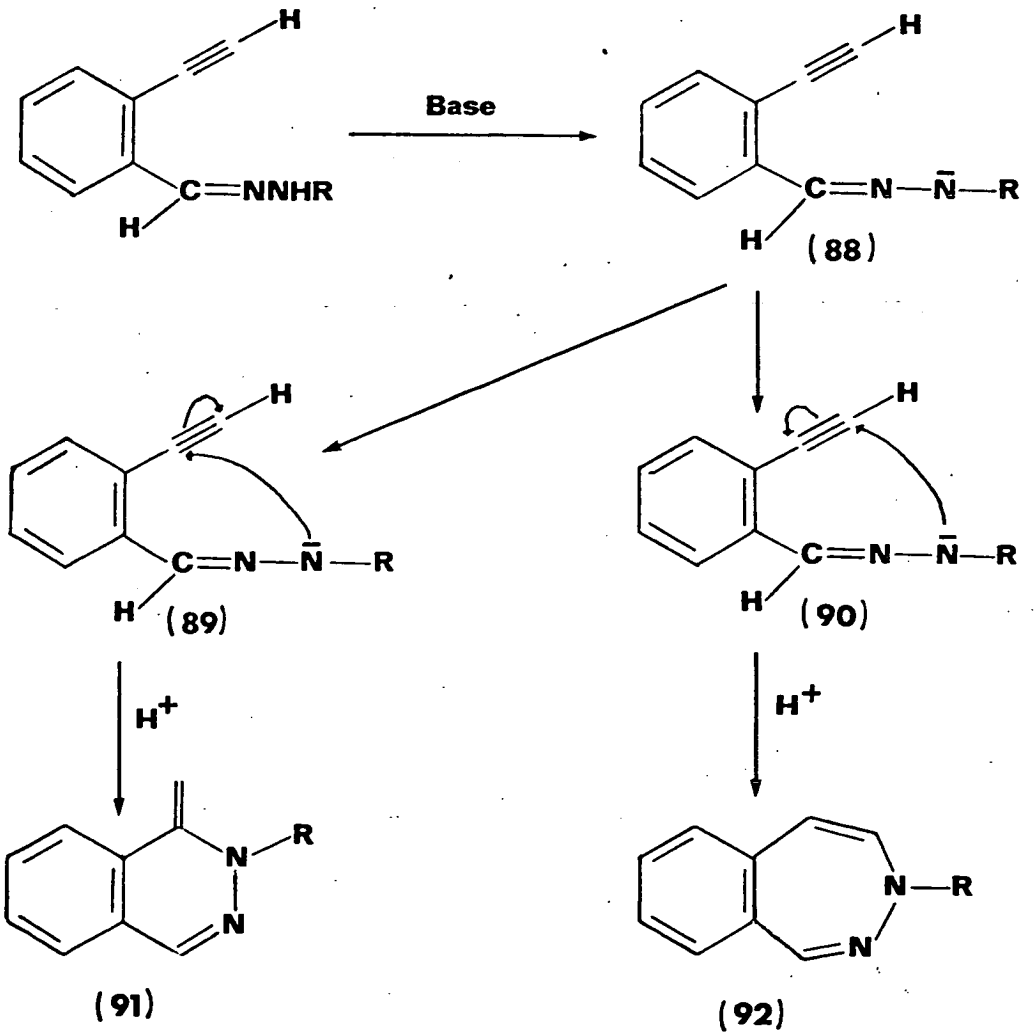
a. R = Ts
b = SO_2Ph
c = SO_2Me
d = COPh
e = $CONH_2$
f = 2,4-DNP

When R = $-SO_2-X$ (87a-c) the nitrogen atom is very acidic and deprotonation will be a facile process. When R = -COPh (87d) the nitrogen atom will be less acidic and thus a stronger base i.e. D.B.U. will be needed for the deprotonation; (87e) and (87f) will be even less activated toward this deprotonation. In the last two cases (87e,f) the cyclisations fail because they cannot be deprotonated by weak bases and stronger bases which can effect this deprotonation are more nucleophilic and therefore can attack the molecule at some other site,

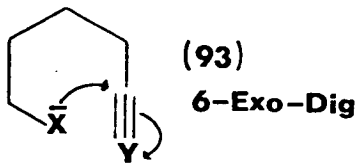
e.g. the triple bond, and will induce polymerisation.

In the base catalysed cyclisation of the hydrazones (87a-d) there are two possible modes of nucleophilic attack on the acetylene moiety, i.e. attack of the nitrogen at either end of the triple bond.

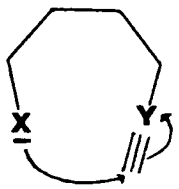
By abstraction of the proton on nitrogen the anion (88) is generated which could either attack the carbon adjacent to the phenyl group (89) or the terminal carbon (90). After proton transfer the products would be the phthalazine derivative (91) or the benzodiazepine (92) respectively.



The former process (89) can be likened to a 6-Exo-Dig process (93), the latter (90) to a 7-Endo-Dig process (94) in Baldwin's rules for ring closure[53] (see Section F of the Introduction). Neither of these processes is disfavoured; however digonal closures are generally of the Endo type[53]. This is in contrast to tetrahedral (Tet) and trigonal (Trig) ring closures which generally proceed by the Exo-modes[53]. This would support ring closure at the terminal carbon of the acetylene, i.e. (90).



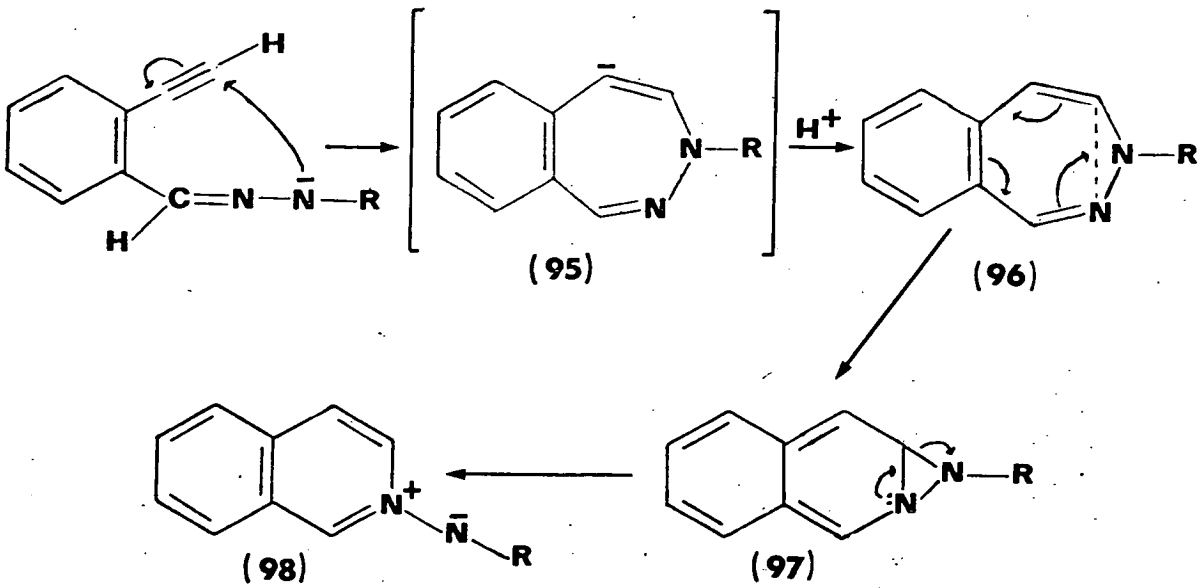
(93)
6-Exo-Dig



(94)
7-Endo-Dig

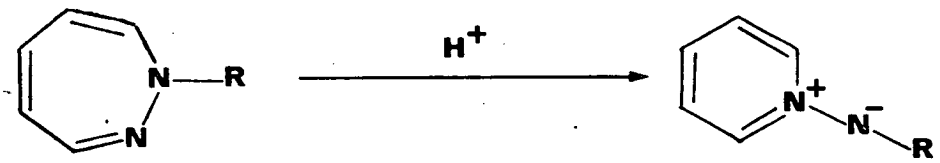
Some polarisation of the triple bond caused by the inductively electron-withdrawing phenyl group may activate the terminal carbon of the acetylene to nucleophilic attack, i.e. (90).

The mechanism favoured here, Scheme 7, is the nucleophilic attack on the terminal carbon of the triple bond to give the intermediate (95) which by proton transfer would give the 3H-2,3-benzodiazepine (96). The benzodiazepine (96) could then collapse via the benzodiaziridine (97) to the isoquinoline N-imine (98).



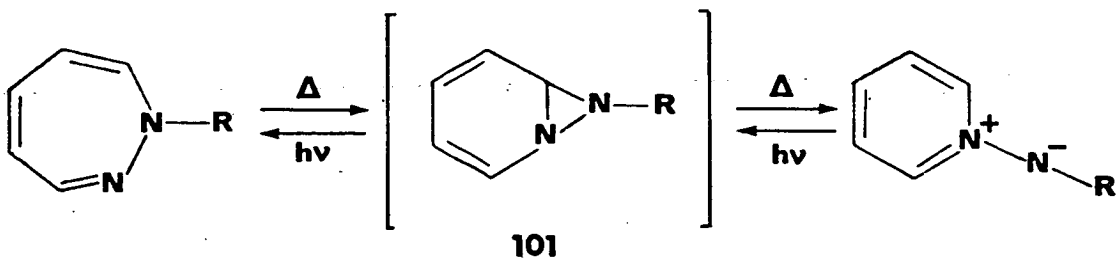
Scheme 7

The 3H-2,3-benzodiazepines (96) postulated here as intermediates have never yet been isolated. The related 1H-1,2-diazepines (99) have been shown to collapse to the pyridine N-imines (100) by treatment with acid[74,88,89].



(99) (100)

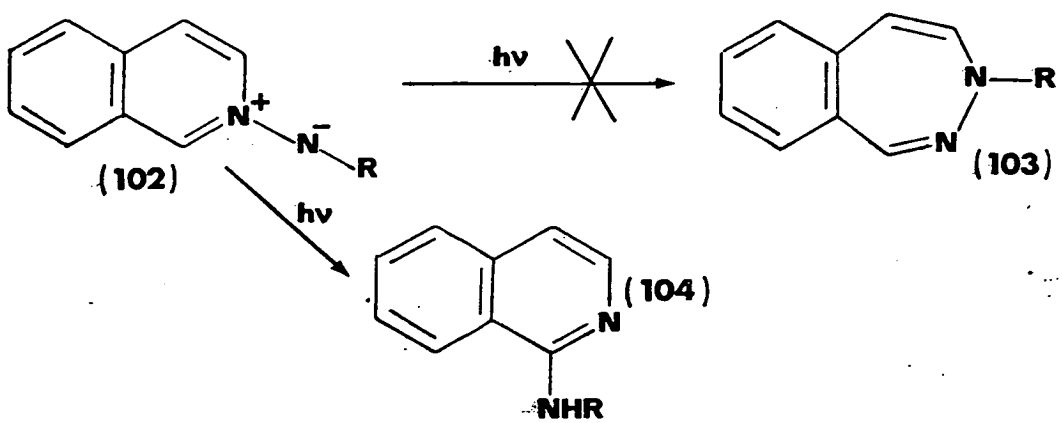
Also, the interconvertablility of 1H-1,2-diazepines and pyridine N-imines is well known[71,75] (see Section G 1a,b) of the Introduction), the reaction proceeding via the diaziridine (101), Scheme 8.



101

Scheme 8

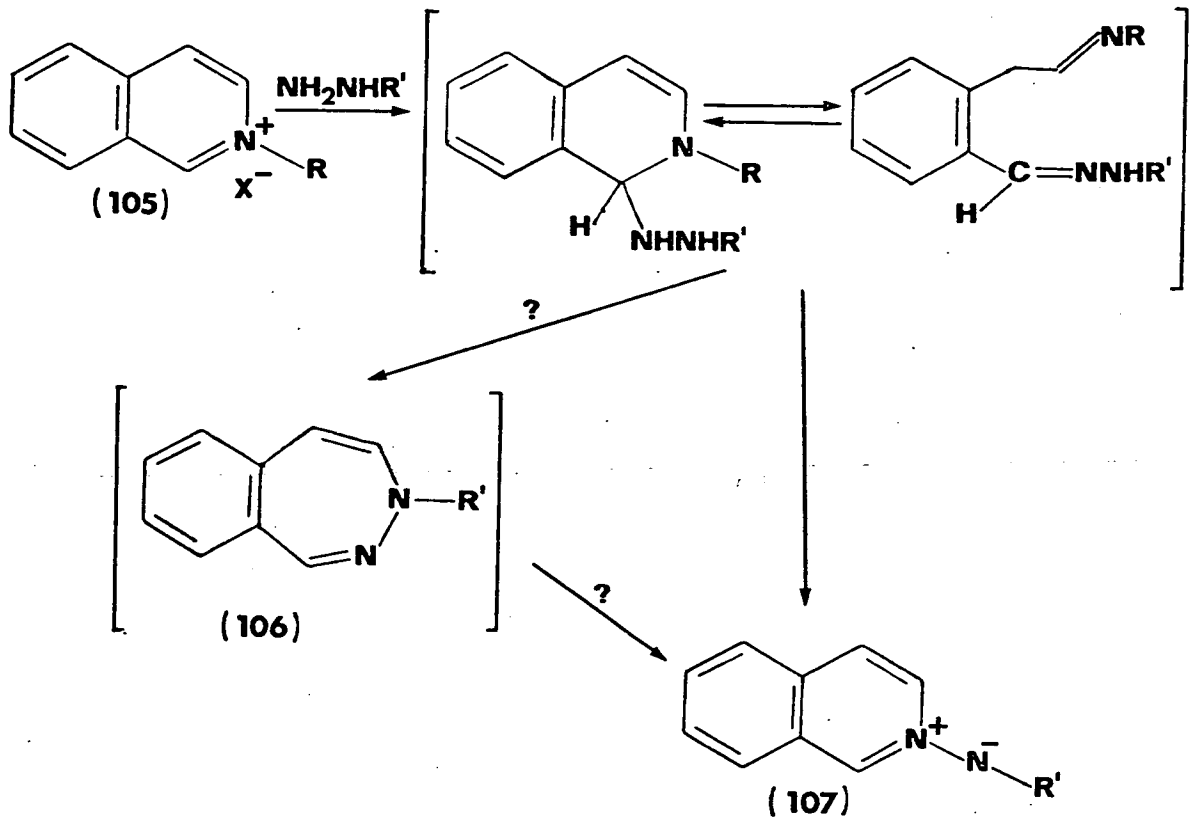
Photolysis of pyridine N-imines gives the 1H-1,2-diazepines, Scheme 8, however photolysis of isoquinoline N-imines (102) does not give the equivalent 3H-2,3-benzodiazepines (103) but rather the 1-substituted aminoisoquinolines[143,144](104).



(102) (103) (104)

This may imply that the 3H-2,3-benzodiazepines (103) are not as stable as their non-benzenoid counterparts (99).

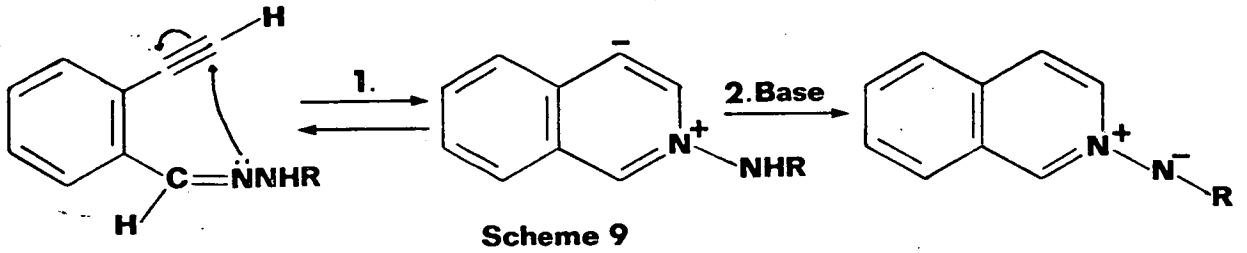
In a recent report it has been postulated[139] that the 3H-2,3-benzodiazepine (106) may be an intermediate involved in the synthesis of isoquinoline N-imines (107) from the hydrazination of isoquinolinium salts (105). However no experimental evidence for the existence of this 3H-2,3-benzodiazepine (106) was given.



The reaction pathway, Scheme 7, to the isoquinoline N-imines thus seems mechanistically reasonable and is in accord with the experimental observation of the dependence of the reaction on the acidity of the N-H group.

The formation of the isoquinoline N-imines via the 6-Exo-Dig ring closure, i.e. from (91), would seem a difficult process and no alternative products were isolated from this Exo cyclisation.

An alternative mechanism for isoquinoline N-imine formation not involving the 3H-2,3-benzodiazepine can be written. This involves the attack of the other nitrogen on the triple bond, Scheme 9, Step(1).



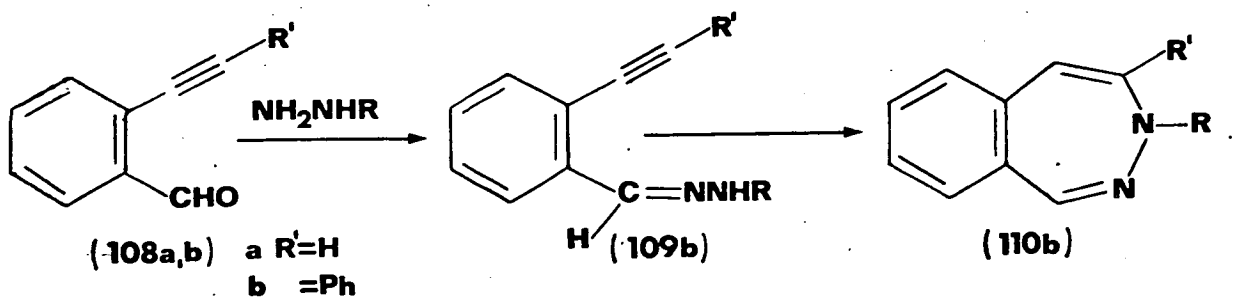
Scheme 9

In this mechanism base is required to catalyse the final proton transfer, Step(2). However this mechanism seems less likely since step(2) would almost certainly proceed spontaneously to the product without base and thus there would be no dependance of cyclisation on the acidity of the N-H group.

Therefore the formation of the isoquinoline N-imines *via* the 3H-2,3-benzodiazepine, Scheme 7, would seem most likely.

C. *The reaction of 2-phenylethynylbenzaldehyde with p-tosylhydrazine and benzoylhydrazide.*

It was hoped to isolate the 3H-2,3-benzodiazepines (110b) from the reaction of 2-phenylethynylbenzaldehyde (108b) and N-substituted hydrazines *via* the hydrazones (109b). The 3H-2,3-benzodiazepines (110b) might be stabilised by the phenyl group on C-4 and thus might be isolated from the reaction rather than the isoquinoline N-imines which were obtained from the reaction of 2-ethynylbenzaldehyde (108a) and N-substituted hydrazines.



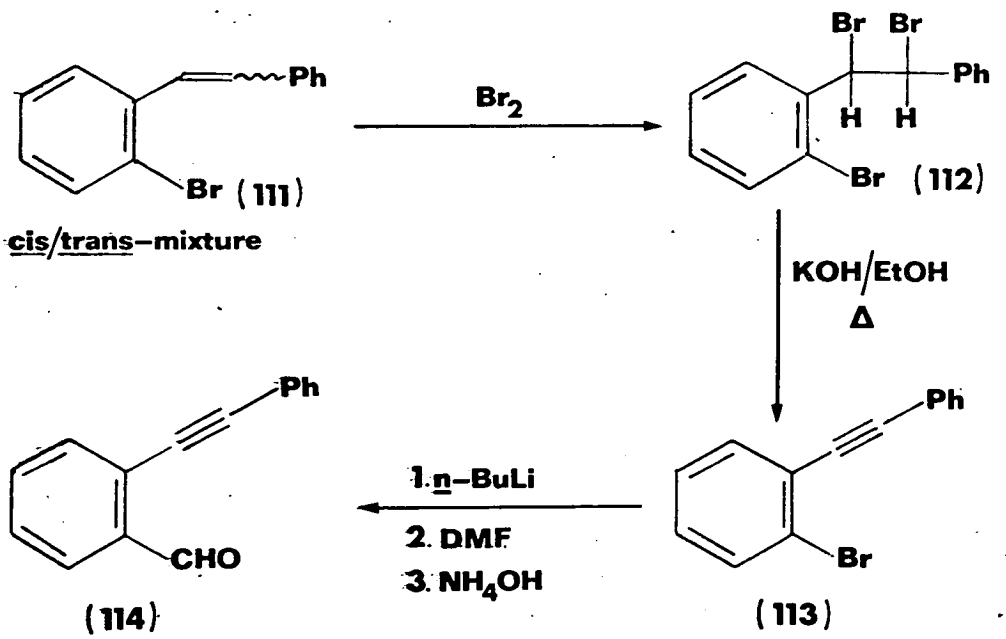
(108a,b) a R'=H
b =Ph

(109b)

(110b)

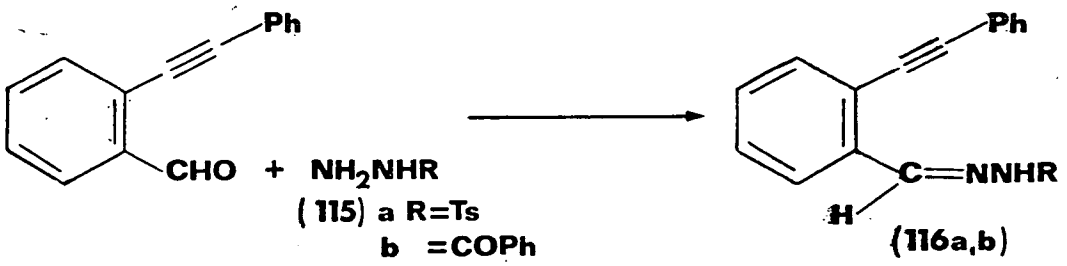
1) Synthesis of 2-phenylethynylbenzaldehyde.

Bromination and dehydrobromination of 2-formylstilbene (cf. the synthesis of 2-ethynylbenzaldehyde (72) from 2-formylstyrene (70)) did not prove successful in the synthesis of 2-phenylethynylbenzaldehyde. However, in the synthesis of trans-2-formylstilbene[170] (see Section 1B 1)) one of the intermediates is the cis/trans-mixture of 2-bromostilbene (111) and this proved to be a good starting point in the synthesis of 2-phenylethynylbenzaldehyde. The cis/trans-mixture of 2-bromostilbene was brominated (thus eliminating any stereochemical consideration) to give 2-bromostilbene dibromide (112) which was dehydrobrominated[181] with potassium hydroxide in refluxing ethanol to give o-bromodiphenylacetylene (113)[182]. o-Bromodiphenylacetylene (113) was then treated with n-butyllithium to give the lithium derivative and this was treated with dimethyl formamide and subsequent hydrolysis gave 2-phenylethynylbenzaldehyde (114); (2-phenylethynylbenzaldehyde was recently mentioned by Straub et al[183] although no experimental data on its synthesis was given).



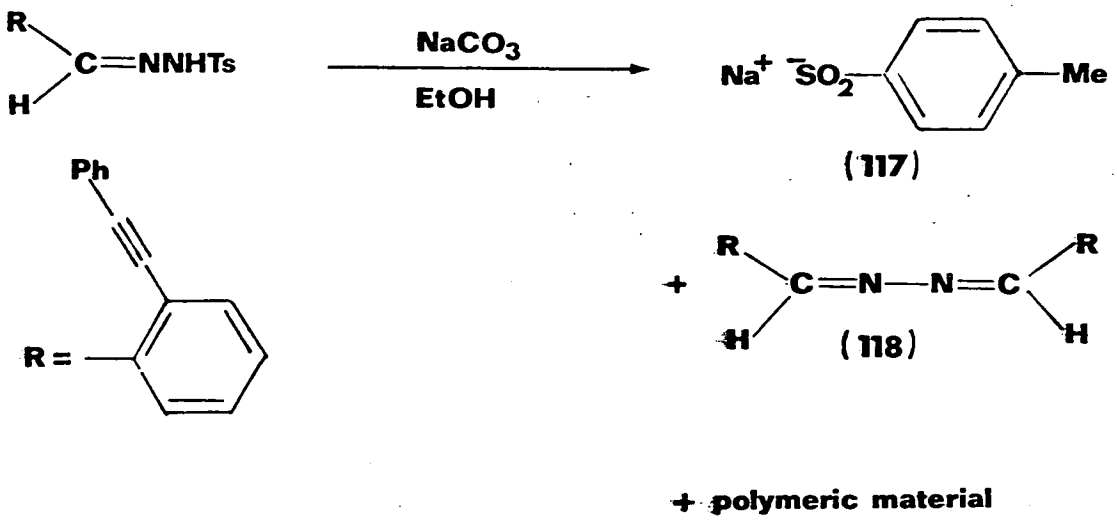
2) Reactions of 2-phenylethynylbenzaldehyde with p-tosylhydrazine and benzoylhydrazide.

When p-tosylhydrazine (115a) and benzoylhydrazide (115b) were stirred in ethanol with a little acid with 2-phenylethynylbenzaldehyde the respective hydrazones (116a,b) were formed.

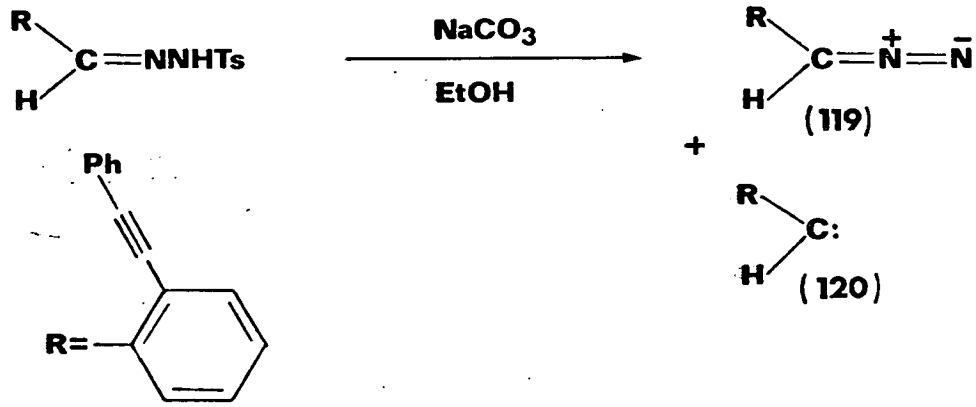


However the hydrazones (116a,b) could not be induced to cyclise under the reaction conditions which were successful for (76a-c,79).

When the tosylhydrazone (116a) was stirred in ethanol with sodium carbonate for 2 days the products obtained after work up were sodium p-toluenesulphinate (117) (87%), a small amount of the azine of 2-phenylethynylbenzaldehyde (118) and a substantial amount of polymeric material.



The production of sodium p-toluenesulphinate (117) is indicative of the decomposition of the tosylhydrazone to the diazoalkane (119) and/or the carbene (120).



The azine (118) and the polymeric material are probably derived from the carbene (119) and/or the diazoalkane (120).

When the tosylhydrazone (116a) was stirred in ethanol with D.B.U. for three days no identifiable material was obtained, the product being a dark yellow powder. It was thought that this was polymeric material derived from D.B.U. and the decomposition products of the tosylhydrazone i.e. diazoalkane (119) and/or carbene (120).

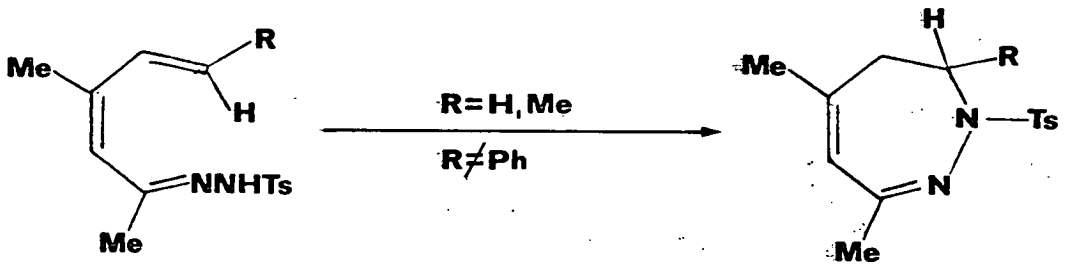
When the tosylhydrazone (116a) was heated under reflux in ethanol with a little cuprous chloride only polymeric material was again obtained.

When the benzoylhydrazone (116b) was stirred in sodium carbonate/ethanol or D.B.U./ethanol only recovered starting material was obtained. When the benzoylhydrazone (116b) was heated under reflux in ethanol with a little cuprous chloride only polymeric material was obtained.

The phenyl group on the terminal carbon of the two hydrazones (116a,b) thus has the surprising effect of completely inhibiting cyclisation. This may partly be due to steric inhibition of the phenyl group, and to the inductive electron withdrawing effect of the

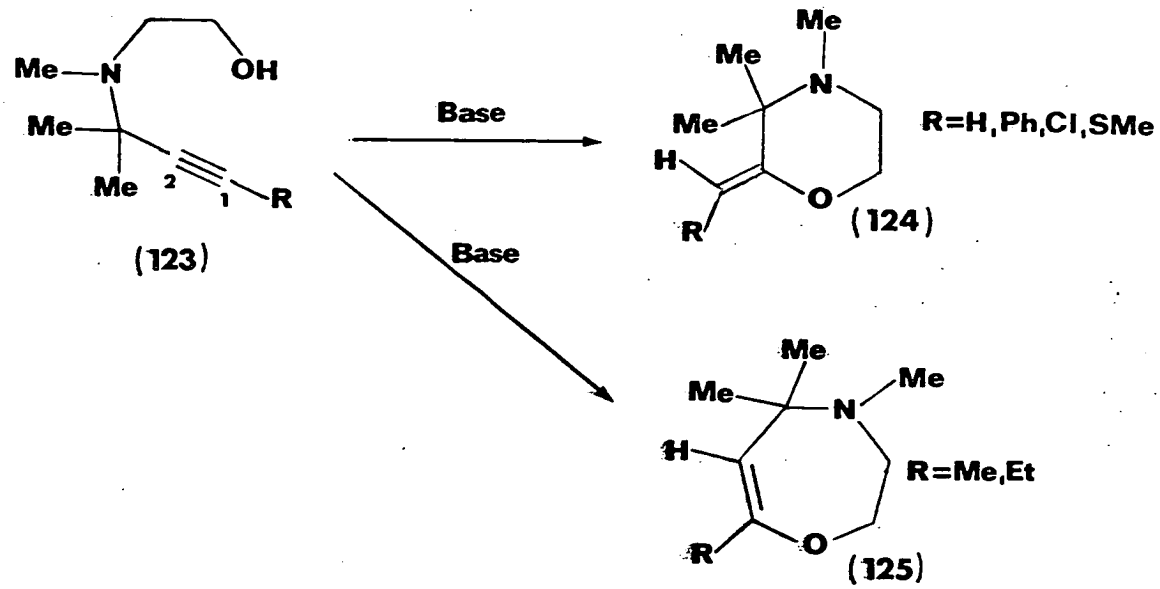
phenyl group which would affect the charge distribution in the triple bond possibly deactivating the terminal carbon to nucleophilic attack.

It has been shown[172,173], see Section 3, in the reaction of the tosylhydrazones of the αβ,γδ-unsaturated ketones (121), that the diazepines (122) are formed when R=H, Me, However when R=Ph no cyclisation occurs. It is postulated, see Section 3E 3), that this failure to cyclise may be due to an electronic effect of the phenyl group as well as steric hindrance.



(121) (122)

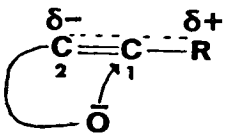
An example which supports the idea of a phenyl group being able to polarise acetylenic bonds is in the cyclisation of N-(β-hydroxy-ethyl)-2-propynylamines (123)[58].



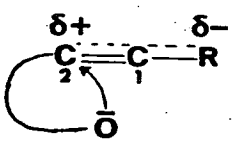
(123) (124) (125)

When R=Me, Et in (123) the products of the cyclisation are the seven-membered rings (125), i.e. a 7-Endo-Dig ring closure. However when R=H, Ph, Cl, SMe in (123) the products obtained are the six-membered rings (124) i.e. the less common 6-Exo-Dig ring closure[53].

It would appear that with inductively electron-releasing groups i.e. Me, Et the transition state is polarised such that C-2 of (123) is deactivated to nucleophilic attack, i.e. (126), thus allowing attack at C-1 to give seven membered rings (125). In the other case with inductively electron-withdrawing groups i.e. Ph, Cl, SMe the transition state is polarised such that C-2 is activated to nucleophilic attack, i.e. (127), thus giving six-membered rings (124).



(126) R=Me, Et

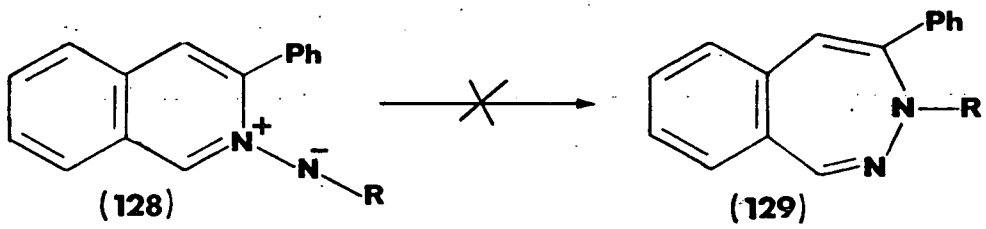


(127) R=Ph, Cl, SMe

Thus the addition of the terminal phenyl groups in the acetylenic hydrazones (116a,b) is counterproductive, the terminal carbon of the triple bond probably being deactivated toward nucleophilic attack and thus the hydrazones (116a,b) are either non-reactive or react by other pathways, e.g. polymerisation.

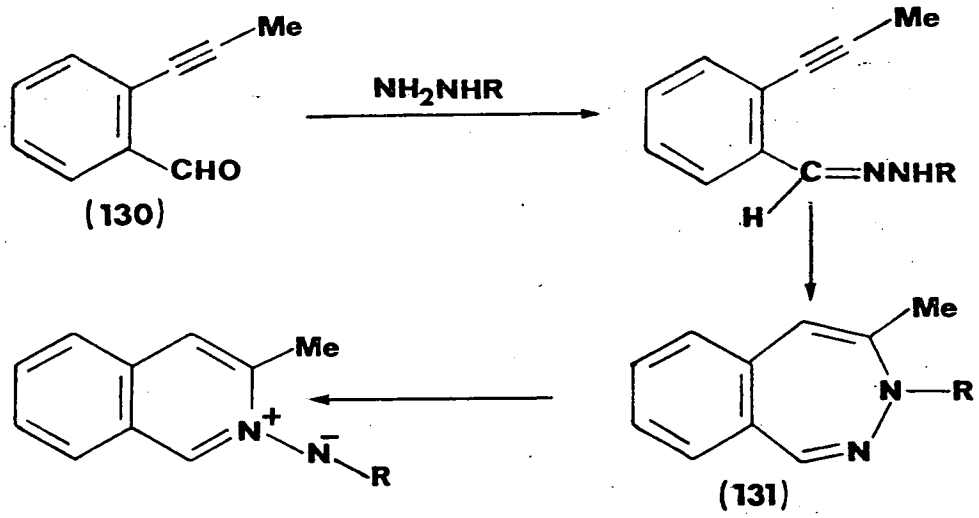
The possible isoquinoline N-imine product (128) from 2-phenylethynylbenzaldehyde has now been prepared by an alternative route[184] and is stable and does not convert to the 3H-2,3-benzodiazepine (129).

In order to extend the synthesis of acetylenic aldehydes and hydrazines it would prove useful to synthesise those acetylenes which have an electron-releasing group e.g. a methyl group attached to



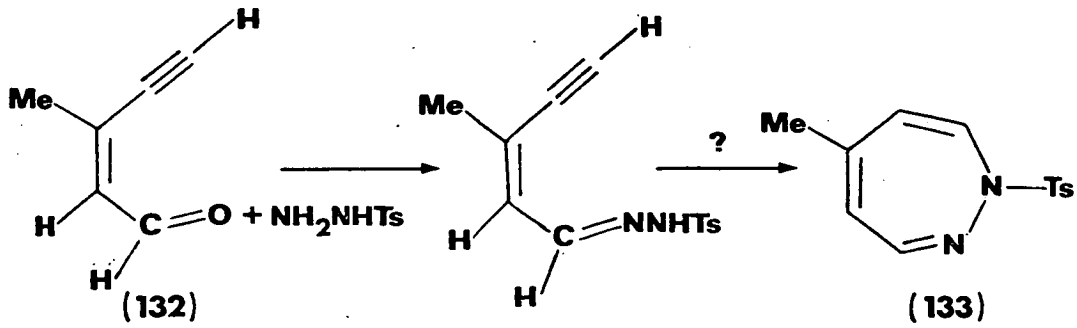
R=COPh

the terminal carbon, i.e. (130), thus further deactivating, to nucleophilic attack, the carbon adjacent to the phenyl group and therefore making cyclisation to the terminal carbon more likely. However an electron-releasing substituent would not stabilise the possible 2,3-benzodiazepine (131) thus the substituted isoquinoline N-imine would probably be the product.

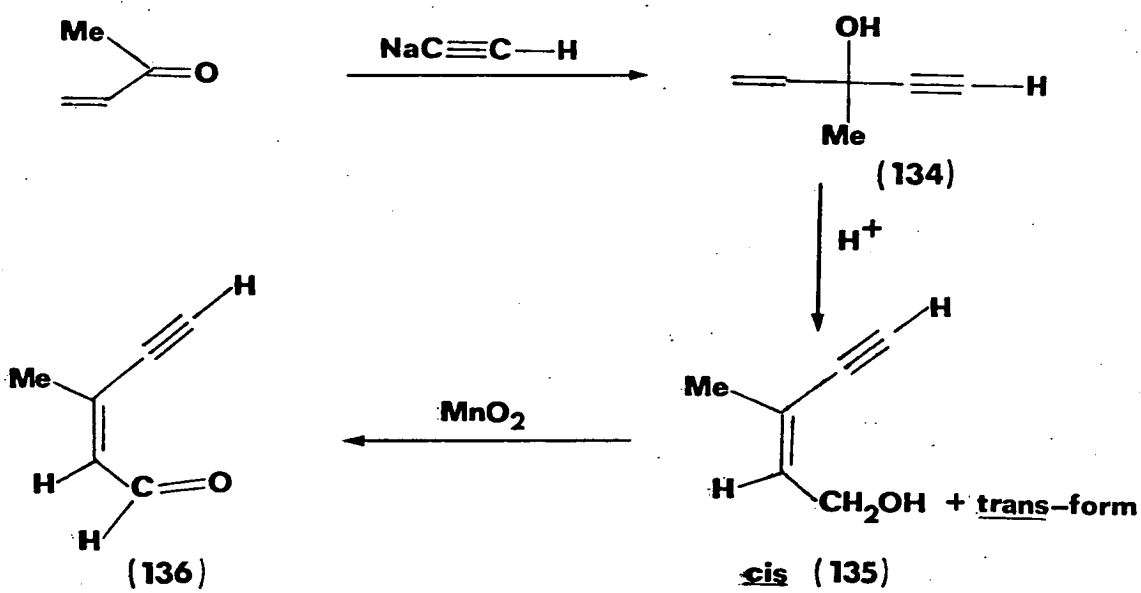


D. Synthesis of cis-3-methylpent-2-en-4-yn-1-al and its reaction with p-tosylhydrazine.

After the failure to obtain 3H-2,3-benzodiazepines from the previous reactions it was of interest to examine the reactivity of a non-benzenoid acetylenic aldehyde i.e. (132) with p-tosylhydrazine, the possible cyclisation product being the known and isolable 1H-1,2-diazepine (133).

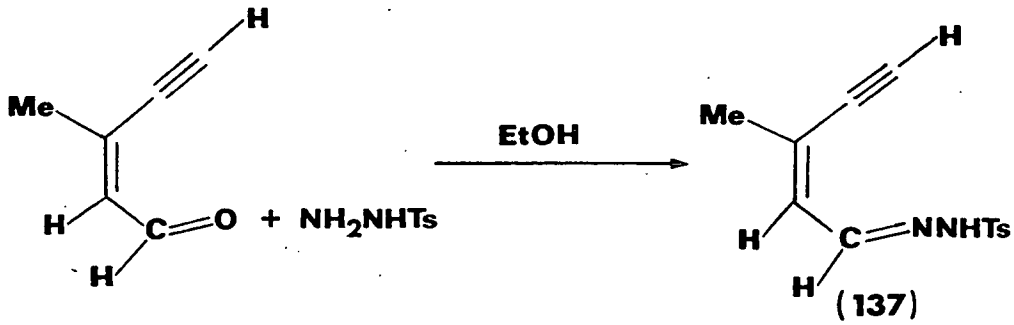


cis-3-Methylpent-2-en-4-yn-1-al was prepared as follows: 3-methylpent-4-en-1-yn-3-ol (134) was prepared by the reaction of methyl vinyl ketone with sodium acetylide[185] and the alcohol (134) was then treated with acid[185] which gave 3-methylpent-2-en-4-yn-1-ol (135) by allylic rearrangement which by distillation could be separated into the cis- and trans-forms[186]. Oxidation of the cis-form with manganese dioxide[187] gave cis-3-methylpent-2-en-4-yn-1-al (136).

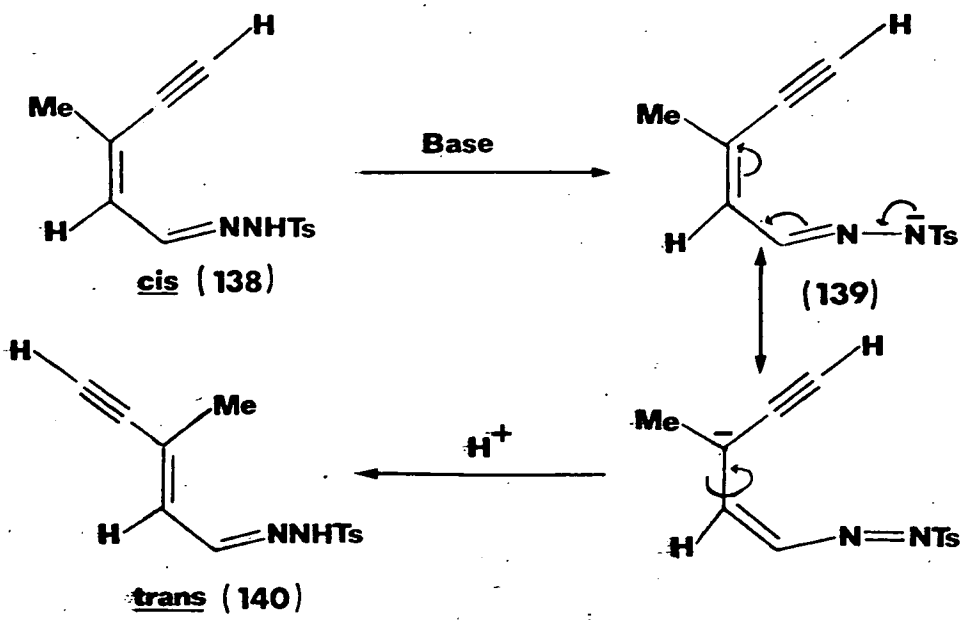


When cis-3-methylpent-2-en-4-yn-1-al (136) was reacted with p-tosylhydrazine in ethanol a pink solution was obtained. T.l.c. of this showed the consumption of the aldehyde (136). The ethanol was

removed under high vacuum and the resulting oil was confirmed by its ^{1}H n.m.r. spectrum to be the tosylhydrazone (137).



This tosylhydrazone (137) could not be purified, only darkening on handling. A variety of cyclisation procedures were attempted, however no cyclisation of (137) could be obtained. When the tosylhydrazone (137) was stirred in ethanol with sodium carbonate or sodium ethoxide T.l.c. showed the consumption of the tosylhydrazone (137) but chromatography of the reaction mixtures failed to yield any products. Formation of the carbene and/or the diazoalkane, leading to polymerisation is possible and the failure to cyclise could also be attributed to an isomerisation of the cis-tosylhydrazone (138), via the anion (139) to the trans-tosylhydrazone (140), i.e. the wrong stereochemistry for cyclisation and would react by other reaction pathways i.e. polymerisation.



In the intramolecular cyclisation of 2-ethynylbenzaldehyde hydrazones the benzene ring would maintain the hydrazone in the correct stereochemistry. When the tosylhydrazone (137) was treated with D.B.U./ethanol there was no reaction by T.l.c. This would appear to be an anomalous result as it would be expected that the same process of isomerisation i.e. (138) ⟶ (140) would occur, leading to polymerisation.

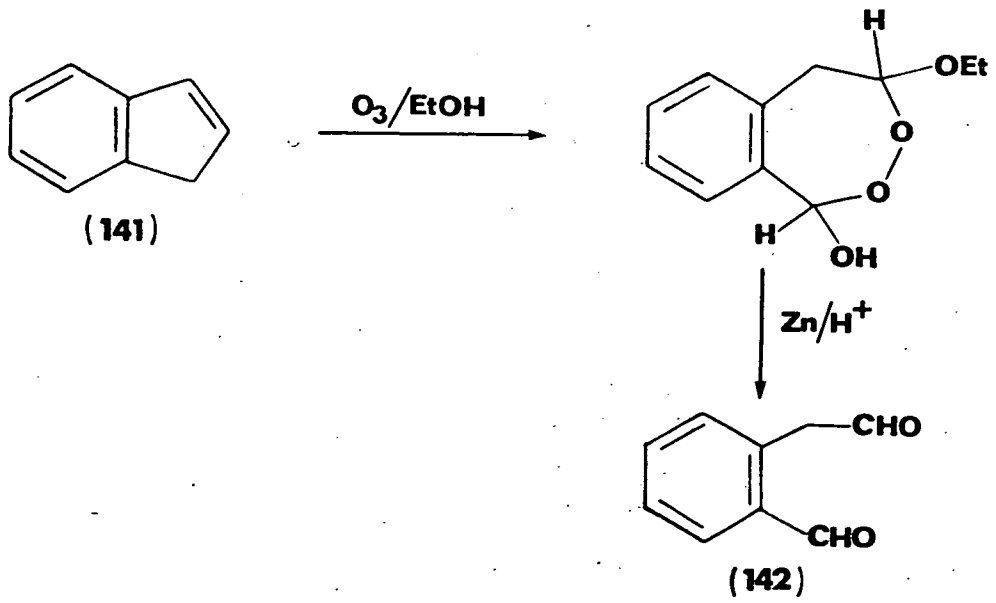
When the tosylhydrazone (137) was heated under reflux with cuprous chloride T.l.c. showed the consumption of the starting material however work up gave an unidentified yellow powder which was probably polymeric.

E. The reaction of homophthalaldehyde with hydrazines.

These reactions were first performed by H.R. Sood. However the products obtained were never fully characterised and in the light of the 2-ethynylbenzaldehyde/N-substituted hydrazines reaction it was decided that a reinvestigation would prove worthwhile.

1) Synthesis of homophthalaldehyde.

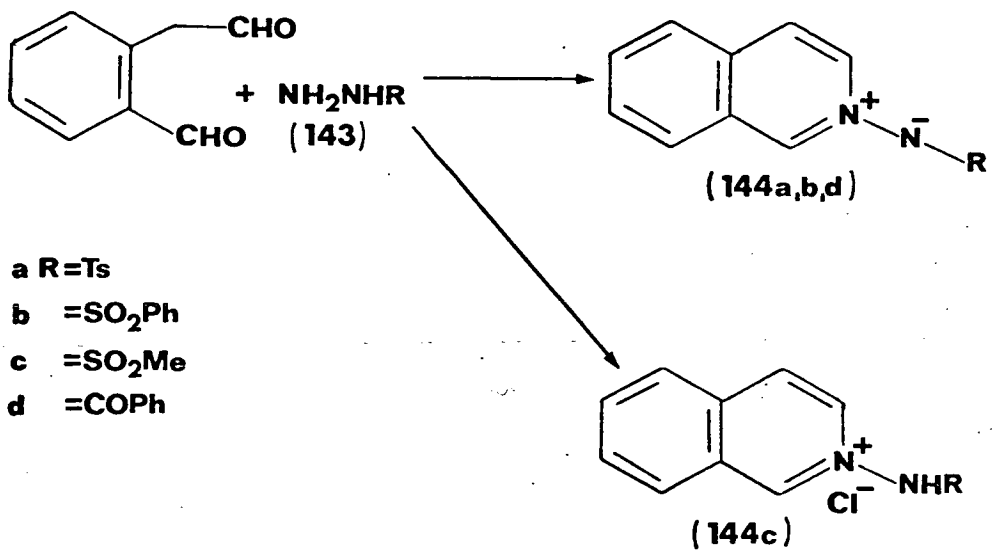
Homophthalaldehyde (142) was prepared by the method of Warnell and Shriner[189] by the ozonolysis of indene (141) and reduction of the resulting ozonide with zinc and acetic acid.



(141) (142)

2) Reactions of homophthalaldehyde with hydrazines.

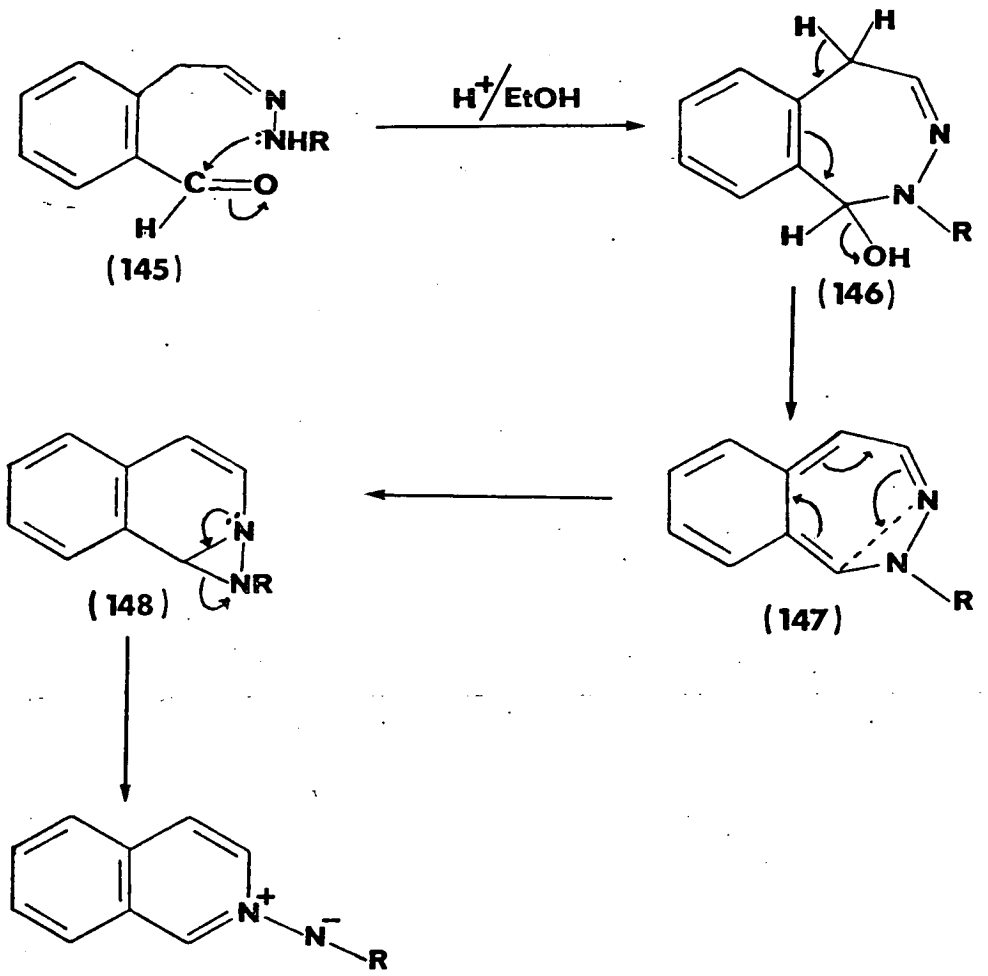
When homophthalaldehyde (142) was reacted with the hydrazines (143a-d) in ethanol with a little acid clear solutions were obtained rapidly. The solutions were then left in the dark for a few days and the resultant crystals filtered off and recrystallised from ethanol the products being the isoquinoline N-imines (144a,b,d) except in the case of methanesulphonylhydrazine (143c) where the product obtained was the hydrochloride salt of the isoquinoline N-imine (144c).



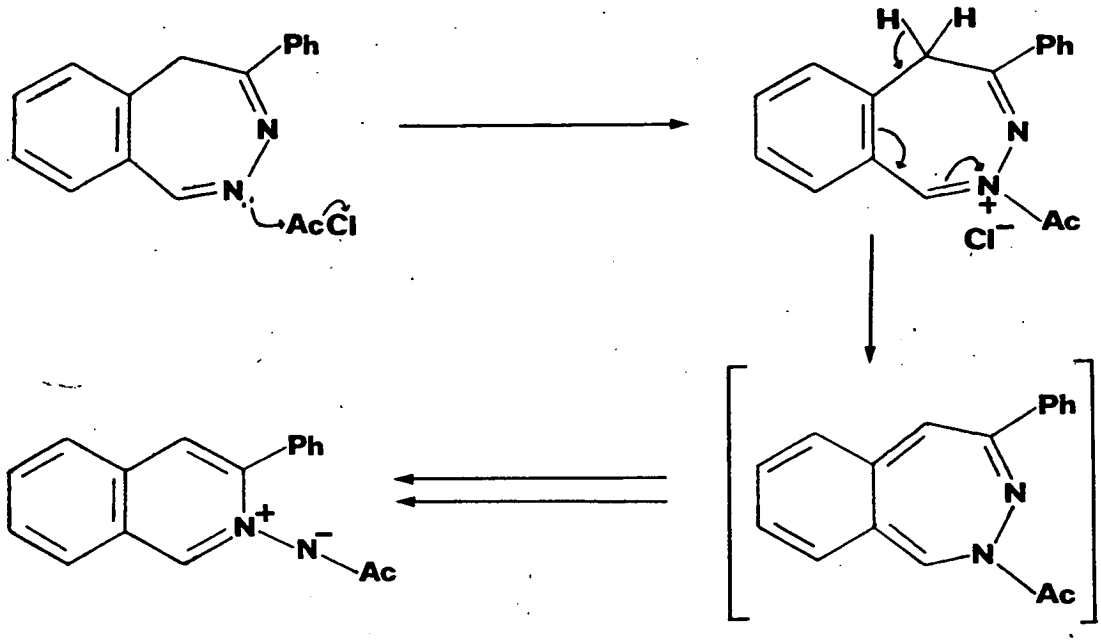
The yields of the isoquinoline N-imines (144a,b,d) were R=Ts (43%), R=SO_2Ph (37%) and R=COPh (42%), the yield of (144c) was 33%.

Homophthalaldehyde has two aldehyde groups and in its reaction with hydrazines a mixture of the two hydrazones (145), (149) could be formed. Two mechanisms for the cyclisation are possible. The first mechanism involves the initial condensation of the aliphatic aldehyde with the N-substituted hydrazine (aliphatic aldehydes are normally more reactive than aromatic aldehydes). The hydrazone could then cyclise to give the 1-hydroxybenzodiazepine (146) which by loss of

water would give the non-aromatic intermediate (147) which could rearomatise to give the benzodiaziridine (148). This benzodiaziridine (148) could then collapse to the isoquinoline N-imine.

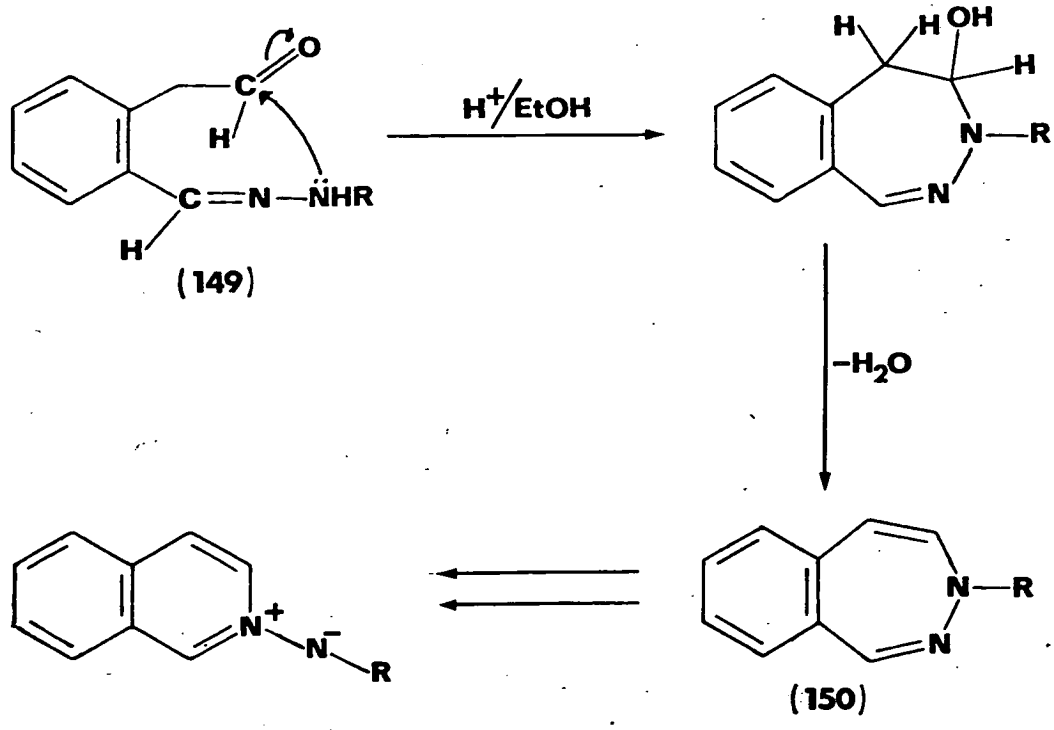


Intermediates of the type (147) are probably involved in the formation of the isoquinoline N-imine in the acylation of the 5H-2,3-benzodiazepine[184], Scheme 10.



Scheme 10

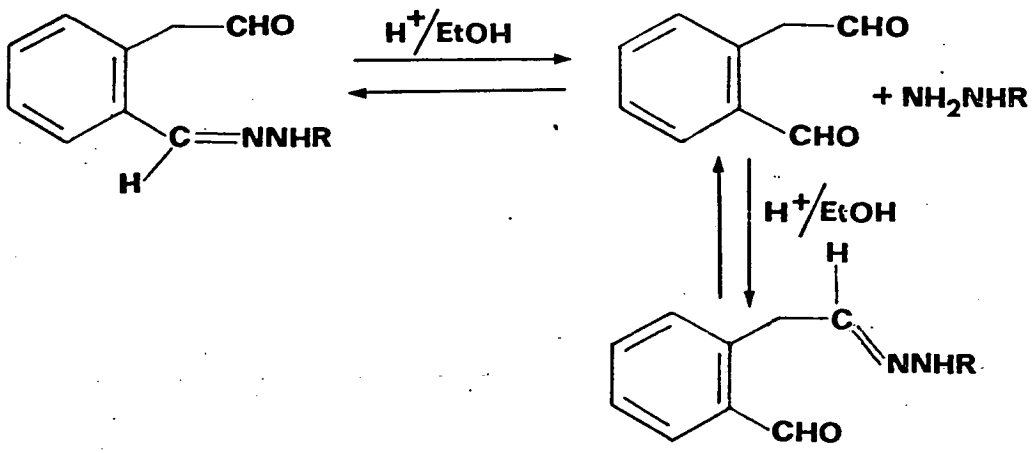
The second mechanism involves condensation of the aromatic aldehyde with the N-substituted hydrazines, i.e. (149), ring closure followed by loss of water would give the 3H-2,3-benzodiazepine (150) which would then collapse to the isoquinoline N-imine as described before.



(149)

(150)

It can be seen that the two mechanisms lead to the same isoquinoline N-imine and it is probably not possible to differentiate between them. In acidic media the imine bond of the two hydrazones (145), (149) will be readily hydrolisable and even if one of the hydrazones is produced to the virtual exclusion of the other it is possible that the minor form may be the precursor to cyclisation via an equilibrium process, Scheme 11.



Scheme 11

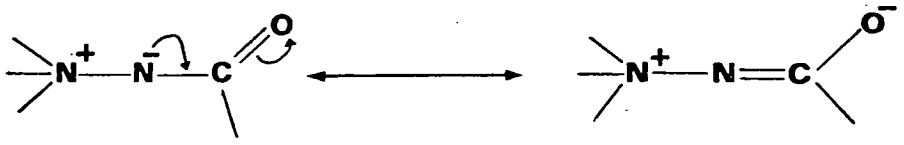
The yields of the isoquinoline N-imines (144a-d) from the reaction of homophthalaldehyde and hydrazines are modest but considering the other possible side reactions e.g. the reaction of two molecules of homophthalaldehyde and one molecule of the hydrazine leading to the complications of cross-condensation and polymerisation it is perhaps remarkable that they are formed at all.

The isolation of the hydrochloride salt of isoquinoline N-methanesulphonylimine (144c) is caused by the reaction of the isoquinoline N-imine with the hydrochloric acid (used to effect the condensation reaction) in the reaction mixture. It is not understood why it is only in this case the hydrochloride salt is obtained, although

greater stabilisation may be offered to the isoquinoline N-imine when the group attached to the nitrogen is tosyl-,benzenesulphonyl- or benzoyl- than when the group is methanesulphonyl-, thus for stability the isoquinoline N-methanesulphonylimine forms its hydrochloride salt (144c).

The structures of the isoquinoline N-imines were confirmed by comparison of their spectral data to that reported[141] and to that obtained for the isoquinoline N-imines prepared from the 2-ethynylbenzaldehyde/hydrazines reaction.

The i.r. spectra of the isoquinoline N-imines are very characteristic. In the isoquinoline N-benzoylimine the absorption of the C=O bond is shifted from the normal 1650cm^{-1} to a much lower wave number, i.e. 1550cm^{-1}. This bathochromic shift is due to the delocalisation of the electron pair of the imino nitrogen into the C=O bond thus giving it more single bond character, thus lengthening the bond and leading to the lower wave number absorption, Scheme 12.



Scheme 12

In the isoquinoline N-sulphonylimines the same sort of bathochromic shift is apparent. The normal O=S=O absorptions i.e. 1320-1340 and 1160-1170cm^{-1} [142,191] are shifted to lower wave number i.e. 1270-1285 and 1130-1140cm^{-1}.

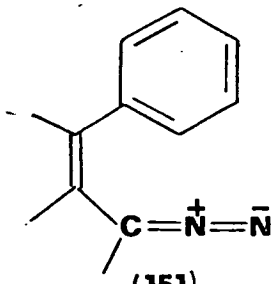
In the isoquinoline N-methanesulphonylimine hydrochloride no such delocalisation is possible and the O=S=O absorptions are in the normal range i.e. 1360 and 1155cm^{-1}.

The non-isolation of the elusive 3H-2,3-benzodiazepines is probably due to their instability, but it is possible that modification of the intermediates used here might still lead into this system, e.g. the addition of phenyl groups as substituents.

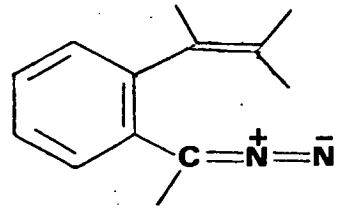
3. Reactions of αβ,γδ-unsaturated ketones with hydrazines.

A. Introduction.

Sharp and his co-workers have recently described routes to the 3H-1,2-benzodiazepines[160,161] and 1H-2,3-benzodiazepines[127] via the 8π-electron cyclisation of (151) and (152).



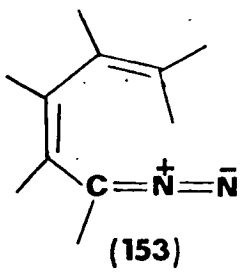
(151)



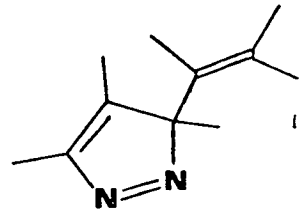
(152)

These reactions are described in greater detail in Section 1A.

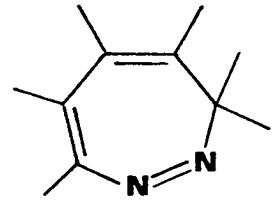
Both of the above systems have aromatic unsaturation thus it was of interest to examine the reactivity of analagous compounds with only olefinic unsaturation e.g. (153).



(153)



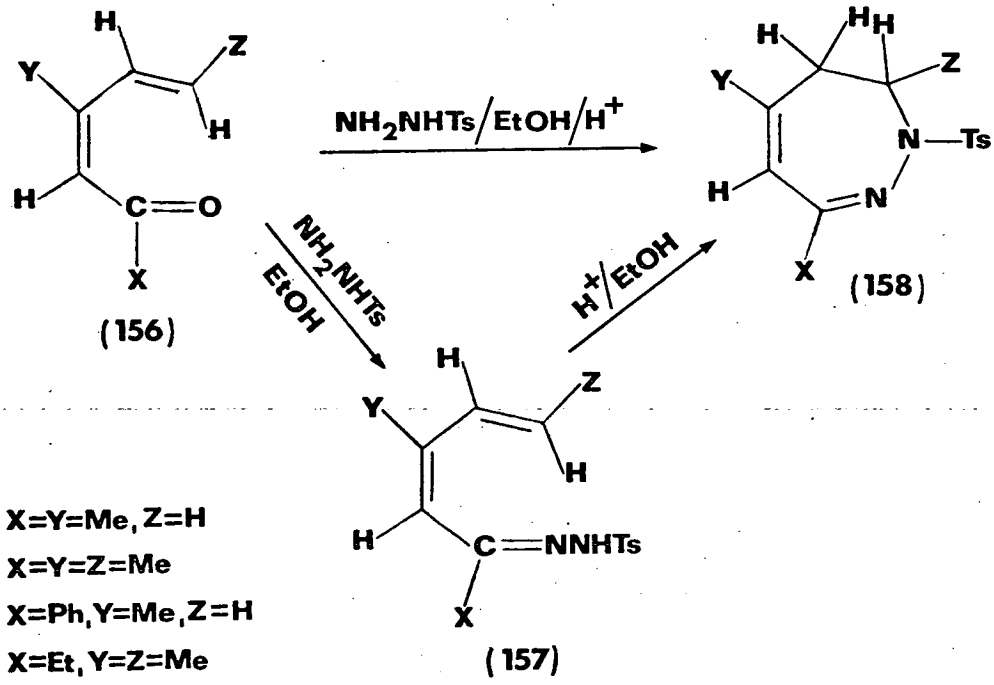
(154)



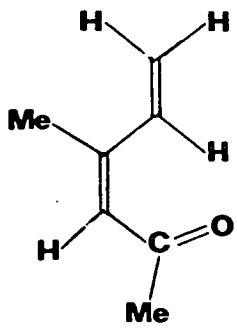
(155)

These compounds (153) could undergo ring closure to give either 3-vinyl-3H-pyrazoles (154) or the virtually unknown 3H-1,2-diazepines (155). (One 3H-1,2-diazepine has been suggested as the thermal

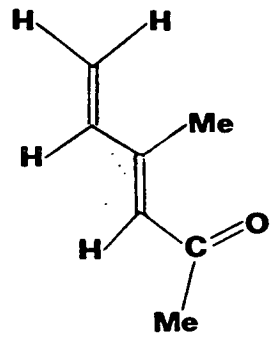
rearrangement product of a diazanorcaradiene but little information is available[192]). However, it was found [172,173] that the ketones (156) (mixtures of cis and trans isomers) were not converted into the required tosylhydrazone precursors (157) when treated with p-toluene-sulphonylhydrazine but rather reacted under acid conditions in ethanol to give the 2-tosyl-3,4-dihydro-1,2-diazepines (158) in yields of 55-77%.



In this cyclisation reaction it is notable that both the E and Z dienones react to give the diazepines. For (156a) the dienone consisted of a ca 2.2:1 ratio of the E (159) to Z (160) isomers[173] by its ^{1}H n.m.r. spectrum (see Appendix).



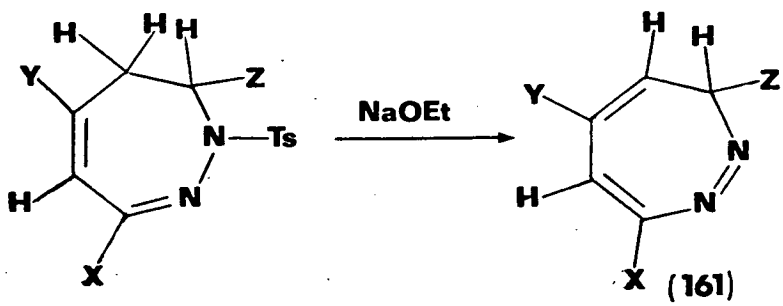
Z(160)



E(159)

The intermediacy of the tosylhydrazone (157) in the cyclisation was demonstrated in one case. The dienone (156a) when treated with p-tosylhydrazine for 18h in the absence of acid was converted mainly to the tosylhydrazone (157a) (mixed E and Z isomers) together with a little (13%) of the diazepine (158a). The tosylhydrazone (157a) when dissolved in ethanol was then rapidly converted to the diazepine (158a) by the addition of a small amount of sulphuric acid. Thus it was postulated that there were two mechanisms for diazepine formation: a slow cyclisation of the Z tosylhydrazone occuring in the absence of acid and a fast acid-catalysed reaction in which protonation of the tosylhydrazone allows E to Z conversion before ring closure.

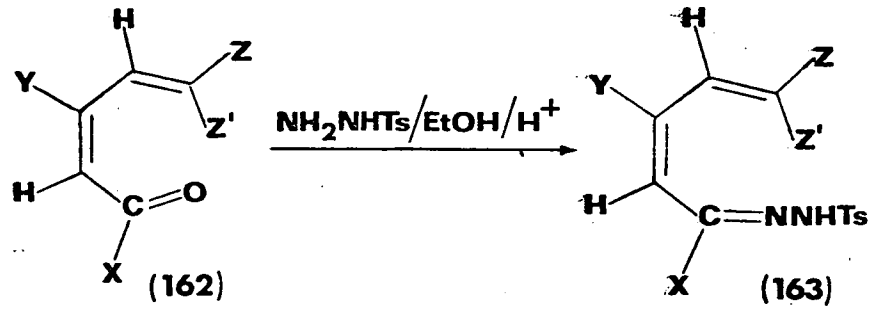
The 2-tosyl-3,4-dihydro-1,2-diazepines could by base induced elimination of p-toluenesulphinic acid be converted into the 3H-1,2-diazepines (161) in high yields[172,193]. This is the only synthetically useful route yet devised to the 3H-1,2-diazepines[172,193].



(161)

a X=Y=H, Z=Me
b X=Y=Z=Me
c X=Ph, Y=Me, Z=H
d X=Et, Y=Z=Me

Although the reaction of 2,4-dienones with p-tosylhydrazine proceeds smoothly to the diazepines (158) in the cases shown, it has been found[173] that certain 2,4-dienones (162) give only the p-toluenesulphonylhydrazones (163) when reacted under identical acid-catalysed conditions. These tosylhydrazones could not be induced to cyclise although a variety of acid/solvent/temperature combinations were tried.



a X=Z=Me, Y=Z'=H
b X=Z'=H, Y=Z=Me
c X=Z'=H, Y=Me, Z=Ph
d X=Y=Me, Z=Ph, Z'=H
e X=Y=Z'=Me, Z=Ph

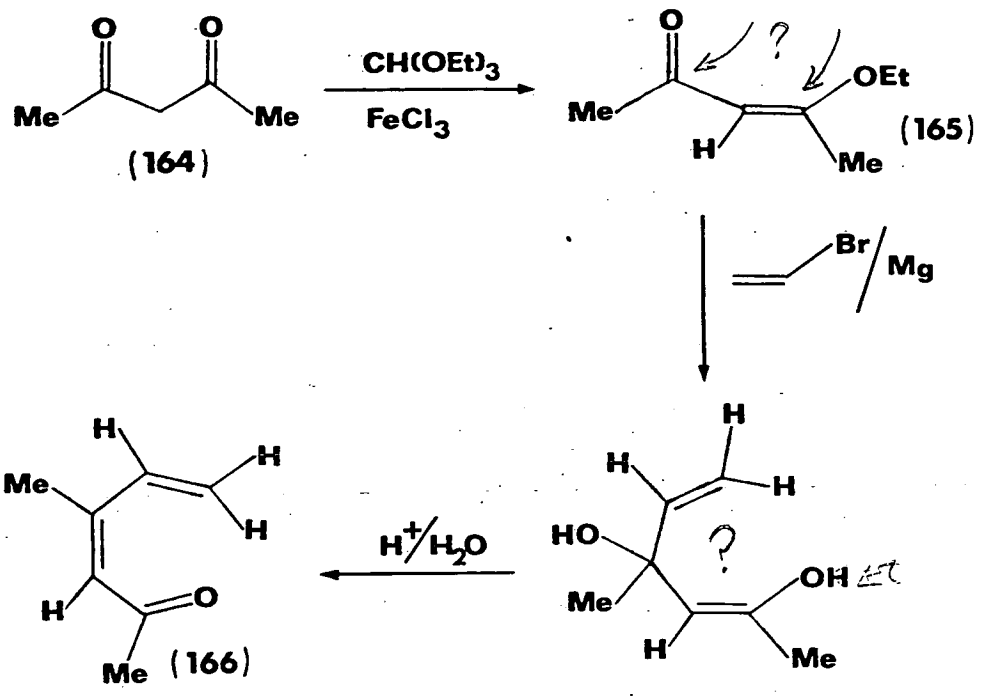
The failure of the tosylhydrazones (163a,b) to cyclise is notable since they differ from (157b) only in the absence of methyl groups at C-2 and C-4 respectively. The other three tosylhydrazones (163c-e) have large (phenyl) groups attached to the terminus of the diene and it is perhaps less surprising that they fail to cyclise as Michael type additions are known to be sensitive to steric hindrance.

Thus this section of work was an attempt to extend the synthesis to other N-substituted 1,2-diazepines, to better understand the failure of tosylhydrazones (163) to cyclise and to clarify the role of the acid catalyst in promoting the cyclisation of tosylhydrazones (157).

B. The reaction of 4-methylhexa-3,5-dien-2-one with hydrazines.

1) Synthesis of starting materials.

4-Methylhexa-3,5-dien-2-one (166)[196] was prepared by the reaction of the Grignard reagent of vinyl bromide and 4-ethoxypent-3-en-2-one (165). The latter was prepared from the reaction of acetyl acetone (164), triethyl orthoformate and ferric chloride in ethanol[194,195].



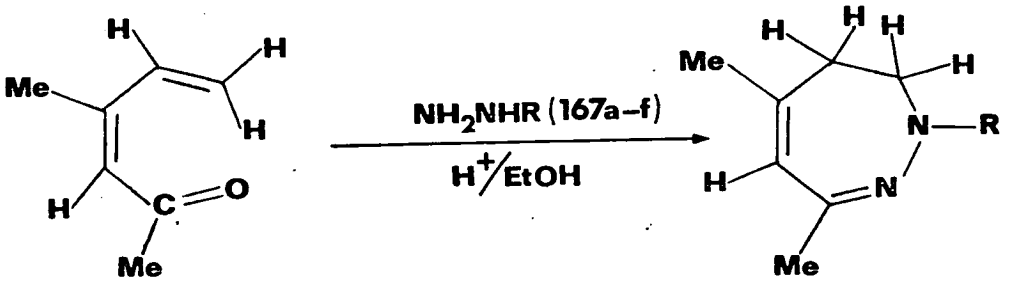
p-Toluene-, benzene- and methanesulphonylhydrazine were prepared by the reaction of hydrazine hydrate on the respective sulphonylchloride[177,178,179].

Acetyl- and benzoylhydrazide were prepared by the reaction of the respective ethyl ester with hydrazine hydrate[180,197].

2) Reactions of 4-methylhexa-3,5-dien-2-one with hydrazines.

As discussed previously the reaction of 4-methylhexa-3,5-dien-2-one with p-tosylhydrazine (167a) in ethanol with a catalytic amount of acid gave the 2-tosyl-3,4-dihydro-5,7-dimethyl-1,2-diazepine (168a)[172,173].

Under the same conditions a variety of other N-substituted hydrazines (167b-f) also gave the N-substituted 1,2-diazepines (168b-f). The results are summarised below.



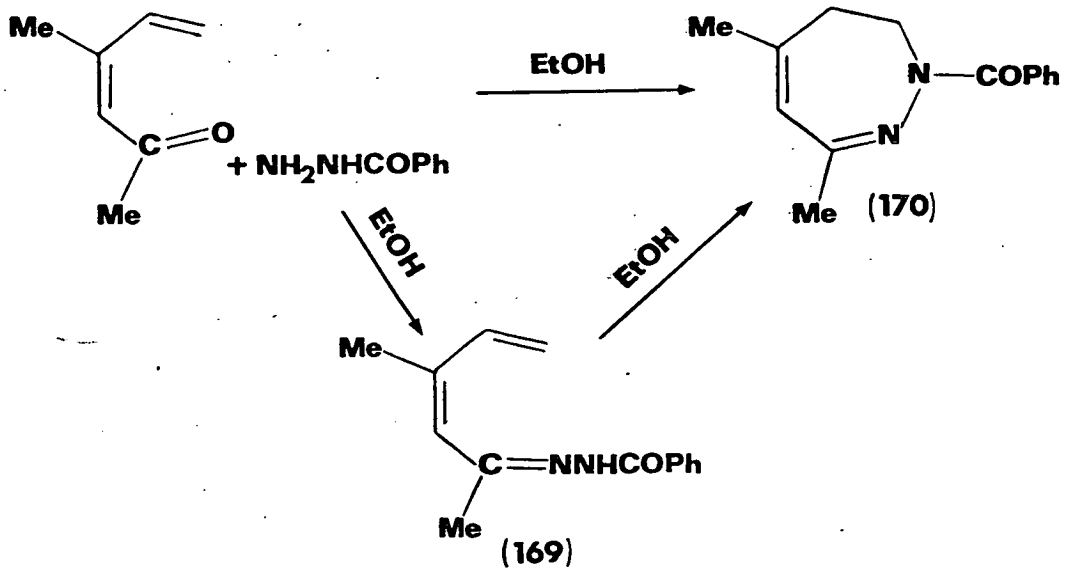
(168a-f)

	R	Yield
a)	-Ts	77%
b)	$-SO_2Ph$	65%
c)	$-SO_2Me$	60%
d)	-COPh	44%
e)	-COMe	46%
f)	$-CO_2Et$	43%

The reaction using benzenesulphonylhydrazine (167b) gave a white precipitate of 2-benzenesulphonyl-3,4-dihydro-5,7-dimethyl-1,2-diazepine (168b) in 65% yield. This is similar to the p-tosyl-hydrazine (167a) which gave a precipitate of the tosyldiazepine (168a) in 77% yield.

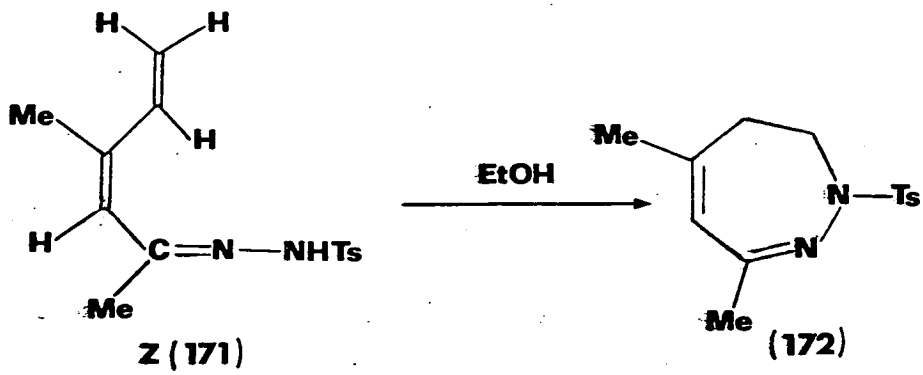
The reaction of methanesulphonylhydrazine (167c) with 4-methyl-hexa-3,5-dien-2-one was different in that no precipitate was obtained on stirring overnight in ethanol with acid. However, after chromatography the 2-methanesulphonyl-3,4-dihydro-5,7-dimethyl-1,2-diazepine (168c) was obtained as an oil in 60% yield which solidified on standing.

The reaction of benzoylhydrazide (167d) and 4-methylhexa-3,5-dien-2-one was studied in greater detail.



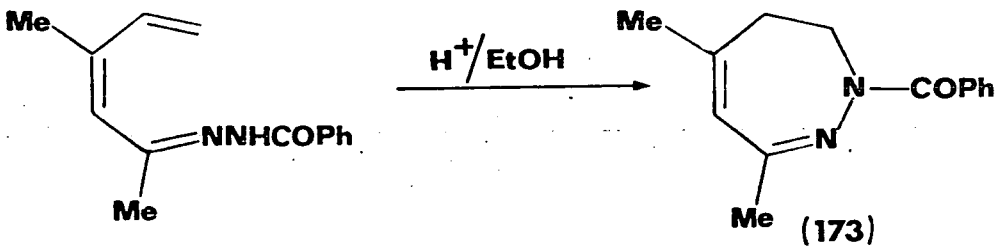
Firstly, benzoylhydrazide was reacted with 4-methylhexa-3,5-dien-2-one in ethanol overnight. The solvent was then evaporated off and the resulting oil separated by medium pressure liquid chromatography. The products obtained were 2-benzoyl-3,4-dihydro-5,7-dimethyl-1,2-diazepine (170) (12%), 4-methylhexa-3,5-dien-2-one benzoylhydrazone (169)(26%) and unreacted benzoylhydrazide (54%).

This reaction is similar to the reaction of p-tosylhydrazine and 4-methylhexa-3,5-dien-2-one in ethanol without acid[173]. In that case a small amount of the tosyldiazepine (172) (13%) is formed presumably through a slow cyclisation of the Z tosylhydrazone (171).



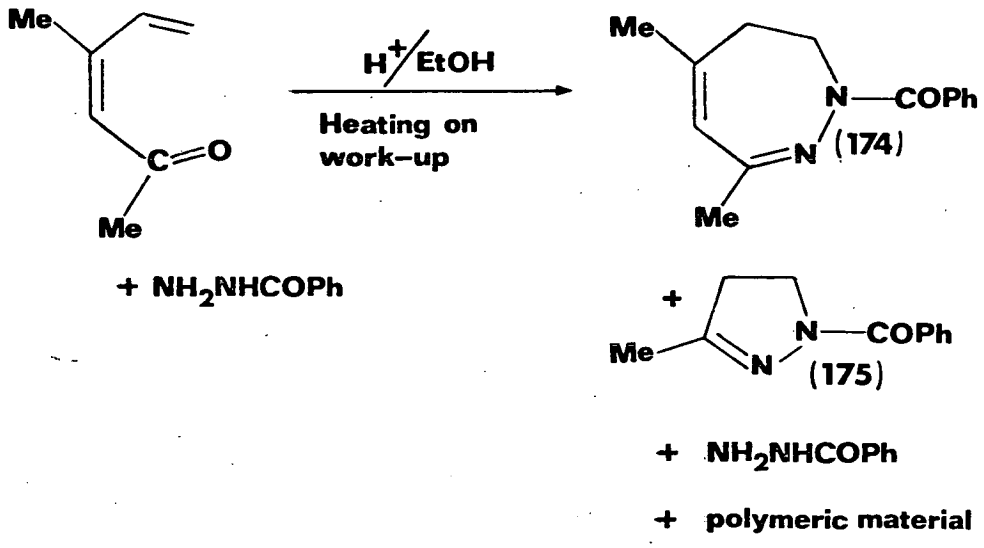
Thus the benzoyldiazepine (170) is probably similarly derived from the Z benzoylhydrazone. The yield of the benzoylhydrazone (169) itself is low. However, the condensation between benzoylhydrazide and the dienone is probably competing with a polymerisation process of the dienone. In the reaction of p-tosylhydrazine with the dienone it appears that the tosylhydrazone (171) is formed more readily in non-acidic conditions than the benzoylhydrazone (169).

The benzoylhydrazone which was isolated was converted to the benzoyldiazepine (173) by treatment with a little acid in ethanol. After chromatography the benzoyldiazepine (173) was obtained in 60% yield.



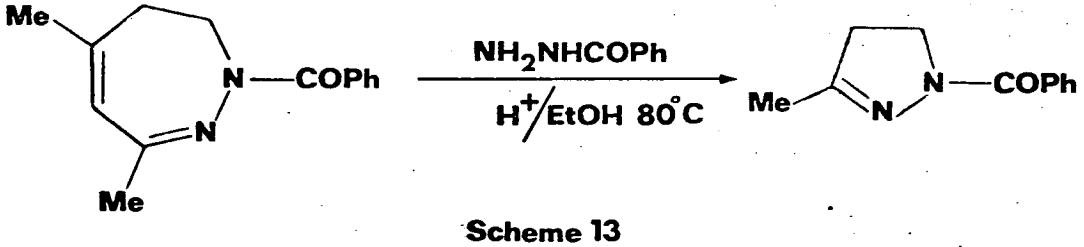
(173)

When 4-methylhexa-3,5-dien-2-one was stirred with benzoylhydrazide (167d) in ethanol with acid for four hours and after chromatography of the reaction mixture, the benzoyldiazepine (168d) was obtained in 44% yield. The only other material obtained from the reaction mixture was an intractable tar. It was found to be most important in the work-up of this reaction i.e. evaporation of the solvent, to keep any heating to a minimum. For example in one preparation of the benzoyldiazepine where heating was used in evaporation of the solvent the products obtained after chromatography were the benzoyldiazepine (174) (37%), 1-benzoyl-3-methylpyrazol-2-ine (175) (26%), benzoylhydrazide (8%) and also polymeric material.



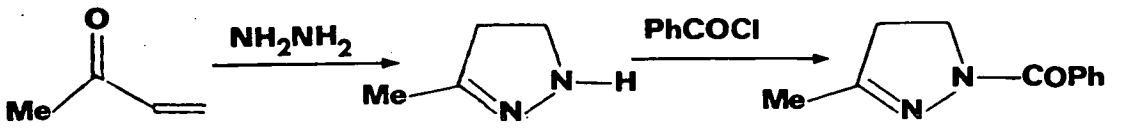
It was shown that the pyrazol-2-ine (175) was not a primary product, but rather a decomposition product of the benzoyldiazepine (174).

When the benzoyldiazepine was heated under reflux in ethanol containing acid and benzoylhydrazide it was converted to the benzoyl-pyrazoline in 56% yield, Scheme 13.



Scheme 13

1-Benzoyl-3-methylpyrazol-2-ine (175) is a known compound[199] and an authentic sample of it was prepared by the action of benzoyl chloride on 3-methyl-2-pyrazoline[198,199] which in turn was synthesised from methyl vinyl ketone and hydrazine hydrate, Scheme 14[198].

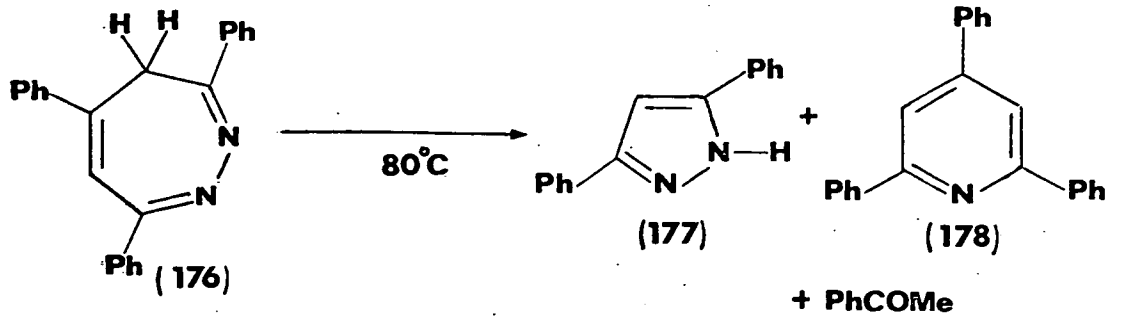


Scheme 14

The physical and spectral properties of the authentic benzoylpyrazoline and the one obtained from the benzoyldiazepine were identical and mixed melting points showed no depression.

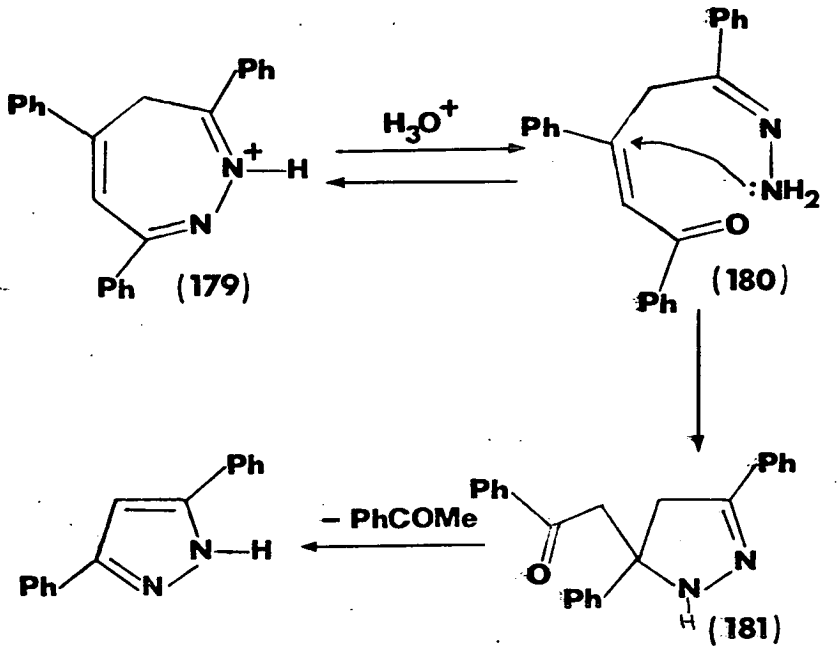
This type of rearrangement of a 1,2-diazepine to a five-membered diazaheterocycle is not entirely unknown.

Snieckus et al[200] have demonstrated that the fully unsaturated 3,5,7-triphenyl-4H-1,2-diazepine (176) when heated under reflux in 5N ethanolic HCl solution gives acetophenone, 3,5-diphenylpyrazole (177) and 2,4,6-triphenylpyridine (178). The 3,5-diphenylpyrazole (177) was obtained in 80% yield, the 2,4,6-triphenylpyridine (178) being a minor product.



It was postulated[200] that the rearrangement to the pyrazole proceeds in the following manner: protonation of the diazepine gives the 4H-1,2-diazepinium cation (179) which could by hydrolytic ring opening provide the non-cyclic intermediate (180). This latter type of compound is known to produce pyrazolines (181) in refluxing ethanol

solution under acidic conditions[201]. Furthermore the acid-catalysed reverse aldol reaction of pyrazolines to pyrazoles is known[202,203,204].



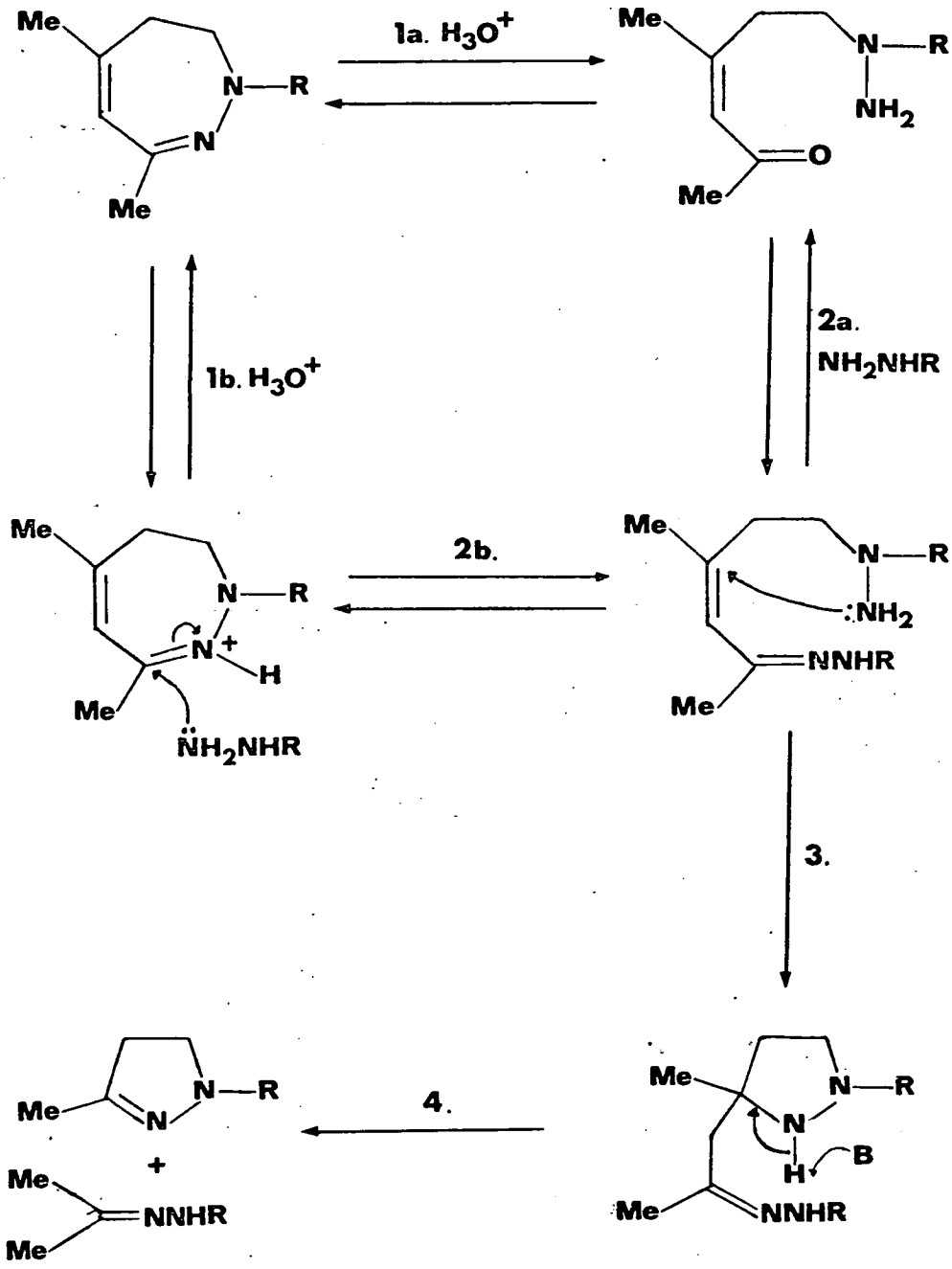
The 2,4,6-triphenylpyridine (178) is formed by ring contraction of the diazepine (176) to a diaziridine, ring cleavage to a pyridine N-imine and loss of a nitrogen fragment to give the substituted pyridine.

So with the rearrangement of a 4H-1,2-diazepine to a pyrazole in mind it is possible to postulate a somewhat similar mechanism for the rearrangement of 2-benzoyl-3,4-dihydro-5,7-dimethyl-1,2-diazepine to 1-benzoyl-3-methylpyrazol-2-ine, Scheme 13. However, this rearrangement is rather different in that it does not proceed in refluxing ethanol with acid, polymerisation occuring in this case; but the rearrangement does proceed when the diazepine is heated under reflux in ethanol containing acid and benzoylhydrazide. No reaction occurs if the diazepine is heated under reflux in ethanol containing benzoylhydrazide alone.

The conditions for the control reaction of diazepine to pyrazoline i.e. the amount of benzoylhydrazide and acid were chosen to approximate

to those present in the synthesis of the diazepine from benzoylhydrazide and the 2,4-dienone.

Two possible mechanisms proposed are shown in Scheme 15.



R=COPh

Scheme 15

Step 1a is the hydrolysis of the imine bond. The equilibrium in this step probably lies well to the left i.e. the diazepine is favoured. This is illustrated in a deuteration experiment (see Section 3E 2i)) where the tosyldiazepine analogue (R=Ts) was stirred in CH_3OD with acid at room temperature. No deuteration was obtained, the ring opened structure would have allowed deuterium incorporation *via* a keto-enol mechanism. Also, Snieckus[200] in his conversion of (176) ⟶ (177) used forcing conditions i.e. refluxing 5N ethanolic HCl for 24h. The benzoylhydrazide would thus be needed to drive the equilibrium to the right *via* formation of the hydrazone, Step 2a. The alternative mechanism, Step 1b, involves a primary protonation at nitrogen followed by nucleophilic attack by the benzoylhydrazide and ring opening to give the benzoylhydrazone, Step 2b.

Step 3 is the nucleophilic attack of the primary nitrogen on the carbon of the double bond bearing the methyl group in an intramolecular Michael-type condensation.

Step 4 produces the pyrazoline *via* abstraction of the proton on nitrogen and loss of acetone benzoylhydrazone by a reverse aldol-type of reaction. Acetone benzoylhydrazone was never isolated from this reaction, therefore re-examination of the reaction residues is necessary to confirm its formation.

The rearrangement of the 4*H*-1,2-diazepine (176) has the extra driving force of forming the fully aromatic final product (177), no such driving force being present in this rearrangement, Scheme 15.

The reaction of acetylhydrazide (167e) with 4-methylhexa-3,5-dien-2-one and acid in ethanol gave 2-acetyl-3,4-dihydro-5,7-dimethyl-1,2-diazepine (168e) as a yellow oil in 46% yield. The only other product obtained was polymeric material.

In the reaction of ethyl carbazate (167f) under the same conditions, with evaporation of the solvent carried out with little heating, the products obtained after chromatography were 2-carboethoxy-3,4-dihydro-5,7-dimethyl-1,2-diazepine (167f) as an oil (43%), 1-carboethoxy-3-methylpyrazol-2-ine (6%) and other polymeric material. The carboethoxy-pyrazoline is presumably formed from the diazepine in the same manner as the formation of the benzoylpyrazoline, Scheme 15.

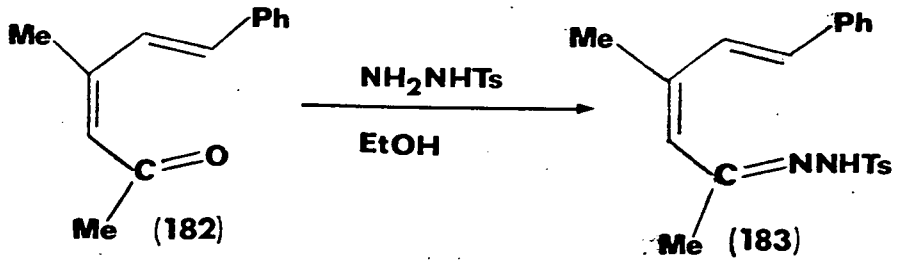
In all these diazepine syntheses some polymeric material was formed. This can be accounted for since 4-methylhexa-3,5-dien-2-one itself as shown later (Section 3 E 2ii)) is very susceptible to acid-catalysed polymerisation.

The spectral data of the diazepines (168b-f) was consistent with the assigned structures and was in agreement with the analagous tosyl-diazepine (168a)[173]. The spectral data of the benzoylhydrazone (169) and the pyrazolines (175) was consistent with the assigned structures.

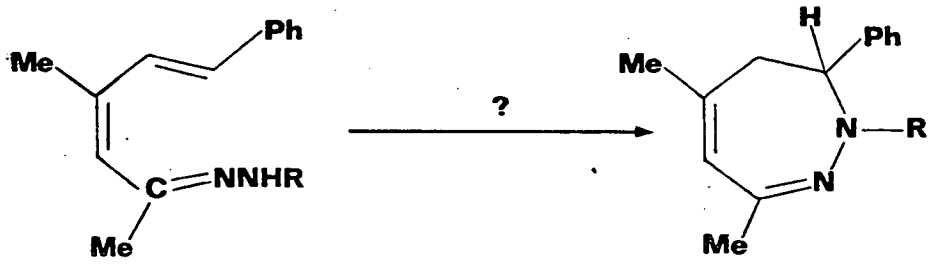
C. <u>The reaction of 4-methyl-6-phenylhexa-3,5-dien-2-one with methane-sulphonylhydrazine and acetylhydrazide.</u>

In the reaction of 2,4-dienones with p-tosylhydrazine there are a number of cases which give only the tosylhydrazones (163) rather than the tosyldiazepines[173] (see Section 3A).

One of these, is the reaction of 4-methyl-6-phenylhexa-3,5-dien-2-one (182) which gives the tosylhydrazone (183) only.



It was postulated[173] that this failure to cyclise to the diazepine might be due to steric hindrance of the phenyl group. When the phenyl group is replaced by a methyl group or by a hydrogen the diazepine is formed smoothly. It was thought possible that steric hindrance to the cyclisation might alternatively be reduced by decreasing the size of the N-substituent on the hydrazine so allowing the formation of the 3-phenyldiazepine, Scheme 16.

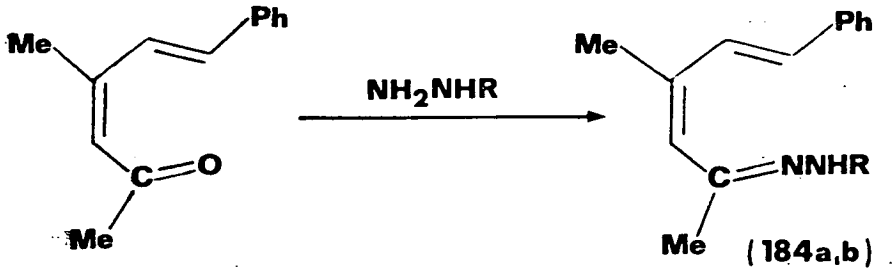


Scheme 16

The two groups chosen were the methanesulphonyl and acetyl.

1) Reactions of 4-methyl-6-phenylhexa-3,5-dien-2-one with methanesulphonylhydrazine and acetylhydrazide.

Under exactly the same conditions which allow the cyclisation to the diazepines (168a-f) of 4-methylhexa-3,5-dien-2-one and the hydrazines (167a-f), the hydrazones (184a,b) only were obtained in the reaction of the hydrazines (167c,e) with 4-methyl-6-phenylhexa-3,5-dien-2-one (182) (prepared in a multi-step sequence[173,205,206]).



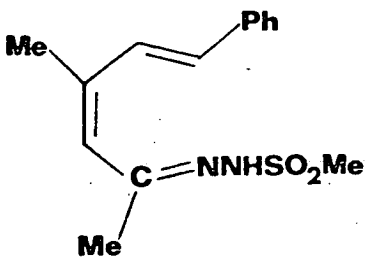
a R=SO_2Me
b =COMe

The spectral data of the hydrazones (184a,b) was consistent with the assigned structures and was comparable to that reported for (183)[173].

2) Attempted cyclisation of the methanesulphonylhydrazone (184a).

The hydrazone (184a) was stirred in methanol with a little acid for 2 days. T.l.c. of the reaction mixture showed at least 7 product spots. After chromatography the only pure material which was isolated was unreacted hydrazone (184a). Much polymeric material was also obtained.

A series of small scale reactions were performed under varying conditions and the reaction mixtures examined by T.l.c. The results of the attempted cyclisations of hydrazone (184a) are summarised below.

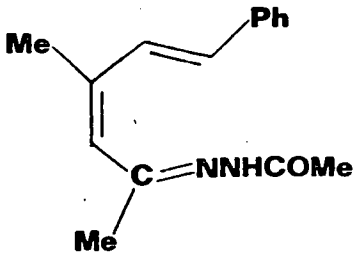


Conditions	Result
Reflux EtOH	No reaction
Reflux EtOH $+H^+$	Reversion to ketone and $MeSO_2NHNH_2$
D.B.U./ EtOH	No reaction
BF_3/MeOH	No products detected (loss of hydrazone)
BF_3/Et_2O	No reaction
BF_3/Et_2O Reflux	No products detected (loss of hydrazone)

In boiling ethanol, D.B.U. in ethanol and BF_3/ether the hydrazone was unchanged and no product spots could be detected. In boiling ethanol with acid there was reversion back to the ketone and methanesulphonylhydrazide and some polymerisation. Treatment with BF_3/Et_2O in the cold gave no reaction, although the hydrazone was complexed to the BF_3. Both BF_3/MeOH and BF_3/Et_2O (reflux) gave loss of the hydrazone but no products could be detected. These experiments parallel the work carried out on the tosylhydrazone (183)[173] which failed to cyclise under a variety of conditions.

3) Attempted cyclisation of the acetylhydrazone (184b).

The results of the attempted cyclisations of the hydrazone (184b) are summarised below (reaction mixtures examined by T.l.c.).



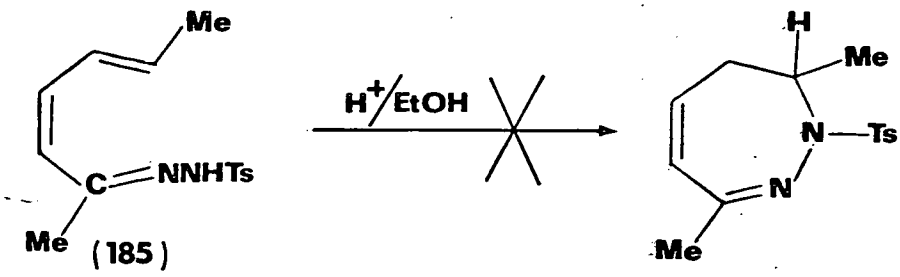
Conditions	Result
Reflux EtOH $+H^+$	Reversion to ketone and $COMeNHNH_2$ + polymerisation
D.B.U./EtOH	No reaction
BF_3/Et_2O	No reaction
BF_3/EtOH	No products detected (loss of hydrazone)
p-toluene-sulphonic acid /EtOH	No reaction

The results of the attempted cyclisations of the acetylhydrazone (184b) are similar to those of the methanesulphonylhydrazone (184a); treatment in refluxing ethanol with acid gave back ketone and hydrazide with polymerisation; D.B.U. in ethanol, BF_3/Et_2O and p-toluenesulphonic acid in ethanol gave no reaction. Treatment with BF_3/EtOH gave loss of the hydrazone but no product spots could be detected.

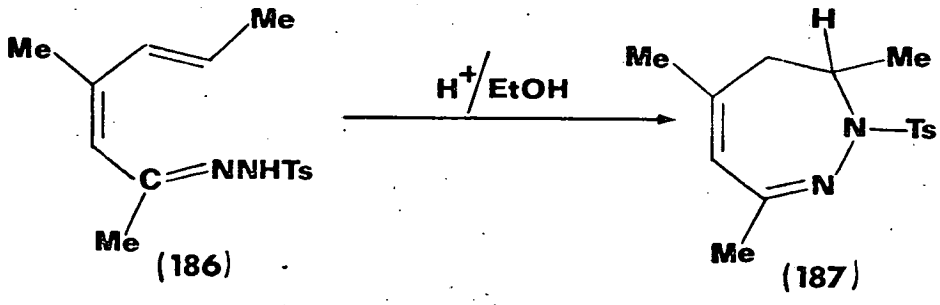
The results of the attempted cyclisation reactions of the hydrazones (183), (184a,b) are similar, i.e. under varying conditions no diazepines are formed. This failure of the smaller N-substituted hydrazones (184a,b) to cyclise to the 3-phenyldiazepines does not completely negate the hypothesis that it is steric hindrance of the phenyl group which prevents this cyclisation, but it does seem possible that other factors may be involved e.g. the electronic effect of the phenyl group. This is discussed in more detail in Section 3 E 3).

D. The reaction of hepta-3,5-dien-2-one with acetylhydrazide.

Hepta-3,5-dien-2-one tosylhydrazone (185) does not cyclise to the diazepine[173] under the standard reaction conditions.



This falure to cyclise to the diazepine is notable in that the hydrazone (185) differs from 4-methylhepta-3,5-dien-2-one tosylhydrazone (186) only in the absence of a methyl group at C-4, the tosylhydrazone (186) cyclising to the diazepine (187) smoothly in ethanol with a little acid.

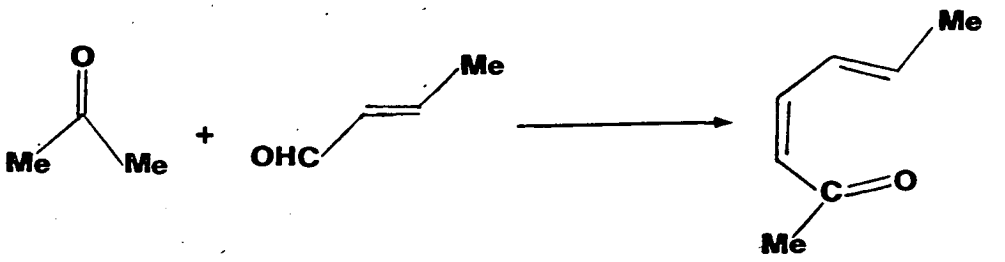


Obviously steric hindrance at the ring-closure site is not involved in the failure of the tosylhydrazone (185) to cyclise but it was thought worthwhile to check the generality of this result by using different hydrazones. The acetylhydrazone of hepta-3,5-dien-2-one was chosen for study.

1) Synthesis of hepta-3,5-dien-2-one and its reaction with acetylhydrazide.

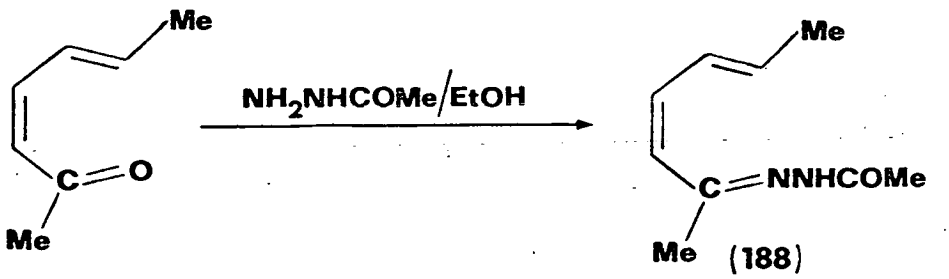
Hepta-3,5-dien-2-one was prepared by the reaction of acetone and

crotonaldehyde,[209] Scheme 17.



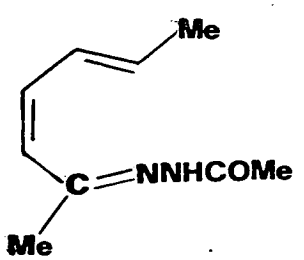
Scheme 17

When hepta-3,5-dien-2-one was stirred in ethanol with acetylhydrazide a precipitate of the acetylhydrazone (188) (56%) was formed. The spectral data of (188) was consistent with the assigned structure.



2) Attempted cyclisation of the acetylhydrazone (188).

A series of small scale reactions were performed to see if cyclisation could be obtained, the reactions were monitored by T.l.c. and the results are summarised below.



Conditions	Result
EtOH/dil H^+	Reversion to ketone and acetylhydrazide and polymerisation
EtOH/conc H^+	Reversion to ketone and acetylhydrazide and polymerisation

Conditions	Result
D.B.U./EtOH	No reaction
BF_3/Et_2O	Reversion to ketone and acetylhydrazide
BF_3/MeOH	No products detected (loss of hydrazone)

Treatment of the acetylhydrazone of hepta-3,5-dien-2-one (188) with acid in ethanol gave only reversion back to the starting materials and polymerisation. D.B.U./EtOH gave no reaction; although in BF_3/Et_2O the hydrazone was complexed to the BF_3 on work up only reversion back to ketone and acetylhydrazide was obtained. Treatment with BF_3/MeOH showed consumption of the hydrazone but no products could be detected.

Neither the tosyl- or the acetylhydrazone of hepta-3,5-dien-2-one (185), (188) will cyclise to the diazepine, consideration of this failure to cyclise on stereoelectronic grounds is given in Section 3 E 3).

E. Deuterium study of the reaction of 2,4-dienones with p-tosylhydrazine.

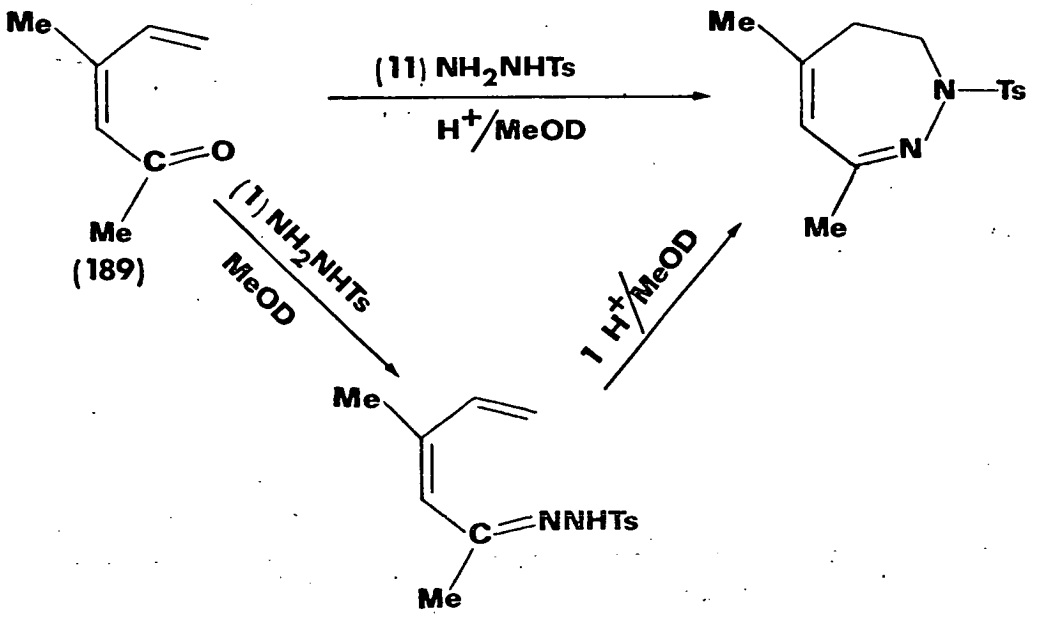
In an attempt to better understand the failure of some of the hydrazones (162a-e; 184a,b; 185) to cyclise to diazepines and to clarify the role of the acid catalyst in promoting the cyclisation of other hydrazones (157a-d, varying hydrazones of (156)) the reaction of 4-methylhexa-3,5-dien-2-one with p-tosylhydrazine in deuteromethanol (CH_3OD) was carried out in the presence and absence of acid.

1) Reactions of 4-methylhexa-3,5-dien-2-one with p-tosylhydrazine in deuteromethanol.

The amount of deuteration in the cyclised products was measured by the integrals of their ^1H n.m.r. spectra. Each integral was performed four times and the average taken. (The integral values are tabulated in the Appendix). The amount of deuteration was then

calculated from the integrals assuming no deuterium incorporation in the aromatic and methyl protons of the tosyl group.

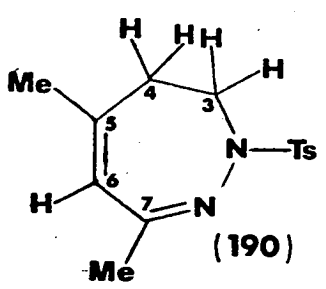
Two routes for the cyclisation to the diazepine were investigated (1) the indirect route and (11) the direct route (Scheme 18).



Scheme 18

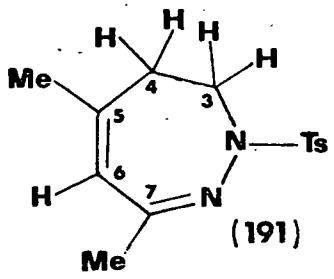
(1) Indirect route.

A mixture of the ketone (189) was stirred with p-tosylhydrazine in deuteromethanol overnight in the dark under nitrogen. A small amount of diazepine (190) (~6%) was formed even in the absence of acid. The reaction was repeated twice more, and the deuterium incorporation from their ^{1}H n.m.r. spectra is shown below.



Deuteration	C-3	C-4	C-6	5-Me	7-Me
	30%	45%	19%	16%	0%
	26%	46%	25%	16%	0%
	26%	38%	25%	12%	0%

To the filtrate in this reaction, containing the tosylhydrazone of 4-methylhexa-3,5-dien-2-one, was added sulphuric acid and the mixture was stirred in the dark under nitrogen at room temperature for 2h and the precipitated diazepine (191) was filtered off. This was repeated twice more and the ^{1}H n.m.r. spectra showed the deuterium incorporation, as shown below.



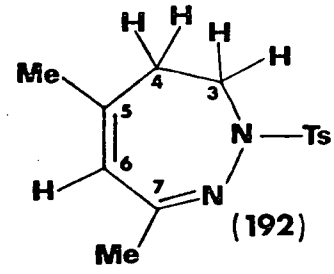
(191)

Deuteration

C-3	C-4	C-6	5-Me	7-Me
0%	58%	72%	9%	26%
0%	38%	61%	7%	22%
0%	42%	60%	5%	17%

(11) Direct route.

A mixture of the ketone (189), p-tosylhydrazine and sulphuric acid was stirred in deuteromethanol in the dark at room temperature under nitrogen for 2h and the precipitated diazepine (192) was filtered off. The deuterium incorporation was calculated from its ^{1}H n.m.r. spectrum. These results and those of a repeat* reaction are shown below.



(192)

Deuteration

C-3	C-4	C-6	5-Me	7-Me
0%	38%	64%	11%	15%
*0%	36%	76%	8%	18%

*Performed by C. D. Anderson.

2) Control experiments (For the integral values, see Appendix)

A number of control experiments were performed:-

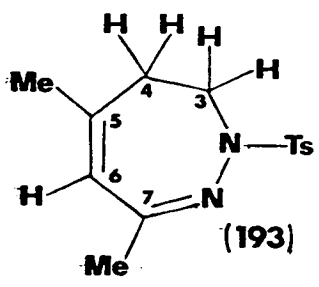
i) 2-Tosyl-3,4-dihydro-5,7-dimethyl-1,2-diazepine (158a) was not deuterated under the reaction conditions.

ii) 4-Methylhexa-3,5-dien-2-one (189) underwent acid catalysed exchange of its methyl protons (ca 17% deuteration after 10min) but not of the C-3 or other vinylic hydrogens. After 24h all the absorptions had diminished relative to that of the internal standard, probably due to acid-catalysed polymerisation. In a similar experiment the reaction mixture was distilled and the ketone (189) showed ca 25% deuteration of the methyl groups.

iii) 4-Methyl-6-phenylhexa-3,5-dien-2-one tosylhydrazone (183) only sparingly soluble in the acidified deuteromethanol was recovered in 77% yield after 18h and found to be deuterated in both methyl groups (ca 20%).

iv) Hepta-3,5-dien-2-one tosylhydrazone (185) was also sparingly soluble in acidified deuteromethanol, but was consumed more rapidly, only 37% being recovered after 1h. The recovered material showed no deuterium incorporation. In a similar reaction of duration 18h all the tosylhydrazone had dissolved and no pure product could be obtained.

3) Analysis of the results of the deuteration experiments.

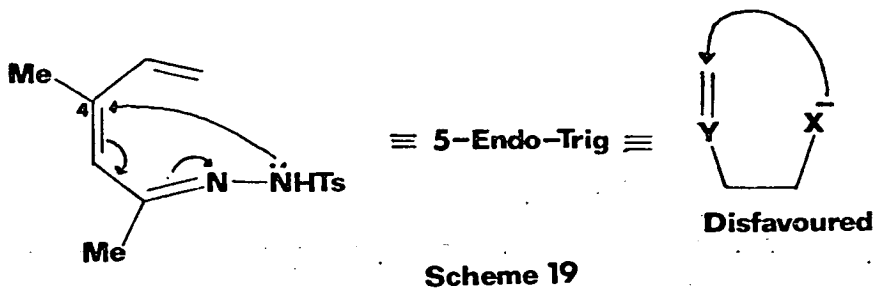


(193)

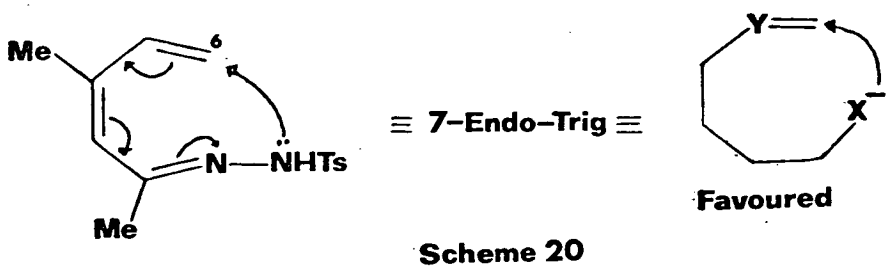
In the acid catalysed reactions both the direct and indirect routes (Scheme 18) gave diazepine products (193) with extensive deuteration at

C-4 and C-6 and some deuterium incorporation into the methyl groups at C-5 and C-7. There was no deuteration at C-3 but the ^1H n.m.r. absorption for this methylene group was changed from the triplet of the all-proton case to a doublet superimposed on a triplet showing that C-4 was predominantly mono- rather than di-deuterated.

Before proposing possible mechanisms for this cyclisation reaction it is interesting to look at it in the light of Baldwin's"Rules for ring closure"[53] (see Section F of the Introduction). Two internal Michael-type additions are possible for the hydrazone.



Scheme 19



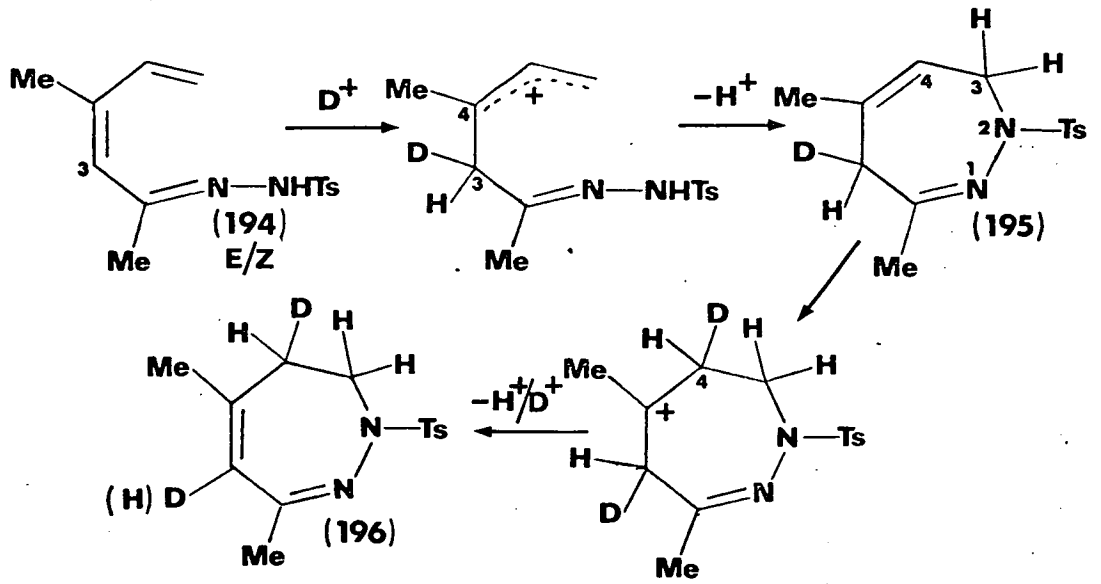
Scheme 20

One involves nucleophilic attack of the nitrogen on C-4 leading to a five-membered system, Scheme 19, this can be likened to a 5-Endo-Trig process in Baldwin's Rules. The other involves attack on C-6 leading to a seven-membered system, Scheme 20, this can be likened to a 7-Endo-Trig process.

Baldwin's rules state that a 5-Endo-Trig process is disfavoured whereas a 7-Endo-Trig process is favoured. This agrees with the experimental evidence i.e. diazepines are formed rather than the five membered pyrazolines.

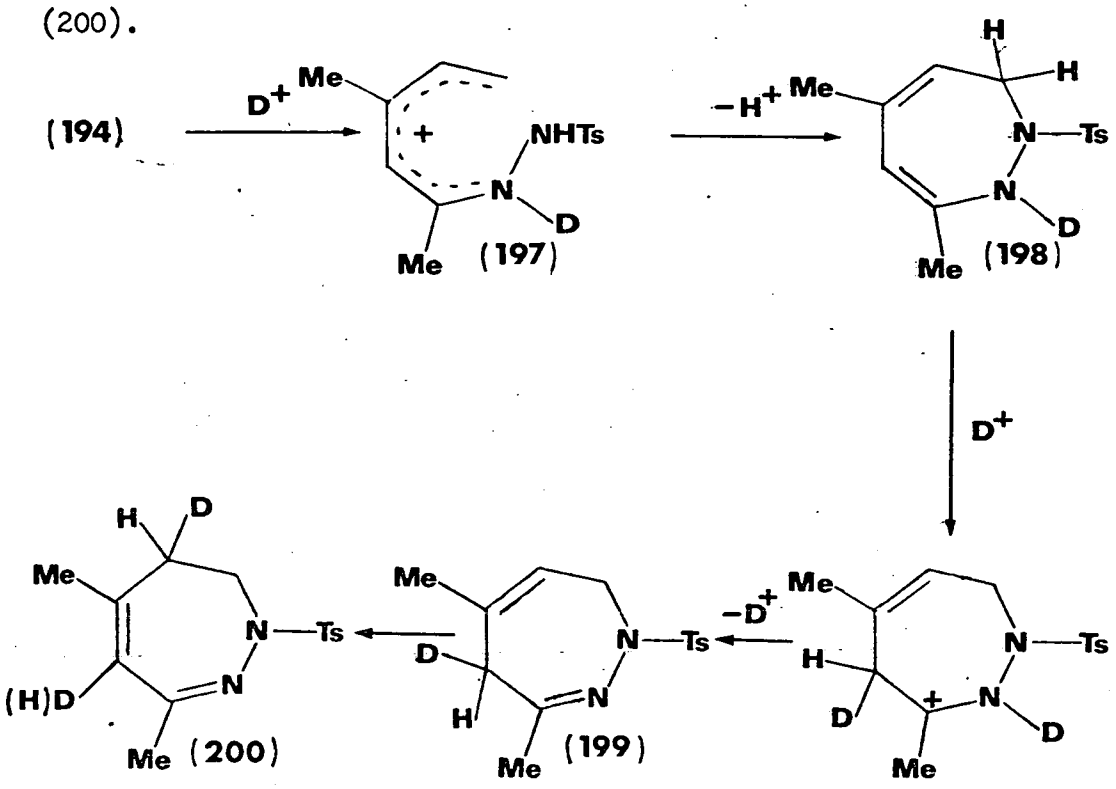
Two possible cyclisation mechanisms which are consistent with the deuteration study and with the formation of the diazepine from both the E and Z isomers of the ketone are shown in Schemes 21 and 22.

The first, Scheme 21, involves primary protonation at C-3 of the tosylhydrazone (194) which then allows rotation about the 3-4 bond, followed by ring closure and loss of the proton on nitrogen to give (195). Further protonation on C-4 of the ring would then allow its isomerisation to the conjugated and presumably more stable final product (196).



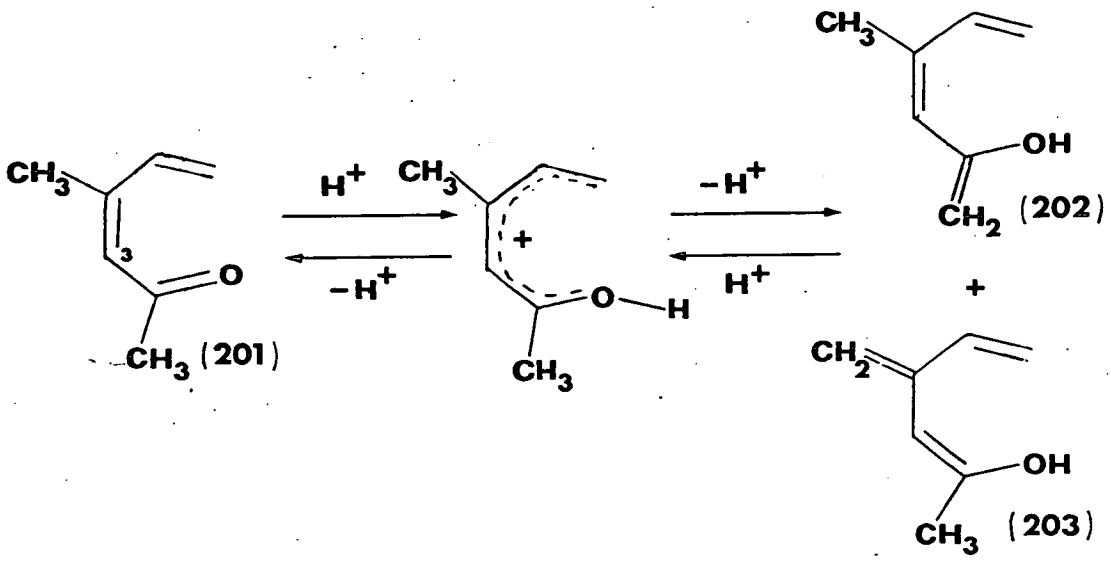
Scheme 21

The other mechanism, Scheme 22, involves initial protonation on nitrogen to give the highly delocalised carbonium ion (197) which on cyclisation would give (198). This compound, an ene-hydrazone analogue would isomerise to the hydrazone analogue (199) and then to the diazepine (200).

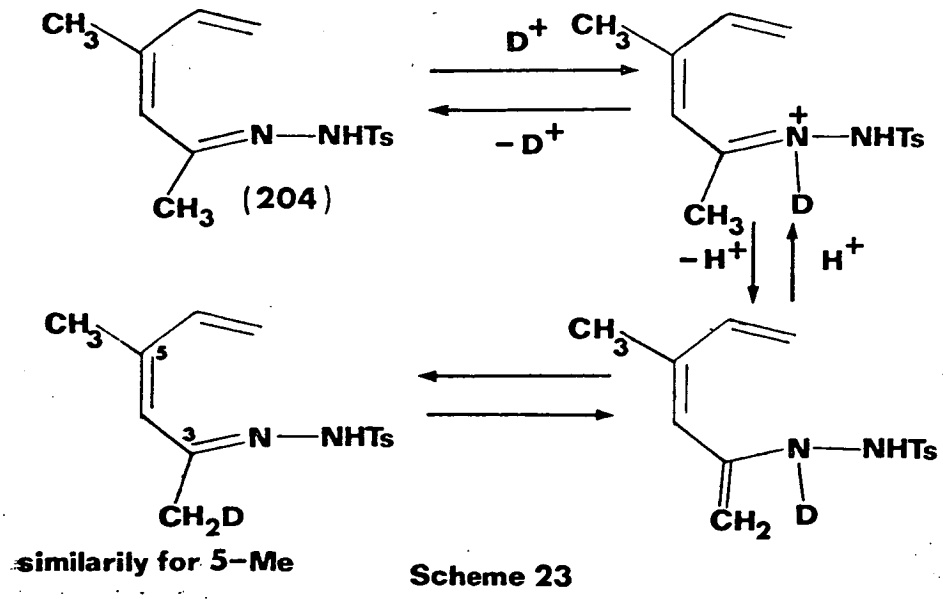


Scheme 22

The experimental results do not allow a conclusive differentiation between these two schemes. However the second of the schemes i.e. Scheme 22 is supported by the observation that 4-methylhexa-3,5-dien-2-one (201) protonates at oxygen rather than at C-3 i.e. there was deuterium incorporation into the methyl groups but not into the vinylic protons. The formation of the enol (202) and the extended enol (203) explains the deuterium incorporation into both methyl groups.



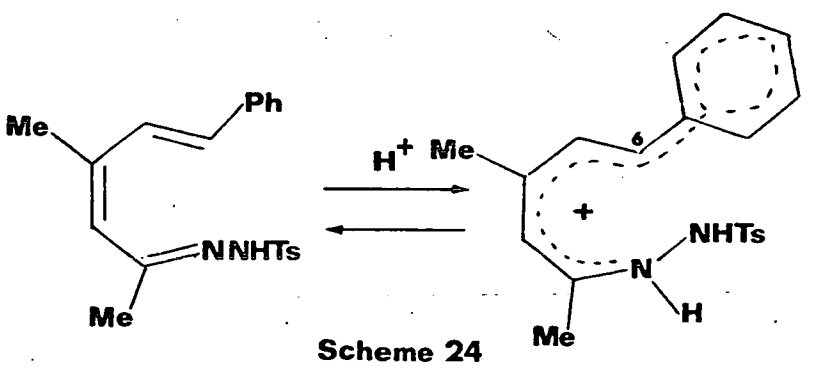
It seems likely that the hydrazone (204) will similarly protonate preferentially at nitrogen. That this does occur is supported by the observation that deuterium is incorporated into both methyl groups, via exchange in the hydrazone, Scheme 23,



Scheme 23

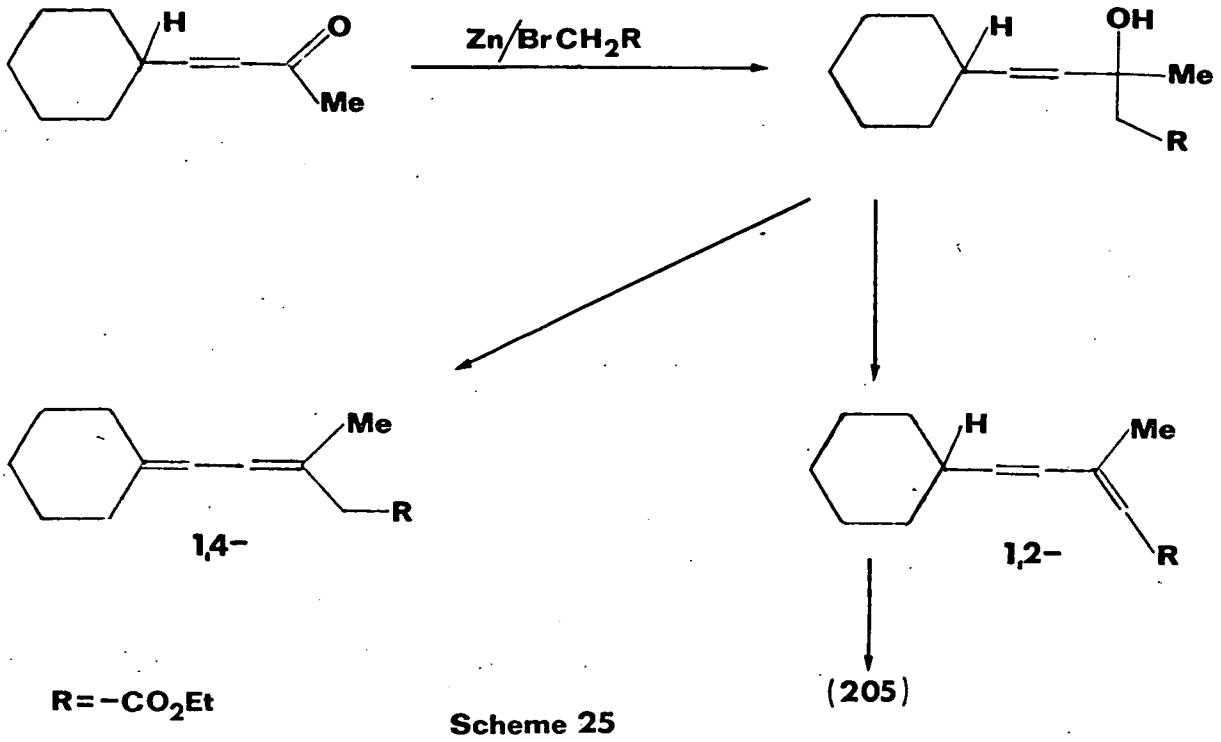
This exchange process explains the deuterium incorporation into both methyl groups, whereas the mechanism of Scheme 21 would lead to deuteration only in the 5-methyl group.

The deuteration experiments on the non-cyclisable tosylhydrazones (183),(185) help clarify the situation. The tosylhydrazone (183), when subjected to the reaction conditions that allow cyclisation of tosylhydrazone, Scheme 18, was found to be deuterated in both methyl groups indicating protonation at nitrogen. The non-cyclisation of (183) is therefore not a failure to give the protonated hydrazone but it may be due either to the conjugating effect of the phenyl group in reducing the positive charge density at C-6, Scheme 24, or to steric inhibition of ring closure.



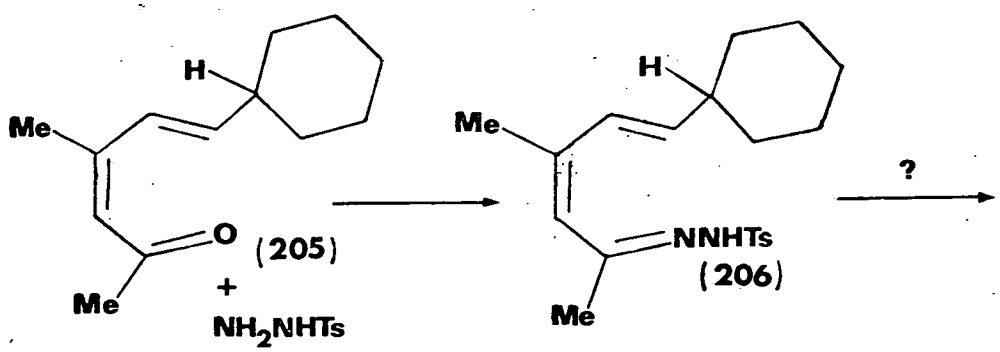
Scheme 24

To clarify this point i.e. to test for the conjugating effect of the phenyl group an attempt was made to prepare 4-methyl-6-cyclohexyl-hexa-3,5-dien-2-one (205). The method attempted was as for the preparation of 4-methyl-6-phenylhexa-3,5-dien-2-one; however this failed at the dehydration stage of the Reformatsky reaction, a number of isomers being formed due to 1,4-dehydration as well as the expected 1,2-dehydration, Scheme 25.

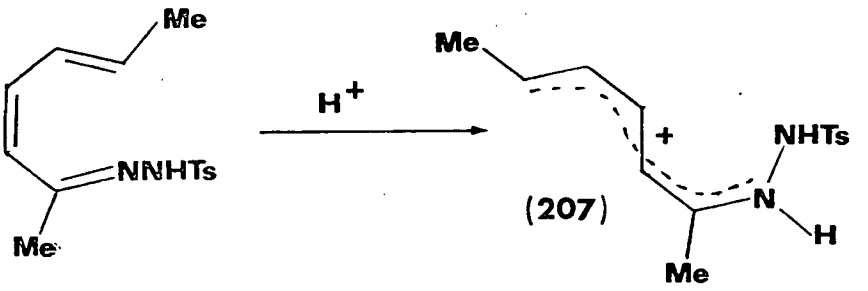


Scheme 25

Synthesis of the cyclohexylketone (205) is important because if cyclisation of its tosylhydrazone (206) to the diazepine were to occur it would imply that the reason for the failure of the tosylhydrazone (183) to cyclise was the conjugating effect of the phenyl group rather than steric inhibition by the phenyl group.



Under the reaction conditions that allow cyclisation, Scheme 18, the recovered tosylhydrazone (185) was found to have no deuterium incorporation. It seems possible however that protonation gives a species (207) which since it lacks the methyl group on the β-carbon atom possessed by all the cyclisable ketones[173], has a stereochemistry unfavourable to cyclisation and reacts rapidly by some other pathway - probably polymerisation.



In the slow non-acid catalysed cyclisation of 4-methylhexa-3,5-dien-2-one tosylhydrazone to the diazepine (190) the use of deuteromethanol as solvent did not produce any positive mechanistic information. The product diazepine (190) was extensively deuterated possibly due to the operation of ring closure/ring opening equilibria preceding product formation.

The cyclisation reaction, (157) ⟶ (158), has been extended to other N-substituted 1,2-diazepines and the mechanism rationalised by a study of the reaction in H^+/CH_3OD.

EXPERIMENTAL

INSTRUMENTATION

Thin-layer Chromatography (T.l.c.) - Chromatograms were obtained on 0.33mm layers of alumina (Merck Aluminium oxide G) containing Woelm fluorescent green indicator (0.5%). Preparative T.l.c. was performed with 1mm layers of the same alumina. Components in the developed chromatograms were detected by their quenching of fluoresence under u.v. light and/or their staining by iodine.

Column Chromatography - Alumina was Laporte Industries, Grade H, 100/200 mesh, prepared to the desired activity.

Medium Pressure Liquid Chromatography - These separations were obtained using Merck silica gel 60 (40-60 μm), tap-fill packed in glass columns (250x15mm, 1000x15mm, 1000x25mm (Quickfit Ltd.)) fitted with solvent resistant connectors and tubing (Jobling Corning) and safety valve (50p.s.i. : Budenburg Guage Co. Ltd.). The samples were preabsorbed onto silica and packed onto 250x15mm columns, these being used as 'pre-columns'.

The solvent systems used were based on petroleum ether 40/60 with varying amounts of ether. The flow rates (pump: Metering Pumps Ltd.) used were 5-20ml min^{-1} depending on column size and the separation required.

The eluent was monitored at 280nm (U.V. meter: Laboratory Data Control) and collected in a fraction collector (Central Ignition Company Ltd.). The fractions were also examined by T.l.c.

Nuclear Magnetic Resonance Spectroscopy (n.m.r.).

(a) Proton ^{1}H n.m.r spectra of routine samples were obtained on a Varian EM360 spectrometer. Spectra of new compounds and deuterium

studies were obtained on a Varian H100 spectrometer operated by Mr. J. Miller. Chemical shifts are recorded as delta (δ values) in parts per million, tetramethylsilane (δ=0.0) being the internal standard. (b) Carbon thirteen ^{13}C n.m.r. spectra were obtained on a Varian CFT20 spectrometer operated by Mr. J. Miller. Chemical shifts are recorded in parts per million, tetramethylsilane (=0.0) being the internal reference.

Mass Spectroscopy - Mass spectra were obtained using an Associated Electrical Industries MS902 instrument (70eV) using a direct insertion probe, operated by Mr. D. Thomas.

Infrared Spectroscopy (i.r.) - Liquid samples were examined as thin films and solid samples as Nujol mulls on a Perkin-Elmer 157G Grating Spectrophotometer.

Melting Points (m.p.)- The melting points of all compounds were obtained using a Kofler hot-stage apparatus.

Elemental Analysis - These were carried out in the Chemistry Department, University of Edinburgh, by Mr. J. Grunbaum using a Perkin-Elmer model 240 analyser.

SOLVENTS.

Solvents were normally redistilled and dried under the recommended conditions. The ethanol used was "Absolute alcohol" and was not dried. Deuterated solvents were obtained from the Aldrich Chemical Co. Ltd.

SYMBOLS AND ABBREVIATIONS.

The abbreviations used in this thesis are those in common usage.

EXPERIMENTAL.

1. Preparation of starting materials.

1) Benzalazine.

Benzalazine was prepared by the method of Curtius and Jay[165]. Freshly distilled benzaldehyde (85.11g, 0.802 mole) was stirred in ethanol (85ml). The reaction vessel was cooled in ice and hydrazine hydrate (20.72g, 0.414 mole) was added dropwise with stirring. A yellow precipitate was formed and this was filtered off and dried to yield benzalazine (83.50g,98.5%) m.p. 93°C (lit.[165], 93°C).

2) 1,2-Dibenzylhydrazine hydrochloride.

1,2-Dibenzylhydrazine hydrochloride was prepared by the method of Curtius[164]. Benzalazine (41.44g, 0.199 mole) was dissolved in ethanol (96%, 800ml) and reduced with vigorous stirring by sodium amalgam (37.55g Na, 890g Hg). Water (250ml) was added and the reaction mixture separated from the sodium amalgam. The reaction mixture was acidified with concentrated hydrochloric acid and the precipitate of 1,2-dibenzylhydrazine hydrochloride filtered off. This was recrystallised from ethanol as white plates (15.42g, 31%) m.p. 222-5°C (lit[164], 220-225°C), i.r. (Nujol) 3200cm^{-1} (N-H). ^{1}H N.m.r. (TFA) δ 4.50 (s, 4H, benzylic), 7.45 (s, 10H, aromatic).

The free 1,2-dibenzylhydrazine[164] was obtained by reaction of the hydrochloride salt with sodium hydroxide solution.

3) 1,1-Dibenzylhydrazine hydrochloride.

1,1-Dibenzylhydrazine hydrochloride was prepared by the method of Busch and Weiss[166]. Hydrazine hydrate (10g, 0.200mole) and benzyl

chloride (10g, 0.079mole) were heated under reflux in ethanol (80ml) under nitrogen for 1h. Hydrazine hydrochloride was filtered off and the filtrate was diluted with water (200ml) and extracted with ether (2 x 100ml). The ether extract was dried over magnesium sulphate, filtered and evaporated under reduced pressure to give a white solid which was recrystallised from ethanol to give 1,1-dibenzylhydrazine (2.40g, 10%). The 1,1-dibenzylhydrazine was acidified to give the hydrochloride and recrystallised from ethanol as white crystals (1.19g) m.p. 195-6°C (lit.[166], 200°C). ^{1}H N.m.r. (TFA) **δ** 4.60(s, 4H, benzylic), 7.61(s, 10H, aromatic).

4) 1-Methyl-2-phenylacetylhydrazine.

1-Methyl-2-phenylacetylhydrazine was prepared by the method of Theuer and Moore[168]. Ethyl phenylacetate (31.0g, 0.189 mole) and methylhydrazine (8.7g, 0.189 mole) were heated under reflux in ethanol (16ml) for 16h. The reaction mixture was cooled and the product precipitated out. This was filtered off and recrystallised from ethanol/ether to give 1-methyl-2-phenylacetylhydrazine (6.27g, 20%) m.p. 123-124°C (lit.[168], 126-127°C), i.r. (Nujol) 3250cm^{-1} (N-H), 1650cm^{-1} (C=O).

5) 2-Bromobenzyl bromide.

2-Bromobenzyl bromide was prepared by the method of Shoesmith and Slater[162] from 2-bromotoluene (48.7g, 0.285 mole) and bromine (48g, 0.6 mole) yielding (53.5g, 75%) b.p. 72-76°C at 0.4mm Hg (lit.[162], b.p. 129°C at 19mm Hg).

6) 2-Bromobenzyltriphenylphosphonium bromide.

2-Bromobenzyltriphenylphosphonium bromide was prepared by the

reaction of 2-bromobenzyl bromide (53.5g, 0.214 mole) with triphenylphosphine (56.1g, 0.214 mole) in boiling benzene (125ml). After 1.5h the product was filtered off and washed with benzene (106.8g, 97.5%) m.p. 195-197°C (lit.[163], 195-197°C).

7) 2-Bromostilbene as cis/trans mixture.

2-Bromostilbene was prepared by the reaction of 2-bromobenzyltriphenylphosphonium bromide (106.8g, 0.209 mole) with benzaldehyde (21.2g, 0.199 mole) in the presence of sodium ethoxide (sodium (4.76g, 0.207 mole) in R.R. ethanol (150ml) and benzene (600ml)).

The cis/trans mixture of 2-bromostilbene was obtained by distillation (39.3g, 73%) b.p. 117°C-122°C at 0.25mm Hg.

The cis/trans mixture was either brominated thus losing its stereochemistry or converted into the pure trans-form.

8) trans-2-Bromostilbene.

The cis/trans mixture of 2-bromostilbene (39.3g, 0.152 mole) was isomerised to the trans-form in boiling nitrobenzene (125ml) containing 2 crystals of iodine in 6h. Distillation gave the pure trans-isomer (33.5g, 85%) b.p. 114-120°C at 0.15-0.18mm Hg, m.p. 27.5-28°C (lit.[169], m.p. 27-28°C).

9) trans-2-Formylstilbene.

This was prepared by the method of Smith and Bayliss[170] using the Grignard reaction of trans-2-bromostilbene (31.2g, 0.122 mol) and magnesium (3.07g, 0.128 mole) in dry T.H.F. (50ml) and dry dimethylformamide (8.90g, 0.122 mole). The product, purified by dry-column chromatography, was obtained as a pale yellow oil (56%) b.p. 135-144°C at 0.20-0.26mm Hg, m.p. 80-82°C (lit.[171] m.p. 83°C).

^{1}H N.m.r. ($CDCl_3$)δ10.35 (s, 1H), 6.85-8.25 (m, 11H), i.r. (Nujol) 1690cm^{-1} (C=O).

10) 2-Bromostilbene dibromide.

To a cooled solution (salt/ice bath) of the cis/trans mixture of 2-bromostilbene (12.25g, 0.047 mole) in chloroform (15ml) was added dropwise with stirring a solution of bromine (2.25 ml, 0.087 mole) in chloroform (20ml). After the addition of the bromine solution the reaction mixture was allowed to warm up to room temperature. The reaction mixture was evaporated under reduced pressure to give a pale yellow powder of the dibromide which was recrystallised from ethanol (17.25g, 84%) m.p. 179-180°C (lit.[182], 179-181°C). ^{1}H N.m.r. ($CDCl_3$) δ 5.55 and 6.20(q, 2H, J_{HA-HB} 11Hz), 7.0-7.9 (m, 9H, aromatic).

11) o-Bromodiphenylacetylene.

The dehydrobromination was carried out following the procedure of Smith and Falkof[181]. 2-Bromostilbene dibromide (17.25g, 0.041 mole) was added slowly to a solution of potassium hydroxide (19g, 0.340 mole) in ethanol (35ml). As the dibromide was added the solvent started to boil. When all the dibromide had been added the reaction mixture was heated under reflux overnight. The reaction mixture was then cooled, poured into water (150ml) and extracted with ether (3x50ml), washed with water (2x25ml) and dried over magnesium sulphate. The ether extract was then filtered and evaporated under reduced pressure to give an orange oil (10.20g) which was distilled to give o-bromodiphenylacetylene (9.15g, 86%) b.p. 130°C at 0.15mm Hg (lit.[182], 155-160°C at 0.7mm Hg). ^{1}H N.m.r. ($CDCl_3$) δ 7.0-7.8 (m).

12) 2-Phenylethynylbenzaldehyde.

o-Bromodiphenylacetylene (2.00g, 7.8mmole) was stirred in sodium dried ether (5ml) under nitrogen at -30°C. To this was added slowly n-butyllithium (9.95ml of 1.58M solution in hexane, 15.7mmole). The solution was then stirred for 45min and a yellow suspension was formed. The reaction mixture was allowed to warm up to 0°C and stirred for 1h. Dry dimethyl formamide (1.2ml) was then added dropwise. The suspension went clear but after stirring for 5min a precipitate was formed. The reaction mixture was stirred overnight at room temperature. Saturated ammonium chloride (25ml) was added and the reaction mixture extracted with benzene (3x50ml), washed with water (2x25ml) and dried over magnesium sulphate. The solution was filtered and evaporated under reduced pressure to give an orange oil (2.0g).

The oil was distilled to give 2-phenylethynylbenzaldehyde as an orange oil (1.20g,75%) b.p. 150°C at 0.1mm Hg (Found: C, 87.2; H, 5.2. $C_{15}H_{10}O$ requires C, 87.35; H, 4.9). ^{1}H N.m.r. ($CDCl_3$) δ 10.64 (s, 1H, aldehydic), 7.1-8.0 (m, 9H, aromatic), i.r. (Film) 2200cm^{-1} (C≡C), 1690cm^{-1} (C=O).

13) N-β-Phenylethylformamide.

N-β-Phenylethylformamide was prepared by the method of Decker et al[175] from 2-phenylethylamine and formic acid in 87% yield b.p. 117-120°C at 0.5mm Hg (lit.[210], 192-196°C at 20mm Hg)

14) 3,4-Dihydroisoquinoline.

3,4-Dihydroisoquinoline was prepared by the method of Dale et al[176] from N-β-phenylethylformamide and polyphosphoric acid in 61% yield b.p. 50-52°C at 0.15mm Hg (lit.[176], 69-72°C at 2mm Hg).

15) 2-Formylstyrene.

2-Formylstyrene was prepared by the method of Dale et al[176] from the reaction of 3,4-dihydroisoquinoline with sodium hydroxide solution and dimethyl sulphate in 48% yield b.p. 105-107°C at 9mm Hg (lit.[176], 113-115°C at 18mm Hg). ^{1}H N.m.r. ($CDCl_3$) δ 10.30(s, 1H, aldehydic), 7.2-7.9 (m, 5H, aromatic), 5.3-5.8 (d-d, J 1.5Hz, J' 17Hz; d-d, J 1.5Hz, J" 11Hz; 3H, olefinic).

16) 2-(1,2-Dibromoethyl)benzaldehyde diethyl acetal.

This was prepared by an adaptation of the method of Ojima et al[174]. To a cooled solution of bromine (10ml, 0.377 mole) in chloroform (100ml) (salt-ice bath) a solution of 2-formylstyrene (24.0g, 0.185 mole) and hydroquinone (as an antioxidant)(0.20g) in chloroform (40ml) was added dropwise with stirring under nitrogen.

After the addition was complete the reaction mixture was allowed to warm up and the chloroform was removed under reduced pressure to give a dark green oil of the crude dibromide (72.5g).

The crude dibromide (72.5g), p-toluenesulphonic acid (1.56g, 0.009 mole), triethyl orthoformate (52ml, 0.313 mole) and ethanol (3ml) were heated under reflux in benzene (130ml) overnight under nitrogen. The reaction mixture was then cooled and stirred with potassium carbonate (10g, 0.09 mole) for 1h. The solution was filtered and stirred with decolourising charcoal for 10min. The solution was filtered and the solvent evaporated under reduced pressure to give a dark oil which on distillation yielded the acetal dibromide (45.22g, 68%) b.p. 115-120°C at 0.05mm Hg (lit.[174], value not quoted). ^{1}H N.m.r. ($CDCl_3$) δ 1.25 (t, J 8Hz, 6H), 3.60(q, J 7Hz, 4H), 4.05 (d, J 8Hz, 2H), 5.60(s, 1H), 6.01(t, J 7Hz, 1H) 7.1-8.0 (m, 4H).

17) 2-Ethynylbenzaldehyde.

2-Ethynylbenzaldehyde was prepared by an adaptation of the method of Ojima et al[174]. Potassium (5g, 0.128 mole) was dissolved in dry t-butyl alcohol (120ml). The excess t-butyl alcohol was evaporated under reduced pressure leaving potassium t-butoxide as a white powder. To this was added sodium dried benzene (100ml) and then 2-(1,2-dibromoethyl)benzaldehyde diethyl acetal (10g, 0.027 mole). The mixture was heated under reflux for 2h, cooled, and then poured into 6M hydrochloric acid (100ml) and heated under reflux for 1min. Ether (50ml) was added and the organic layer separated from the aqueous layer. The aqueous layer was further extracted with ether (2x50ml) and the organic fractions combined, washed with water (2x50ml) and dried over magnesium sulphate. The solution was filtered and the solvent removed under reduced pressure to give a dark brown solid (3.48g). Short path distillation gave 2-ethynylbenzaldehyde as white crystals (2.64g, 71%) b.p. 60°C at 0.1mm Hg, m.p 60°C (lit.[174], m.p. 60-60.5°C). ^{1}H N.m.r. ($CDCl_3$) δ 3.45 (s, 1H, acetylenic), 10.45 (s, 1H, aldehydic), 7.1-8.0 (m, 4H, aromatic).

18) 3-Methylpent-4-en-1-yn-3-ol.

This was prepared by the method of Cymerman et al[185]. A solution of methyl vinyl ketone (24g, 0.343 mole) in dry ether (250ml) was added with cooling (acetone/CO_2 bath) and stirring over 1.5h to a solution of sodium acetylide in ammonia prepared from sodium (35g, 1.52 mole) in liquid ammonia (1l) by the method of Vaughn et al[188]. After the addition was complete the reaction was stirred and cooled for a further 1.5h. Ammonium chloride (100g, 1.87 mole) was then added, and the ammonia allowed to evaporate off overnight.

The product was extracted with ether and distilled to give 3-methylpent-4-en-1-yn-3-ol (6.5g, 20%) b.p. 63-65°C at 100mm Hg (lit.[185], 63.5-64.5°C at 100mm Hg).

19) cis-3-Methylpent-2-en-4-yn-1-ol.

This was prepared by the method of Cymerman et al[185]. 3-Methylpent-2-en-4-yn-1-ol (6.5g, 0.067 mole) was shaken with sulphuric acid (110ml, 10% v/v) for 48h at room temperature under nitrogen. Ether extraction and distillation yielded the cis-3-methylpent-2-en-4-yn-1-ol (3.0g, 46%) b.p. 62-64°C at 9mm Hg (lit.[186], 65°C at 9.4mm Hg).

20) cis-3-Methylpent-2-en-4-yn-1-al.

This was prepared by the method of Boehm et al[187]. cis-3-Methylpent-2-en-4-yn-1-ol (2g, 0.021 mole) was shaken with manganese dioxide (20g, 0.230 mole) in methylene chloride (75ml) in the dark. The reaction was monitored by G.l.c. (2½% Carbowax 80°C). When all the alcohol had been consumed (3h) the reaction mixture was filtered and the manganese dioxide washed with hot methylene chloride. The solvent was removed under reduced pressure and distillation yielded the aldehyde (0.8g, 41%) b.p. 55-57°C at 10mm Hg (lit.[187], 58-60°C at 10mm Hg) as a pale yellow liquid. ^{1}H N.m.r. ($CDCl_3$) δ 2.15 (d, J 2Hz, 3H, $-CH_3$), 3.57 (s, 1H, acetylenic), 6.22 (d-q, J 2Hz, J' 8Hz, 1H, olefinic), 9.12(d, J 8Hz, 1H, aldehydic).

21) Homophthalaldehyde.

This was prepared by the method of Warnell and Shriner[189]. Freshly distilled indene (11.6g, 0.1 mole) in dry ethanol (500ml) was treated with ozone (3% solution in O_2) to give the ozonide. This was reduced by treatment with zinc and acetic acid. After

extraction with ether, homophthalaldehyde was distilled as a clear liquid (4.1g, 28%) b.p. 83°C at 0.1mm Hg (lit.[190], 93°C at 0.4mm Hg). ^{1}H N.m.r. ($CDCl_3$) δ 4.31(d, J 0.5Hz, 2H, benzylic), 7.2-8.1 (m, 4H, aromatic), 9.90(t, J 0.5Hz, 1H, aldehydic), 10.15 (s, 1H, aldehydic).

22) p-Toluenesulphonylhydrazine.

This was prepared by the method of Friedmann et al[177] (75%) m.p. 100-101°C (lit.[177],101-104°C).

23) Benzenesulphonylhydrazine.

This was prepared by the method of Friedmann et al[177] (60%) m.p. 103-105°C (lit.[178], 104-106°C).

24) Methanesulphonylhydrazine.

This was prepared by the method of Kloes[179]. A solution of methanesulphonyl chloride (22.9g, 0.2 mole) in dioxane (75ml) was added gradually to a mixture of hydrazine hydrate (17.5g, 0.35 mole) and sodium hydroxide (0.85g, 0.02 mole) in dioxane (100ml). The reaction mixture was then left standing for two days at room temperature. The precipitate formed was filtered off and the dioxane solution dried over potassium carbonate. The dioxane solution was filtered and evaporated under reduced pressure to give a yellow oil (17g) which solidified on standing. This was recrystallised from ethanol/ethyl acetate as white crystals (15.6g, 71%) m.p. 50°C (lit.[179], 52°C) of methanesulphonylhydrazine.

25) Benzoylhydrazide.

This was prepared by heating under reflux equimolar quantities of ethyl benzoate and hydrazine hydrate for 4h. After cooling and leaving overnight benzoylhydrazide (63%) was filtered off as white

plates m.p. 111-113°C (lit.[180] , 112.5°C).

26) Acetylhydrazide.

This was prepared by the method of Kost and Sagitullin[197] by heating under reflux a mixture of hydrazine hydrate, ethyl acetate and ethanol. Distillation gave the product (70%) b.p. 129-131°C at 18mm Hg (lit.[197] , 129-131°C at 18mm Hg).

27) Ethyl carbazate: was obtained from the Aldrich Chemical Co. Ltd.

28) 4-Ethoxypent-3-en-2-one.

This was prepared by the method of Claisen[194] from acetyl acetone, triethylorthoformate and ferric chloride in ethanol (23%) b.p. 78-81°C at 18mm Hg (lit.[195], 71-72°C at 15mm Hg).

29) 4-Methylhexa-3,5-dien-2-one.

This was prepared by the method of Normant[196] from the Grignard reagent of vinyl bromide in tetrahydrofuran and 4-ethoxypent-3-en-2-one (49%) b.p. 60°C at 15mm Hg (lit.[196], 55-56°C at 15mm Hg).

30) Hepta-3,5-dien-2-one.

This was prepared by the method of Meerwein[209] from acetone and crotonaldehyde (15%) b.p. 70°C at 12mm Hg (lit.[209], 70°C at 16mm Hg).

31) Ethyl 3-methyl-5-phenylpenta-2,4-dienoate.

This was prepared by the method of Cawley and Nelan[205] from the Reformatsky reaction of ethyl bromoacetate, benzalacetone and zinc in dry benzene (60%) b.p. 130-132°C at 0.4mm Hg (lit.[205] ,160-163°C at 4mm Hg).

32) 3-Methyl-5-phenylpenta-2,4-dienoic acid.

This was prepared by the method of Cawley and Nelan[205]. A mixture of ethyl 3-methyl-5-phenylpenta-2,4-dienoate (38g, 0.18 mole), potassium hydroxide (20g, 0.43 mole) and water (22.5ml) in ethanol (175ml) was kept overnight at room temperature. The reaction mixture was then heated almost to boiling point, cooled, washed with ether and acidified with concentrated hydrochloric acid to give the dienoic acid which was filtered off (27g) and recrystallised from ethanol (23.2g, 86%) m.p. 123-124°C (lit.[205], 125-125.5°C).

33) 3-Methyl-5-phenylpenta-2,4-dienoic acid chloride.

3-Methyl-5-phenylpenta-2,4-dienoic acid (23.2g, 0.12 mole) was stirred in dry benzene (130ml) and to this was added dropwise thionyl chloride (28.8g, 0.29 mole). This was stirred overnight and then heated under reflux for 1.3h. The benzene and excess thionyl chloride were evaporated under reduced pressure to give a brown solid (25g) which was distilled to give the acid chloride (19.7g, 77%) b.p. 130-133°C at 0.14mm Hg (lit.[173], 128-130°C at 0.09mm Hg).

34) 4-Methyl-6-phenylhexa-3,5-dien-2-one.

This was prepared using a method based on that of Heilbron et al[207]. A Grignard reagent was prepared from methyl iodide (15.8g, 0.111 mole) and magnesium (2.58g, 0.106 mole) in ether (60ml). This was cooled in ice to 0°C and anhydrous cadmium chloride (10.2g, 0.053 mole) added in one batch with vigorous mechanical stirring. After 30min at room temperature 3-methyl-5-phenylpenta-2,5-dienoic acid chloride (11.0g, 0.053 mole) in ether (80ml) was dripped in, and the reaction mixture was heated under reflux for 2h. After cooling the hydrolysis was carried out by the careful addition of

ammonium chloride (10%, 100ml). The aqueous layer was washed with ether (2x50ml) and the ether extracts combined with the organic layer, dried over magnesium sulphate, and evaporated under reduced pressure to give an oil (9.1g). Short path distillation gave the dienone as a yellow oil (5.3g, 54%) b.p. 103-105°C at 0.15mm Hg (lit.[208], 79-83°C at 0.03mm Hg).

35) 3-Methyl-2-pyrazoline.

This was prepared by the method of Elguero and Jacquier[198]. Methyl vinyl ketone (21g, 0.31 mole) was added dropwise with stirring to a solution of hydrazine hydrate (45g, 0.9 mole) in ethanol (15ml) and cooled in an ice bath. After the addition was complete the reaction mixture was heated under reflux for 2h. The solvent was then removed under reduced pressure, ether added, and then washed with a saturated solution of potassium carbonate. The ether extract was dried over potassium carbonate, filtered, evaporated under reduced pressure and distilled to give 3-methyl-2-pyrazoline (2.5g, 10%) b.p. 56°C at 15mm Hg (lit.[198], 58°C at 17mm Hg). ^{1}H N.m.r. ($CDCl_3$) δ 2.03 (d, J 1Hz, 3H, $-CH_3$), 2.65 (d-t, J 10Hz, J' 1Hz, 2H, $-CH_2$), 3.35 (d-t, J 10Hz, J' 2Hz, 2H, $-CH_2$), 4.91(s, broad, 1H, NH).

36) 1-Benzoyl-3-methylpyrazol-2-ine.

This was prepared by the method of Auwers and Ludewig[199]. 3-Methyl-2-pyrazoline (0.5g, 5.9mmole) was mixed with ice cold dry pyridine (2ml). Benzoyl chloride (0.9g, 6.4mmole) was added cautiously dropwise. There was a vigorous reaction and a precipitate was formed. This was left at room temperature for 30min. Ether (10ml) was added and to this dilute sulphuric acid (5ml) was added dropwise with stirring. The precipitate was filtered off and recrystallised from ethanol (0.76g, 68%) m.p. 98.5°C-99°C (lit.[199], 98.5-99.5°C). ^{1}H N.m.r., i.r., mass spectra, see Appendix.

2. Reactions of aromatic aldehydes with 1,2-dibenzylhydrazine.

I) trans-2-Formylstilbene.

1,2-Dibenzylhydrazine hydrochloride (1.79g, 7.20mmole), pyridine (0.571g, 7.22mmole) and trans-2-formylstilbene were heated under reflux in dry toluene (25ml) with stirring under nitrogen for 1h. T.l.c. (alumina, petroleum ether(40/60)/ether: 95%/5%) of the reaction mixture showed the consumption of the trans-2-formylstilbene and the formation of a single product. The solution was cooled and washed with water (2x50ml), dried over magnesium sulphate, filtered, and the filtrate evaporated under reduced pressure to give a yellow oil (1.85g) which slowly solidified. This was recrystallised from ethanol to give benzaldehyde benzyl(2-stilbenylbenzyl)hydrazone as off-white crystals (1.41g, 73%) m.p. 98.5-99°C. (Found: C, 86.5; H, 6.5; N, 7.0. $C_{29}H_{26}N_2$ requires C, 86.2; H, 6.5; N, 7.0%). ^1H N.m.r., i.r., mass spectra, see Appendix.

II) p-Chlorobenzaldehyde.

a) With pyridine.

1,2-Dibenzylhydrazine hydrochloride (1.36g, 5.47mmole), pyridine (0.435g, 5.50mmole) and p-chlorobenzaldehyde (0.514g, 3.66mmole) were heated under reflux with stirring in sodium dried toluene (25ml) under nitrogen for 1h. The insoluble material was filtered off and the filtrate evaporated under reduced pressure to give a yellow oil (1.15g). This was crystallised from ethanol to give benzaldehyde benzyl(p-chlorobenzyl)hydrazone as whitecrystals(0.464g, 38%) m.p. 65-67°C. ^1H N.m.r., i.r., mass spectra, see Appendix.

b) With sodium carbonate.

1,2-Dibenzylhydrazine hydrochloride (0.683g, 2.75mmole), anhydrous

sodium carbonate (0.319g, 3.01mmole) and p-chlorobenzaldehyde (0.258g, 1.84mmole) were heated under reflux with stirring in sodium dried toluene (15ml) under nitrogen for 2h. T.l.c. (alumina, petroleum ether(40/60)/ether: 95%/5%) showed the loss of p-chlorobenzaldehyde and the formation of the hydrazone. The inorganic residue was filtered off and the filtrate evaporated under reduced pressure to give an oil (0.817g) which was crystallised from ethanol to give white crystals of benzaldehyde(p-chlorobenzyl)hydrazone (0.488g, 80%) m.p. 67-67.5°C. (Found:C, 75.1; H, 5.7; N, 8.3. $C_{21}H_{19}N_2Cl$ requires C, 75.3; H, 5.7; N, 8.4%). ^1H N.m.r., ^{13}C n.m.r., i.r., mass spectra, see Appendix.

c) With free 1,2-dibenzylhydrazine.

1,2-Dibenzylhydrazine (0.610g, 2.87mmole) and p-chlorobenzaldehyde (0.392g, 2.80mmole) were heated under reflux with stirring in sodium dried toluene (15ml) under nitrogen for 3h.

T.l.c. showed the loss of p-chlorobenzaldehyde and the formation of the hydrazone. The toluene was evaporated under reduced pressure to give a yellow oil (0.690g). This could not be crystallised from ethanol. The oil was purified by chromatography (alumina Grade I, petroleum ether(40/60)/ether: 90%/10%). The oil (0.420g) so obtained was crystallised from ethanol to give benzaldehyde benzyl(p-chlorobenzyl) hydrazone (0.405g, 45%) m.p. 60.5-62°C with impurities of benzaldehyde dibenzylhydrazone and p-chlorobenzaldehyde benzyl(p-chlorobenzyl) hydrazone ca 13% by H.p.l.c. (15x0.5cm S5y Spherisorb silica, 50% water saturated hexane: dioxane/10:1, 2.5ml min^{-1}). ^1H N.m.r., ^{13}C n.m.r., i.r., mass spectra, see Appendix.

d) Exchange reaction of benzaldehyde dibenzylhydrazone with p-chlorobenzaldehyde.

Benzaldehyde dibenzylhydrazone (0.250g, 0.833mmole) and p-chlorobenzaldehyde (0.587g, 4.18mmole) were heated under reflux in dry toluene (15ml) under nitrogen with stirring for 5h. The toluene was evaporated under reduced pressure and the hydrazone (0.207g) recovered by 'dry column' chromatography (alumina, Grade III, benzene).

The hydrazone was recrystallised from ethanol as a white powder (0.125g, 50%) m.p. 75-76°C. Mass spectral examination showed this was mostly benzaldehyde dibenzylhydrazone but did contain ca 0.5% of p-chlorobenzaldehyde dibenzylhydrazone. Mass spectrum, see Appendix.

III) p-Methoxybenzaldehyde.

1,2-Dibenzylhydrazine hydrochloride (0.733g, 2.95mmole), sodium carbonate (0.333g, 3.14mmole) and p-methoxybenzaldehyde (0.284g, 2.09mmole) were heated under reflux with stirring in sodium dried toluene (15ml) under nitrogen for 3h. T.l.c. (alumina, petroleum ether (40/60)/ether: 95%/5%) of the reaction mixture showed the loss of p-methoxybenzaldehyde. The insoluble material was filtered off and the toluene removed under reduced pressure to give an oil (0.896g). This was crystallised from ethanol to give benzaldehyde benzyl(p-methoxybenzyl)hydrazone as white crystals (0.497g, 72%) m.p. 89.5-90.5°C. (Found: C, 79.8; H, 6.7; N, 8.4. $C_{22}H_{22}N_2O$ requires C, 80.0 ; H, 6.7; N, 8.5%). ^1H N.m.r., i.r., mass spectra, see Appendix.

IV) Benzaldehyde.

a) With sodium carbonate.

1,2-Dibenzylhydrazine hydrochloride (0.466g, 1.87mmole), sodium carbonate (0.233g, 2.20mmole) and freshly distilled benzaldehyde

(0.132g, 1.24mmole) were heated under reflux with stirring in dry toluene (10ml) under nitrogen for 1h. The inorganic residue was filtered off and the filtrate evaporated under reduced pressure to give a yellow oil (0.501g). This was crystallised from ethanol to give benzaldehyde dibenzylhydrazone as white crystals (0.288g, 77%) m.p. 80-81°C. ^{1}H N.m.r., i.r., mass spectra, see Appendix.

b) Equimolar reaction in the presence of sodium carbonate.

1,2-Dibenzylhydrazine hydrochloride (0.306g, 1.23mmole) and sodium carbonate (0.065g, 0.613mmole) were heated under reflux in degassed, sodium dried toluene (10ml) with stirring under nitrogen for 5min. This was cooled and benzaldehyde (0.131g, 1.23mmole) was added. The reaction mixture was heated under reflux for 1h. It was then cooled, the inorganic residue was filtered off and the filtrate evaporated under reduced pressure to give an oil (0.320g). This was crystallised from ethanol to give benzaldehyde dibenzylhydrazone as white crystals (0.246g, 64%) m.p. 79.5-80.5°C.

c) In the absence of base.

1,2-Dibenzylhydrazine hydrochloride (73mg, 0.293mmole) and benzaldehyde (21mg, 0.198mmole) were heated under reflux in sodium dried toluene (5ml) under nitrogen. The reaction mixture was filtered and evaporated under reduced pressure to give an oil (45mg). This was crystallised from ethanol to give benzaldehyde dibenzylhydrazone as white crystals (25mg, 50%) m.p. 80-81°C.

d) In the presence of base and dimethyl fumarate.

1,2-Dibenzylhydrazine hydrochloride (0.933g, 3.75mmole), pyridine (0.327g, 4.14mmole), benzaldehyde (0.266g, 2.51mmole) and dimethyl fumarate (0.434g, 2.52mmole) were heated under reflux with stirring

in dry toluene (15ml) under nitrogen for 1h. The reaction mixture was cooled and filtered and the filtrate evaporated under reduced pressure to give a yellow oil. The dimethyl fumarate was removed under high vacuum to give an oil (1.150g). This oil was triturated with petroleum ether (40/60) to yield a white solid which was filtered and recrystallised from ethanol to give benzaldehyde dibenzylhydrazone (0.701g, 93%) m.p. 74-75°C. Further recrystallisation (87% recovery, overall yield 80%) from ethanol gave m.p. 81-82°C.

Preparation of authentic benzaldehyde dibenzylhydrazone.

1,1-Dibenzylhydrazine hydrochloride (0.185g, 0.744mmole), sodium acetate (0.110g, 1.34mmole) and benzaldehyde (0.079g, 0.744mmole) were stirred in dry toluene (10ml) in the cold for 2h. T.l.c. (alumina, petroleum ether(40/60)/ether: 95%/5%) showed the consumption of the benzaldehyde. The inorganic residue was filtered off, and the filtrate evaporated under reduced pressure to give a yellow oil (0.249g) which solidified on standing. This was recrystallised from ethanol to give benzaldehyde dibenzylhydrazone as white crystals (0.185g, 66%) m.p. 80-81°C (lit.[167], 85°C), ^{1}H n.m.r., i.r., mass spectra, see Appendix.

V) Deuterium labeling study of the reaction of 1,2-dibenzylhydrazine hydrochloride and trans-2-formylstilbene.

a) 1,2-Dibenzylhydrazine hydrochloride (0.302g, 1.21mmole) was dissolved in boiling deuterium oxide (10ml) under dry nitrogen. The solution was cooled and the 1,2-dibenzylhydrazine hydrochloride crystallised out. This was repeated and the deuterated 1,2-dibenzylhydrazine hydrochloride (0.127g) was obtained m.p. 220-223°C (lit.[164], 220-225°C). Mass spectral data showed this to be 72% tri-deuterated, 18% di-deuterated and 10% mono-deuterated on the nitrogen atoms; mass spectrum, see Appendix.

The deuterated 1,2-dibenzylhydrazine hydrochloride (0.127g, 0.505mmole) was heated under reflux with trans-2-formylstilbene (0.072g, 0.346mmole) and sodium carbonate (0.059g, 0.555mmole) in dry toluene (10ml) with stirring under nitrogen for 1h. The reaction mixture was cooled and the inorganic residue filtered off and washed with a little toluene. The filtrate was evaporated under reduced pressure to give a yellow oil (0.166g) which solidified on standing. This was recrystallised from ethanol to give benzaldehyde benzyl(2-stilbylbenzyl)hydrazone (0.060g, 43%). A repeat experiment on the same scale gave (0.076g, 55%). The hydrazone by its ^{1}H n.m.r. spectrum was ca 55% deuterated in one of the benzyl protons of the 2-stilbylbenzyl group. ^{1}H N.m.r., mass spectra, see Appendix.

b) Control experiments.

1) Benzaldehyde benzyl(2-stilbylbenzyl)hydrazone (0.053g, 0.132mmole), deuterated 1,2-dibenzylhydrazine hydrochloride (0.034g, 0.135mmole), sodium carbonate (0.016g, 0.151mmole) and D_2O (2.6µl) were heated under reflux with stirring in toluene (10ml) for 1h under nitrogen. The reaction mixture was cooled, filtered and the filtrate evaporated under reduced pressure to give a yellow oil (0.083g) which was crystallised from ethanol as a white powder (0.026g, 50% recovery) of benzaldehyde benzyl(2-stilbylbenzyl)hydrazone, the ^{1}H n.m.r. spectrum showed no deuteration. ^{1}H N.m.r. spectrum, see Appendix.

2)The deuterated hydrazone (0.026g, 0.006mmole) was recrystallised twice from ethanol to yield (0.009g, 35%), the ^{1}H n.m.r. spectrum showed no loss of deuteration on recrystallisation. ^{1}H N.m.r. spectrum see Appendix.

3. The reaction of 1-methyl-2-phenylacetylhydrazine with trans-2-formylstilbene.

1-Methyl-2-phenylacetylhydrazine (0.967g, 5.90mmole) and trans-2-formylstilbene (1.178g, 5.66mmole) were heated under reflux with stirring in tertiary-butylbenzene (20ml) under nitrogen for 6h. A Soxhlet extractor with molecular sieve was used to aid the condensation reaction. The reaction mixture was cooled and the solvent removed under reduced pressure to give an oil (2.032g). This oil was triturated with ether to give a white powder (0.314g). The remaining oil (1.710g) was analysed by dry column chromatography (alumina Grade III, benzene); 4 fractions were obtained.

The first, (0.116g) was unreacted trans-2-formylstilbene. The second (0.306g) contained 5 components by T.l.c. (alumina, petroleum ether (40/60)/ether: 70%/30%). The third, (0.233g) was by T.l.c. (as above) the same product as obtained by trituration. These were combined and recrystallised from ethanol to give white crystals (0.400g) m.p. 118°C. ^{1}H N.m.r, ^{13}C n.m.r., i.r., mass spectra see Appendix. The fourth, (0.615) by T.l.c. (alumina, petroleum ether (40/60)/ether: 30%/70%) contained 6 spots including unreacted 1-methyl-2-phenylacetylhydrazine.

4. Reactions of 2-ethynylbenzaldehyde with hydrazines and cyclisation reactions of the hydrazones.

I) p-Toluenesulphonylhydrazine.

a) Preparation of hydrazone.

2-Ethynylbenzaldehyde (0.600g, 4.61mmole), p-toluenesulphonylhydrazine (0.900g, 4.83mmole) and concentrated hydrochloric acid (2 drops) were stirred in ethanol (15ml) in the dark under nitrogen

for 1 hour at room temperature. T.l.c. (alumina, petroleum ether (40/60)/ether: 95%/5%) showed the loss of 2-ethynylbenzaldehyde and the appearance of a slower running spot.

The solvent was removed under reduced pressure to give the crude 2-ethynylbenzaldehyde p-toluenesulphonylhydrazone (1.373g, 98%) as a yellow oil. (Found: m/e 298.075473. $C_{16}H_{14}N_2O_2S$ requires m/e 298.077554). ^1H N.m.r., mass spectra, see Appendix. Attempts at purification of the hydrazone failed, yielding only tarry material.

The crude hydrazone (1.373g) was dissolved in ethanol (15ml) and to this was added sodium carbonate (4g, 0.04 mole) and water (2ml). The reaction mixture was then stirred in the dark under nitrogen for 18h at room temperature. Water (50ml) was added and the mixture was extracted with methylene chloride (2x50ml). The organic extract was dried over magnesium sulphate, filtered and the solvent removed under reduced pressure to give a slightly yellow powder (1.20g) which was recrystallised from ethanol to give isoquinoline N-p-toluenesulphonylimine (0.642g, 47%) m.p. 226-227°C (lit.[141], 228-229°C). The ^1H n.m.r. and i.r. spectra were identical to those reported[141].

On evaporation of the mother liquors a dark oil (0.558g) was obtained. This however, appeared to be polymeric in nature and chromatography (alumina Grade I) yielded no identifiable products.

b) Cyclisation with sodium carbonate.

2-Ethynylbenzaldehyde (0.200g, 1.54mmole), p-toluenesulphonylhydrazine (0.300g, 1.61mmole) and concentrated hydrochloric acid (2 drops) were stirred at room temperature in the dark in ethanol (10ml) under nitrogen for 1h. T.l.c. (alumina, petroleum ether (40/60)/ether: 95%/5%) showed the loss of 2-ethynylbenzaldehyde

and the appearance of a slower running spot corresponding to the tosylhydrazone of 2-ethynylbenzaldehyde.

Sodium carbonate (3g, 0.03 mole) and water (1ml) were added and the reaction mixture was stirred in the dark for a further 24h at room temperature. T.l.c. showed the loss of the hydrazone intermediate. Water (25ml) was added and then extracted with methylene chloride (2x 50ml). The methylene chloride extract was dried over magnesium sulphate, filtered and the solvent evaporated under reduced pressure to give an off-white solid (0.372g). Recrystallisation from ethanol gave isoquinoline N-p-toluenesulphonylimine as white crystals (0.218g, 48%) m.p. 226.5-228.5°C (lit.[141], 228-229°C). The analytical sample was recrystallised from n-propanol. (Found:C, 64.2; H, 4.75. N, 9.2. $C_{16}H_{14}N_2O_2S$ requires C, 64.4; H, 4.7; N, 9.4%). ^1H N.m.r., i.r., mass spectra, see Appendix.

The remaining mother liquors (0.183g) were examined by T.l.c. This showed 5 spots. On attempted isolation by prep. T.l.c., the spots when isolated gave only further spots by T.l.c., indicating the remaining products were probably unstable. Indeed on work up the mother liquors became black and tarry.

c) Cyclisation with 1,5-diazabicylclo(5,4,0)undec-5-ene (D.B.U.).

2-Ethynylbenzaldehyde (0.100g, 0.77mmole), p-toluenesulphonylhydrazine (0.150g, 0.80mmole) and concentrated hydrochloric acid (1 drop) in ethanol (10ml) were stirred in the dark under nitrogen for 1h at room temperature. The acid was then neutralised with sodium bicarbonate and 1,5-diazabicyclo(5,4,0)undec-5-ene (D.B.U.) (60mg, 0.4mmole) was added and the reaction mixture stirred in the dark under nitrogen for 2 days at room temperature. The reaction mixture was filtered and the solid filtered off extracted with

methylene chloride (60ml). The ethanolic and methylene chloride fractions were combined and evaporated under reduced pressure to give a dark oil (0.350g) which was crystallised from ethanol to give isoquinoline N-p-toluenesulphonylimine as white crystals (0.080g, 35%) m.p. 226-228°C (lit.[141], 228-229°C).

II) Benzenesulphonylhydrazine.

a) Preparation of hydrazone.

Again the intermediate hydrazone was unstable and could not be isolated pure. 2-Ethynylbenzaldehyde (0.100g, 0.77mmole), benzenesulphonylhydrazine (0.133g, 0.77mmole) and concentrated hydrochloric acid (1 drop) were stirred in ethanol (5ml) in the dark and under nitrogen for 1h. T.l.c. (alumina, benzene/ether: 75%/25%) showed the consumption of the aldehyde and the appearance of a slower running spot. The solvent was removed under reduced pressure to give 2-ethynylbenzaldehyde benzenesulphonylhydrazone (0.215g, 97%) as a yellow oil. (Found: m/e 284.062791. $C_{15}H_{12}N_2O_2S$ requires m/e 284.061945). ^1H N.m.r., mass spectra, see Appendix.

b) Cyclisation with sodium carbonate.

2-Ethynylbenzaldehyde (0.200g, 1.54mmole), benzenesulphonylhydrazine (0.265g, 1.54mmole) and concentrated hydrochloric acid (2 drops) were stirred in ethanol (10ml) in the dark under nitrogen for 1h at room temperature. T.l.c. (alumina, benzene/ether: 75%/25%) showed the loss of 2-ethynylbenzaldehyde and the appearance of a slower running spot corresponding to the hydrazone. Sodium carbonate (3g, 0.03 mole) and water (2ml) were added and the mixture stirred in the dark under nitrogen for 2 days at room temperature. T.l.c. showed the loss of the hydrazone. Water (25ml) was added and the mixture was extracted with methylene chloride (2x50ml). The methylene

chloride extract was dried over magnesium sulphate, filtered and the solvent removed under reduced pressure to yield an off-white powder (0.354g) which was recrystallised from ethanol to give isoquinoline N-benzenesulphonylimine as off-white crystals (0.178g, 40%) m.p. 258-260°C (with decomposition). The analytical sample was recrystallised from n-butanol. (Found:C, 63.2; H, 4.35; N, 9.6. $C_{15}H_{12}N_2O_2S$ requires C, 63.4; H, 4.25; N, 9.85%). ^1H N.m.r., i.r., mass spectra, see Appendix.

III) Methanesulphonylhydrazine.

a) Preparation of hydrazone.

This hydrazone appears to be even less stable to isolation than the p-toluenesulphonyl and benzenesulphonylhydrazones and thus was only obtained in a crude form. 2-Ethynylbenzaldehyde (0.200g, 1.54mmole), methanesulphonylhydrazine (0.170g, 1.54mmole) and concentrated hydrochloric acid (1 drop) were stirred in ethanol (10ml) at room temperature in the dark under nitrogen for 1.5h. T.l.c. (alumina, benzene/ether: 75%/25%) showed the loss of 2-ethynylbenzaldehyde and the appearance of a slower running spot. The solvent was removed under reduced pressure to give 2-ethynylbenzaldehyde methanesulphonylhydrazone (0.321g, 94%) as a yellow oil. ^1H N.m.r. spectrum, see Appendix.

b) Cyclisation with sodium carbonate.

2-Ethynylbenzaldehyde (0.600g, 4.61mmole), methanesulphonylhydrazine (0.510g, 4.63mmole) and concentrated hydrochloric acid (2 drops) in ethanol (20ml) were stirred at room temperature in the dark for 2h. T.l.c. (alumina, benzene/ether: 75%/25%) showed the loss of 2-ethynylbenzaldehyde and the appearance of a spot corresponding to the hydrazone. Sodium carbonate (4g, 0,04 mole) was added and the reaction mixture was stirred in the dark at room

temperature for 2 days. T.l.c. showed the loss of the hydrazone. The reaction mixture was filtered and the material that was filtered off washed with hot methylene chloride (50ml) and hot ethanol (50ml). The extracts were combined and evaporated under reduced pressure to give an off-white powder (1.050g) which was recrystallised from ethanol to yield isoquinoline N-methanesulphonylimine as a pink powder (0.401g, 40%). Further recrystallisation from n-propanol for the analytical sample gave pink needles m.p. 220°C. (Found: C, 53.9; H, 4.5; N, 12.5. $C_{10}H_{10}N_2O_2S$ requires C, 54.0; H, 4.5; N, 12.6%). ^{1}H N.m.r., i.r., mass spectra, see Appendix.

IV) Benzoylhydrazide.

a) Preparation of hydrazone.

2-Ethynylbenzaldehyde (0.204g, 1.57mmole), benzoylhydrazide (0.214g, 1.57mmole) and concentrated hydrochloric acid (3 drops) were stirred in the dark in ethanol (10ml) under nitrogen at room temperature. A white precipitate was formed after 5min. This was filtered off as a white powder (0.368g) and recrystallised from ethanol to give 2-ethynylbenzaldehyde benzoylhydrazone (0.236g, 61%) as a white powder. m.p. 162-164°C. (Found:C, 77.2; H, 4.75; N, 11.2. $C_{16}H_{12}N_2O$ requires C, 77.4; H, 4.9; N, 11.3%). ^{1}H N.m.r., i.r., mass spectra, see Appendix.

b) Cyclisation with 1,5-diazabicyclo (5,4,0) undec-5-ene (D.B.U.).

1) From 2-ethynylbenzaldehyde and benzoylhydrazide.

Benzoylhydrazide (0.158g, 1.16mmole), 2-ethynylbenzaldehyde (0.151g, 1.16mmole) and concentrated hydrochloric acid (2 drops) were stirred at room temperature in the dark in ethanol (10ml) under nitrogen for 5min. A white precipitate was formed and T.l.c. (alumina, benzene/ether: 75%/25%) showed the consumption of

2-ethynylbenzaldehyde and the production of the benzylhydrazone. The acid was neutralised with sodium bicarbonate and D.B.U. (40mg, 0.27mmole) was added and the reaction stirred over 4 days. T.l.c. (alumina, ether/ethanol: 95%/5%) showed the loss of the benzoylhydrazone and the appearance of a product spot. The reaction mixture was filtered and the residue extracted with methylene chloride (80ml). The two extracts were combined and evaporated under reduced pressure to give a dark oil which crystallised on scratching with a glass rod.

The solid was recrystallised from ethanol to give isoquinoline N-benzoylimine as off white crystals (0.149g, 50%) m.p. 189.5-190.5°C (lit.[141], 188°C). (Found:C, 77.1; H, 4.95; N, 11.3. $C_{16}H_{12}N_2O$ requires C, 77.4; H, 4.9; N, 11.3%). ^1H N.m.r., i.r., mass spectra, see Appendix.

2) From the benzoylhydrazone.

2-Ethynylbenzaldeyde benzoylhydrazone (0.100g, 0.403mmole) and D.B.U. (80mg, 0.6mmole) were stirred as a slurry in ethanol (5ml) in the dark at room temperature under nitrogen for 3 days. T.l.c. (alumina, ether/ethanol: 95%/5%) showed the loss of the benzoylhydrazone and the appearance of a product spot. The precipitate was filtered off to give the isoquinoline N-benzoylimine (0.040g, 40%). The filtrate was evaporated under reduced pressure to give a dark solid which was recrystallised from ethanol to give a further (0.037g) of the isoquinoline N-benzoylimine (Total yield 77%) m.p. 187-188°C.

3) Control experiment for the effect of sodium bicarbonate.

2-Ethynylbenzaldehyde (0.109g, 0.837mmole), benzoylhydrazide (0.113g, 0.830mmole) amd concentrated hydrochloric acid (3 drops) were stirred in the dark under nitrogen in ethanol (10ml) at room

temperature for 5min. The benzoylhydrazone was formed as before. The acid was neutralised with excess sodium bicarbonate and stirred for 3 days. T.l.c. (alumina, ether/ethanol: 95%/5%) showed only the benzoylhydrazone and none of the isoquinoline N-imine. D.B.U. (60mg, 0.4mmole) was then added and the mixture stirred for a further 4 days. The reaction mixture was then filtered and the precipitate washed with methylene chloride (50ml). The filtrate and washings were combined and evaporated under reduced pressure to give a dark solid which was recrystallised from ethanol to give isoquinoline N-benzoylimine as white crystals (0.062g, 30%) m.p. 183-184°C.

c) Cyclisation with cuprous chloride of the benzoylhydrazone.

2-Ethynylbenzaldehyde benzoylhydrazone (0.100g, 0.403mmole) and cuprous chloride (3mg) were stirred overnight in the dark in ethanol (10ml) at room temperature under nitrogen. T.l.c. (alumina, ether/ethanol: 95%/5%) showed no reaction. The reaction mixture was then heated under reflux for 30min. T.l.c. showed the consumption of starting hydrazone and production of the isoquinoline N-imine. After cooling, methylene chloride (30ml) was added and the inorganic residue filtered off. The filtrate was evaporated under reduced pressure to give a purple powder which was washed with petroleum ether (40/60)/ ether (10ml) to give a light purple powder (0.060g). This was recrystallised from ethanol to give slightly purple crystals (0.016g, 16%) m.p. 187-188°C of the isoquinoline N-benzoylimine. The mother liquor was evaporated under reduced pressure. Dry column chromatography (alumina, Grade III: ether) of the residue gave a purple powder (0.040g) which was recrystallised from ethanol to give slightly purple crystals (0.012g, 12%) m.p. 187-188°C; of the isoquinoline N-benzoylimine; total yield (28%).

V) Semicarbazide hydrochloride.

a)Preparation of semicarbazone.

2-Ethynylbenzaldehyde (0.154g, 1.18mmole), semicarbazide hydrochloride (0.132g, 1.18 mmole) and concentrated hydrochloric acid (2 drops) were stirred in the dark at room temperature in ethanol (5ml) under nitrogen for 2h. A white precipitate formed and this was filtered off (0.182g). Recrystallisation from ethanol gave 2-ethynylbenzaldehyde semicarbazone (0.149g, 67%) as white crystals m.p. 188.5-190°C. (Found:C, 64.3; H, 4.9; N, 22.4. $C_{10}H_9N_3O$ requires C, 64.2; H, 4.85; N, 22.5%). ^{1}H N.m.r., i.r., mass spectra, see Appendix.

b) Attempted cyclisation reactions.

1) With sodium carbonate.

2-Ethynylbenzaldehyde (0.186g, 1.43mmole) and semicarbazide hydrochloride (0.160g, 1.43mmole) were stirred in ethanol (10ml) for 2h under nitrogen. T.l.c. (alumina, petroleum ether (40/60)/ether: 95%/5%) showed the loss of 2-ethynylbenzaldehyde. Sodium carbonate (3g, 0.03 mole) was added and the reaction stirred overnight. T.l.c. (alumina, ether/ethanol: 95%/5%) showed no loss of the semicarbazone. The precipitate was filtered off and washed with methylene chloride (50ml). The filtrate and washings were combined and evaporated under reduced pressure to give a white powder (0.192g). This was recrystallised from ethanol to give the semicarbazone (0.153g, 50%) m.p. 188-189°C.

2) With D.B.U.

The semicarbazone (0.054g, 0.289mmole) was stirred with D.B.U. (40mg, 0.27mmole) in ethanol (5ml) for 4 days. T.l.c. (alumina, ether/ethanol: 95%/5%) showed no loss of the semicarbazone. The solid was filtered off and was the semicarbazone (0.048g, 90%) m.p. 188-189°C.

3) With cuprous chloride.

The semicarbazone (0.108g, 0.577mmole) and cuprous chloride (5mg) were stirred under nitrogen in ethanol (10ml) overnight at room temperature. T.l.c. showed there had been no reaction. The reaction mixture was then heated under reflux for 5 min. T.l.c. showed that the semicarbazone had been consumed. The inorganic residue was filtered off and washed with methylene chloride (50ml) and the solvent evaporated under reduced pressure to give a dark powder (0.090g). T.l.c. of this material did not show any new product spot. Chromatography (alumina Grade I, (wet column), ether with increasing amounts of ethanol) yielded only a small recovery of unidentified material. Most of the material was irreversibly adsorbed on the alumina.

4) With sodium ethoxide.

The semicarbazone (0.051g,0.272mmole) was dissolved in ethanol (5ml) and sodium ethoxide (0.1ml of a solution of sodium (0.5g) in ethanol (10ml))and heated under reflux for 2h. T.l.c. showed the consumption of the semicarbazone. Water (10ml) was added and the ethanol evaporated under reduced pressure. The aqueous fraction left was extracted with methylene chloride (2x50ml), and the organic extract was dried over magnesium sulphate, filtered and evaporated under reduced pressure to give a dark oil (0.061g). From the ^{1}H n.m.r. spectrum of the material it appeared polymeric in nature.

VI) 2,4-Dinitrophenylhydrazine.

a) Preparation of hydrazone.

2-Ethynylbenzaldehyde (0.240g, 1.84mmole), 2,4-dinitrophenylhydrazine (0.365g, 1.84mmole) and concentrated hydrochloric acid (2drops) were stirred in ethanol (10ml) at room temperature.

After a few minutes an orange precipitate was formed. This was filtered off as an orange powder (0.541g) which was recrystallised from ethanol to give 2-ethynylbenzaldehyde 2,4-dinitrophenylhydrazone as orange crystals (0.443g, 77%) m.p. 200-205°C. (Found:C, 57.8: H, 3.3; N, 17.9. $C_{15}H_{10}N_4O_4$ requires C, 58.1; H, 3.25; N, 18.1%). ^1H N.m.r., i.r., mass spectra, see Appendix.

b) Attempted cyclisation reactions.

1) With D.B.U.

2-Ethynylbenzaldehyde (0.133g, 1.02mmole), 2,4-dinitrophenylhydrazine (0.204g, 1.03mmole) and concentrated hydrochloric acid (2 drops) were stirred in ethanol (10ml) under nitrogen for 15min. An orange precipitate was formed and T.l.c. (alumina, benzene/ether: 75%/25%) showed the loss of 2-ethynylbenzaldehyde and the formation of the 2,4-dinitrophenylhydrazone. The acid in the solution was neutralised with sodium bicarbonate and D.B.U. (40mg, 0.3mmole) was added. The reaction mixture was stirred for 2 days under nitrogen. T.l.c. showed that no reaction had occured. The reaction mixture was then extracted with methylene chloride (50ml) and the inorganic material filtered off. The filtrate was evaporated under reduced pressure to give an orange powder (0.300g). This was recrystallised from ethanol to yield the 2,4-dinitrophenylhydrazone (0.198g, 62%) m.p. 200-203°C.

2) With sodium carbonate.

The hydrazone (0.092g, 0.297mmole) in dry benzene (15ml) with sodium carbonate (2g, 0.02 mole) was heated under reflux with stirring under nitrogen for 16h. T.l.c. showed no reaction. The reaction mixture was filtered off and washed with methylene chloride

(30ml). The solvent was removed under reduced pressure to give the hydrazone (0.085g, 92%) m.p. 198-200°C.

3) With D.B.U. in benzene.

The hydrazone (0.026g, 0.082mmole) was stirred in dry benzene (5ml) with D.B.U. (20mg, 0.13mmole) for 2 days; T.l.c. showed no reaction had taken place.

4) With D.B.U. in boiling benzene.

The hydrazone (0.042g, 0.135mmole) was heated under reflux in dry benzene (10ml) with D.B.U. (40mg, 0.27mmole) for 10h; T.l.c. showed no reaction had taken place.

5) With sodium ethoxide.

The hydrazone (0.091g,0.294mmole) was heated under reflux in ethanol (10ml) and sodium ethoxide (0.2ml of a solution of sodium (0.5g) in ethanol (10ml)) for 3h. T.l.c. showed the loss of the 2,4-dinitrophenylhydrazone but no new product spot. Water (20ml) was added and the ethanol removed under reduced pressure. The residue was extracted with methylene chloride (2x50ml) and the extract dried over magnesium sulphate, filtered and evaporated under reduced pressure to give a black polymeric material (0.085g).

5. Reactions of 2-phenylethynylbenzaldehyde with hydrazines.

I) p-Toluenesulphonylhydrazine.

a) Preparation of hydrazone.

2-Phenylethynylbenzaldehyde (0.451g, 2.19mmole), p-toluene-sulphonylhydrazine (0.408g, 2.19mmole) and concentrated hydrochloric acid (2 drops) were stirred in ethanol (20ml) at room temperature under nitrogen in the dark. A white precipitate was formed in a few minutes. This was filtered off (0.705g) and recrystallised

from ethanol to give 2-phenylethynylbenzaldehyde p-toluenesulphonylhydrazone as white crystals (0.630, 77%) m.p. 158-161°C. (Found: C, 70.8; H, 4.9; N, 7.4. $C_{22}H_{18}N_2O_2S$ requires C, 70.6; H, 4.85; N, 7.5%). ^1H N.m.r., i.r., mass spectra, see Appendix.

b) Attempted cyclisation reactions.

1) With sodium carbonate.

2-Phenylethynylbenzaldehyde p-toluenesulphonylhydrazone (0.250g, 0.668mmole) was stirred in ethanol (10ml) with sodium carbonate (2g, 0.02 mole) in the dark under nitrogen for 2 days. T.l.c. (alumina, benzene/ether: 75%/25%) showed the loss of the tosylhydrazone The reaction mixture was filtered and washed with ethanol (50ml) and the filtrate evaporated under reduced pressure to give a slightly orange powder (0.240g). This was washed with a little ether and filtered to give a white powder (0.096g, 81%) of sodium p-toluenesulphinate.

The filtrate was evaporated under reduced pressure to give an orange gum (0.141g) which after chromatography (alumina, Grade I) gave orange crystals (15mg) m/e 408 which was probably the azine of 2-phenylethynylbenzaldehyde. The remaining material obtained was a dark oil (0.099g), m/e (140°C) 208, m/e (200°C) 409, possibly polymeric material originating from the diazoalkane and the carbene produced by the elimination of p-toluenesulphinic acid from 2-phenylethynylbenzaldehyde tosylhydrazone.

2) With D.B.U.

The tosylhydrazone (0.100g, 0.267mmole) was stirred in ethanol (10ml) and D.B.U. (40mg, 0.27mmole) was added. The reaction mixture was stirred under nitrogen for 3 days. T.l.c. showed the loss of

the hydrazone. The ethanol was removed under reduced pressure to give an oil (0.131g) which on trituration with a little ether gave a yellow powder (0.090g) m/e (120°C) 218 (53), 190 (60), 189 (100), 178 (50), 152 (62), 151 (100), 137 (25), 123 (30), 99 (38), 97 (52) 95 (23%). This is possibly polymeric material derived from D.B.U. and the breakdown products of 2-phenylethynylbenzaldehyde tosylhydrazone. The mother liquor was evaporated under reduced pressure to give an intractible tar (0.040g).

3) With cuprous chloride.

The tosylhydrazone (0.100g, 0.267mmole) was heated under reflux in ethanol (10ml) with cuprous chloride (5mg) for 30min under nitrogen. T.l.c. showed the loss of the hydrazone. The inorganic residue was filtered off and washed with ethanol (20ml). The filtrate was evaporated under reduced pressure to give a dark gum which was triturated with ether to a dark yellow powder (0.058g). From mass spectral evidence this appeared to be polymeric in nature.

II) Benzoylhydrazide.

a) Preparation of hydrazone.

2-Phenylethynylbenzaldehyde (0.522g, 2.53mmole), benzoylhydrazide (0.345g, 2.53mmole) and concentrated hydrochloric acid (2 drops) were stirred in ethanol (10ml) under nitrogen at room temperature for 10min. A thick white precipitate was obtained. This was stirred for another 30min. and then filtered off (0.805g). Recrystallisation from ethanol gave 2-phenylethynylbenzaldehyde benzoylhydrazone as a white powder (0.659g, 80%) m.p. 178-180°C. (Found: C, 81.2; H, 5.0; N, 8.6. $C_{22}H_{16}N_2O$ requires C, 81.5; H, 5.0; N, 8.6%). ^1H N.m.r., i.r., mass spectra, see Appendix.

b) Attempted cyclisation reactions.

1) With sodium carbonate.

The benzoylhydrazone (0.200g, 0.617mmole) and sodium carbonate (2g, 0.02 mole) were stirred in ethanol (10ml) under nitrogen in the dark for 6 days at room temperature. T.l.c. (alumina, benzene/ether: 75% /25%) showed no reaction had taken place. The sodium carbonate was filtered off and washed with hot ethanol (30ml). The filtrate was evaporated under reduced pressure to give a yellow oil which was triturated with ether to give back the hydrazone (0.160g, 80%) m.p. 178-179°C.

2) With D.B.U.

The hydrazone (0.200g, 0.617mmole) and D.B.U. (40mg, 0.27mmole) were stirred in ethanol (10ml) for 4 days. T.l.c. showed there had been no reaction. Water (10ml) was added and then acidified with dilute hydrochloric acid. The reaction mixture was then extracted with benzene (2x25ml), dried over magnesium sulphate, filtered and evaporated under reduced pressure to give back the hydrazone (0.181g, 90.5%) m.p. 178-180°C.

3) With cuprous chloride.

The hydrazone (0.100g, 0.309mmole) and cuprous chloride (6mg) in ethanol (15ml) were heated under reflux for 2h. T.l.c. showed the loss of the hydrazone. The inorganic residue was filtered off and washed with hot ethanol (25ml) and the filtrate evaporated under reduced pressure to give an oil (0.095g) which was triturated with a small amount of ether to give a yellow powder (0.050g). From mass spectral data this appeared to be polymeric in nature.

6. The reaction of cis-3-methylpent-2-en-4-yn-1-al with p-toluenesulphonylhydrazine.

a) Preparation of hydrazone.

cis-3-Methylpent-2-en-4-yn-1-al (0.100g, 1.06mmole) and p-toluenesulphonylhydrazine (0.198g, 1.06mmole) were stirred in ethanol (5ml) in the dark under nitrogen for 30min. A pink solution was obtained. T.l.c. (alumina, benzene/ether: 75%/25%) showed the loss of the aldehyde and the appearance of a spot due to the p-toluenesulphonylhydrazone. The ethanol was removed under reduced pressure to give the crude hydrazone (0.285g, 99%) as a red oil which could not be crystallised. ^{1}H N.m.r. spectrum, see Appendix.

b) Attempted cyclisation reactions.

1) With sodium carbonate.

The aldehyde (0.126g. 1.29mmole) and p-toluenesulphonylhydrazine (0.249g, 1.33mmole) were stirred in ethanol (10ml) in the dark under nitrogen for 30min. T.l.c. showed the production of the hydrazone. Sodium carbonate (3g, 0.03 mole) was added and the reaction mixture stirred for 4 days. T.l.c. indicated that the hydrazone had been consumed. The sodium carbonate was filtered off and washed with methylene chloride (2x25ml) and the filtrate evaporated under reduced pressure to give a yellow gummy solid (0.381g). Chromatography (alumina, Grade I, ether with increasing amounts of ethanol) yielded only a small recovery of unidentified material. Most of the material was irreversibly adsorbed on the alumina.

2) With sodium ethoxide.

The aldehyde (0.107g, 1.13mmole) and p-toluenesulphonylhydrazine (0.212g, 1.14mmole) were stirred in ethanol (10ml) for 30min.

To this was added sodium ethoxide (0.15ml of a solution of sodium (0.5g) in ethanol (10ml)) and the reaction mixture stirred for 2 days. T.l.c. indicated the loss of the hydrazone intermediate. Water (20ml) was added and the ethanol removed under reduced pressure. The aqueous fraction left was extracted with methylene chloride (2x50ml), dried over magnesium sulphate, filtered and evaporated under reduced pressure to give a dark oil (0.301g).

Column chromatography (alumina, Grade I, ether with increasing amounts of ethanol) failed to yield any pure products. Most of the material was irreversibly adsorbed on the alumina.

3) With D.B.U.

The aldehyde (0.068g, 0.723mmole) and p-toluenesulphonylhydrazine (0.134g, 0.720mmole) were stirred in ethanol (10ml) for 30min. To the hydrazone formed was added D.B.U. (20mg, 0.13mmole) and the reation mixture was stirred for 3 days under nitrogen in the dark. T.l.c. showed that no reaction had taken place.

4) With cuprous chloride.

The aldehyde (0.159g, 1.69mmole) and p-toluenesulphonylhydrazine (0.314g, 1.69mmole) were stirred in ethanol (15ml) for 30min. Cuprous chloride (5mg) was added and the reaction mixture heated to boiling point and cooled. T.l.c. showed the loss of the hydrazone. The inorganic residue was filtered off and washed with methylene chloride (25ml) and the filtrate evaporated under reduced pressure to give a yellow-brown powder (0.414g). ^{1}H N.m.r. and mass spectral data indicated that the material was polymeric in nature.

7. Reactions of homophthalaldehyde with hydrazines.

I) p-Toluenesulphonylhydrazine.

Homophthalaldehyde (0.229g, 1.55mmole), p-toluenesulphonylhydrazine (0.288g, 1.55mmole) and concentrated hydrochloric acid (4 drops) were stirred in ethanol (10ml) for 10min under nitrogen. A clear yellow solution was obtained. This was left standing in the dark for 2 days and white crystals precipitated out. These were filtered off (0.247g) and recrystallised from ethanol to give isoquinoline N-p-toluene-sulphonylimine as fluffy white crystals (0.198g, 43%) m.p. 226-228°C (lit.[141], 228-229°C). The analytical sample was recrystallised from n-propanol. (Found:C, 64.6; H, 4.8; N, 9.6. $C_{16}H_{14}N_2O_2S$ requires C, 64.4; H, 4.7; N, 9.4%). ^{1}H N.m.r., i.r., mass spectra, see Appendix.

II) Benzenesulphonylhydrazine.

Homophthalaldehyde (0.360g, 2.43mmole), benzenesulphonylhydrazine (0.414g, 2.41mmole) and concentrated hydrochloric acid (4 drops) were stirred in ethanol (10ml) for 10min under nitrogen. A clear yellow solution was obtained. This was left standing in the dark for 2 days, gold coloured crystals precipitated out. These were filtered off (0.439g) and recrystallised from ethanol to give isoquinoline N-benzenesulphonylimine as gold-coloured crystals (0.251g, 37%) m.p. 258-260°C. The analytical sample was recrystallised from n-butanol. (Found:C, 63.65; H, 4.4; N, 9.8. $C_{15}H_{12}N_2O_2S$ requires C, 63.4; H, 4.25; N, 9.85%). ^{1}H N.m.r., i.r., mass spectra, see Appendix.

III) Methanesulphonylhydrazine.

Homophthalaldehyde (0.360g, 2.43mmole), methanesulphonylhydrazine (0.269g, 2.44mmole) and concentrated hydrochloric acid (4 drops)

were stirred in ethanol (10ml) under nitrogen for 10min. A clear yellow solution was obtained and this was left standing for 2 days in the dark. A precipitate was obtained and this was filtered off (0.337g) and recrystallised from ethanol to give isoquinoline N-methanesulphonylimine hydrochloride (0.209g, 33%) m.p. 195°C. The analytical sample was recrystallised from n-propanol. (Found: C, 46.6; H, 4.3; N, 10.8. $C_{10}H_{11}N_2ClO_2S$ requires C, 46.6; H, 4.3; N, 10.8%). ^1H N.m.r., i.r., mass spectra, see Appendix.

IV) Benzoylhydrazide.

Homophthalaldehyde (0.500g, 3.37mmole), benzoylhydrazide (0.460g, 3.38mmole) and concentrated hydrochloric acid (2 drops) in ethanol (8ml) were stirred for 5min under nitrogen. A clear yellow solution was obtained and on standing in the dark for 2 days white crystals (0.431g) were obtained and recrystallisation from ethanol gave isoquinoline N-benzoylimine (0.401g, 42%) m.p. 188-189°C (lit.[141], 188°C). (Found: C, 77.3; H, 4.85; N, 11.5. $C_{16}H_{12}N_2O$ requires C, 77.4; H, 4.9; N, 11.3%). ^1H N.m.r., i.r., mass spectra, see Appendix.

8. Reactions of αβ,γδ-unsaturated ketones with hydrazines.

A) 4-Methylhexa-3,5-dien-2-one.

I) Benzenesulphonylhydrazine.

4-Methylhexa-3,5-dien-2-one (0.500g, 4.55mmole), benzenesulphonylhydrazine (0.780g, 4.54mmole) and concentrated hydrochloric acid (0.25ml) were stirred in ethanol (8ml) under nitrogen overnight. A white precipitate was formed. This was filtered off to give the diazepine (0.781g, 65%). Recrystallisation from ethanol gave 2-benzenesulphonyl-3,4-dihydro-5,7-dimethyl-1,2-diazepine as white crystals (0.651g) m.p. 132-133°C. (Found: C, 59.2; H, 6.2; N, 10.6.

$C_{13}H_{16}N_2O_2S$ requires C, 59.1; H, 6.1; N, 10.6%). ^1H N.m.r., i.r., mass spectra, see Appendix.

II) Methanesulphonylhydrazine.

4-Methylhexa-3,5-dien-2-one (1.00g, 9.10mmole), methanesulphonylhydrazine (1.00g, 9.10mmole) and concentrated hydrochloric acid (0.5ml) were stirred in ethanol (15ml) under nitrogen in the dark for 2 hours. The solvent was removed under reduced pressure to give an oil (1.95g). Wet column chromatography (alumina Grade II, petroleum ether (40/60)/ether: 50%/50%) gave 2-methanesulphonyl-3,4-dihydro-5,7-dimethyl-1,2-diazepine (1.11g, 60%) as an oil which solidified on standing. The analytical sample was prepared by recrystallisation from hexane/ethanol m.p. 73-73.5°C. (Found:C, 47.2; H, 6.9; N, 13.7. $C_8H_{14}N_2O_2S$ requires C, 47.5; H, 6.7; N, 13.85%). ^1H N.m.r., i.r., mass spectra, see Appendix.

III) Benzoylhydrazide.

a) With no acid.

4-Methylhexa-3,5-dien-2-one (1.00g, 9.10mmole) and benzoylhydrazide (1.24g, 9.11mmole) were stirred overnight in ethanol (15ml) in the dark under nitrogen. The ethanol was evaporated under reduced pressure and the resulting oil separated by medium pressure liquid chromatography to give 2-benzoyl-3,4-dihydro-5,7-dimethyl-1,2-diazepine (0.24g, 12%) as a yellow oil which solidified on standing and recrystallisation from hexane gave yellow cubes, m.p. 44-46°C: (Found:C, 73.8; H, 7.2; N, 12.1. $C_{14}H_{16}N_2O$ requires C, 73.7; H, 7.1; N, 12.3%) (^1H n.m.r., i.r., mass spectra, see Appendix); and 4-methylhexa-3,5-dien-2-one benzoylhydrazone (0.54g, 26%) as yellow needles recrystallised from ethanol m.p. 112°C (decomposition starting at 100°C): (Found:C, 73.5;

H, 7.2; N, 12.3. $C_{14}H_{16}N_2O$ requires C, 73.7; H, 7.1; N, 12.3%) (^1H n.m.r., i.r., mass spectra, see Appendix); and unreacted benzoylhydrazide (0.67g, 54%).

b) With acid.

4-Methylhexa-3,5-dien-2-one (0.500g, 4.55mmole), benzoylhydrazide (0.620g, 4.55mmole) and concentrated hydrochloric acid (0.25ml) were stirred in ethanol (8ml) for 4h in the dark under nitrogen. The solvent was removed under high vacuum in the cold. The resultant oil was separated by medium pressure liquid chromatography to give 2-benzoyl-3,4-dihydro-5,7-dimethyl-1,2-diazepine (0.46g, 44%) m.p. 44-46°C and an intractable tar (0.35g).

c) Formation of the diazepine from the intermediate hydrazone.

4-Methylhexa-3,5-dien-2-one benzoylhydrazone (0.100g, 0.439mmole) was stirred in ethanol (0.5ml) with concentrated sulphuric acid (2 µl) for 4h in the dark under nitrogen. The ethanol was evaporated under reduced pressure at room temperature and the resulting oil separated by medium pressure liquid chromatography to give 2-benzoyl-3,4-dihydro-5,7-dimethyl-1,2-diazepine (0.060g, 60%) and no other products.

d) With acid (with heating on work up).

4-Methylhexa-3,5-dien-2-one (1.00g, 9.10mmole), benzoylhydrazide (1.24g, 9.11mmole) and concentrated hydrochloric acid (0.5ml) were stirred in ethanol (15ml) under nitrogen in the dark overnight. The ethanol was removed under vacuum (water pressure) with heating. The resulting oil was separated by medium pressure liquid chromatography to give 2-benzoyl-3,4-dihydro-5,7-dimethyl-1,2-diazepine (0.77g, 37%); 1-benzoyl-3-methylpyrazol-2-ine (0.26g, 15%) as white crystals from ethanol (0.17g) m.p. 98-99°C mixed m.p. 98-99°C (lit.[199], 98.5-99°C)

(^{1}H n.m.r., i.r., mass spectra, see Appendix); benzoylhydrazide (0.10g, 8%) and polymeric material (0.88g).

e) Formation of the pyrazol-2-ine from the diazepine.

2-Benzoyl-3,4-dihydro-5,7-dimethyl-1,2-diazepine (0.200g, 0.807mmole) was heated under reflux in a solution of ethanol (4ml) containing benzoylhydrazide (0.120g, 0.882mmole) and concentrated hydrochloric acid (0.2ml) for 1h. T.l.c. (alumina, benzene/ether: 75%/25%) indicated the consumption of the diazepine and production of the pyrazol-2-ine. The ethanol was removed under vacuum and the resulting solid separated by medium pressure liquid chromatography to give 1-benzoyl-3-methylpyrazol-2-ine (0.092g, 56%) as white crystals from ethanol (0.052g) m.p. 98-99°C (lit.,[199] 98.5-99°C).

IV) Acetylhydrazide.

4-Methylhexa-3,5-dien-2-one (1.00g, 9.10mmole), acetylhydrazide (0.68g, 9.18mmole) and concentrated hydrochloric acid (0.5ml) were stirred in ethanol (15ml) under nitrogen in the dark for 2h. The ethanol was removed under high vacuum at a low temperature. The resulting oil was separated by medium pressure liquid chromatography to give 2-acetyl-3,4-dihydro-5,7-dimethyl-1,2-diazepine (0.70g, 46%) as a yellow oil. (Found:C, 64.8; H, 8.5; N, 17.1. $C_9H_{14}N_2O$ requires C, 65.0; H, 8.5; N, 16.85%) (^{1}H n.m.r., i.r., mass spectra, see Appendix) and polymeric material (0.61g).

V) Ethyl carbazate.

4-Methylhexa-3,5-dien-2-one (1.00g, 9.10mmole), ethyl carbazate (0.95g, 9.13mmole) and concentrated hydrochloric acid (0.5ml) were stirred in ethanol (15ml) in the dark under nitrogen for 1h. The

ethanol was removed under high vacuum with little heating and the resulting oil was separated by medium pressure liquid chromatography to give 2-carboethoxy-3,4-dihydro-5,7-dimethyl-1,2-diazepine (0.76g, 43%) as a yellow oil. (Found:C, 61.1; H, 8.0; N, 14.2. $C_{10}H_{16}N_2O_2$ requires C, 61.2; H, 8.2; N, 14.3%) (^{1}H n.m.r., i.r., mass spectra, see Appendix); 1-carboethoxy-3-methylpyrazol-2-ine (0.09g, 6%) as an oil. (Found m/e 156.089620. $C_7H_{12}N_2O_2$ requires m/e 156.089872) (^{1}H n.m.r. i.r., mass spectra, see Appendix); and polymeric material (0.75g).

B) 4-Methyl-6-phenylhexa-3,5-dien-2-one.

I) Methanesulphonylhydrazine.

4-Methyl-6-phenylhexa-3,5-dien-2-one (1.00g, 5.37mmole), methanesulphonylhydrazine (0.590g, 5.37mmole) and concentrated hydrochloric acid (2 drops) were stirred in ethanol (15ml) under nitrogen in the dark for 20min. A precipitate formed and this was filtered off (1.28g, 86%) and was recrystallised from ethanol to give 4-methyl-6-phenylhexa-3,5-dien-2-one methanesulphonylhydrazone (0.86g, 58%) m.p. 137-138°C as white crystals. (Found:C, 60.3; H, 6.5; N, 10.1. $C_{14}H_8N_2O_2S$ requires C, 60.4; H, 6.5; N, 10.1%). ^{1}H N.m.r., i.r., mass spectra, see Appendix.

II) Acetylhydrazide.

4-Methyl-6-phenylhexa-3,5-dien-2-one (0.500g, 2.68mmole), acetylhydrazide (0.199g, 2.69mmole) and concentrated hydrochloric acid (1 drop) were stirred in ethanol (10ml) under nitrogen in the dark for 20min. A precipitate formed and this was filtered off (0.550g, 85%) and was recrystallised from ethanol to give light yellow crystals of 4-methyl-6-phenylhexa-3,5-dien-2-one acetylhydrazone (0.309g, 48%)

m.p. 147-148.5°C. (Found:C, 74.2; H, 7.5; N, 11.6. $C_{15}H_{18}N_2O$ requires C, 74.35; H, 7.5; N, 11.6%). ^1H N.m.r., i.r., mass spectra, see Appendix.

III) p-Toluenesulphonylhydrazine.

4-Methyl-6-phenylhexa-3,5-dien-2-one p-toluenesulphonylhydrazone was prepared by stirring 4-methyl-6-phenylhexa-3,5-dien-2-one with an equimolar quantity of p-toluenesulphonylhydrazine in ethanol overnight and the resulting precipitate filtered off and recrystallised from ethanol (70%) m.p. 136-137.5°C (lit.[173], 136-137.5°C).

C) Hepta-3,5-dien-2-one.

I) Acetylhydrazide.

Hepta-3,5-dien-2-one (0.500g, 4.55mmole) and acetylhydrazide (0.340g, 4.59mmole) were stirred in ethanol (10ml) under nitrogen in the dark for 5h. A precipitate formed and this was filtered off (0.310g, 56%) and recrystallised from ethanol to give white crystals of hepta-3,5-dien-2-one acetylhydrazone (0.247g, 45%) m.p. 161-163°C. (Found:C, 64.85; H, 8.4; N, 16.7. $C_9H_{14}N_2O$ requires C, 65.0; H, 8.5; N, 16.85%). ^1H N.m.r., i.r., mass spectra, see Appendix.

II) p-Toluenesulphonylhydrazine.

Hepta-3,5-dien-2-one p-toluenesulphonylhydrazone was prepared by stirring hepta-3,5-dien-2-one with an equimolar quantity of p-toluenesulphonylhydrazine in ethanol for 1h. The resulting precipitate was filtered off and recrystallised from ethanol (55%) m.p. 147-149°C (lit.[173], 147-149°C).

D) Attempted cyclisation of hydrazones of αβ,γδ-unsaturated ketones.

I) 4-Methyl-6-phenylhexa-3,5-dien-2-one methanesulphonylhydrazone.

The hydrazone (0.500g, 1.80mmole) was stirred in methanol (10ml) with concentrated sulphuric acid (3drops) in the dark at room temperature under nitrogen for 2 days. T.l.c. (alumina, benzene/ether: 75%/25%) showed at least 7 products. The solvent was removed under reduced pressure and the resulting oil was chromatographed on silica; the only pure product isolated was the recovered hydrazone (0.12g, 24%) m.p. 137-138°C. Elution with ethyl acetate gave polymeric material (0.21g).

A series of small scale reactions were performed and the reaction mixtures examined by T.l.c. (alumina, benzene/ether: 75%/25%).

1. The hydrazone (10mg) was heated under reflux in ethanol (0.5ml) for 2h. T.l.c. showed no reaction.

2. The hydrazone (10mg) was heated under reflux in ethanol (0.5ml) with concentrated hydrochloric acid (1 drop) for 2h. T.l.c. showed reversion back to the ketone and methanesulphonylhydrazine.

3. The hydrazone (10mg) was stirred in ethanol (0.5ml) with D.B.U. (20mg, 0.13mmole) for 3 days. T.l.c. showed no reaction.

4. The hydrazone (10mg) was dissolved in a BF_3/methanol solution (0.5ml). The hydrazone was complexed to the BF_3. The solution was left overnight but on aqueous work up although the hydrazone had been consumed no products could be detected by T.l.c.

5. The hydrazone (10mg) was dissolved in a BF_3/ether solution (0.5ml). The solution was left overnight but on aqueous work up only unreacted hydrazone could be detected by T.l.c.

6. The hydrazone (10mg) was dissolved in a BF_3/ether solution (0.5ml) and heated under reflux for 2h. On aqueous work up however although the hydrazone had been consumed no products could be detected by T.l.c.

II) 4-Methyl-6-phenylhexa-3,5-dien-2-one acetylhydrazone.

A series of small scale reactions were performed and the reaction mixtures examined by T.l.c. (alumina, benzene/ether: 75%/25%).

1.The hydrazone (10mg) was dissolved in ethanol (0.5ml) and concentrated hydrochloric acid (1 drop) added and left overnight. The solution went dark red and T.l.c. showed the loss of the hydrazone, a small amount of reversion back to ketone and acetylhydrazide but mostly a spot at R_f = 0 consistant with the polymeric material obtained from other similar reactions.

2.The hydrazone (10mg) was stirred overnight in ethanol (0.5ml) with D.B.U. (20mg, 0.13mmole). T.l.c. showed no reaction.

3.The hydrazone (10mg) was dissolved in BF_3/ether solution (0.5ml) and left overnight . After aqueous work up only unreacted hydrazone could be detected by T.l.c.

4.The hydrazone (10mg) was dissolved in BF_3/methanol solution (0.5ml) and left overnight. On aqueous work up although the hydrazone had been consumed no product could be detected by T.l.c.

5.The hydrazone (10mg) was stirred overnight in ethanol (0.5ml) with p-toluenesulphonic acid (2mg), T.l.c. showed no reaction.

III) Hepta-3,5-dien-2-one acetylhydrazone.

A series of small scale reactions were performed and the reaction mixtures examined by T.l.c. (alumina, benzene/ether: 75%/25%).

1.The hydrazone (10mg) was dissolved in ethanol (0.5ml) and concentrated hydrochloric acid (1 drop) was added. The solution went red and was left overnight. T.l.c. showed the loss of the hydrazone, a small amount of reversion back to ketone and acetylhydrazide but no product spot, only material R_f = 0.

2.The hydrazone (10mg) was stirred in ethanol (0.5ml) with D.B.U. (20mg, 0.13mmole) overnight. T.l.c. showed no reaction.

3.The hydrazone (10mg) was dissolved in ethanol (0.5ml) and dilute hydrochloric acid (1drop) was added. This was left overnight and T.l.c. showed reversion back to ketone and acetylhydrazide and some material $R_f = 0$.

4.The hydrazone (10mg) was dissolved in a BF_3/ether solution (0.5ml) and left overnight. After aqueous work up T.l.c. only showed decomposition to ketone and acetylhydrazide.

5.The hydrazone (10mg) was dissolved in a BF_3/methanol solution (0.5ml) and left overnight. After aqueous work up it appeared by T.l.c. that the hydrazone had been consumed but no products could be detected.

E) Reactions of 4-methylhexa-3,5-dien-2-one with p-tosylhydrazine in deuteromethanol (CH_3OD).

I) Indirect route.

The ketone (0.500g, 4.55mmole) and p-tosylhydrazine (0.846g, 4.55mmole) were stirred in deuteromethanol (5ml) in the dark at room temperature under nitrogen overnight. The precipitated diazepine (0.082g, 6%) was then filtered off, washed with deuteromethanol and dried under vacuum. Its ^1H n.m.r. spectrum showed deuterium incorporation at C-3 (30%), C-4 (45%), C-6 (19%), 5-Me (16%) and are given in Table 1, see Appendix.

To the filtrate, containing the tosylhydrazone of 4-methylhexa-3,5-dien-2-one, was added concentrated sulphuric acid (25 µl) and the mixture was stirred in the dark under nitrogen at room temperature for 2h. The precipitated diazepine (0.329g, 26%) was filtered off, washed with deuteromethanol and dried under vacuum. Its ^1H n.m.r. spectrum showed deuterium incorporation at C-4 (58%), C-6 (72%), 5-Me (9%), 7-Me (26%) and are given in Table 2, see Appendix.

Two repeat experiments were performed:-

1. On the same scale giving the diazepine before acid was added (0.070g, 5.5%). Its ^{1}H n.m.r. spectrum showed deuterium incorporation at C-3 (26%), C-4 (40%), C-6 (25%), 5-Me (16%) and are given in Table 1, see Appendix. And the diazepine formed after acid was added (0.325g, 26%). Its ^{1}H n.m.r. spectrum showed deuterium incorporation at C-4 (42%), C-6 (60%), 5-Me (5%), 7-Me (17%) and are given in Table 2, see Appendix.

2. On half scale giving the diazepine before acid was added (0.047g, 7%). Its ^{1}H n.m.r. spectrum showed deuterium incorporation at C-3 (17%), C-4 (24%), C-6 (28%), 5-Me (12%) and are given in Table 1, see Appendix. And the diazepine formed after acid was added (0.159g, 25%). Its ^{1}H n.m.r. spectrum showed deuterium incorporation at C-4 (57%), C-6 (62%), 5-Me (11%), 7-Me (22%) and are given in Table 2, see Appendix.

II) Direct route.

The ketone (0.500g, 4.55mmole), p-tosylhydrazine (0.846g, 4.55mmole) and concentrated sulphuric acid (25 µl) were stirred in deuteromethanol (5ml) in the dark at room temperature under nitrogen for 2h. The precipitated diazepine (0.487g, 38%) was filtered off, washed with deuteromethanol and dried under high vacuum. Its ^{1}H n.m.r. spectrum showed deuterium incorporation at C-4 (38%), C-6 (64%), 5-Me (11%), 7-Me (15%) and are given in Table 3, see Appendix. A repeat experiment on 0.2 scale gave the diazepine (0.13g, 48%). Its ^{1}H n.m.r. spectrum showed deuterium incorporation at C-4 (36%), C-6 (76%), 5-Me (8%), 7-Me (18%) and are given in Table 3, see Appendix.

III) Control experiments.

a) A slurry of 2-tosyl-3,4-dihydro-5,7-dimethyl-1,2-diazepine (0.108g, 0.389mmole), sulphuric acid (2.5 µl) and deuteromethanol (0.5ml) was stirred at room temperature in the dark under nitrogen for 24h. The diazepine was then filtered off (0.092g, 85%) and dried under high vacuum. The ^{1}H n.m.r. spectrum showed no deuterium incorporation, Table 4, see Appendix.

b) A solution of 4-methylhexa-3,5-dien-2-one (0.50g, 4.55mmole) in deuteromethanol (CD_3OD) (0.4ml) containing cyclohexane (5 µl) was made up in an n.m.r. tube and the ^{1}H n.m.r. spectrum run. Concentrated sulphuric acid (2 µl) was added and the ^{1}H n.m.r. spectrum was run again after 10min and after 24h. After 10min the absorptions of the vinyl protons were not affected but those of the methyl groups had diminished by ca 17%, Table 5, see Appendix. After 24h all the absorptions had diminished, probably due to acid catalysed polymerisation, Table 5, see Appendix.

c) A mixture of 4-methylhexa-3,5-dien-2-one (0.250g, 2.23mmole), deuteromethanol (2ml) and concentrated sulphuric acid (10 µl) was kept for 18h at room temperature in the dark. The solvent was removed under reduced pressure and distillation at 10mm Hg yielded the ketone (0.035g, 14%), the residue being polymeric. A solution of this ketone (obtained from the distillation) (0.025g, 0.223mmole) in deutero-methanol (CD_3OD) (0.2ml) containing cyclohexane (2.5 µl) as an internal standard was made up and its ^{1}H n.m.r. spectrum run. This showed ca 25% deuteration of the methyl groups, Table 5, see Appendix.

F) Exchange reaction of 4-methyl-6-phenylhexa-3,5-dien-2-one tosylhydrazone in deuteromethanol.

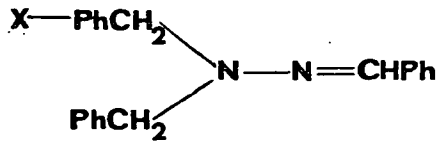
A slurry of 4-methyl-6-phenylhexa-3,5-dien-2-one tosylhydrazone (0.138g, 0.390mmole), concentrated sulphuric acid (2.5 µl) and deuteromethanol (0.5ml) was stirred at room temperature in the dark under nitrogen for 18h. The tosylhydrazone was filtered off, washed with deuteromethanol and dried under high vacuum (0.100g, 72%). The amount of deuteration in the tosylhydrazone was investigated by its ^{1}H n.m.r. spectrum. This showed ca 20% deuteration of the 1- and 3- methyl groups, Table 6 see Appendix.

G) Exchange reaction of hepta-3,5-dien-2-one tosylhydrazone in deuteromethanol.

A slurry of hepta-3,5-dien-2-one tosylhydrazone (0.216g, 0.777mmole), concentrated sulphuric acid (5 µl) and deuteromethanol (1ml) was stirred at room temperature in the dark under nitrogen for 1h. The tosylhydrazone was filtered off, washed with deuteromethanol and dried under high vacuum (0.081g, 38%). The amount of deuteration in the tosylhydrazone was investigated by its ^{1}H n.m.r. spectrum. This showed no deuterium incorporation, Table 7, see Appendix. In a similar reaction of duration 18h all the tosylhydrazone had dissolved and no pure product could be obtained.

APPENDIX I

Benzaldehyde benzyl(substituted-benzyl)hydrazones.



^{1}H N.m.r. spectral data $CDCl_3$ δ (28°C).

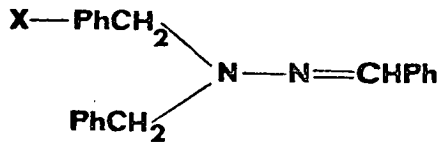
X	Benzyl protons	Aromatic and imine protons	
o-styryl	4.50s, 2H 4.68s, 2H	7.0-8.7m, 22H	
p-Cl	4.41s, 2H 4.45s, 2H	7.0-7.5m, 15H	
p-OMe	4.45s, 4H	6.5-7.5m, 15H	3.70s, 3H, -OMe
H	4.50s, 4H	7.1-7.5m, 16H	
H (authentic)	4.50s, 4H	7.1-7.5m, 16H	

I.r. spectral data (Nujol) cm^{-1}.

X = o-styryl 1585 (C=N); p-Cl, 1590 (C=N); p-OMe, 1585 (C=N); H, 1590 (C=N); H (authentic), 1590 (C=N).

APPENDIX II

Benzaldehyde benzyl(substituted-benzyl)hydrazones.

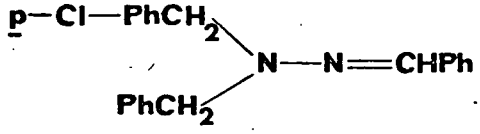


Mass spectral data.

	m/e (relative abundance %).
X = o-styryl (140°C)	57(28), 71(20), 91(98), 115(83), 178(35), 181(15), 192(18), 193(100), 194(25), 208(13), 210(25), 298(23), 311(65), 312(19), 402(30).
X = p-Cl (115°C)	91(100), 103(6), 105(5), 125(56), 127(20), 165(4), 166(5), 181(16), 215(3), 217(1), 334(64), 336(24).
X = p-OMe (140°C)	77(7), 78(5), 90(7), 91(31), 102(4), 121(100), 165(2), 166(3), 181(6), 211(4), 220(10), 300(11), 330(33).
X = H (140°C)	90(10), 91(100), 92(12), 103(10), 165(5), 166(8), 181(20), 300(80).
X = H (authentic, 130°C)	90(12), 91(100), 92(12), 103(10), 165(7), 166(10), 181(20), 300(80).

APPENDIX III

Benzaldehyde benzyl(p-chlorobenzyl)hydrazones.



^{13}C N.m.r. data (p.p.m. from Me_4Si) $CDCl_3$.

a) from 1,2-dibenzylhydrazine hydrochloride, sodium carbonate and p-chlorobenzaldehyde.

CH_2, 57.8; CH_2, 57.4; aromatic, 137.3 (tert),136.75 (tert), 136.2 (tert), 132.9 (tert), 129.0, 128.6, 128.4, 127.6, 127.4, 125.6; CH=N , 132.3.

b) from 1,2-dibenzylhydrazine and p-chlorobenzaldehyde.

CH_2, 57.7; CH_2, 57.3; aromatic, 137.3 (tert), 136.7 (tert), 136.1 (tert), 132.9 (tert), 129.0, 128.6, 128.4, 127.6, 127.3, 125.6; CH=N , 132.3.

From 1,2-dibenzylhydrazine and p-chlorobenzaldehyde.

^1H N.m.r. spectral data $CDCl_3$ δ (28°C).

4.41, 4.45, 4.50 (benzyl protons, containing impurity of benzaldehyde dibenzylhydrazone) 7.0-7.5m (aromatic and imine protons).

I.r. spectral data (Nujol) cm^{-1}.

1595 (C=N).

Mass spectral data.

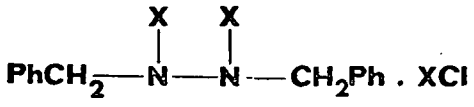
m/e (relative abundance %).

(160°C)

91(100), 103(6), 105(6), 125(37), 127(13), 165(3), 166(4), 181(12), 215(2), 217(1), 300(20), 334(50), 336(16), 368,370,372(1).

APPENDIX IV

1,2-Dibenzylhydrazine hydrochloride.

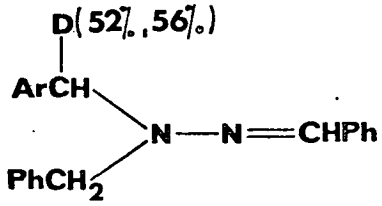


Mass spectral data.	m/e (relative abundance %).
X = H (160°C)	91(100), 123(10), 211(0), 212(19).
X = D (160°C)	91(100), 123(10), 212(0), 213(6), 214(24).

The mass spectrum (X = D) has peaks m/e 213(6%) and 214(24%). This shows that the free 1,2-dibenzylhydrazine has D_2 80% and D_1 20%. Assuming the same deuteration ratio in the hydrochloride moiety the overall deuteration in 1,2-dibenzylhydrazine hydrochloride is D_3 72%, D_2 18%, D_1 10%.

APPENDIX V

Deuterium labelling study of the reaction of 1,2-dibenzylhydrazine hydrochloride and trans-2-formylstilbene.



Ar = o-styryl

^{1}H N.m.r. spectral data $CDCl_3$ δ (28°C).

Deuterium labelling experiments.

	Aromatic protons	Unchanged benzyl protons	Expanded integration	o-Styryl benzyl protons
Integral Expt 1	160 (22H)	14 (2H)	46 (2H)	34
Integral Expt 2.	86 (22H)	8 (2H)	64 (2H)	46

Therefore % deuteration of one hydrogen of the o-styrylbenzyl group = Expt 1 52%, Expt 2 56%.

Control experiments.

	Aromatic protons	Unchanged benzyl protons	Expanded integration	o-Styryl benzyl protons
Integral Control (1)	163 (22H)	14 (2H)	38 (2H)	38
Integral Control (2)	80 (22H)	7 (2H)	56 (2H)	41

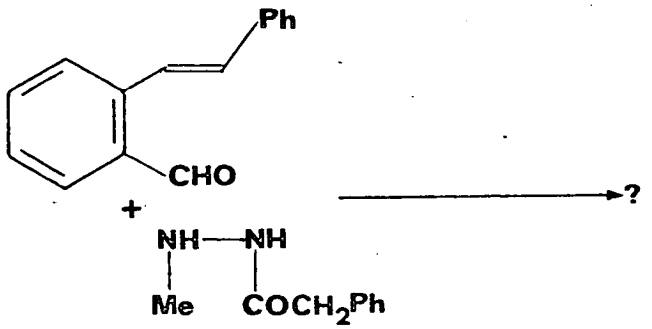
Control (1) showed no deuterium incorporation into the undeuterated hydrazone under the reaction conditions; Control (2) showed no loss of deuteration on recrystallisation from ethanol.

Mass specral data (160°C) m/e (relative abundance %).

91(100), 115(48), 116(26), 178(24), 179(15), 181(12), 184(21), 193(71), 194(50), 210(17), 298(11), 299(9), 311(33), 312(27), 402(12), 403(11).

APPENDIX VI

The product of the reaction between trans-2-formylstilbene and 1-methyl-2-phenylacetylhydrazine.



^{1}H N.m.r. spectral data $CDCl_3$ δ (28°C).

1.70(integration; 3), 2.09 (16), 2.31(7), 3.35 (3), 3.39 and 3.40 (9), 3.46 (6), 3.65 (3), 4.75 (2), 4.90(5), 5.21(2), 6.22 (6), 6.75-6.8 (multiplet, 14), 7.0-7.6 (multiplet, 97).

^{13}C N.m.r. data (p.p.m. from Me_4Si) $CDCl_3$.

Possible tertiary carbon atoms noted.

39.4, 40.3 (tert), 42.9, 63.1 (tert), 64.2, 65.65, 67.5 (tert), 71.3, 121.1 (tert), 122.3, 123.4, 126.0 (tert), 126.2, 126.6, 126.75 (tert), 127.0, 127.2, 127.4, 127.8, 127.9, 128.4, 128.55, 128.6, 129.5, 135.05, 136.0 (tert), 141.2 (tert), 141.35 (tert), 141.6, 174.4 (tert).

Mass spectral data (130°C) m/e (relative abundance %).

91(90), 116(45), 129(33), 130(52), 131(24), 144(33), 145(62), 159(19), 165(17), 178(48), 191(60), 192(88), 206(95), 207(19), 219(38), 220(100), 221(52), 235(71), 248(21),263(67), 277(45), 349(14), 354(74).

I.r. spectral data (Nujol).

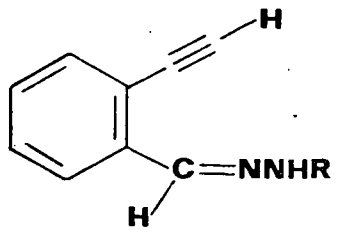
1650cm^{-1} (C=O).

APPENDIX VII

Acetylenic hydrazones.

^{1}H N.m.r. spectral data (28°C) δ.

2-Ethynylbenzaldehyde hydrazones



R	Solvent	Acetylenic	H-C=N	N-H	Aromatic	$-CH_3$	
Ts	$CDCl_3$	3.01s, 1H	8.25s, 1H	8.07s, 1H	7.1-80m, 8H	2.41s, 3H	
SO_2Ph	$CDCl_3$	3.28s, 1H	8.31s, 1H	8.80s, 1H	7.1-8.1m, 8H		
SO_2Me	$CDCl_3$	3.40s, 1H	8.37s, 1H	8.50s, 1H	7.1-8.1m, 4H	3.15s, 3H	
COPh	$DMSOd_6$	4.30s, 1H	8.91s, 1H		7.2-8.2m, 10H(including N-H)		
$CONH_2$	$DMSOd_6$	4.22s, 1H	8.32s, 1H		7.1-8.2m, 5H(including N-H)		6.40s, 2H $-NH_2$
2,4-DNP	$DMSOd_6$	4.65s, 1H	9.01s, 1H		7.3-8.9m, 8H(including N-H)		

2-Phenylethynylbenzaldehyde tosylhydrazone ($CDCl_3$)

8.30 (s, 1H, H-C=N); 8.15 (s, 1H, N-H); 7.1-8.0 (m, 13H, aromatic); 2.25 (s, 3H, $-CH_3$).

2-Phenylethynylbenzaldehyde benzoylhydrazone ($CDCl_3$)

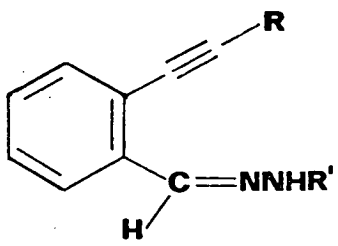
9.45(s, 1H, H-C=N); 8.70 (s, 1H, N-H), 7.1-8.0 (m, 14H, aromatic).

cis-3-Methylpent-2-en-4-yn-1-al tosylhydrazone ($CDCl_3$)

8.20 (s, 1H, N-H); 7.83 (d, J8Hz, 1H, H-C=N); 7.52 (q, J7Hz, 4H, aromatic); 6.30 (dd, J8Hz, J'1Hz, 1H, vinylic); 3.30 (s, 1H, acetylenic); 2.41 (s, 3H, aromatic -Me); 1.95 (d, J1Hz, 3H, vinylic -Me).

APPENDIX VIII

Acetylenic hydrazones.



I.r. spectral data (Nujol) cm^{-1}.

a) R = H, R' = COPh; 3230 (N-H), 1650 (C=O), 1610 (C=N).

b) R = H, R' = $CONH_2$; 3470, 3260 and 3140 (N-H and NH_2), 1700 (C=O).

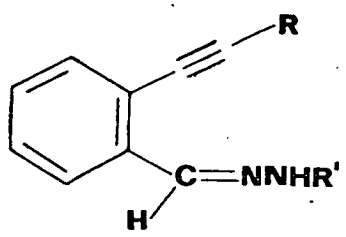
c) R = H, R' = 2,4-DNP; 3260 (N-H), 1610 (C=N).

d) R = Ph, R' = Ts; 3220 (N-H), 1600 (C=N), 1320 and 1165 (O=S=O).

e) R = Ph, R' = COPh; 3180 (N-H), 1645 (C=O), 1610 (C=N).

APPENDIX IX

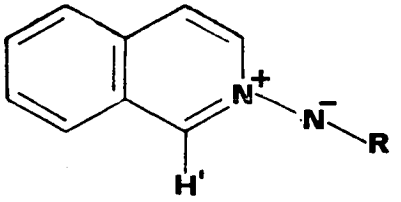
Acetylenic hydrazones.



Mass spectral data.	m/e (relative abundance).
a) R = H, R' = Ts (170°C)	39(36), 50(18), 51(33), 63(28), 65(59), 77(26), 89(23), 91(100), 92(46), 102(28), 115(97), 129(82), 139(46), 155(26), 156(36), 171(21), 278(18), 298(3).
b) R = H, R' = SO_2Ph (180°C)	93(24), 94(17), 102(34), 109(54), 115(17), 125(83), 128(24), 129(100), 141(46), 157(24), 218(15), 250(39), 284(5).
c) R = H, R' = COPh (180°C)	51(20), 77(75), 104(30), 105(100), 129(35), 145(75), 171(20), 247(62), 248(40).
d) R = H, R' = $CONH_2$ (180°C)	44(13), 51(10), 63(13), 75(10), 89(14), 90(13), 115(14), 116(14), 117(10), 128(14), 143(17), 144(19), 145(100), 170(5), 171(4), 187(5).
e) R = H, R' = 2,4-DNP (200°C)	51(26), 63(29), 75(37), 77(26), 101(42), 128(95), 129(39), 190(26), 217(71), 218(100), 264(74), 298(34), 310(45).
f) R = Ph, R' = Ts (180°C)	65(13), 91(26), 139(10), 156(13), 165(5), 178(4), 189(33), 191(100), 205(6), 218(5), 282(4), 346(6).
g) R = Ph, R' = COPh (190°C)	51(18), 77(88), 104(28), 105(100), 121(10), 143(14), 144(20), 189(13), 221(85), 243(23), 244(30), 245(30), 247(10), 323(8), 324(8).

APPENDIX X

Isoquinoline N-imines.



^{1}H N.m.r. spectral data (28°C) δ .

From 2-ethynylbenzaldehyde and hydrazines.

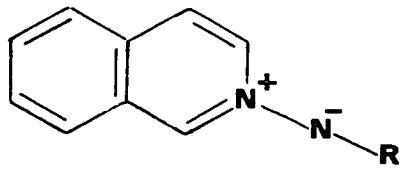
R	Solvent	H'	Aromatic Protons		
Ts	$DMSOd_6$	9.52s, 1H	7.7-8.5m, 6H	7.32q, J8Hz, 4H	2.33s, 3H
SO_2Ph	$DMSOd_6$	9.53s, 1H	7.1-8.5m, 11H		
SO_2Me	$DMSOd_6$	9.70d, J1Hz, 1H	7.8-8.6m, 6H	2.70s, 3H	
COPh	$CDCl_3$	9.85s, 1H	7.1-8.5m, 11H		

From homophthalaldehyde and hydrazines.

R	Solvent	H'	Aromatic Protons		
Ts	$DMSOd_6$	9.53s, 1H	7.7-8.5m, 6H	7.31q, J8Hz, 4H	2.32s, 3H
SO_2Ph	$DMSOd_6$	9.53s, 1H	7.1-8.5m, 11H		
SO_2Me (hydrochloride)	$DMSOd_6$	9.70s, 1H	7.8-8.6m, 6H	2.70s, 3H	
COPh	$CDCl_3$	9.85s, 1H	7.1-8.5m, 11H		

APPENDIX XI

Isoquinoline N-imines.



I.r. spectral data (Nujol) cm^{-1}.

From 2-ethynylbenzaldehyde and hydrazines.

a) R = Ts 1605 (C=N), 1285 and 1130 (O=S=O).

b) R = SO_2Ph 1605 (C=N), 1285 and 1130 (O=S=O).

c) R = SO_2Me 1605 (C=N), 1275 and 1120 (O=S=O).

d) R = COPh 1590 (C=N), 1550 (C=O).

From homophthalaldehyde and hydrazines.

a) R = Ts 1605 (C=N), 1285 and 1130 (O=S=O).

b) R = SO_2Ph 1605 (C=N), 1285 and 1130 (O=S=O).

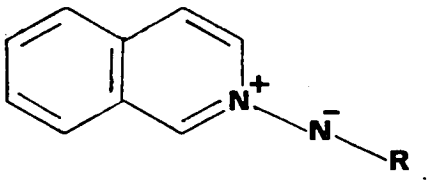
c) R = SO_2Me 2450 (broad, N-H), 1360 and 1155 (O=S=O).
(hydrochloride)

d) R = COPh 1590 (C=N), 1550 (C=O).

APPENDIX XII

Isoquinoline N-imines.

From 2-ethynylbenzaldehyde and hydrazines.



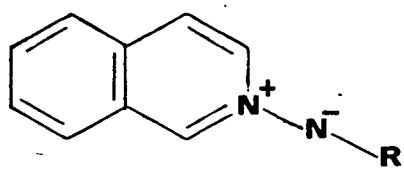
Mass spectral data.

Compound.	m/e (relative abundance %).
a) R = Ts (240°C)	39(43), 50(20), 51(26), 63(49), 65(57), 89(50), 91(57), 102(23), 105(37), 115(43), 116(100), 129(83), 130(43), 143(24), 233(19), 234(31), 298(36).
b) R = SO_2Ph (230°C)	39(20), 50(20), 51(40), 63(20), 65(16), 77(56), 89(20), 91(24), 102(24), 115(23), 116(68), 129(100), 143(44), 219(32), 220(32), 284(74).
c) R = SO_2Me (200°C)	39(15), 50(15), 51(24),63(22), 65(10), 89(19), 102(34), 115(26), 116(53), 128(19), 129(100), 143(30), 207(29), 222(47).
d) R = COPh (180°C)	44(6), 51(8), 76(4), 77(15), 102(8), 103(8), 105(6), 116(4), 128(9), 129(40), 130(5), 171(30), 172(4), 247(100), 248(73).

APPENDIX XIII

Isoquinoline N-imines.

From homophthalaldehyde and hydrazines.

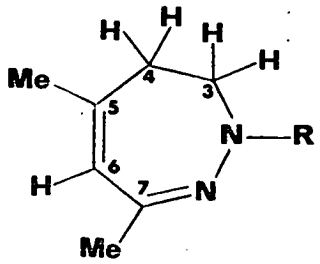


Mass spectral data.

Compound.	m/e (relative abundance %).
a) R = Ts (210°C)	39(20), 50(10), 51(20), 63(21), 65(26), 89(22), 91(45), 102(20), 105(23), 115(20), 116(45), 129(100), 130(29), 143(30), 233(20), 234(15), 298(73).
b) R = SO_2Ph (220°C)	39(17), 50(19), 51(42), 63(18), 65(16), 77(63), 89(21), 91(13), 102(26), 115(19), 116(53), 129(100), 143(28), 219(20), 220(26), 284(53).
c) R = SO_2Me (hydrochloride, 190°C)	36(100), 38(30), 39(7), 50(9), 51(13), 63(43), 65(33), 89(33), 102(14), 115(20), 116(50), 128(9), 129(40), 143(40), 207(33), 222(56).
d) R = COPh (170°C)	44(5), 51(9), 63(4), 76(4), 77(17), 102(9), 103(6), 105(8), 128(11), 129(37), 130(6), 171(37), 172(7), 247(100), 248(66).

APPENDIX XIV

3,4-Dihydro-1,2-diazepines.



^{1}H N.m.r. spectral data (28°C) $CDCl_3$ (δ).

R	3-H_2	4-H_2	5-CH_3	6-H	7-CH_3	
) SO_2Ph	3.39t, J6Hz, 2H	2.60t, J6Hz, 2H	1.88s, 3H	5.65s, 1H	2.00s, 3H	7.35-8.1m, 5H, aromatic
) SO_2Me	3.58t, J7Hz, 2H	2.62t, J7Hz, 2H	1.90s, 3H	5.70s, 1H	2.06s, 3H	2.98s, 3H, SO_2-Me
) COPh	3.92t, J5Hz, 2H	2.60t, J5Hz, 2H	1.95s, 3H	5.71s, 1H	2.03s, 3H	7.1-8.7m, 5H, aromatic
) COMe	3.79t, J5Hz, 2H	2.41t, J5Hz, 2H	1.88s, 3H	5.65s, 1H	2.10s, 3H	2.19s, 3H, COMe
) $CO_2C_2H_5$	3.75t, J5Hz, 2H	2.50t, J5Hz, 2H	1.89s, 3H	5.70s, 1H	2.12s, 3H	1.28t, J6Hz, 3H 4.20q, J6Hz, 2H

I.r. spectral data (Nujol) cm^{-1}.

a) R = SO_2Ph, 1640 (C=C), 1590 (C=N), 1360 and 1165 (O=S=O).

b) R = SO_2Me, 1640 (C=C), 1595 (C=N), 1340 and 1155 (O=S=O).

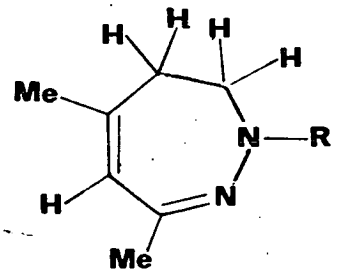
c) R = COPh, 1645 (C=O), 1595 (C=N).

d) R = COMe, 1660 (C=O), 1580 (C=N).

e) R = $CO_2C_2H_5$, 1700 (C=O), 1635 (C=C), 1580 (C=N).

APPENDIX XV

3,4-Dihydro-1,2-diazepines.

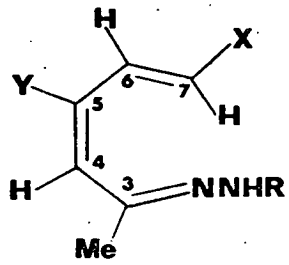


Mass spectral data.	m/e (relative abundance %).
a) R = SO_2Ph (120°C)	39(9), 42(12), 43(13), 51(9), 53(8), 55(13), 67(7), 77(17), 79(7), 80(5), 81(60), 94(8), 123(100),124(15), 264(25).
b) R = SO_2Me (*)	39(19), 41(27), 42(27), 43(10), 53(15), 55(23), 67(13), 69(8), 77(8), 79(9), 82(10), 94(8), 95(6), 105(9), 111(8), 123(100), 124(15), 202(27).
c) R = COPh (*)	39(15), 41(15), 42(12), 50(9), 51(25), 53(11), 55(10), 77(93), 78(12), 79(9), 96(12), 104(9), 105(100), 106(20), 107(10), 108(12), 109(9), 124(23), 228(50).
d) R = COMe (*)	39(16), 41(14), 42(13), 43(25), 53(11), 55(9), 67(12), 82(14), 94(19), 95(25), 96(100), 109(23), 123(15), 124(25), 151(4), 166(56).
e) R = $CO_2C_2H_5$ (*)	29(42), 39(16), 41(20), 43(25), 53(10), 55(17), 67(12), 82(15), 94(22), 95(24), 96(50), 108(12), 109(20), 123(50), 137(10), 196(100).

* room temperature and heat.

APPENDIX XVI

Hydrazones of αβ,γδ-unsaturated ketones.



^{1}H N.m.r. spectral data (28°C) $CDCl_3$ (δ).

a) X = H, Y = Me, R = COPh; 1.85-2.15 (m, 2xMe); 4.7-6.5 (m, 4H, olefinic); 7.3-8.0 (m, 5H, aromatic); 8.7 (bs, 1H, N-H).

b) X = Ph, Y = Me, R = SO_2Me; 1.99(s, 3H, 3-Me); 2.20(d, J0.5Hz, 3H, 5-Me); 3.11 (s, 3H, SO_2Me); 5.99 (d, J0.5Hz, 1H, C-4); 6.73 (d, J2Hz, 2H, C-6 and C-7.1-7.5 (m, 5H, aromatic); 7.65 (bs, 1H, N-H).

c) X = Ph, Y = Me, R = COMe; 2.00 (s, 3H, 3-Me); 2.25 (d, J0.5Hz, 3H, 5-Me); 2.30 (s, 3H, COMe); 5.97 (d, J0.5Hz, 1H, C-4); 6.75 (d,J2Hz, 2H, C-6 and C-7) 7.1-7.5 (m, 5H, aromatic), 9.0 (bs, 1H, N-H).

d) X = Me, Y = H, R = COMe; 1.77 (d, J6Hz, 3H, 7-Me); 1.90 (s, 3H, 3-Me); 2.28 (s, 3H, COMe); 5.6-6.7 (m, 4H, olefinic); 8.45 (bs, 1H, N-H).

I.r. spectral data (Nujol) cm^{-1}.

a) X = H, Y = Me, R = COPh; 3200 (N-H), 1650 (C=O), 1600 (C=N), 1580 (C=C).

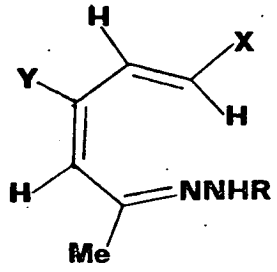
b) X = Ph, Y = Me, R = SO_2Me; 3210 (N-H), 1605 (C=N), 1315 and 1150 (O=S=O).

c) X = Ph, Y = Me, R = COMe; 3160 (N-H), 1660 (C=O), 1605 (C=N).

d) X = Me, Y = H, R = COMe; 3180 (N-H), 1670 (C=O).

APPENDIX XVII

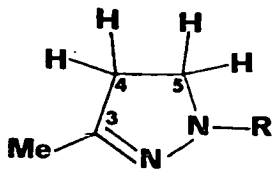
Hydrazones of αβ,γδ-unsaturated ketones.



Mass spectral data.	m/e (relative abundance %).
a) X = H, Y = Me, R = COPh.	39(9), 40(8), 41(7), 51(14), 77(53), 105(100), 107(38), 109(53), 123(12), 213(12), 227(11), 228(12).
b) X = Ph, Y = Me, R = SO_2Me.	31(100), 63(32), 65(82), 71(32), 80(43), 91(25), 95(20), 97(36), 104(34), 158(25), 175(19), 199(57), 263(4), 278(9).
c) X = Ph, Y = Me, R = COMe.	39(7), 41(8), 42(12), 43(31), 51(6), 56(5), 77(14), 91(17), 102(16), 115(15), 123(26), 127(7), 128(17), 129(7), 140(11), 142(9), 165(66), 168(65), 183(100), 199(12), 227(81), 242(30).
d) X = Me, Y = H, R = COMe.	39(20), 41(25), 43(55), 83(36), 107(39), 108(32), 109(84), 123(34), 151(100), 166(35).

APPENDIX XVIII

3-Methylpyrazol-2-ines.



^{1}H N.m.r. spectral data (28°C) $CDCl_3$ (δ).

	R	3-CH_3	4-H_2	5-H_2	
a)	COPh	2.01 bs, 3H	2.80t, J9Hz, 2H	4.06t, J9Hz, 2H	7.1-7.9m, 5H
a)	COPh (authentic)	2.01bs, 3H	2.80t, J9Hz, 2H	4.06t, J9Hz, 2H	7.1-7.9m, 5H
b)	$CO_2C_2H_5$	2.04d, J0.5Hz, 3H	2.80t, J9Hz, 2H	3.85t, J9Hz, 2H	1.30t, J9Hz, 3H 4.25q, J9Hz, 2H

I.r spectral data (Nujol) cm^{-1}.

a) R = COPh; 1620 (C=O), 1595 (C=N).

a) R = COPh (authentic); 1620 (C=O), 1595 (C=N).

b) R = $CO_2C_2H_5$; 1690 broad (C=O); 1620 ; 1595 (C=N); 1570

Mass spectral data.	m/e (relative abundance %).
a) R = COPh (90°C)	188(62), 106(16), 105(100), 78(6), 77(58), 51(14), 50(8).
a) R = COPh (authentic, 120°C)	188(41), 106(13), 105(100), 78(6), 77(61), 51(17), 50(6).
b) R = $CO_2C_2H_5$ (room temperature)	156(100), 111(88), 97(98), 84(100), 83(100), 70(15), 69(27), 56(35), 55(23), 42(83), 29(100).

APPENDIX XIX

^{1}H N.m.r. spectra of the deuterated diazepine formed with no acid.

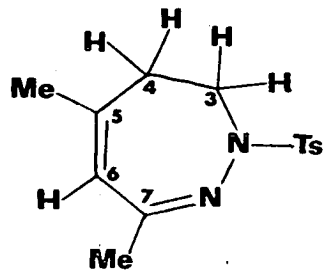
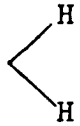


Table 1.

Position	Average Integration	Integration per proton	Standard Integration*	% Deuteration	
3 	24.5	12.25	14.5	30	
	19.6	9.8	11.3	26	Ave = 27
	22.0	11.0	12.4	24	
4 	23.5	11.25		45	
	17.5	8.7		46	Ave = 43
	20.0	10.0		38	
5 $-CH_3$	36.5	12.2		16	
	31.5	10.5		16	Ave = 15
	32.75	10.9		12	
6 -H	11.8	11.8		19	
	8.5	8.5		25	Ave = 23
	9.25	9.25		25	
7 $-CH_3$	43.5	14.5		0	
	33.6	11.2		0	Ave = 0
	37.25	12.4		0	

* The standard integration per proton is calculated from the aromatic and methyl groups of the p-tosyl group assuming no deuterium incorporation.

APPENDIX XX

^{1}H N.m.r. spectra of the deuterated diazepine formed with acid by the indirect route.

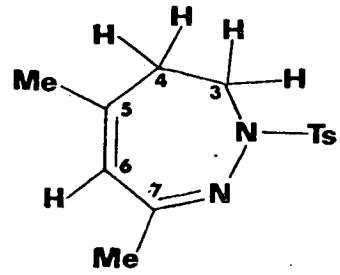
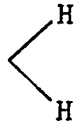


Table 2.

Position	Average Integration	Average per proton	Standard Integration	% Deuteration	
3 	33.8	16.9	17.5	0	
	27.1	13.55	13.5	0	Ave = 0
	23.25	11.6	11.7	0	
4 	24.6	12.3		58	
	22.3	11.15		38	Ave = 46
	18.6	9.3		42	
5 $-CH_3$	47.5	15.8		9	
	37.8	12.6		7	Ave = 7
	33.3	11.1		5	
6 -H	4.9	4.9		72	
	5.3	5.3		61	Ave = 64
	4.7	4.7		60	
7 $-CH_3$	38.5	12.8		26	
	26.1	8.7		22	Ave = 22
	29.1	9.7		17	

APPENDIX XXI

^{1}H N.m.r. spectra of the deuterated diazepines formed with acid by the direct route.

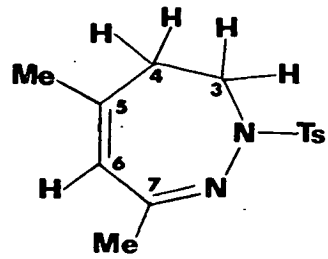


Table 3.

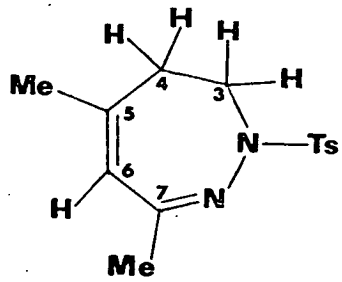
Position	Average Integration	Integration per proton	Standard Integration	% Deuteration	
3 $-CH_2-$	23.1	11.6	11.85	0 * 0	Ave = 0.
4 $-CH_2-$	19.25	9.6		38 * 36	Ave = 37
5 $-CH_3$	31.5	10.5		11 * 8	Ave = 10
6 -H	4.25	4.25		64 * 76	Ave = 70
7 $-CH_3$	30.0	10.0		15 * 18	Ave = 17

* Performed by C.D. Anderson.

Control i. ^{1}H N.m.r. spectrum of the non-deuterated diazepine stirred in H^+/CH_3OD.

Table 4.

Position	Average Integration	Integration per proton
3 $-CH_2-$	23.5	11.8
4 $-CH_2-$	24.8	12.4
5 $-CH_3$	35.5	11.8
6 -H	11.8	11.8
7 $-CH_3$	37.2	12.4
$-C_6H_4$	49.9	12.5
$Ar-CH_3$	35.5	11.8

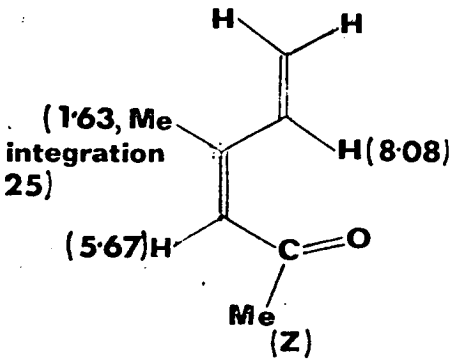


Average per proton = 12.1 $\pm$ 0.3

Error = $\pm$ 3%

APPENDIX XXII

^{1}H N.m.r. spectrum (δ) of 4-methylhexa-3,5-dien-2-one.



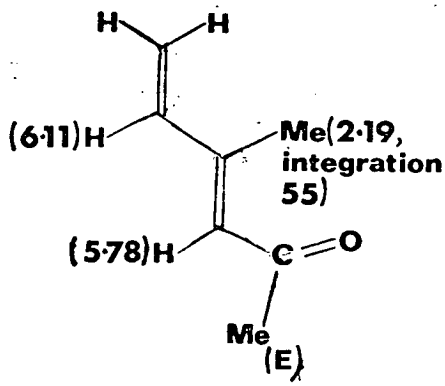


Table 5. E:Z = 2.2:1

Control ii: 4-methylhexa-3,5-dien-2-one in H^+/CH_3OD

H's	Average integral					
	t = 0	t = 10min		t = 24h	redistilled	
2 x Me, 6H	137.3	98.6		56.1	100.2	
vinylic, 4H	91.2	82.7		53.5	89.3	
cyclo-hexane	37.6	31.8		33.5	35.8	
	Ratio of integrals		Deuteration	Ratio of integrals		Deuteration
vinylic / 2 x Me	0.66	0.80	-	0.95	0.84	-
2 x Me / c/hexane	3.7	3.1	17%	1.7	2.8	24%
vinylic / c/hexane	2.4	2.6	~0%	1.6	2.5	~0%

Control iii: 4-Methyl-6-phenylhexa-3,5-dien-2-one tosylhydrazone: H^+/CH_3OD.

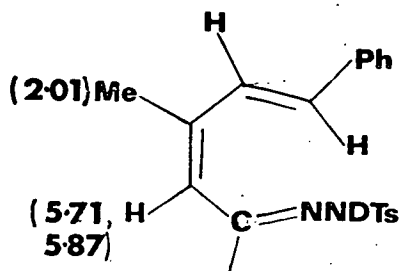


Table 6.

H's δ	Average Integral	Deuteration
1.77 and 1.90, Me, 3H	33	20%
2.01, Me, 3H	33	20%
2.38, Me, 3H	42	= 0%
5.71, 5.87, vinylic, 1H	14	0%
6.60, 6.79, vinylic, 2H	28	0%

Control iv: Hepta-3,5-dien-2-one tosylhydrazone: H^+/CH_3OD.

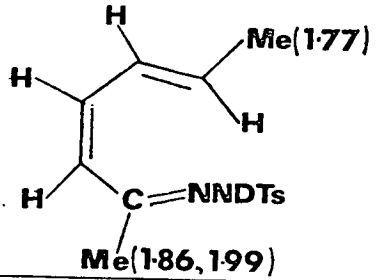


Table 7.

H's, δ	Average Integral	Deuteration
1.77, Me, 3H	38	0%
1.86 and 1.99 Me, 3H	38	0%
2.38, Me, 3H	38	= 0%
5.7-6.6, vinylic, 4H	52	0%

BIBLIOGRAPHY

1. J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structures", International Student Edn., McGraw-Hill Kogakusha, Ltd., Japan, 1968 pp. 562-573.

2. P.B.D. de la Mare and R. Bolton, "Electrophilic Additions to Unsaturated Systems", American Elsevier Publishing Company, New York, 1966.

3. J.I.G. Cadogan and M.J. Perkins in "The Chemistry of Alkenes", ed. S. Patai, Interscience Publishers Inc., New York, 1964, pp. 585-632.

4. S. Patai in "The Chemistry of Alkenes", ed. S. Patai, Interscience Publishers Inc., New York, 1964, pp. 469-584.

5. E.D. Bergmann, D. Ginsburg and R. Pappo, Organic Reactions, 1959, 10, 179.

6. A. Hochstetter and M. Kohn, Monatsh. Chem., 1903, 24, 773.

7. D. Aelony and W.J. McKillip, U.S. 3,876,657 (Chem. Abs., 1975, 83, 58825c).

8. R. Baltzly, E. Lorz, P.B. Russell and F.M. Smith, J. Amer. Chem. Soc., 1955, 77, 624.

9. S.R. Buc, J.H. Ford and E.C. Wise, J. Amer. Chem. Soc., 1945, 67, 92.

10. J.H. Ford, S.R. Buc and J.W. Greiner, J. Amer. Chem. Soc., 1947, 69, 844.

11. R. Blank, Ber., 1895, 28, 145.

12. T.L. Jacobs in Heterocyclic Compounds Vol. V, ed. R.C. Elderfield, John Wiley and Sons, New York, 1957, p.45.

13. K.v. Auwers and H. Mauss, Ber., 1926, 59, 611.

14. T.F. Rutledge, "Acetylenes and Allenes: Addition, Cyclisation and Polymerisation Reactions", Reinhold Book Corp., New York, 1969.

15. E. Winterfeldt in "The Chemistry of the Acetylenes", ed. H.G. Viehe, Marcel Deker Inc., New York, 1969, pp. 267-334.

16. R. Fuks and H.G. Viehe in "The Chemistry of the Acetylenes", ed. H.G. Viehe. Marcel Deker Inc., New York, 1969, pp. 425-495.

17. R. Paul and H. Normant, Bull. Soc. chim. France, 1944, 365.

18. J. Cologne and R. Gelin, Bull. Soc. chim. France, 1954, 799.

19. R. Paul and S. Tchelitcheff, Compt. rend., 1950, 230, 1872.

20. G. Eglinton, E.R.H. Jones and M.C. Whiting, J. Chem. Soc., 1952, 2873.

21. K.E. Schulte, J. Reisch and D. Bergenthal, Angew. Chem. Internat. Edn., 1965, 4, 1082.

22. K.E. Schulte, J. Reisch and D. Bergenthal, Ber., 1968, 101, 1540.

23. J. Reisch, Arch. Pharm., 1965, 298, 591.

24. F. Ya. Perveev, E.M. Vekshina and L.N. Surenkova, Zh. obshchei Khim., 1957, 27, 1526 (Chem. Abs., 1958, 52, 3767g).

25. F. Ya. Perveev and V.M. Demidova, Zh. org. Khim., 1965, 1, 2244 (Chem. Abs., 1966, 64, 11095d).

26. J. Chauvelier, Ann. chim. (Paris), 1948, 3, 410.

27. J. Chauvelier, Bull. Soc. chim. France, 1954, 734.

28. J. Chauvelier, Bull. Soc. chim. France, 1966, 1721.

29. T. Metler, A. Uchida and S.I. Miller, Tetrahedron, 1968, 24, 4285.

30. K.E. Schulte, J. Reisch and H. Lang, Ber., 1963, 96, 1470.

31. J. Reisch, Pharmazie, 1966, 21, 770.

32. J. Reisch, Ber., 1964, 97, 2717.

33. G. Coispeau, J. Elguero and R. Jacquier, Bull. Soc chim. France, 1970, 689.

34. L.I. Vereshchagin, L.D. Gavrilov, E.I. Titova, S.R. Buzilova, N.V. Sushkova, A.V. Maksikova, Zh. org. Khim., 1975, 11, 47 (Chem. Abs., 1975, 82, 139997s).

35. V. Bardakos, W. Sucrow and A. Fehlauer, Ber., 1975, 108, 2161.

36. R. Huisgen, Angew. Chem. Internat. Edn., 1963, 2, 565, 633.

37. R. Huisgen, R. Grashey and J. Sauer in "The Chemistry of Alkenes", ed. S. Patai, Interscience Publishers Inc., New York, 1964, pp. 806-878.

38. R. Huisgen, J. Org. Chem., 1968, 33, 2291.

39. R. Huisgen, Angew. Chem. Internat. Edn., 1968, 7, 321.

40. R. Huisgen, J. Org. Chem., 1976, 41, 403.

41. R.A. Firestone, J. Org. Chem., 1968, 33, 2285.

42. R.A. Firestone, J. Org. Chem., 1972, 37, 2181.

43. R.A. Firestone, Tetrahedron, 1977, 33, 3009.

44. K.N. Houk, J. Amer. Chem. Soc., 1972, 94, 8953.

45. K.N. Houk, J. Sims, R.E. Duke, R.W. Strozier and J.K. George, J. Amer. Chem. Soc., 1973, 95, 7287.

46. K.N. Houk, J. Sims, C.R. Watts and L.J. Luskins, J. Amer. Chem. Soc., 1973, 95, 7301.

47. J. Sims and K.N. Houk, J. Amer. Chem. Soc., 1973, 95, 5798.

48. R.D. Harcourt, Tetrahedron, 1978, 34, 3125.

49. A. Padwa, Angew. Chem. Internat. Edn., 1976, 15, 123.

50. W. Oppolzer, Angew. Chem. Internat. Edn., 1977, 16, 10.

51. N.A. Lebel and J.J. Whang, J. Amer. Chem. Soc., 1959, 81, 6334.

52. N.A. Lebel, Trans. New York Acad. Sci., 1965, 27, 858.

53. J.E. Baldwin, J.C.S. Chem. Comm., 1976,734.

54. A.C. Knipe and C.J.M. Stirling, J. Chem. Soc. (B), 1968, 66.

55. L. Tenud, S. Faroog, J. Seible and A. Eschenmoser, Helv. Chim. Acta., 1970. 53, 2059.

56. J.E. Baldwin, J. Cutting, W. Dupont, L. Kruse, L. Silberman and R.C. Thomas, J.C.S. Chem. Comm., 1976, 736.

57. S.A. Kandil and R.E. Dessy, J. Amer. Chem. Soc., 1966, 88, 3027.

58. R.E. Dillard and N.R. Easton, J. Org. Chem., 1966, 31, 122.

59. G.L. Hekkert and W. Drenth, Rec. Trav. Chim., 1961, 80, 1285.

60. A.T. Bottini, F.P. Carson and E.F. Bottner, J. Org. Chem., 1965, 30, 2988.

61. H.B. Burgi, J.D. Dunitz, J.M. Lehn and G. Wipff, Tetrahedron, 1974, 30, 1563.

62. G. Wegner, Polymer Letters, 1971, 9, 133.

63. R.H. Baughman, J. Appl. Phys., 1972, 43, 4362.

64. E. Rouvier, J.C. Giacomoni and A. Cambon, Bull. Soc, chim. France, 1971, 1717.

65. K. v. Auwers and E. Lammerhirt, Annalen, 1920, 421, 30.

66. G. Claeson and H.-G. Jonsson, Arkiv Kemi., 1968, 28, 167 (Chem. Abs., 1968, 68, 87083e).

67. J.E. Baldwin and L.I. Kruse, J.C.S. Chem. Comm., 1977, 233.

68. J.E. Baldwin and J.A. Reiss, J.C.S. Chem. Comm., 1977, 77.

69. J.E. Baldwin, J.C.S. Chem. Comm., 1976, 738.

70. F.D. Popp and A.C. Noble, Adv. Heterocyclic Chem., 1967, 8, 21.

71. M. Nastasi, Heterocycles, 1976, 4, 1509.

72. J.A. Moore, Trans. New York Acad. Sci., 1965, 27, 591.

73. J. Streith and J.M. Cassal, Angew. Chem. Internat. Edn., 1968, 7, 129.

74. J. Streith and J.M. Cassal, Tetrahedron Letters, 1968, 4541.

75. H.-J. Timpe, Adv. Heterocyclic Chem., 1974, 17, 213.

76. G.G. Spence, E.C. Taylor and O. Buchardt, Chem. Rev., 1970, 70, 231.

77. Y. Tamura, J. Minamikawa, Y. Miki, S. Matsugashita and M. Ikeda, Tetrahedron letters, 1972, 4133.

78. Y. Tamura, J. Minamikawa, Y. Kita, J.H. Kim and M. Ikeda, Tetrahedron, 1973, 29, 1063.

79. Y. Tamura, Y. Miki and M. Ikeda, J. Heterocyclic Chem., 1973, 10, 447.

80. E. Klingsberg, Abstracts of the Amer. Chem. Soc. Meeting, September 1965, p66s.

81. V. Snieckus and G. Kan, J.C.S. Chem. Comm., 1970, 1208.

82. D.J. Harris, G. Y-P. Kan, V. Snieckus and E. Klingsberg, Canad. J. Chem., 1974, 52, 2798.

83. T. Tsuchiya and V. Snieckus, Canad. J. Chem., 1975, 53, 519.

84. J. Streith and B. Willig, Bull. Soc. chim. France, 1973, 2847.

85. A Balasubramanian, J.M. McIntosh and V. Snieckus, J. Org. Chem., 1970, 35, 433.

86. T. Sasaki, K. Kanematsu, A. Kakehi, I. Ichikawa and K. Hayakawa, J. Org. Chem., 1970, 35, 426.

87. M. Nastasi and J. Streith, Bull. Soc. chim.France, 1973, 635.

88. J. Streith, J.P. Luttringer and M. Nastasi, J. Org. Chem., 1971, 36, 2962.

89. J. Streith and J.M. Cassal, Bull. Soc. chim. France, 1969, 2175.

90. G. Kan, M.T. Thomas and V. Snieckus, J.C.S. Chem. Comm., 1971, 1022.

91. J.P. Luttringer, N. Perol and J. Streith, Tetrahedron, 1975, 31, 2435.

92. D.J. Harris and V. Snieckus, J.C.S. Chem. Comm., 1976, 844.

93. H. Prinzback and D.H. Martin, Chimia, 1969, 23, 37.

94. J.-J. Koenig and C.-G. Wermuth, Tetrahedron Letters, 1973, 603.

95. G. Wittig, W. Joos and P. Rathfelder, Annalen, 1957, 610, 180.

96. G. Zinner and W. Deucker, Arch. Pharm., 1962, 295, 526.

97. S. Wawzonek and J.G. Stephanie, J. Org. Chem., 1971, 36, 2467.

98. C.D. Anderson, J.T. Sharp, E. Stefaniuk and R.S. Strathdee, Tetrahedron Letters, 1976, 305.

99. H.E. Zimmermann and W. Eberbach, J. Amer. Chem. Soc., 1973, 95, 3970.

100. H.D. Fuhlhuber and J. Sauer, Tetrahedron Letters, 1977, 4393.

101. H. Kolbinger, G. Reissenweber and J. Sauer, Tetrahedron Letters 1976, 4321.

102. M. Lipp, F. Dallacker and S. Munnes, Annalen, 1958, 618, 110.

103. K.W. Merz and H. Richter, Arch. Pharm., 1937, 275, 294.

104. L.A. Carpino, J. Org. Chem., 1965, 30, 736.

105. E.E. Blaise and H. Gault, Bull. Soc. chim. France, 1907, 75.

106. C.G. Overberger and J.J. Monagle, J. Amer. Chem. Soc., 1956, 78, 4470.

107. C.G. Overberger and J.G. Lombardino, J. Amer. Chem. Soc., 1958, 80, 2317.

108. C.G. Overberger, J.G. Lombardino, I. Tashlick and P.G. Hiskey, J. Amer. Chem. Soc., 1957, 79, 2662.

109. R.G. Amiet, R.B. Johns and K.R. Markham, J.C.S. Chem. Comm., 1965, 128.

110. G.A. Archer and L.H. Sternbach, Chem. Rev., 1968, 68, 747.

111. S.J. Childress and M.I. Glickman, J. Pharm. Sci., 1964, 53, 577.

112. L.H. Sternbach, L.O. Randall, R. Banziger and H. Lehr in, "Medicinal Research Series" Vol 2, Drugs Affecting the Central Nervous System, ed. A. Burger, Marcel Deker Inc., New York, 1968, p. 237.

113. J. Gottlieb, Ber., 1899, 32, 958.

114. H. Wolbling, Ber., 1905, 38, 3845.

115. A. Lieck, Ber., 1905, 38, 3853.

116. H.P. Buu-Hoi, Compt. rend., 1939, 209, 321.

117. W.F. Whitmore and R.C. Cooney, J. Amer. Chem. Soc., 1944, 66, 1237.

118. L. Legrand and N. Lozac'h, Bull. Soc. chim. France, 1970, 2237.

119. J.O. Halford, R.W. Raiford and B. Weissman, J. Org. Chem., 1961, 26, 1898.

120. C. -G. Wermuth and M. Flammang, Tetrahedron Letters, 1971, 4293.

121. A. Sotiriadis, P. Catsoulacos and D. Theodoropoulos, J. Heterocyclic Chem., 1974, 11, 401.

122. M. Flammang and C. -G. Wermuth, Eur. J. Med. Chem., 1977, 12, 121.

123. M. Flammang, Compt. rend., 1978, 286c, 671.

124. E. Schmitz and R. Ohme, Ber., 1962, 95, 2012.

125. C. v.d. Stelt, P.S. Hofman and W. Th. Nauta, Rec. Trav. Chim., 1965, 84, 633.

126. J.T. Sharp and P.B. Thorogood, J.C.S. Chem. Comm., 1970, 1197.

127. A.A. Reid, J.T. Sharp, H.R. Sood and P.B. Thorogood, J.C.S. Perkin I, 1973, 2543.

128. A.A. Reid, J.T. Sharp and S.J. Murray, J.C.S. Chem.Comm., 1972, 827.

129. J. Korosi and T. Lang, Ber., 1974, 107, 3883.

130. A. Neszmelyi, E. Gacs-Baitz, G. Horvath, T. Lang and J. Korosi, Ber., 1974, 107, 3894.

131. G. Zolyomi, D. Banfi, T. Lang and J. Korosi, Ber., 1974, 107, 3904.

132. Y. Tamura, J. Minamikawa, H. Matsushima and M. Ikeda, Synthesis, 1973, 3, 159.

133. R. Huisgen, R. Grashey and R. Krischke, Tetrahedron Letters, 1962, 387.

134. Y. Tamura, N. Tsiyimoto and M. Uchimura, Chem. Pharm. Bull., 1971, 19, 143.

135. Y. Tamura and N. Tsiyimoto, Chem.and Ind., 1970, 926.

136. Y. Tamura, S. Matsugashita, M. Ishibashi and M. Ikeda, Tetrahedron, 1973, 29, 2359.

137. T. Zincke and G. Weisspfennig, Annalen, 1913, 396, 103.

138. V.S. Garkusha-Bozhko, S.N. Baranov and O.P. Shvaika, U.S.S.R. 430,098 (Chem. Abs., 1974, 81, 63502h)

139. V.S. Garkusha-Bozhko, O.P. Shvaika, L.M. Kapkan and S.N. Baranov, Khim. Geterotsikl. Soedin., 1974; 7, 961 (Chem. Abs., 1974, 81, 152189d).

140. V.S. Garkusha-Bozhko, O.P. Shvaika and S.N. Baranov, Tezisy Dokl.-Simp. Khim. Tekhnol. Geterotsikl. Soedin. Goryuch. Iskop. 2nd., 1973, 68 (Chem. Abs., 1977, 86, 29774s).

141. B. Agai and K. Lempert, Tetrahedron, 1972, 28, 2069.

142. R.A. Abramovitch and T. Takaya, J. Org. Chem., 1972, 37, 2022.

143. Y. Tamura, H. Ishibashi, N. Tsujimoto and M. Ikeda, Chem. Pharm. Bull., 1971, 19, 1285.

144. J. Becher and C. Lohse, Acta. Chem. Scand., 1972, 26, 4041.

145. R. Huisgen, R. Fleischmann and A. Eckell, Tetrahedron Letters, 1960, 1.

146. R. Huisgen and A. Eckell, Tetrahedron Letters, 1960, 5.

147. E. Schmitz, Ber., 1958, 91, 1495.

148. R. Huisgen, R. Grashey, P. Laur and H. Leitermann, Angew. Chem., 1960, 72, 416.

149. R. Grashey, R. Huisgen, K.K. Sun and R.M. Moriarty, J. Org. Chem., 1965, 30, 74.

150. W. Oppolzer, Tetrahedron Letters, 1970, 2199.

151. W. Oppolzer, Tetrahedron Letters, 1972, 1707.

152. W. Oppolzer, Tetrahedron Letters, 1970, 3091.

153. J.W. Lown and B.E. Landberg, Canad. J. Chem., 1975, 53, 3782.

154. G. Cauquis and B. Chabaud, Tetrahedron, 1978, 34, 903.

155. J.C. Earl and A.W. Mackney, J. Chem. Soc., 1935, 899.

156. G.L. Closs, L.E. Closs and W.A. Boll, J. Amer. Chem. Soc., 1963, 85, 3796.

157. G.L. Closs and W.A. Boll, Angew. Chem.Internat. Edn., 1963, 2, 399.

158. R.H. Findlay, J.T. Sharp and P.B. Thorogood, J.C.S. Chem. Comm., 1970, 909.

159. J.L. Brewbaker and H. Hart, J. Amer. Chem. Soc., 1969, 91, 711.

160. J.T. Sharp, R.H. Findlay and P.B. Thorogood, J.C.S. Perkin I, 1975, 102.

161. J. Dingwall and J.T. Sharp, J.C.S. Chem. Comm., 1975, 128.

162. J.B. Shoesmith and R.H. Slater, J. Chem. Soc., 1926, 214.

163. E. Stefaniuk, Ph.D. Thesis, University of Edinburgh, 1976.

164. T. Curtius, J. prakt. Chem., 1900, 62, 83.

165. T. Curtius and R. Jay, J. prakt. Chem., 1889, 39, 27.

166. M. Busch and B. Weiss, Ber., 1900, 33, 2701.

167. T. Curtius and H. Franzen, Ber., 1901, 34, 552.

168. W.J. Theuer and J.A. Moore, J. Org. Chem., 1964, 29, 3734.

169. D.F. Detar and L.A. Carpino, J. Amer. Chem. Soc., 1956, 78, 475.

170. L.I. Smith and M. Bayliss, J. Org. Chem., 1941, 6, 437.

171. S. Natelson and S.P. Gottfried, J. Amer. Chem. Soc., 1941, 63, 487.

172. C.D. Anderson, J.T. Sharp, H.R. Sood and R.S. Strathdee, J.C.S. Chem. Comm., 1975, 613.

173. C.D. Anderson, P.N. Anderson and J.T. Sharp, J.C.S. Perkin I, 1979, 1640.

174. J. Ojima, Tad. Yokomachi and Tai. Yokomachi, Chem. Letters, 1972, 7, 633.

175. H. Decker, Annalen, 1913, 395, 282.

176. W.J. Dale, L. Starr and C.W. Strobel, J.Org. Chem., 1961, 26, 2225.

177. L. Friedmann, R.L. Little and R. Reichle, Org. Synth., 1960, 40, 93.

178. T. Curtius and F. Lorenzen, J. prakt. Chem., 1898, 58, 160.

179. H. Kloes, Ger. 1,069,637 (Chem. Abs., 1962, 56, 327f).

180. T. Curtius and G. Struve, J. prakt. Chem., 1894, 50, 295.

181. L.I. Smith and M.M. Falkof, Org. Synth., 1942, 22, 50.

182. R.T. Letsinger, T.E. Feare, T.J. Savereide and J.R. Nazy, J. Org. Chem., 1961, 26, 1271.

183. W. Munzenmaier and H. Straub, Synthesis, 1976, 1, 49.

184. D.P. Munro and J.T. Sharp, unpublished observations.

185. J. Cymerman, I.M. Heilbron and E.R.H. Jones, J. Chem. Soc., 1945, 90.

186. W. Oroshnik, J. Amer. Chem. Soc., 1956, 78, 2651.

187. E.E. Boehm, V. Thaller and M.C. Whiting, J. Chem. Soc., 1963, 2535.

188. T.H. Vaughn, R.R. Vogt and J.A. Nieuwland, J. Amer. Chem. Soc., 1934, 56, 2120.

189. J.L. Warnell and R.L. Shriner, J. Amer. Chem. Soc., 1957, 79, 3165.

190. K.T. Potts and R. Robinson, J. Chem. Soc., 1955, 2675.

191. L.J. Bellamy, The Infrared Spectra of Complex Molecules, Methuen, London, 1958.

192. J. Sauer and G. Heinrichs, Tetrahedron Letters, 1966, 4979.

193. C.D. Anderson, J.T. Sharp and R.S. Strathdee, J.C.S. Perkin I, in press.

194. L. Claisen, Ber., 1907, 40, 3903.

195. R. West, J. Amer. Chem. Soc., 1958, 80, 3246.

196. C. Crisan and H. Normant, Bull. Soc. chim. France, 1957, 1451.

197. A.N. Kost and R.S. Sagitullin, Zh. obshchei Khim., 1957, 27, 3338 (Chem. Abs., 1958, 52, 9071c).

198. J. Elguero and R. Jacquier, Bull. Soc. chim. France, 1965, 769.

199. K.v. Auwers and H. Ludewig, Ber., 1936, 69, 2347.

200. D.J. Harris, M.T. Thomas, V. Snieckus and E. Klingsberg, Canad. J. Chem., 1974, 52, 2805.

201. A.T. Balaban, Tetrahedron, 1970, 26, 739.

202. J. Elguero, Bull. Soc. chim. France, 1971, 1925.

203. G. Coispeau, J. Elguero, R. Jacquier and D. Tizane, Bull. Soc. chim. France, 1970, 1581.

204. H. Ferres, M.S. Hamdam and W.R. Jackson, J.C.S. Perkin II, 1973, 936.

205. J.D. Cawley and D.R. Nelan, J. Amer. Chem. Soc, 1955, 77, 4130.

206. R. Kuhn and M. Hoffer, Ber., 1932, 65, 651.

207. I.M. Heilbron, E.R.H. Jones and D.G. O'Sullivan, J. Chem. Soc., 1946, 866.

208. C.H. Eugster, C. Garbers and P. Karrer, Helv. Chim. Acta, 1952, 35, 1179.

209. H. Meerwein, Annalen, 1908, 358, 85.

210. H.E. Baumgarten, F.A. Bower, R.A. Setterquist and R.E. Allen, J. Amer. Chem. Soc., 1958, 80, 4588.