THE SYNTHESIS AND REACTIVITY
OF 2,3-BENZODIAZEPINES

A Thesis presented for the degree of Doctor of Philosophy in the
Faculty of Science of the
University of Edinburgh

by

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October 1973
TO MY WIFE JEAN

AND

MY PARENTS
The synthesis of a series of 1H-2,3-benzodiazepines has been carried out by the ring closure of the corresponding \( \alpha \)-(o-alkenylation) diazoalkenes in aprotic solvents. The structure of these compounds has been deduced from their n.m.r. and mass spectral data, and a mechanism has been proposed for the reaction. A new series of 5H-2,3-benzodiazepines has been prepared from the base catalysed, and in one case the thermal isomerisation of the 1H-compounds. A study of ring inversion by n.m.r. was carried out on the 5H- and suitable 1H-2,3-benzodiazepines. The free energies of activation for inversion were calculated and compared with related systems.

The photolysis of the 1H-2,3-benzodiazepines was investigated, and found to afford fast, quantitative isomerisation to 4H-\( [1,2] \)diazeto[3,2-a]isoindoles; a new heterocyclic ring system. Spectral, structural and theoretical evidence for this structure is presented. In contrast, the one example of 5H-2,3-benzodiazepine photolysis studied, reacted via loss of nitrogen to give a hydrocarbon product.

The kinetics of thermolysis of 1-phenyl-1H-2,3-benzodiazepine was studied by n.m.r. spectroscopy with a view to elucidation of the mechanism of decomposition. The Arrhenius activation energy was calculated along with/...
with the thermodynamic parameters $\Delta G^+$ and $\Delta S^+$. These values were compared with literature values for related compounds, and evidence against decomposition via a carbenic mechanism was produced.

An attempt was made to extend the electrocyclic ring closure to the formation of triazepines from o-azido-stilbene. This was unsuccessful, as the reaction took an alternative path leading to an indole. The decomposition of a \( \beta,\beta \)-dimethyl substituted \( \alpha \)-(o-alkenyl-aryl) diazoalkene was also studied, and found to take place via a carbenic mechanism.
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<table>
<thead>
<tr>
<th>CONTENTS</th>
<th>PAGE NO.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INTRODUCTION</strong></td>
<td>1</td>
</tr>
<tr>
<td>I  Base-induced decomposition of toluene-p-sulphonylhydrazones</td>
<td>2</td>
</tr>
<tr>
<td>II Diazaoalkanes</td>
<td>11</td>
</tr>
<tr>
<td>III Benzodiazepines and benzotriazepines</td>
<td>26</td>
</tr>
<tr>
<td>IV Photochemistry of conjugated dienes</td>
<td>32</td>
</tr>
<tr>
<td>V  Thermolysis of azo-compounds</td>
<td>39</td>
</tr>
<tr>
<td>VI Ring inversion studies by nuclear magnetic resonance</td>
<td>46</td>
</tr>
<tr>
<td><strong>EXPERIMENTAL</strong></td>
<td>52</td>
</tr>
<tr>
<td>1. Preparation of starting materials</td>
<td>62</td>
</tr>
<tr>
<td>2. Synthesis of toluene-p-sulphonylhydrazones</td>
<td>77</td>
</tr>
<tr>
<td>3. Synthesis of 1H-2,3-benzodiazepines</td>
<td>81</td>
</tr>
<tr>
<td>4. Synthesis of 5H-2,3-benzodiazepines</td>
<td>86</td>
</tr>
<tr>
<td>5. Photolysis of 1H-2,3-benzodiazepines</td>
<td>89</td>
</tr>
<tr>
<td>6. Photolysis of 5H-2,3-benzodiazepines</td>
<td>92</td>
</tr>
</tbody>
</table>
7. Attempted cyclisation of 2-formyl-5-ethoxy-β,β-dimethylstyrene toluene-p-sulphonylhydrazone 93

8. Attempted thermal cyclisation of trans-stilbene-2-azide 98

9. Thermolysis studies 96

APPENDICES 106-116

DISCUSSION 118

I 2,3-benzodiazepines 123

A. Synthesis 123

B. Reactions 142

II Possible extensions of the cyclisation 163

A. Attempted cyclisation of trans-stilbene-2-azide 163

B. Attempted cyclisation of 2-formyl-5-ethoxy-β,β-dimethylstyrene toluene-p-sulphonylhydrazone 165
# INTRODUCTION

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>BASE-INDUCED DECOMPOSITION OF TOLUENE-p-SULPHONYLHYDRAZONES</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>A. Effect of Solvent Protonicity.</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>B. Effect of Base Concentration</td>
<td>8</td>
</tr>
<tr>
<td>II</td>
<td>DIAZOALKANES</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>1. Carbene Formation</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>2. 1,3-Dipolar Cycloaddition Reactions</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>3. Intramolecular Electrocyclic Reactions</td>
<td>20</td>
</tr>
<tr>
<td>III</td>
<td>BENZODIAZEPINES AND BENZOTRIAZEPINES</td>
<td>26</td>
</tr>
<tr>
<td>IV</td>
<td>PHOTOCHEMISTRY OF CONJUGATED DIENES</td>
<td>32</td>
</tr>
<tr>
<td>V</td>
<td>THERMOLYSIS OF AZO-COMPOUNDS</td>
<td>39</td>
</tr>
<tr>
<td>VI</td>
<td>RING INVERSION STUDIES BY NUCLEAR MAGNETIC RESONANCE</td>
<td>46</td>
</tr>
</tbody>
</table>
INTRODUCTION

I - BASE-INDUCED DECOMPOSITION OF TOLUENE-p-SULPHONYLHYDRAZONES

It was observed by Escales in 1885 that warm alkali effected the decomposition of benzenesulphonylphenyl-hydrazide (I) to benzene, nitrogen and benzenesulphinate anion.

\[
\text{PhSO}_2\text{-NH-NH-} + \text{OH}^- \rightarrow \text{PhSO}_2^- + \text{N}_2 + \text{PhSO}_2^- \]

As a result of this, Bamford and Stevens unsuccessully attempted to obtain olefins from the toluene-p-sulphonylhydrazones of readily enolisable ketones. However, on examining the toluene-p-sulphonylhydrazones of not readily enolisable aliphatic ketones (II), they found that olefins were produced in good yield from decompositions of the sodium salts in ethylene glycol.

\[
\text{Me-C=NH-NH-SO}_2\text{Ar} \xrightarrow{\text{Na}} \text{CH}_2=\text{CHMe} + \text{N}_2 + \text{ArSO}_2^-\text{Na}^+ \]
On the other hand, toluene-\(\text{p}\)-sulphonylhydrazones of aromatic aldehydes and ketones afforded aromatic diazo-compounds or their decomposition products. Subsequent work has revealed that decompositions can occur with or without nitrogen loss, and has opened up versatile syntheses of compounds as diverse as diazoalkanes, olefins, cyclopropanes, cyclopropenes, pyrazoles, diazepines and other heterocyclic compounds.

Investigation of the mechanism of decomposition has shown that it is both solvent and base dependent. In protic solvents the reactive intermediates are carbonium ions, whereas in aprotic media, carbene reactions are favoured. When excess of strong base is used at low temperature, a mechanism involving carbanionic species operates. Much of the early work involved elucidating the mechanisms of toluene-\(\text{p}\)-sulphonylhydrazone decomposition was done using camphor toluene-\(\text{p}\)-sulphonylhydrazone. The effect of solvent protonicity and base concentration on the mechanism will now be discussed.

A - EFFECT OF SOLVENT PROTONICITY

The decomposition of camphor toluene-\(\text{p}\)-sulphonylhydrazone (III) was carried out by Bamford and Stevens\(^2\) using two equivalents of base in ethylene glycol.

\[
\begin{align*}
\text{III} & \quad \frac{\text{N-NH-Ts} \quad 2\text{NaOMe}}{\Delta} \quad \text{IV}
\end{align*}
\]
They found that optically active camphene (IV) was formed, and since Heubaum and Noyes had previously shown that diazocamphene (V) decomposed to give tricyclene (VI),

\[ \text{V} \quad \xrightarrow{\text{N}=\text{N}} \quad \text{VI} \]

they rejected the possibility that the mechanism of toluene-\(p\)-sulphonylhydrazone decomposition always involved breakdown to an aliphatic diazo-compound and sulphinate ion, as optically active camphene would not result even if subsequent isomerisation of tricyclene did occur. Bamford and Stevens suggested that the mechanism of the decomposition of toluene-\(p\)-sulphonylhydrazones involved removal of a proton by alkoxide ion, followed by release of sulphinate anion, leaving the rest of the molecule either (a) intact as a diazo-compound, or (b) to undergo fission into the corresponding olefin and nitrogen with concomitant migration of one of the groups attached to the \(\alpha\)-carbon.
In 1959, Powell and Whiting investigated the mechanism of the Bamford-Stevens reaction, by comparing the base-induced decomposition of cyclohexanone toluene-\(\text{p}\) sulphonylhydrazone and camphor toluene-\(\text{p}\)-sulphonylhydrazone under the same reaction conditions. They found that both decomposed at virtually the same rate, and had the same activation energy. In conflict with the above mechanism, they therefore postulated that the rate determining step in the Bamford-Stevens reaction was unimolecular elimination from the sulphonylhydrazone anion to give the diazo-compound, and was independent of alkane stereochemistry. They rejected the possibility of direct olefin formation by means of a cyclic transition state in which a \(\beta\)-hydrogen atom is removed by the departing sulphinate residue, since camphor toluene-\(\text{p}\)-sulphonylhydrazone, unable to utilise its two \(\alpha\)-hydrogen atoms for steric reasons would be unable to decompose by this/...
Fig I
this route, and would thus employ an alternative mechanism and hence a different rate. Using the technique of gas liquid chromatography, Powell and Whiting also found that the decomposition product of camphor toluene-p-sulphonylhydrazone (III) using sodium in ethylene glycol was not pure camphene as stated by Bamford and Stevens, but a mixture of camphene (V): tricyclene (VI) in a 4:1 ratio. Earlier, Meerwein and van Emster had reported that a small amount of camphene was formed along with tricyclene in the decomposition of diazo-camphene. Therefore, if it could be shown that changing the solvent markedly changed the camphene:tricyclene ratios in either reaction, then this would support their mechanism. Powell and Whiting therefore tested the mechanism by studying the decomposition of diazo-camphene in protic and aprotic solvents, and came to the conclusion that the decomposition could take place in two ways. In both routes, the toluene-p-sulphonylhydrazone decomposed to give diazo-camphene which in protonating solvents formed a diazonium cation and/or a carbonium ion. This underwent a Wagner-Meerwein rearrangement to give camphene (Fig. I). In aprotic solvents the diazo-compound decomposed directly to a carbene, which gave tricyclene via intramolecular C-H insertion (Fig. I). Thus tricyclene only accounted for 12% of the reaction product in protic media (e.g. glycerol) whereas it was 99% in acetamide. It should be noted at this point however that acetamide is of intermediate protonating/...
protonating ability, and the low yield of camphene obtained is due to the reluctance of diazocamphene to be protonated. In the case of the base-induced decomposition of pinacolone toluene-\(p\)-sulphonylhydrazone (VII, Fig. II) in acetamide, 50% of the carbonium ion rearrangement product\(^8\) is obtained.

\[
\begin{align*}
\text{Me-C-C-Me} & \quad \overset{\text{OMe}^-}{\longrightarrow} \quad \text{H}_2\text{C} &= \text{C-C-Me} + \quad \begin{array}{c}
\text{H} \\
\text{Me} \\
\text{Me}
\end{array} \\
\text{NMe} & \quad \text{NHTs}
\end{align*}
\]

VII

Fig II

50% Reactions run in acetamide and considered to be carbenoid on the basis of the camphor experiments must therefore be regarded with some suspicion.

Friedman and co-workers\(^9\) initiated a study in order to obtain further information concerning the relative 'protonicity', i.e. proton donor ability of various representative hydroxylic solvents in diazoalkane thermolysis. They found that protonicity is a function of the (a) relative acidity (pKa), and (b) proton equivalence (P.E.) defined as milliequivalents of hydroxyl per gram of solvent. These conclusions were arrived at by studying the product ratios obtained from the decomposition of 2-methylpropanal and 2,2-dimethylpropanal toluene-\(p\)-sulphonylhydrazones in various hydroxylic and non hydroxylic solvents.
B - EFFECT OF BASE CONCENTRATION

Shapiro\textsuperscript{10} and co-workers, having studied the decomposition of diazocamphene, came to the conclusion that the two hydrocarbon products could be generated from two distinct intermediates depending on the conditions of the reaction. The ratio of camphene:tricyclene was found to decrease with increasing base concentration as well as decreasing solvent polarity. It was found that although solvent polarity is a major factor in determining the camphene:tricyclene ratio, the relative amount of base present is even more important e.g. in the base-induced decomposition of camphor toluene-\(p\)-sulphonylhydrazone, the use of less than an equimolar amount of base resulted in a higher percentage of camphene than with an equimolar ratio, and with base to toluene-\(p\)-sulphonylhydrazone ratios of 1.25:1 or above, tricyclene was the sole product. Shapiro\textsuperscript{10} concluded that the earlier workers had not taken base concentration into account, Bamford and Stevens\textsuperscript{2} having used approximately two equivalents of base in their reactions, while Powell and Whiting\textsuperscript{4} had used an average of more than four. Thus in these cases tricyclene formation was favoured.

When less than one equivalent of base was used in an aprotic solvent, camphene was the main decomposition product. The question then arose as to the origin of the proton required for protonation of the diazocamphene intermediate. Using deuterium labelling experiments, Shapiro\textsuperscript{10} verified the previous proposal of Friedman\textsuperscript{11} and/...
**Fig III**

* Wagner Meerwein rearrangement
and co-workers, that the proton originated from unreacted toluene-$p$-sulphonylhydrazone. These experiments also led Shapiro to the conclusion that tricyclene could be formed not only from a carbene intermediate as previously proposed, but also via a carbonium ion. At high base concentration it is formed by transannular insertion of the intermediate carbene, (Fig. III) while at low base concentration the diazonium cation is favoured, which can decompose to form both camphene and tricyclene via the carbonium ion as shown in Fig. III. The key step in the mechanism is the equilibrium between diazocamphene and its corresponding diazonium ion. When less than one equivalent of base is used, excess of methanol solvent will push the reaction equilibrium in favour of the diazonium ion, following the law of mass action. Conversely, excess base will favour the diazo-compound. Under the relatively severe reaction conditions, both intermediates can lose nitrogen to give a carbene or carbonium ion which give products as indicated.

The effect of using excess strong base at low temperature was simultaneously reported by Shapiro$^{12}$ and Friedman$^{13}$. Shapiro and Heath prepared good yields of olefins from aliphatic toluene-$p$-sulphonylhydrazones containing $\alpha$-hydrogen atoms using two or more equivalents of methyl lithium in ether at 25$^\circ$.

![Diagram](image-url)
Fig IV
In this way 2-bornene (VIII) was prepared in quantitative yield from camphor toluene-$p$-sulphonylhydrazone (III). The mechanism proposed (Fig. IV) involved a carbanionic species. This was supported by deuterium labelling experiments.
II - DIAZOALKANES

The preparative significance and intensive study of this class of compounds is reflected in the extensive literature on the subject. The most important aspects of their chemistry include generation of carbenes from their photolysis and thermolysis\(^\text{14}\), and cycloaddition reactions\(^\text{15}\). Since diazoalkanes have been shown to constitute the primary products in the base-induced decomposition of toluene-\(p\)-sulphonylhydrazones\(^2\), they are of direct relevance to the work reported in this thesis.

The simplest diazoalkane, diazomethane, has the molecular formula \(\text{CH}_2\text{N}_2\). In 1889, Curtius proposed the cyclic diazirine (IX) structure which was replaced in 1911 with the open chain structure (X).

\[
\text{IX} \quad \text{X}
\]

Diazomethane is best represented as a resonance hybrid of the three canonical forms shown in (Fig. V).

\[
\text{Fig V}
\]
The π system produced by the overlap of the p orbitals is shown in (XI).

\[
\text{XI}
\]

It is a highly toxic, yellow gas which is explosive at room temperature. The stability of higher diazo-compounds is markedly dependent on the nature of the substituent on the α-carbon. Conjugating substituents always increase stability regardless as to whether they are electron releasing or withdrawing, e.g. carbonyl, aryl or nitrile. Electron withdrawing substituents favour a resonance structure having a formal carbanion (\(\text{C}-\text{N}≡\text{N}^{-}\)) whereas electron releasing substituents favour a formal positive charge on the carbon atom (\(\text{C}-\text{N}=\text{N}^{+}\)). Non-conjugating substituents in the α-position increase stability if they are electron withdrawing, because such a group can delocalise the negative charge of forms such as \(\text{C}-\text{N}≡\text{N}^{-}\).

Diazo-compounds can be detected by their reaction with alkyl and aryl phosphines. This was shown by Staudinger and Meyer\(^{16, 17}\) in 1919, when they found that diazofluorene (XII), the first stable diazo-compound to be prepared, reacted with phosphines additively to give the corresponding phosphazines\(^{17}\) (XIII). These could then decompose on/...
R_3P + \text{N=N=C} \xrightarrow{\Delta} R_3P=\text{N-N=C} \xrightarrow{\text{H}_2\text{O}} R_3P=\text{O} + R_2\text{C=NNH}_2

\text{N}_2 + R_3\text{P}=\text{C} \xrightarrow{\Delta} R_3P=\text{O} + R_2\text{C=NNH}_2

\text{PX}_2Y \xrightarrow{\text{Y=X=Ph}} \text{YX=Et} \xrightarrow{\text{Y=X=E t}} \text{PX}_2Y

\text{XII} \quad \text{XIII}
on heating to give phosphoranes and nitrogen, or hydrolyse to give the corresponding phosphine oxide and hydrazone (Fig. VI).

Cava and Napier\(^\text{18}\) have used the base-induced decomposit-
ion of toluene-\(p\)-sulphonylhydrazones to prepare isolable diazoketones (Fig. VII).
1. Carbene Formation

When diazoalkanes are thermally or photolytically decomposed in aprotic solvents in the presence of excess base, carbenes are generally produced with loss of nitrogen. In protic solvents and at low base concentration the intermediate is more likely to be a carbonium ion, due to initial protonation of the diazoalkane.

The literature on carbenes is vast, and it is not proposed to go into any of their reactions in great detail. They can undergo any or all of the following reactions: C-H insertion, cycloaddition, rearrangement, abstraction and reaction with their diazoalkane precursor to give an azine. Dimerisation of carbenes is statistically unlikely, and isolation of dimers can often be explained by a more likely mechanism e.g. consider the dimer formed from diazofluorene (XIV) which is produced by carbene attack on its diazo-compound precursor.

![Diagram](image.png)
The two non-bonding electrons of a carbene may have parallel spins (triplet state) or anti-parallel spins (singlet state) (Fig. VIII).

Cycloaddition to olefins is one of the most characteristic reactions of carbenes. This is usually stereospecific for singlet carbenes and non stereospecific for triplet carbenes.

Singlet carbenes are electron deficient species comparable to carbonium ions. They also have a non-bonding pair of electrons like carbanions, thus their electrophilic or nucleophilic properties are determined largely by the electronic effects of the groups attached to the carbene carbon.

Carbene precursors are important in the preparation of cyclopropanes and many bicyclic and tricyclic ring systems.
<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azides</td>
<td>$\overset{\ddagger}{\text{N=N-N}} \leftrightarrow \overset{\ddagger}{\text{N=N-N}}$</td>
</tr>
<tr>
<td>Nitrones</td>
<td>$\overset{\ddagger}{\text{C-N}} \leftrightarrow \overset{\ddagger}{\text{C=O}}$</td>
</tr>
<tr>
<td>Ozone</td>
<td>$\overset{\ddagger}{\text{O-O-O}} \leftrightarrow \overset{\ddagger}{\text{O=O=O}}$</td>
</tr>
<tr>
<td>Nitrous oxide</td>
<td>$\overset{\ddagger}{\text{N=N-O}} \leftrightarrow \overset{\ddagger}{\text{N=N-O}}$</td>
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</table>

Fig IX
2. 1,3- Dipolar Cycloaddition Reactions

A variety of 1,3- additions of diazoalkanes, azides and ozone to alkenes and alkynes e.g. the formation of (XVI) had been known for many years before the generality of the reaction was recognised by Huisgen. In a brilliant series of researches during which many new reactions were predicted and discovered, Huisgen showed that diazoalkanes are only one of a large class of 1,3-dipolar molecules, some examples of which are shown as zwitterionic structures (Fig. IX).

Cycloadditions can be classified according to the number of new $\sigma$ bonds formed, or the size of the ring formed. Most frequently, two new $\sigma$ bonds are created at the expense of two $\pi$ bonds. A $3+2\rightarrow 5$ cycloaddition (Fig. X) leading to an uncharged five membered ring obviously cannot occur with octet stabilised reactants having no formal charges. A 1,3- dipole $a$-$b$-$c$ must be defined, where atom (a) possesses an electron sextet and atom (c) an unshared electron pair.

Combination of this 1,3- dipole with a multiple bond system (d-e), called the dipolarophile is known as 1,3-dipolar cycloaddition. For example, diazomethane and methyl/...
methyl methacrylate (XV) react to give pyrazoline (XVI) in greater than 90% yield.

\[
\begin{align*}
\text{Me} & \\
\text{CH}_2\text{C} & \quad \text{CO}_2\text{Me} \\
\text{XV} & + \\
\text{CH}_2\text{N} & \quad \text{N} \\
\text{N} & \\
\text{XVI} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

Ledwith and Parry\textsuperscript{24} studied the kinetics and mechanism of this reaction, and found that reaction rates were essentially independent of solvent polarity, while enthalpies of activation were low and entropies of activation high. Other common features of the cycloadditions are the retention of olefin stereochemistry, increase in reaction rates with conjugation in the dipolarophile, and decrease in reaction rates with increasing steric effects.

The mechanism of 1,3- dipolar cycloaddition has aroused much interest, and there are currently two schools of thought. The original mechanism of Huisgen\textsuperscript{15} involves a single-step concerted addition (Fig. XIa). In 1967, Firestone\textsuperscript{25} proposed an alternative mechanism; a two step reaction with a spin-paired diradical as intermediate (Fig. XIb), and the first step rate determining.
The following year a reply by Huisgen\textsuperscript{22} refuted Firestone's argument on the grounds that the available evidence, i.e. activation parameters, \textit{cis}-stereospecificity and solvent dependence, fitted the concerted mechanism. Woodward and Hoffmann\textsuperscript{26} have since published rules for the conservation of orbital symmetry which supply a theoretical basis for Huisgen's earlier predictions.

In 1972, another publication by Firestone\textsuperscript{27} appeared in support of the diradical mechanism. In this he argued that the unidirectionality of orientation exhibited by most 1,3-dipoles towards electron-rich and electron-poor dipolarophiles was a natural consequence of the diradical mechanism, as seen by analysis of both transition-state structure and prereaction complexes. Steric effects also favoured the diradical theory. Linnet structures for the diradical intermediates possess partial formal charges which account for (1) the nature of the diradicals (2) the dual orientation of azides and (3) the competition between cyclo and extended conformations of diradicals in reactions that exhibit concurrent cycloaddition and condensation with hydrogen transfer. Firestone concluded that the present/...
present weight of evidence favours the diradical mechanism.
3. Intramolecular Electrocyclic Reactions

Having discussed 1,3-dipolar additions in general terms, it is now proposed to give an account of additions where both the dipole and the dipolarophile are incorporated in the same molecule. Such additions constitute what are generally known as electrocyclic reactions.

In 1935, it was briefly reported that 3-diazopropene (XVII) slowly decomposed at room temperature to give 1H-pyrazole (XVIII)\(^{28,29}\).

\[
\text{CH}_2=\text{CH}-\text{CH}=\overset{+}{\text{N}=\text{N}} \rightarrow \overset{+}{\text{H}} \rightarrow \overset{+}{\text{H}} \quad \text{XVII} \rightarrow \overset{+}{\text{XIX}} \rightarrow \overset{+}{\text{XVIII}}
\]

Adamson and Kenner\(^{28}\) also noted that the decomposition was unimolecular and accelerated by light. Ledwith and Parry\(^{30}\), in 1967, reported the results of a more detailed investigation of the relatively modest effect of light on the rate at which 3-diazopropene cyclises, and found evidence for the intermediacy of the unstable 3H-pyrazole (XIX). Adamson and Kenner also observed that the red colour of an ethereal solution of trans-1-diazo-2-butene slowly faded at room temperature. The product of this decomposition was not identified, but later, Curtin and Gerber\(^{31}\) showed it to be 3-methylpyrazole (XX).
Me₂C=C_H  →  OMe, diglyme  →  Me₂C≡N—N—Ts  \( \xrightarrow{160^\circ} \) Me₂

XXIa

Me₂C=C_H  →  diethyl carbitol  \( \xrightarrow{180^\circ} \) Me₂

XXIb

Me₂C≡N—N—Ts  \( \xrightarrow{160^\circ} \) Me₂

4%

XXII

Me₂C≡N—N—Ts  \( \xrightarrow{180^\circ} \) Me₂

H

Me₂

Me

XXII

Major
In the decomposition of some diazoalkenes there is competition between routes involving loss of nitrogen and reactions in which it is retained, for example in the base-induced decomposition of the toluene-\(\alpha\)-sulphonylhydrazones of some \(\alpha, \beta\)-unsaturated compounds first reported by Closs, Closs and Boll\(^{32}\). They found that decompositions of toluene-\(\alpha\)-sulphonylhydrazones of type (XXI) using two equivalents of sodium methoxide in diglyme or diethyl carbitol at 160\(^0\), afforded alkyl-substituted cyclopropenes as well as pyrazoles. Cyclopropene yields varied from good to poor depending on the degree of \(\sigma\)-substitution of the toluene-\(\alpha\)-sulphonylhydrazone. Thus a lower yield was obtained when only one alkyl group was present at the \(\beta\)-position, and no cyclopropene was formed at all when two hydrogens were at the \(\beta\)-position. In this case an aromatic 1H-pyrazole was the only product. They examined the possibility of a 3H-pyrazole intermediate (XXII) in the formation of cyclopropene, but this was rejected on the grounds that on preparation of the 3H-pyrazole, it was perfectly stable at the temperatures at which cyclopropene formation took place. This supported the intermediacy of alkylcarbene in cyclopropene formation. By lowering the reaction temperature, they were able to isolate the intermediate diazoalkenes which were found to give the same products on pyrolysis as the high temperature/...
Me,

\[ \text{Me} \cdot \text{C} = \text{C} \cdot \text{H} \]

\[ \text{C} = \text{N} \cdot \text{N} - \text{Ts} \]

\[ \text{Me} \cdot \text{H} \]

\[ \text{H} \cdot \text{C} = \text{N} = \text{N} \cdot \text{Me} \]

\[ \text{XXIII} \]

\[ \text{Me} \cdot \text{C} = \text{C} \cdot \text{H} \]

\[ \text{H} \cdot \text{C} = \text{C} \cdot \text{C} \cdot \text{Me} \]

\[ \text{C} = \text{N} - \text{N} \cdot \text{Me} \]

\[ \text{Me} \]

\[ \text{Me} \]

\[ \text{H} \cdot \text{C} = \text{C} \cdot \text{H} \]

\[ \text{Me} \]

\[ \text{C} = \text{N} = \text{N} \cdot \text{Me} \]

\[ \text{Me} \]

\[ \text{XXIV} \quad R = \text{H} \]

\[ \text{XXV} \quad R = \text{CH}_3 \]
temperature decomposition of the toluene-$p$-sulphonyl-hydrazone salts. Closs and his co-workers concluded that increasing substitution at the $p$-carbon atom would retard cyclisation due to steric hindrance, and that the electron releasing effects of the alkyl groups would facilitate elimination of nitrogen.

This conclusion was supported by the work of Bartlett and Stevens$^{33}$ who studied the base-induced decomposition of toluene-$p$-sulphonylhydrazones of $\alpha,p$-unsaturated ketones containing either a hydrogen or a phenyl at the $p$-position. Thus they succeeded in forming the corresponding pyrazoles from the decomposition of toluene-$p$-sulphonylhydrazones of crotonaldehyde (XXIII), cinnamaldehyde (XXIV) and methylstyryl ketone (XXV) in ethylene glycol (protic) at 160°.

In 1969, Brewbaker and Hart$^{34}$, investigating the mechanism of cyclisation found that the 3-diazoalkenes (XXVI) spontaneously cyclised at room temperature to form $1H$-pyrazoles (XXVII) in essentially quantitative yield.

![Chemical structures](image_url)
The rate of cyclisation was measured, and substituents attached to the dipolarophile were found to have very little effect on the rate. Thus it was concluded that the mechanism of pyrazole formation fitted the general class of 1,3-dipolar additions as described by Huisgen\textsuperscript{15}. In 1970, Sharp and co-workers\textsuperscript{35} investigated steric effects in the cyclisation of diazoalkenes formed from the toluene-$\mu$-sulphonylhydrazone sodium salts of methylene-cyclohexanone and methylenecyclopentanone derivatives. They found that the methylenecyclohexanone derivatives cyclised to give 1$H$- or 3$H$- pyrazoles in good yield (Fig. XII).

The reaction course was little affected by solvent protonicity, which showed that the cyclisation of the diazoalkene/...
diazoalkene intermediate is fast compared with competing protonation by the solvent. However, when the methylenecyclopentanone derivatives were examined, 1H-pyrazoles were only obtained when \( R_1 \) or \( R_2 = H \) (Fig. XIII). When \( R_1 \) and \( R_2 \) were both alkyl groups, the diazoalkene reacted only via loss of nitrogen, the products depending on the protonicity of the solvent. In aprotic solvents, the diazoalkene reacted via loss of nitrogen to give the carbene which underwent a hydride shift to give a diene (Fig. XIV). In protic solvents on the other hand, protonation occurred to give a diazonium ion which decomposed as shown (Fig. XIV). It was postulated that this difference in reactivity was due to steric factors making the transition state for cyclisation more difficult to attain in the case of the five than the six membered ring, and which would lead initially in the former case to a more strained 3H-pyrazole. Thus the diazacyclopentanone derivative preferentially decomposed via carbenic or carbonium ion routes except when \( R_1 \) or \( R_2 = H \). Electro-cyclic ring closure to give the 3H-pyrazole is a priori a reversible reaction and although the equilibrium (Fig. XIII) may well lie to the left because of steric reasons, when \( R_2 = H \) the 3\( \bar{H} \)-pyrazole can undergo a fast hydrogen migration to give the aromatic 1H-pyrazole in high yield. It was also found that when \( R_1 \) and \( R_2 \) were aryl groups, the decomposition could take yet another course, resulting in the formation of a 1,2-benzodiazepine (Fig. XV). In this case, carbene formation was less favourable/...
favourable due to stabilisation of the intermediate diazoalkane by conjugation with the aryl group. Cyclisation to a pyrazole was unfavourable sterically, as in the previous example and it was found that an alternative electrocyclic ring closure took place to give a seven membered ring, followed by a $[1,5]$ sigmatropic hydrogen migration, restoring the aromaticity of the benzene ring.

Sharp and Thorogood$^{36}$ then carried out a brief investigation into the thermal decomposition of the toluene-$\pi$-sulphonylhydrazone salts of $\omega$-alkenylaryl ketones, and found that nitrogen was again retained, the product being a 2,3- benzodiazepine (Fig. XVI).

![Diagram](image)

This reaction will be considered in detail in the Discussion section of this thesis.
Benzodiazepines are bicyclic, heterocyclic compounds having a benzene nucleus fused to a seven membered ring containing two nitrogen atoms. Six basic ring structures can result from changing the positions of the nitrogen atoms in the seven membered ring e.g.

Thus, the synthesis and reactions of each class of compound differ considerably, and although this thesis is primarily concerned with 2,3- benzodiazepines, some of the other classes will be briefly mentioned.

The chemistry of diazepines has been reviewed by Popp and Noble\textsuperscript{37}, and that of benzodiazepines by Sternbach and Archer\textsuperscript{38}. Of all the groups, 1,4- benzodiazepines have been most extensively studied due to the discovery of\textsuperscript{39,40} their/...
their biological activity as psychosedatives and tranquillising agents. The other groups of benzodiazepines have attracted less interest, and of these, the 1,5-benzodiazepines have been fairly well explored\textsuperscript{41,42,43}, due to their relative ease of synthesis from common starting materials. Relatively little work has been done on 1,3-benzodiazepines and 2,4-benzodiazepines. Reactions involving 1,2-benzodiazepines are discussed in other sections of the Introduction. (See Parts II, II and V).

The literature on 2,3-benzodiazepines is also not extensive. In 1905, 2,5-dihydro-4-phenyl-1H-2,3-benzodiazepin-1-one (XXVIII) was prepared from the reaction of p-desoxybenzoin-o-carboxylic and or 3-phenylisocoumarin with hydrazine\textsuperscript{47}.

\[
\text{CO}_2\text{H} \quad \text{CH}_2\text{COR} \quad \text{NH}_2\text{NH}_2 \quad \text{NH} \quad \text{O} \quad \text{N} \quad \text{E} \quad \text{XXVIII}
\]

Analogues where \( R = \text{m-tolyl} \textsuperscript{48} \) and \( R = \text{p-hydroxyphenyl} \textsuperscript{49} \) were also obtained in this way from the corresponding isocoumarins.

Whitmore/...
Whitmore and Cooney\textsuperscript{50} found that treatment of homophthalic anhydride (XXIX) with hydrazine in boiling ethanol gave 2,3-benzodiazepine-5H-1,4-(2H,3H)-dione (XXX).

In 1961, Halford and co-workers\textsuperscript{51} found that intramolecular condensation of o-acetylphenylacetic acid phenylhydrazone (XXXI) gave mixtures containing 3,5-dihydro-1-methyl-3-phenyl-4H-2,3-benzodiazepine-4-one (XXXII) and 1-methyl-2-phenylamino-3(2H)-isoquinolone (XXXIII), the benzodiazepine being the major product of the reaction at 190°.
In the same manner, the analogue (XXXIV) was obtained by pyrolysis of o-acetylphenylacetic acid semicarbazone (XXXV) or the corresponding azine (XXXVI).

In 1962, Schmitz and Chme\textsuperscript{52} reported that pyrolysis of the diisoquinolinotetrazine (XXXVII) alone, or in isoquinoline as solvent gave 4,5-dihydro-3H-2,3-benzodiazepine (XXXVIII) which could be reduced by catalytic hydrogenation to 2,3,4,5-tetrahydro-1H-2,3-benzodiazepine (XXXIX). This tetrahydro compound could also be prepared by the reaction of phthaloyl hydrazide and o-chloromethyl-2-phenylethyl chloride (XL), followed by cleavage of the diazepine product (XLI) with base.

Reaction of substituted benzophenones with hydrazines was also found to give 2,3-benzodiazepines: 2-(2-bromoethyl) benzophenone (XLII), $X = H$ gave 4,5-dihydro-1-phenyl-3H-2,3-benzodiazepine (XLIII), $X = R = H$ on treatment with hydrazine\textsuperscript{53}. 
The synthesis of 1H-2,3-benzodiazepines from the cyclisation of o-alkenylaryl diazoalkenes will be considered in detail in the Discussion section.

4. Benzotriazepines

In 1971, Rees and co-workers in attempting to prepare dibenzo-1,2,3-triazepine (XLIV) from 2,2'-diaminobiphenyl and pentyl nitrite in refluxing benzene, isolated the isomeric iminobenzocinnolinium ylide (XLV).
They suggested an equilibrium between the ylide and dibenzotriazepine in which the latter is unstable with respect to the former. The following year, the same workers confirmed this by isolation of (XLIV), the first example of the 1,2,3-triazepine system. The compound was obtained as a pale yellow solid by addition of excess dilute aqueous ammonia to a solution of tetrazotised 2,2'-diaminobiphenyl in 2N hydrochloric acid at 0°C.

In 1972, Bowie and Thomason reported the formation of a 1,3,4-benzotriazepine system. By treating 4-chloro-quinazolines (XLVI) with hydrazine hydrate at 150°C in a sealed tube, they succeeded in isolating 4-amino-4'H-1,2,4-triazoles (XLVII). These were found to undergo ring closure with triethyl orthoesters (a) and aldehydes and ketones (b) to afford the 1,3,4-benzotriazepine system.
IV PHOTOCHEMISTRY OF CONJUGATED DIENES

The field and scope of photochemistry has increased greatly in recent years, and a complete review of the subject would indeed be a formidable task. Therefore, only photochemical reactions of direct relevance to this thesis will be considered.

In 1961, Dauben and Cargill\textsuperscript{57} studied photochemical transformations in cycloheptadiene and cycloheptatriene. They found that irradiation of 1,3-cycloheptadiene (XLVIII) in ether gave the photoisomer (XLIX) in 42\% yield.

\[ \text{XLVIII} \xrightleftharpoons[\Delta]{h\nu} \text{XLIX} \]

This photoisomer reverted to cycloheptadiene on pyrolysis at 400\textdegree. They then went on to investigate the photochemical reaction of 1,3,5-cycloheptatriene (L), and found that a similar intramolecular cyclisation occurred giving bicyclo [3,2,0] heptadiene (LI).

\[ \text{L} \xrightleftharpoons{h\nu} \text{LI} \]

During the 1960's, many light-induced conversions of cycloheptatrienes/...
cycloheptatrienes to bicyclo[3,2,0] hepta-2,6-dienes were reported, and it became clear that such reactions generally proceeded via an excited singlet state and could be interpreted after Woodward and Hoffmann\textsuperscript{58} as symmetry allowed electrocyclic processes, which occurred via a \([\pi 2s + \pi 2s]\) disrotatory mode.

In 1970, Brember and co-workers\textsuperscript{59} investigated the directive effect of substituents on ring closure in cycloheptatrienes. They noted that when two paths were open to ring closure, the reaction was highly selective. They attempted to show that this was due to unsymmetrical charge distribution in the excited state, by considering the two extreme cases in cycloheptatriene (LII) and (LIII).

The arrows show the nature of a substituent (electron withdrawing or donating) required to stabilise the 1,4-polarised species with respect to the 3,6-polarised species. Substituents at 1,3,4 and 6 will obviously have the greatest effect. Thus the following rules were drawn up:
Electron donating substituents at 1,3 or 5 positions or electron withdrawing substituents at 2,4 or 6 will result in 1,4 ring closure.

The reverse applies for 3,6 ring closure.

Substituents in 1,3,4 or 6 direct ring closure when opposed by substituents in 2 or 5.

They found that this analysis not only fitted their own results, but all other previous examples of cycloheptatriene ring closure.

Paquette and Barret studied the photoisomerisation of the heterocyclic analogues of cycloheptatriene, and found parallel reactions. Thus, N-carbethoxyazepine (LIV) was completely decomposed in 2-3 days with formation of the photoproduct (LV) in 43% yield.

Similarly, irradiation of 2,7-dimethyloxepin (LVI) for 6 days gave (LVII) as the major product. Both photoproducts underwent facile thermal reversal to starting material/...
LVIIIa

\[
\begin{align*}
\text{hv} & \quad \text{hv} \\
\text{hv} & \quad \text{hv} \\
\end{align*}
\]

LVIIIb

1:1

LVIIIc

1.5:1
material. Paquette and Barret found that the introduction of an electronegative hetero-atom caused variations in the magnitude of long range n.m.r. coupling. They deduced this to be a direct consequence of the effect of the hetero-atom on the bonding in the molecule. Such effects can be produced by direct inductive effects on the C-H bond, changes in hybridisation of the C-H bond, and the like. Therefore, any attempt to utilize the dihedral angle dependence of allylic coupling constants in structural analysis must allow for variation as a function of other substituents in the particular molecule.

In 1969, Paquette and Kuhla \(^{61} \) studied the irradiation of 2-, 3-, and 4-methyl-N-carbomethoxyazepines (LVIII a,b,c). In each case, a mixture containing both possible bicyclic tautomers was produced. The products were considered to arise by disrotatory cyclisation from the lowest lying excited states of the three azepines. However, only in the case of LVIII a) was high product selectivity observed (see ratios). They explained that this selectivity was based on non-bonded interactions between the methyl group, and the bulky substituent on nitrogen as disrotation begins. They noted that an angular methyl was not in itself a deterrent to product formation, as shown in the case of LVIII c).

The photoisomerisation of a diazepine system was investigated by Moore and co-workers \(^{62} \), who reported that photoisomerisation of 2,3-dihydro-1,2-diazepine ketones e.g. (LIX)/...
(LIX), and carbinols e.g. (LX) gave high yields of 1,2-diazabicyclo[3,2,0]-6-hepten-4-ones and -4-ols, (LXI) and (LXII) respectively.

In each case the major photoalcohols were shown to be the exo isomers.

Similarly Snieckus and co-workers\textsuperscript{63} have photolysed highly substituted 1H-1,2-diazepines (LXIII a,b,c) and obtained the corresponding diaza [3,2,0] bicycloheptadienes (LXIV a,b,c).

\[ \text{LXIII a,b,c} \quad \text{LXIV a,b,c} \quad a; R=\text{Me} \quad b; R=\text{CO}_2\text{Et} \]
In the case of (LXIII a), the product isolated was a pyrazole (LXV) which was produced by non-concerted loss of phenylacetylene from (LXIV a). Thus the butadiene unit reacts preferentially to the 1-azabutadiene unit in ring closure when the two modes are available.

A few years previous to this, Closs and Boll had studied irradiation of alkyl-substituted 31-1-pyrazoles (LXVI) which contain a 1,2-diazabutadiene unit, and found that in all cases nitrogen elimination occurred and cyclopropenes were produced in variable yield.

\[
\text{LXVI}
\]

However, when they studied the low temperature irradiation of fully alkylated pyrazoles (LXVII), they found little or no nitrogen evolution.

\[
\text{LXVII} \xrightarrow{h\nu} \text{LXVIII}
\]

N.m.r. data suggested that a photoisomer (LXVIII) had been produced which reverted to pyrazole on warming to room temperature.

Recently/...
Recently, it has been observed\textsuperscript{65} that 3\textit{H}-1,2-benzodiazepines of type (LXIX),

\[
\text{LXIX}
\]

which do not contain a non-aromatic conjugated diene structure, do not undergo a \([\pi 2s + \pi 2s]\) cyclisation as discussed above but rather, decompose by loss of nitrogen to give products derived from carbene and diradical intermediates.
V THERMOLYSIS OF AZO-COMPOUNDS

Decomposition reactions of saturated and unsaturated monocyclic and bridged polycyclic azo-compounds is currently an area of intense activity. The most interesting aspects perhaps, are the variable mechanistic features exhibited, and the remarkable stereoelectronic effects observed in many systems.

It is proposed here to give a brief outline of the current ideas on azo-compound thermolysis. Azo-compounds have been used for many years as radical generators, e.g. azobisisobutyronitrile (LXX) decomposes to give radicals at moderate temperatures, and is a useful initiator.

\[
\begin{align*}
\text{Me-C-N=N-C-Me} & \xrightarrow{60-80^\circ} 2\text{Me-C}^* + \text{N}_2 \\
\text{LXX}
\end{align*}
\]

The synthesis and thermolysis of cyclic azo-compounds was the subject of a large number of publications by Overberger and co-workers in the 1950's and early 1960's. In general, these indicated that cis-azo-compounds decomposed considerably faster than their trans-counterparts. In 1958, Overberger and Lombardino studied the kinetics of decomposition of 3,7-diphenyl-1,2-diaza-1-cycloheptene (LXXI) to give mixtures of cis-and trans-1,2-diphenylcyclopentane and 1,5-diphenyl-1-pentene, the products/...
products expected from the non-stereospecific combination or disproportionation of the 1,5-diphenyl-1,5-pentadiyl biradical (LXXII).

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{N} & \quad \text{N} \\
\text{Ph} & \quad \text{Ph}
\end{align*}
\]

LXXI

\[
\begin{align*}
\Delta & \quad \text{Ph} \quad \text{H} \\
\text{Ph-C-(CH}_2)_3 \text{C-Ph} & \quad \text{H} \\
\text{H}
\end{align*}
\]

LXXII

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph}
\end{align*}
\]

cis + trans

The following year, Overberger and Tashlick\textsuperscript{67} reported that 3,8-diphenyl-1,2-diaza-1-cyclooctene (LXXIII) decomposed at a rate 10,000 times less than the corresponding six and seven membered rings.

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{N} & \quad \text{N} \\
\text{Ph} & \quad \text{Ph}
\end{align*}
\]

LXXIII

They concluded that although (LXXIII) had a cis-azo linkage, the phenyl groups were prevented from being coplanar with the C-N=N-C system in the transition state, thereby reducing the labilising effect of the phenyl substituents on the C-N bonds. This illustrates the important role played by steric factors in azo-compound thermolysis.

The/...
The exact mechanism of azo-compound thermolysis has always been in doubt. The main point at issue in the mechanism, is whether loss of nitrogen is a one step, route (a) or a two step, route (b) process (Fig. XVII).

\[ R-N=N-R' \rightarrow R^\bullet + N_2 + R' \quad (a) \]

\[ R-N=N-R' \rightarrow R^\bullet + N=N-R' \]

Fig XVII

\[ R^\bullet + N_2 + R' \quad (b) \]

Among the studies which support a one step loss of nitrogen is work by Ruchardt\textsuperscript{68} on the relations between structure and reactivity in azoalkane decompositions, in which rates of thermolysis are interpreted in terms of bond dissociation energies as well as polar and steric effects.

Seltzer and co-workers\textsuperscript{69,70,71} have shown, by measuring kinetic isotope effects, that there is good evidence for the one step mechanism in the thermolysis of symmetric azo-compounds such as (LXXIV), in solution.

\[ Ph-C-N=N-C-Ph \]
\[ \text{Me} \quad \text{Me} \]
\[ X \]
\[ \text{LXXIV} \]
\[ X=H \]
\[ X=D \]

\[ Ph-C-N=N-C-Me \]
\[ \text{Me} \quad \text{Me} \]
\[ X \]
\[ \text{LXXV} \]
\[ X=Y=H \]
\[ X=D; Y=H \]
\[ X=H, Y=D \]
Isotope effects also indicate that the stepwise mechanism operates in the thermolysis of unsymmetricazo-compounds in solution e.g. (LXXV).

In 1972, Porter and co-workers applied Chemically Induced Dynamic Nuclear Polarisation to a study of the decomposition of unsymmetric azo-compounds (LXXVI) and (LXXVII).

\[
\text{Ph-N=N-C-(CH}_3\text{)}_2\text{-Ph} \quad \text{Ph}_2\text{CH-N=N-CH}_2\text{Ph}
\]

\text{LXXVI} \quad \text{LXXVII}

Results obtained on the decomposition of (LXXVI) supported the previous claims that suitably substituted azo-compounds decompose \textit{via} one-bond scission leading to diazenyl radicals (Fig. XVIII).

\[
R-N=N-R' \rightarrow R^\circ + N=N-R'
\]

\text{Fig XVIII}

In addition to decomposition \textit{via} one or two-bond scission mechanisms giving radicals, diazo-compounds can also decompose \textit{via} a concerted mechanism. Excellent evidence for the loss of nitrogen by a concerted rather than a diradical route was obtained by Allred, who studied the decomposition of exo-6,7-diazatricyclo[3,2,1,0-6]-octene (LXXVIII) to give (LXXIX), and found that its rate of decomposition was $10^{11}$ times that of the related structure (LXXX) which gave the corresponding bicyclo[2,1,0] pentanes. It was argued that if (LXXVIII) reacts/...
Fig XIX

Fig XX
reacts via 1,3-diradical intermediate(s) one would expect at least some ring closure, and a tendency for inversion of configuration to give trans-tricyclo $[3,1,0,0]$ hexane (LXXXI). However, only 1,4-cyclohexadiene (LXXIX) was found with no trace of (LXXXI).

The most plausible mechanism accounting for this involves synchronous nitrogen elimination and 1,4-cyclohexadiene formation. The mechanism employed is an orbital symmetry allowed process. The orbital orientation in the transition state (LXXXII) is thus very favourable to nitrogen departure, resulting in a considerable decrease in activation energy.

![LXXXII](image)

Therefore, it is concluded that a concerted process is allowed for the decomposition of (LXXVIII) but not for (LXXX).

Recent work by Bergmann has shown the existence of competitive pathways in the thermolysis of diazabicyclo $[3,2,0]$ hept-2-enes (LXXXIII) and 2,3-diazabicyclo $[3,1,0]$ hex-2-enes (LXXXIV). Thermal decomposition of the former led to six products, predominant among which were bicyclopentane and 1,4-pentadiene. Product ratios indicated that the major route involved rate determining carbene formation, (possibly via the corresponding diazo-compound) followed by rapid reaction of this material to...
to give characteristic hydrogen-shifted and insertion products (route a). The minor route (b) involves direct nitrogen loss and subsequent bicyclopentane formation, presumably via 1,3-diradicals. The pathways were distinguished by stereochemistry and double position labelling of the dimethyl derivatives of (LXXXIII).

The thermolysis of (LXXXIV) gave hydrocarbon decomposition products whose nature strongly suggested the intervention of carbenes as shown in Fig. (XX). This provides a notable exception to the generally observed reaction modes of bicyclic azo-compounds as the compounds of structure (LXXXIV) were designed as precursors to cyclopropylmethylene diradicals (LXXXV).

Thus this novel reaction mode must be considered to be competitive with simple nitrogen extrusion in strained bicyclic pyrazoline systems, and may also occur in some unstrained monocyclic systems.

Studies on the thermolysis of 3H-1,2-benzodiazepines (LXIX) have recently been reported by McEwan and Sharp77. They found that nitrogen was thermally eliminated in both gas phase and solution, and postulated two different modes of decomposition via diradical and carbene intermediates X and Y.
The diradical intermediate (X) was formed by loss of nitrogen via one or two bond cleavage, or electrocyclic ring opening, and carbene (Y) by a [1,5] sigmatropic hydrogen migration followed by electrocyclic ring opening to the diazoalkene, and loss of nitrogen.
Fig XXI

\[ \Delta G^\ddagger \]

\[ \Delta G_{AB}^\ddagger \]

\[ \Delta G_{BA} \]

\[ \Delta G_0 \]

(A)  \hspace{1cm} \rightleftharpoons \hspace{1cm} (B)
VI  RING INVERSION STUDIES BY NUCLEAR MAGNETIC RESONANCE

Conformational analysis may be said to have started in 1950 when fundamental relationships between conformation and chemical reactivity were pointed out by Barton. Barton and Cookson \(^{78}\), in 1956, reviewed the consequences of preferred conformations in various cyclohexane derivatives and steroid systems.

The use of Nuclear magnetic resonance as a tool for quantitative calculations of free energy of activation for reorientation about bonds, was used by Holm \(^{79}\) in 1956, when he studied the temperature dependent coalescence for the proton doublet in C-NMe\(_2\) for N,N-\(\text{dimethylformamide}\) and N,N-\(\text{dimethylacetamide}\). The values he obtained, 92 and 80 kJ mole\(^{-1}\) respectively, indicated a significant amount of double bond character in C-N.

Nuclear magnetic resonance spectroscopy provides a means of studying intramolecular movements with activation energies of ca. 20-100 kJ mol\(^{-1}\). Processes of this type are so fast that the resulting isomers cannot be separated at room temperature. However they are too slow to be investigated by infra-red and Raman spectroscopy.

In rotation about a bond in a molecule, there are preferred positions for the substituents. Thus if we interconvert the isomers A and B (Fig. XXI) we must supply energy \(\Delta G^\pm_{AB}\) and \(\Delta G^\pm_{BA}\) respectively. If \(\Delta G^\pm\) is \(\geq 96\) kJ mol\(^{-1}\), then the isomers are stable at room/...
Fig XXIV

- $T > T_c$
- $T > T_c$
- $T = T_c$
- $T < T_c$
- $T < T_c$
room temperature. Smaller values of $\Delta G^\pm$ result in rapid thermal isomerisation. Consider structure (LXXXVI).

When $R_1 = R_2$, these give separate signals when $X$ and $Y$ are different, and rotation of groups leads to "exchange". "Slow" isomerisation leads to separate signals (Fig. XXII), whereas "fast" isomerisation gives a peak of intermediate chemical shift (Fig. XXIII).

For thermally induced rotations, n.m.r. spectra are temperature dependent (Fig. XXIV) in the transition region between "slow" and "fast" and the shape of the signal in this region can be used to determine rate constants of inversion $k_1$ and the activation parameters $\Delta G^\pm$, $\Delta H^\pm$, $\Delta S^\pm$ and $E_a$. The coalescence temperature is that temperature at which the two signals just coincide (see Fig. XXIV). The theory of line broadening is/...
is well developed, and several methods of evaluation are available in practice.

1. By approximate equations.
2. By graphical evaluation of certain spectral parameters.
3. Computer matching of measured and calculated spectra.

For the simple situation, when two atoms or groups with initially sharp signals of equal intensity undergo chemical exchange (uncoupled AB case, see Figs. XXII, XXIII), the rate constant $k_c$ of chemical exchange at the coalescence temperature $T_c$ is given by

$$k_c = \frac{\pi \Delta \delta}{\sqrt{2}}$$

$\Delta \delta =$ line separation without exchange.

For the coalescence of an AB-type spectrum we have (disregarding the intrinsic width)

$$k_c = \frac{\pi}{\sqrt{2}} \left( \frac{\Delta \delta^2_{AB} + 6J_{AB}^2}{2} \right)^{\frac{1}{2}}$$

where $J_{AB}$ is the coupling constant in Hz between the nuclei A and B. The rate constant of isomerisation is related to $\Delta G^\pm$ in accordance with the Eyring equation

$$k_c = \frac{k_b T_c}{h} e^{-\frac{\Delta G^\pm}{RT_c}}$$

$k_b =$ Boltzmann const.
$R =$ gas const.
$T_c =$ coalescence temp.
$h =$ Planck const.

Thus a value of $\Delta G^\pm$, the free energy of activation can be obtained with high accuracy, since this is dependent on $T_c$ which can be measured very accurately. Although $\Delta G^\pm$ contains a temperature dependent entropy term, it has/...
has been found to be more useful for comparison of compounds than the Arrhenius activation energy \( E_a \), which cannot be quoted with the same accuracy. This is due to errors in the value of the rate constant \( k \), determined from line-shape analysis. These errors increase with distance from the coalescence temperature, and thus, the gradient of an Arrhenius plot is strongly influenced by small deviations in the \( k \) value.

Computers are necessary for the evaluation of \( k_c \) in more complicated cases, as curve shapes can then be simulated and compared with the experimental spectra.

Hundred rotation and inversion by n.m.r. has been reviewed by Kessler\(^82\).

In 1960, Reeves and Stromme\(^83\) used n.m.r. to study the rates of conversion and populations of the conformers of bromo- and chlorocyclohexane. In the same year, Jensen\(^84\) and co-workers calculated the energy barrier for the chair-chair interconversion of cyclohexane. Refinements to the calculation were made by Harris and Sheppard\(^85\) in 1961, and by Jensen\(^86\) in 1962.

In 1964, Anet\(^87\), using low temperature n.m.r. studies, calculated a value for the free energy of ring inversion of cycloheptatriene (LXXXVII). This was extended to heterocyclic rings in 1967, when energy barriers were calculated for the 1H-azepine (LXXXVIII) and 1,5-benzo-diazepine systems\(^88\) (LXXXIX).
\[
\begin{align*}
\text{LXXXVII} & \quad \rightleftharpoons \quad \text{LXXXVIII} \\
\text{LXXXVIII} & \quad \rightleftharpoons \quad \text{LXXXIX} \\
\text{XC} & \quad \rightleftharpoons \quad \text{XCI} \\
\text{XCI} & \quad \rightleftharpoons \quad \text{XCII}
\end{align*}
\]

**Fig XXV**

<table>
<thead>
<tr>
<th>Compound</th>
<th>( \Delta G^\ddagger ) kJ mole(^{-1} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>LXXXVII</td>
<td>25.2</td>
</tr>
<tr>
<td>LXXXVIII</td>
<td>62.8</td>
</tr>
<tr>
<td>LXXXIX</td>
<td>50.4</td>
</tr>
<tr>
<td>XC</td>
<td>84.0</td>
</tr>
<tr>
<td>XCII</td>
<td>75-90</td>
</tr>
</tbody>
</table>
In 1969, Buchardt and co-workers\textsuperscript{89} investigated the spectra of highly substituted 4H-1,2-diazepines, and found that the energy barrier to inversion between the two degenerate boat forms was exceptionally large (see Fig. XXV). They found no evidence for a valence tautomerisation with the corresponding norcaradiene system (Fig. XXVI).

\begin{center}
\begin{adjustbox}{scale=0.5,center={X_1 X_2 X_1 X_2}}
\begin{tikzpicture}
\node (A) at (0,0) {X_1};
\node (B) at (1,0) {X_2};
\node (C) at (2,0) {X_1};
\node (D) at (1,1) {X_2};
\draw (A) -- (B) -- (C) -- (D) -- (A);
\end{tikzpicture}
\end{adjustbox}
\end{center}

**Fig XXVI**

In a later publication, Svanholm\textsuperscript{90} carried out a full line shape analysis on the spectra of compounds (XC), and calculated the energy barriers for inversion, derived from a comparison of the theoretical and experimental spectra. It was found that substituents in the aryl group in the 5-position of the diazepines had almost no effect on the energy barriers, whereas substitution in the 6-position increased the energy barrier by at least 21 kJ mole\textsuperscript{-1}. This effect is probably due to an increase in the energy of the transition state brought about by increasing steric interactions between the substituents in the planar transition state.

Binsch, Sauer and co-workers\textsuperscript{91} have recently used variable temperature n.m.r. to show that the 4H-azepine system exists/...
exists in the monocyclic form, but 4H-I,2-diazepines (XCI) exists entirely in the bicyclic 3,4-diaza norcaradiene structure (XCII). This is easily explained by the fact that the bond energy of a nitrogen-nitrogen double bond is less than that of a carbon-carbon or carbon-nitrogen double bond by about 210 kJ mole\(^{-1}\). This also explains why the 4H-1,2-diazepine of Buchardt\(^{89}\) exists in the monocyclic form (Fig. XXVI), as this does not suffer from the strong energetic disadvantage of a nitrogen-nitrogen double bond. Binsch and Sauer\(^{91}\) postulated that the observed topomerisations of (XCII) proceed in two reversible steps, a valence isomerisation of the diaz anorcaradiene to the monocyclic form (XCI), followed by ring reversal of the latter.

Some \(\Delta G^\ddagger\) values for the inversion of a few selected ring systems are shown in Fig. XXV.
Preparation and purification of reagents and reference compounds

(1) PREPARATION OF STARTING MATERIALS

I SYNTHESIS OF AMIDES

A. N-Acetyl-2-phenylethylamine
B. N-Acetyl-2-(3,4-dimethoxyphenyl)-ethylamine
C. N-Propionyl-2-phenylethylamine
D. N-Benzoyl-2-phenylethylamine
E. N-Benzoyl-2-(3,4-dimethoxyphenyl)-ethylamine
F. N-Phenylacetetyl-2-phenylethylamine

II SYNTHESIS OF 3,4-DIHYDROISOQUINOLINES

A. 1-Ethyl-3,4-dihydroisoquinoline
B. 6,7-Dimethoxy-3,4-dihydroisoquinoline
C. 1-Methyl-3,4-dihydroisoquinoline
D. 1-Methyl-6,7-dimethoxy-3,4-dihydroisoquinoline
E. 1-Phenyl-3,4-dihydroisoquinoline
F. 1-Phenyl-6,7-dimethoxy-3,4-dihydroisoquinoline
G. 1-Benzyl-3,4-dihydroisoquinoline
III  SYNTHESIS OF 2-ACYLSTYRENES  
A. 2-Formyl-4,5-dimethoxystyrene 
B. 2-Propionylstyrene 
C. 2-Benzoylstyrene 
D. 2-Benzoyl-4,5-dimethoxystyrene 
E. 2-Acetylstyrene 
F. 2-Acetyl-4,5-dimethoxystyrene 
G. 2-Formyl-5-ethoxy-β,β-dimethylstyrene 
H. 2-Phenylacetylstyrene 

IV  SYNTHESIS OF STILBENE DERIVATIVES  
A. Benzal phthalide 
B. trans-Stilbene-2-carboxylic acid 
C. trans-Stilbene-2-carboxylic ethyl ester 
D. trans-Stilbene-2-carboxylic hydrazide 
E. 1-α-Styrylbenzoyl-2-α-toluene-sulphonylhydrazine 
F. Stilbene-2-aldehyde 
G. Benzyltriphenylphosphonium chloride 
H. trans-2-Nitrostilbene 
J. trans-2-Aminostilbene 
K. trans-Stilbene-2-azide 

V  MISCELLANEOUS PREPARATIONS  
A. 3-Phenyl-1-indanone 
B. 3-Phenyl-1-indanol 
C. 1-Phenylindene
(2) SYNTHESIS OF TOLUENE-\(\text{p}\)-SULPHONYLHYDRAZONES

A. 2-Formyl-4,5-dimethoxystyrene toluene-\(\text{p}\)-sulphonylhydrazone
B. 2-Acetylstyrene toluene-\(\text{p}\)-sulphonylhydrazone
C. 2-Propionylstyrene toluene-\(\text{p}\)-sulphonylhydrazone
D. 2-Acetyl-4,5-dimethoxystyrene toluene-\(\text{p}\)-sulphonylhydrazone
E. 2-Benzoylstyrene toluene-\(\text{p}\)-sulphonylhydrazone
F. 2-Benzoyl-4,5-dimethoxystyrene toluene-\(\text{p}\)-sulphonylhydrazone
G. 2-Formylstilbene toluene-\(\text{p}\)-sulphonylhydrazone
H. 2-Formyl-5-ethoxy-\(\beta\),\(\beta\)-dimethylstyrene toluene-\(\text{p}\)-sulphonylhydrazone

(3) SYNTHESIS OF 1H-2,3-BENZODIAZEPINES FROM THE CYCLISATION OF THE CORRESPONDING TOLUENE-\(\text{p}\)-SULPHONYLHYDRAZONE SODIUM SALTS

A. 7,8-Dimethoxy-1H-2,3-benzodiazepine
B. 1-Phenyl-1H-2,3-benzodiazepine
C. 1-Phenyl-7,8-dimethoxy-1H-2,3-benzodiazepine
D. 4-Phenyl-1H-2,3-benzodiazepine
E. 1-Ethyl-1H-2,3-benzodiazepine
F. 1-Methyl-1H-2,3-benzodiazepine
G. 1-Methyl-7,8-dimethoxy-1H-2,3-benzodiazepine
(4) SYNTHESES OF 5H-2,3-BENZODIAZEPINES

A. 1-Phenyl-5H-2,3-benzodiazepine
B. 1-Phenyl-7,8-dimethoxy-5H-2,3-benzodiazepine
C. 1-\textit{p}-Toly1-4-phenyl-5H-2,3-benzodiazepine
D. 1-Methyl-4-phenyl-5H-2,3-benzodiazepine

(5) PHOTOLYSIS OF 1H-2,3-BENZODIAZEPINES

A. 1-Methyl-7,8-dimethoxy-1H-2,3-benzodiazepine
B. 7,8-Dimethoxy-1H-2,3-benzodiazepine
C. 1-Phenyl-1H-2,3-benzodiazepine
D. 1-Methyl-1H-2,3-benzodiazepine
E. 1-Methyl-4-phenyl-1H-2,3-benzodiazepine
F. 4-Phenyl-1H-2,3-benzodiazepine

(6) PHOTOLYSIS OF 5H-2,3-BENZODIAZEPINES

A. 1-Phenyl-5H-2,3-benzodiazepine

(7) ATTEMPTED CYCLISATION OF 2-FORMYL-5-ETHOXY-\textit{p},\textit{p}-DIMETHYLSTYRENE TOLUENE-\textit{p}-SULPHONYLHYDRAZONE SODIUM SALT

A. Decomposition in dimethoxyethane

(8) ATTEMPTED THERMAL CYCLISATION OF trans-STILBENE-2-AZIDE

A. Decomposition in dimethoxyethane
B. Decomposition in toluene
(9) THERMOLYSIS STUDIES

I
1-Phenyl-1H-2,3-benzodiazepine

A. Decomposition of toluene

B. Kinetics of decomposition in diphenyl ether

II
4-Phenyl-4H-[1,2]diazeto [3,2-a]
isoindole

III
1-Phenyl-4H-[1,2]diazeto [3,2-a]
isoindole

IV
1-Phenyl-4-methyl-4H-[1,2]diazeto
[3,2-a]isoindole

APPENDICES OF N.M.R. AND
MASS SPECTRAL DATA
SYMBOLS AND ABBREVIATIONS

The abbreviations used in this thesis are those in common usage. In addition, the following are used:

\[ J \] spin-spin coupling constant

\[ m \] multiplet

\[ bs \] broad singlet

\[ m/e \] mass to charge ratio

\[ R_f \] ratio of distance moved by the substance to distance moved by the solvent front

H.S.L.C. high speed liquid chromatography

C.I.D.N.P. chemically induced dynamic nuclear polarisation
INSTRUMENTATION

Gas-Liquid Chromatography - All analytical investigations were carried out on a Pye Series 104 chromatograph, with a flame ionisation detector, using 2m x 4mm i.d. packed columns. The carrier gas was nitrogen, the flow rate being that recommended by the manufacturer. The following stationary phases, supported on 100-200 mesh celite or silocel were employed; carbowax 20m (CAR) neopentylglycol succinate (NPGS) and apiezon grease (APL).

High Speed Liquid Chromatography (HSLC) - A Dupont 820 liquid chromatograph with a U.V. photometer detector and 1m x 2mm packed columns was used. Samples were run by Dr. J. Done, Chemistry Department, University of Edinburgh.

Thin Layer Chromatography (t.l.c.) - Chromatograms were obtained on 0.33mm layers of alumina (Merck, Aluminium oxide G) or silica gel (Merck, Silica gel G). Components in the developed chromatogram were detected by their fluorescence in U.V. light, or by their reaction with iodine.

Column Chromatography - Alumina was Laporte Industries, Grade H, 100/200 mesh (Brockmann activity 2). Silica gel was Whatman Chromedia SG31. Alumina for dry column chromatography was of activity 3. Nylon tubing was supplied by W. Coles and Co. Ltd., London SE1.
Proton Magnetic Resonance Spectroscopy - Spectra of routine samples were obtained on Perkin-Elmer model R-10 and Varian EM360 spectrometers. Spectra of new compounds, decoupling and variable temperature studies were obtained from a Varian HA100 instrument operated by Mrs. M. Groves and Mr. J. Miller. Chemical shifts are recorded as \( \tau (') \) values in parts per million, tetramethylsilane \( (\tau = 10.0) \) being the internal reference. Spectra were determined on ca. 10% w/v solutions, or as indicated.

Mass Spectroscopy - Mass spectra were obtained using an Associated Electrical Industries MS20 and MS902 instruments.

Infrared Spectroscopy - Liquid samples were examined as thin films or solutions, and solid samples as nujol mulls. Spectrophotometers used were Perkin-Elmer 337 Grating, Perkin-Elmer 157G Grating and a Unicam SP200.

Melting Points - The melting points of all new compounds were obtained using a Kofler hot-stage apparatus.

Photochemical reactions - A Hanovia 125 watt medium pressure mercury arc tube in a quartz envelope was surrounded by the reaction mixture in an appropriately sized pyrex vessel.

Elemental Analysis - These were carried out in the Chemistry Department, University of Edinburgh by Mr. B. Clark and Mr. J. Grunbaum using a Perkin-Elmer Model 240 analyser.
Drying - All organic solutions were dried using anhydrous magnesium sulphate.
PREPARATION AND PURIFICATION OF REAGENTS AND REFERENCE COMPOUNDS

"Super-dry" ethanol was prepared as described by Vogel (Method I)\textsuperscript{92}. Cyclohexane (b.p. 80\textdegreeC at 760mm Hg) and 1,2-dimethoxyethane (b.p. 85\textdegreeC at 760mm Hg) were distilled under nitrogen from calcium hydride immediately before use. Toluene (b.p. 111\textdegreeC at 760mm Hg) was allowed to stand over sodium wire until no further reaction occurred, distilled under dry nitrogen and stored over sodium wire. Diphenyl ether (b.p. 258-259\textdegreeC at 760mm Hg) was degassed in the usual way by freezing/thawing cycles under high vacuum.
PREPARATION OF STARTING MATERIALS

I - SYNTHESIS OF AMIDES -

A. N-Acetyl-2-phenylethylamine - 2-Phenylethylamine (49.3g, 0.407 mole), glacial acetic acid (80ml) and acetic anhydride (80ml) were warmed to 80°C for 0.5 h. After cooling, excess acetic acid was neutralised with potassium hydroxide solution. The product was extracted with ether (5 x 150ml, dried, and the solvent evaporated, giving an oil which solidified on standing. Distillation of this solid afforded N-acetyl-2-phenylethylamine (50.2g, 75%), b.p. 128°C at 0.4mm Hg (lit., 93°C-134°C at 0.6mm Hg). Since the product distilled at constant temperature it was used for the next stage.

B. N-Acetyl-2-(3,4-dimethoxyphenyl)-ethylamine - This compound was prepared by a method identical to N-acetyl-2-phenylethylamine using 2-(3,4-dimethoxyphenyl)-ethylamine (50g, 0.28 mole). The crude solid obtained by evaporation of the ethereal solution was recrystallised from ethanol to give white crystals of N-acetyl-2-(3,4-dimethoxyphenyl)-ethylamine (38g, 62%) m.p. 93-95°C (lit., 94°C-94-95°C)

I.r. (nujol): 3240cm⁻¹ (N-H).
1630cm⁻¹ (C=O).

C. N-Propionyl-2-phenylethylamine - 2-Phenylethylamine (50g, 0.413 mole), propionic anhydride (54g, 0.415 mole) and distilled, dry benzene (100ml) were boiled under reflux/...
reflux for 1 h. After cooling, the reaction solution was transferred to a beaker containing potassium hydroxide solution (32g in 200ml water) and benzene (200ml). The organic layer was collected and the aqueous layer extracted with benzene (2 x 100ml). The combined benzene fractions were washed with water (2 x 150ml), dried and the solvent evaporated giving a white solid. This was crushed, washed with petrol, distilled water and a little cold ether. After recrystallisation from ethanol, N-propionyl-2-phenylethylamine (59.8g, 82%) was obtained as colourless crystals m.p. 73-75°C.

I.r. (nujol): 3240cm⁻¹ (N-H)
1630cm⁻¹ (C=O).

D. N-Benzoyl-2-phenylethylamine - 2-Phenylethylamine (50g, 0.414 mole) was suspended in sodium hydroxide solution (250ml, 15%). Benzoyl chloride (70g) was then cautiously added. The mixture was shaken vigorously in a stoppered vessel for 1 h. The white solid formed was filtered, dried in vacuo, then recrystallised from ethanol to remove excess benzoyl chloride giving N-benzoyl-2-phenylethylamine (79.3g, 85%). m.p. 118-120°C. (lit.⁹⁵ 95, 113-114°C)

I.r. (nujol): 3310cm⁻¹ (N-H)
1640cm⁻¹ (C=O)

E. N-Benzoyl-2-(3,4-dimethoxyphenyl)-ethylamine - This compound was prepared by a method identical to N-benzoyl-2-phenylethylamine using 2-(3,4-dimethoxyphenyl)-ethylamine (50g, 0.28 mole). The white solid collected was/...
was recrystallised from ethanol to give N-benzoyl-2-(3,4-dimethoxyphenyl)-ethylamine (69.8g, 87%) m.p. 91-92°C (lit.96, 90-91°C)

I.r. (nujol): 3300cm⁻¹ (N-H).

1630cm⁻¹ (C=O).

F. N-Phenylacetyl-2-phenylethylamine - Phenylacetyl chloride (30.9g, 0.2 mole) was added dropwise to a suspension of 2-phenylethylamine (24.2g, 0.2 mole) in sodium hydroxide solution (250ml, 15%) with shaking, keeping the temperature below 10°C. After addition was complete, the flask was shaken vigorously for 0.5 h. The solid formed was filtered, washed with water and dried. After recrystallisation from ethanol, N-phenylacetyl-2-phenylethylamine (34.5g, 72.5%) was obtained as a white crystalline solid m.p. 91-93°C (lit.97, 94-95°C)

I.r. (KBr disc): 3250cm⁻¹ (N-H).

1650cm⁻¹ (C=O).
In general, 3,4-dihydroisoquinolines were prepared from the corresponding amides by the method of Whaley and Hartung.\(^9\) Purification was effected by distillation or crystallisation of the free base, or formation of a solid hydrochloride.

A. 1-Ethyl-3,4-dihydroisoquinoline - A mixture of N-propionyl-2-phenylethylamine (25g, 0.142 mole), phosphorus pentoxide (50g, 0.35 mole) and phosphorus oxychloride (70g, 0.455 mole) was heated to reflux in dry xylene (400ml) for 1 h. After cooling, the reaction mixture was treated with ice water (600ml). When all of the residue had dissolved, the aqueous layer was run off and extracted with benzene (2 x 100ml). It was then made strongly alkaline by the addition of 20% sodium hydroxide solution. On cooling, the free base was extracted with benzene (3 x 150ml), dried, and the solvent evaporated. The crude oil was distilled giving 1-ethyl-3,4-dihydroisoquinoline (16g, 72%) b.p. 75° at 3.5mm Hg. (Found: C, 82.9; H, 8.6; N, 8.8. \(C_{11}H_{13}N\) requires C, 83.0; H, 8.3; N, 8.8%).

I.r. (liquid): 1610cm\(^{-1}\) (C=N).

N.m.r. (CDCl\(_3\)): \(\gamma\) 2.5-3.1 (m,4H), 6.4 (t,2H), 7.2-7.8 (m,4H), 8.85 (t,3H).
B. **6,7-Dimethoxy-3,4-dihydroisoquinoline** - This compound was gifted by The Wellcome Research Laboratories, Beckenham, Kent.

C. **1-Methyl-3,4-dihydroisoquinoline** - This was prepared as the free base in 72% yield. b.p. 152-153° at 70mm Hg. (lit.93, 148-150° at 30mm Hg).

I.r. (liquid): 1630cm⁻¹ (C=N).
N.m.r. (CDCl₃): γ 2.4-2.95 (m,4H), 6.35 (t, N-CH₂-), 7.35 (t, -CH₂-CH₂-), 7.65 (s,Me).

D. **1-Methyl-6,7-dimethoxy-3,4-dihydroisoquinoline** - The free base was obtained as a yellow solid after purification by acid extraction. Yield 55%. m.p. 99-101° (lit.94, 106-107°)

I.r. (nujol): 1610cm⁻¹ (C=N)
N.m.r. (CCl₄): γ 3.2 (s,1H), 3.5 (s,1H), 6.2 (two overlapping singlets, 6H), 6.4-6.7 (m,2H), 7.4-7.7 (m,2H), 7.8 (s,Me).

E. **1-Phenyl-3,4-dihydroisoquinoline** - The free base was converted to the hydrochloride due to its high boiling point. This gave 1-phenyl-3,4-dihydroisoquinoline hydrochloride as a pale-green solid m.p. 228-234°. On recrystallisation from petrol/isopropanol a 57% yield of product m.p. 243-244° (lit.98, 245°) was obtained.

I.r. (nujol): 2500-2600cm⁻¹ (broad) (N-H).
1630cm⁻¹ (C=N).
N.m.r. (CDCl₃): γ 2.0-2.5 (m,10H), 5.9 (t, -N-CH₂-), 6.8 (t, -CH₂-CH₂-).
F. 1-Phenyl-6,7-dimethoxy-3,4-dihydroisoquinoline -
The free base was obtained as a yellow solid after
purification by acid extraction. Yield 60%. m.p.
115-117° (lit. ⁹⁶, 120.5-121.5°).

I.r. (nujol): 1600cm⁻¹

N.m.r. (CCl₄): γ 2.3-2.9 (m, 5H), 3.2-3.5 (m, 2H),
6.4 (two overlapping singlets, 6H), 6.2 (m, 2H),
7.2-7.7 (m, 2H).

G. 1-Benzyl-3,4-dihydroisoquinoline - The crude
hydrochloride was obtained by bubbling hydrogen chloride
through a solution of the free base in benzene. This
gave 1-benzyl-3,4-dihydroisoquinoline as a white solid
in 74% yield. m.p. 222-224° (lit. ⁹⁸, 227-229°), after
recrystallisation from isopropanol.

I.r. (nujol): 1610cm⁻¹ (C=N).

ca. 2700cm⁻¹ (broad, N-H).

N.m.r. (CCl₄): γ 2.45-3.1 (m, 9H), 5.95 (s, benzyl 2H),
6.3 (t, -N-CH₂⁻), 7.3 (t, -CH₂-CH₂⁻).
III - SYNTHESIS OF 2-ACYLSTYRENES -

In general, acylstyrenes were prepared from 3,4-dihydroisoquinolines by Gensler's method. The crude products were purified by distillation or recrystallisation.

A. 2-Formyl-4,5-dimethoxystyrene - A mixture of 6,7-dimethoxy-3,4-dihydroisoquinoline (17.3g, 0.096 mole) and dimethylsulphate (82ml) in sodium hydroxide solution (600ml, 30%) was boiled under reflux in an atmosphere of nitrogen for 3 h. After cooling, the product was extracted into ether (3 x 120ml), and the ethereal solution washed with dilute hydrochloric acid (1 x 80ml), and then with water (2 x 80ml). After drying, the ether was removed on a rotary evaporator giving an orange oil. This failed to crystallise on standing, or scratching with ether. Purification was effected by chromatography on a column (1" x 24") silica gel/methylene chloride : benzene 1:1. This gave 2-formyl-4,5-dimethoxystyrene (10.85g, 63%) as an orange solid m.p. 46-48°C (lit., 50-51°C).

I.r. (nujol): 1660cm⁻¹ (C = O).

N.m.r. (CDC1₃): γ -0.25 (s,1H), 2.3-2.9 (m,1H), 2.7 (s,1H), 3.05 (s,1H), 6.05 (s,3H) and 6.1 (s,3H).

The following compounds were prepared by the same method. Chromatography was not necessary.

B. 2-Propionylstyrene - This was obtained as a colourless liquid in 88% yield. b.p. 74°C at 0.05mm Hg. (Found: C, 82.6; H, 7.8. C₁₁H₁₂O requires C, 82.5; H, 7.55%).
I.r. (liquid): $1685\text{cm}^{-1}$ (C=O).
N.m.r. (CDCl$_3$): $\gamma 2.4\text{-}3.1$ (m,5H), 4.3\text{-}4.8 (m,2H), 7.2 (q,2H) and 8.9 (t,3H).

C. 2-Benzoylstyrene - This was obtained as a pale yellow liquid in 69\% yield. b.p. 126° at 0.4mm Hg (lit.$^9$, 159\text{-}161° at 2.5mm Hg).
I.r. (liquid): $1660\text{cm}^{-1}$ (C=O).
N.m.r. (CDCl$_3$): $\gamma 2.05\text{-}2.9$ (m,9H), 2.95\text{-}3.55 (m,1H), and 4.1\text{-}4.95 (m,2H).

D. 2-Benzoyl-4,5-dimethoxystyrene - This was obtained as a white solid in 79\% yield. m.p. 66\text{-}67° (lit.$^9$, 66\text{-}67°). Benzene was used for extraction of product.
I.r.: $1650\text{cm}^{-1}$ (C=O).

E. 2-Acetylstyrene - This was obtained as a colourless liquid in 56\% yield. b.p. 82\text{-}85° at 2mm Hg (lit.$^9$, 96\text{-}100° at 3mm Hg).
I.r. (liquid): $1690\text{cm}^{-1}$ (C=O).
N.m.r. (CDCl$_3$): $\gamma 2.3\text{-}3.1$ (m,5H), 4.2\text{-}4.8 (m,2H), 7.55 (s,3H).

F. 2-Acetyl-4,5-dimethoxystyrene - This was obtained as a pale yellow solid in 69.5\% yield after recrystallisation from methanol. m.p. 76° (lit.$^9$, 77\text{-}78°).
I.r. (nujol): $1670\text{cm}^{-1}$ (C=O).
N.m.r. (CCl$_4$): $\gamma 3.0$ (s,1H), 3.1 (s,1H), 2.45\text{-}3.1 (m,1H), 4.4\text{-}4.9 (m,2H), 6.2 (pair of singlets, 6H), 7.55 (s3H).
G. 2-Formyl-5-ethoxy-\(\beta,\beta\)-dimethylstyrene - This compound was prepared from 3,3-dimethyl-6-ethoxy-3,4-dihydroisoquinoline which was gifted by Dr. F. Copp, Wellcome Research Laboratories, Beckenham, Kent. This 3-substituted 3,4-dihydroisoquinoline had been prepared by the Ritter\(^{100}\) reaction. The styrene was obtained as a water white liquid in 68% yield. b.p. 90\(^0\) at 0.05mm Hg. (Found: C, 76.7; H, 7.7. \(C_{13}H_{16}O_2\) requires C, 76.4; H, 7.9%).

I.r. (liquid): 1680cm\(^{-1}\) (\(C=O\)).

N.m.r. (CDCl\(_3\)): \(\gamma\) -0.1 (s,1H), 2.0-3.6 (m,4H), 5.8 (q,2H), 8.1 (s,3H), 8.3 (s,3H), 8.7 (t,3H). Olefinic methyl split \(J = 2\)Hz.

H. 2-Phenylacetylstyrene - An attempt was made to prepare this compound from 1-benzyl-3,4-dihydroisoquinoline hydrochloride (4.0g, 0.0155 mole), dimethyl sulphate (12.6ml) and sodium hydroxide solution (160ml, 10%) by the usual procedure\(^99\). Distillation of the crude product gave a water-white liquid (2.33g). N.m.r. indicated that 55% of this liquid was 2-phenylacetylstyrene. The other major component was assigned the structure 2-(2-Phenylpropanoyl)styrene. A further distillation using a fractionating column gave no separation of the mixture.
IV - SYNTHESIS OF STILBENE DERIVATIVES -

A. Benzal phthalide - This was prepared by the method of Weiss\textsuperscript{101} from phthalic anhydride, phenylacetic acid and anhydrous sodium acetate. After two recrystallisations from ethanol, benzal phthalide (70.5\%) was obtained as a pale yellow crystalline solid m.p. 93-95\degree C. (lit.\textsuperscript{102}, 97-99\degree C).

B. trans-Stilbene-2-carboxylic acid - This was prepared\textsuperscript{102} by the method of De Tar and Carpino\textsuperscript{102}. After two crystallisations from ethanol, the acid (58.5\%) was obtained as a colourless crystalline solid m.p. 159-160\degree C. (lit.\textsuperscript{102}, 158-160\degree C).

\textit{I.r. (disc): ca. 3000cm\textsuperscript{-1} (O-H).}
\textit{1670cm\textsuperscript{-1} (C=O).}

C. trans-Stilbene-2-carboxylic ethyl ester - This was prepared using the method of Natelson and Gottfried\textsuperscript{103}. The crude ester was distilled to give a 90\% yield of product b.p. 140\degree C at 0.1mm Hg. (lit.\textsuperscript{103}, 215\degree C at 15mm Hg).

D. trans-Stilbene-2-carboxylic hydrazide - A mixture of trans-stilbene-2-carboxylic ethyl ester (36g, 0.143 mole), 99-100\% hydrazine hydrate (8.3g, 0.166 mole) and ethanol (35ml) was boiled under reflux with mechanical stirring for 24 h. On cooling, a white solid mass was obtained. The product was stirred up with benzene to extract unchanged ester, then dried by azeotropic distillation with benzene. Recrystallisation from benzene/...
benzene gave the hydrazide (22.0g, 66%) as a white powdery solid m.p. 134-135° (lit. 103, 135°).

I.r. (nujol): 3340cm⁻¹ (N-H).
   : 1620cm⁻¹ (C=O).

E. 1-o-styrylbenzoyl-2-p-toluenesulphonylhydrazine -
This was prepared by the method of Natelson and Gottfried 103 from trans-stilbene-2-carboxylic hydrazide (21.4g, 0.0915 mole), toluene-p-sulphonyl chloride (17.4g, 0.0915 mole) and anhydrous pyridine (70ml). The crude solid (33.7g) was recrystallised from benzene giving 1-o-styrylbenzoyl-2-p-toluenesulphonylhydrazine (26.1g, 73.5%) as a white crystalline solid. m.p. 184-186° (lit. 103, 190°).

Stilbene-2-aldehyde - This was prepared from 1-o-styrylbenzoyl-2-p-toluenesulphonylhydrazine (17.2g, 0.045 mole), potassium carbonate (14g) and glycerol (85ml) by the method of Natelson and Gottfried 103. The crude product was isolated as a light brown solid (7.6g), which on recrystallisation from aqueous ethanol gave yellow crystals of stilbene-2-aldehyde (5.3g, 57%) m.p. 80-82°. (lit. 103, 83°)

I.r. (nujol): 1690cm⁻¹ (C=O).
N.m.r. (CDCl₃): 1.1 (s,1H aldehydic),
   2.0-3.2 (m,7H).

G. Benzyltriphenylphosphonium chloride - Benzyl chloride (35g, 0.275 mole) and triphenylphosphine (79g, 0.30 mole) were dissolved in D.M.F. (200ml). The solution was boiled/...
boiled under reflux for 2.5 h, cooled and the white crystals formed washed with D.M.F. (X1), ether (X2), and dried giving benzyltriphenylphosphonium chloride (99.8g, 88%). m.p. > 300° (lit. 104, 338°).

H. trans-2-Nitrostilbene - A solution of sodium (3.0g, 0.1305 mole) in ethanol (250ml) was added with brisk stirring to a solution of o-nitrobenzaldehyde (18.5g, 0.1225 mole) and benzyltriphenylphosphonium chloride (47.53g, 0.1225 mole) in ethanol (70ml). After 30min, the solution was heated to reflux for 1 h, and then left overnight. The ethanol was then removed, and the reaction mixture was treated with chloroform/water (250/150ml). The aqueous layer was extracted with chloroform (100ml), the fractions combined and dried. The stilbene isomer ratio was found to be approximately 1:1 by g.l.c. on 2% N.P.G.S. at 208°, cis being eluted before trans. Isomerisation required boiling under reflux in nitrobenzene (120ml) for 3 h in the presence of a few crystals of iodine. When g.l.c. analysis showed the isomerisation to be complete, the nitrobenzene was removed under high vacuum, the residue extracted into chloroform (250ml) and washed with sodium thiosulphate solution. After separation of the layers, the chloroform was dried and removed in vacuo. The crude mixture of trans-stilbene and triphenylphosphine oxide was separated by dry column chromatography on a 20" x 2" alumina column/...
column, eluting with benzene. The yellow band was cut out, extracted into chloroform (3 x 80ml). On removal of the solvent a yellow crystalline solid (22.0g) was obtained. This recrystallised from methanol to give trans-2-nitrostilbene (20.6g, 73%) m.p. 68-70° (lit. 105, 70-72°).

I.r. (nujol): 1340 cm⁻¹, 1530 cm⁻¹ (NO₂).

J. trans-2-Aminostilbene - trans-2-Nitrostilbene (15g, 0.0666 mole), iron powder (15g), ethanol (27ml) and water (27ml) were placed in a 3-necked flask equipped with a mechanical stirrer. Conc. hydrochloric acid (1.6g) was slowly dripped in with vigorous stirring. The contents were then boiled under reflux for 14 h, stirring continuously. The solution was then cooled, made alkaline by the addition of 10% sodium hydroxide solution and filtered through celite. The solid was washed with benzene (200ml), and the combined filtrate washed with water (70ml). The organic layer was dried, and the solvent removed on a rotary evaporator giving a brown solid (9.1g). This was purified by acid extraction, and on regeneration of the free base, recrystallised from ethanol to give trans-2-aminostilbene (7.8g, 60%). m.p. 98-99° (lit. 106, 100°)

I.r. (nujol): 3360, 3430 cm⁻¹ (N-H).

N.m.r. (CDCl₃): 2.3-3.4 (m, 11H), 6.35 (broad, 2 N-H).

K. trans-Stilbene-2-azide - trans-2-aminostilbene (7.1g, 0.0364 mole) was added to conc. hydrochloric acid/...
acid (36.4ml) and water (180ml) with vigorous stirring, resulting in a white suspension of hydrochloride. This was cooled to \(-2.5^\circ\) in an ice-salt bath, and a solution of sodium nitrite (2.73g) in water (18.2ml) dripped in, so that the temperature remained below \(0^\circ\). A solution of sodium azide (2.91g) in water (18.2ml) was then added dropwise, resulting in frothing and precipitation of the azide. After standing 1 h at \(0^\circ\) the solution was allowed to warm up to room temperature. The solid azide was filtered off and dried overnight in vacuo. This was recrystallised from benzene/petrol to give trans-stilbene-2-azide (6.9g, 85.5%) m.p. 92-93\(^\circ\) (lit.\(^{107}\) 94-95.5\(^\circ\)).

I.r. (nujol): \(2110\text{cm}^{-1}\) (azide)
V - MISCELLANEOUS PREPARATIONS -

A. 3-Phenyl-1-indanone - This was prepared in 32% yield by the method of Koelsch, Hochmann and Le Claire\textsuperscript{108} from cinnamic acid, dry benzene and anhydrous aluminium chloride. The crude material was recrystallised from ethanol m.p. 78° (lit.\textsuperscript{109} 78-79°).

I.r. (nujol): 1730cm\(^{-1}\) (C=O).

N.m.r. (CDCl\(_3\)): \(\gamma\) 2.0-3.0 (m,9H), 5.25-5.6 (pair of doublets, 1H), 6.85 (pair of doublets, 1H), 7.35 (pair of doublets, 1H).

B. 3-Phenyl-1-indanol - This was prepared in 73% yield by the method of Miller and Boyer\textsuperscript{109} from 3-phenyl-1-indanone and lithium aluminium hydride in dry ether. A white solid, m.p. 95° (lit.\textsuperscript{109} 95°) was obtained on recrystallisation from ethanol.

I.r. (nujol): 3300cm\(^{-1}\) (O-H).

C. 1-Phenylindene - This was prepared as a colourless oil in 25% yield by the method of Miller and Boyer\textsuperscript{109}, from 3-phenyl-1-indanol, glacial acetic acid and toluene-p-sulphonic acid. The product was purified by chromatography on a 6" x 1" silica gel column eluting with petrol.

N.m.r. (CCl\(_4\)): \(\gamma\) 2.9 (m,9H), 3.3 (pair of doublets, 2H) and 5.5 (t,1H).
A. 2-Formyl-4,5-dimethoxystyrene toluene-\(p\)-sulphonylhydrazone - A mixture of 2-formyl-4,5-dimethoxystyrene (3.0 g, 0.016 mole) and toluene-\(p\)-sulphonylhydrazide (2.95 g, 0.016 mole) in methanol (20 ml) containing conc. hydrochloric acid (0.1 ml) was boiled under reflux for 5 min. The product (5.67 g) deposited on cooling was filtered off and recrystallised from dimethoxyethane to give 2-formyl-4,5-dimethoxystyrene toluene-\(p\)-sulphonylhydrazone (4.95 g) m.p. 75-76 ° (decomp.).

I.r. (KBr disc): 3200 cm\(^{-1}\) (N-H).

Parent ion had mass = 360.114270: \(C_{18}H_{20}N_{2}O_{4}S\) requires 360.114369.

B. 2-Acetylstyrene toluene-\(p\)-sulphonylhydrazone - A solution of 2-acetylstyrene (3.04 g, 0.021 mole) in ethanol (15 ml) was warmed to 50 °, and then added to a solution of toluene-\(p\)-sulphonylhydrazide (3.88 g, 0.021 mole) in ethanol (15 ml) containing conc. hydrochloric acid (0.1 ml). After standing overnight at room temperature, colourless needles (6.7 g) were filtered off. These were recrystallised from ethanol/ethyl acetate to give 2-acetylstyrene toluene-\(p\)-sulphonylhydrazone (5.03 g, 77%) m.p. 146-148 °. (Found: C, 64.85; H, 5.95; N, 8.95. \(C_{17}H_{18}N_{2}O_{2}S\) requires C, 64.9; H, 5.8; N, 8.9%).

I.r. (nujol): 3200 cm\(^{-1}\) (N-H).

N.m.r. spectrum: See Appendix.
C. 2-Propionylstyrene toluene-p-sulphonylhydrazone - A mixture of 2-propionylstyrene (1.6g, 0.01 mole), toluene-p-sulphonylhydrazide (1.86g, 0.01 mole) in ethanol (20ml) containing conc. hydrochloric acid (5 drops) was boiled for 2 min. After standing overnight, the product (2.71g) was filtered off, and recrystallised from ethanol to give 2-propionylstyrene toluene-p-sulphonylhydrazone (2.38g, 73%) m.p. 141-143° (decomp.). (Found: C, 65.7; H, 6.2; N, 8.5. \( \text{C}_{18}\text{H}_{20}\text{N}_{2}\text{O}_{2}\text{S} \) requires C, 65.8; H, 6.1; N, 8.5%).

\[ \text{I.r. (nujol): } 3180\text{cm}^{-1} \text{ (N-H)}. \]

\[ \text{N.m.r. spectrum: See Appendix.} \]

D. 2-Acetyl-4,5-dimethoxystyrene toluene-p-sulphonylhydrazone - A solution of 2-acetyl-4,5-dimethoxystyrene (3.11g, 0.0151 mole) in ethanol (15ml) was warmed to 50° and then added to a solution of toluene-p-sulphonylhydrazide (2.81g, 0.0151 mole) containing concentrated hydrochloric acid (0.1ml). After standing overnight, the product (5.0g) was filtered off. This was recrystallised from methanol giving 2-acetyl-4,5-dimethoxystyrene toluene-p-sulphonylhydrazone (4.2g, 74%) m.p. 166-170° (decomp.). (Found: C, 60.8; H, 6.0; N, 7.6. \( \text{C}_{19}\text{H}_{22}\text{N}_{2}\text{O}_{4}\text{S} \) requires C, 60.9; H, 5.9; N, 7.5%).

\[ \text{I.r. (nujol): } 3250\text{cm}^{-1} \text{ (N-H)}. \]

\[ \text{N.m.r. spectrum: See Appendix.} \]

E. 2-Benzoylstyrene toluene-p-sulphonylhydrazone - A mixture of 2-benzoylstyrene (10.4g, 0.05 mole) and toluene-p-sulphonylhydrazide (9.3g, 0.05 mole) in ethanol/...
ethanol (60ml) containing concentrated hydrochloric acid (1ml) was boiled under reflux for four hours. After cooling, the tacky greenish solid was filtered off and recrystallised from benzene/petroleum ether (60-80°) to give 2-benzoylstyrene toluene-p-sulphonylhydrazone (15.2g, 60%) m.p. 116-120° (decomp.).

(Found: C, 70.2; H, 5.4; N, 7.7. C_{22}H_{20}N_{2}O_{2}S requires C, 70.2; H, 5.4; N, 7.4%).

I.r. (nujol): 3170cm^{-1} (N-H).

N.m.r. spectrum: See Appendix.

F. 2-Benzoyl-4,5-dimethoxystyrene toluene-p-sulphonylhydrazone - A mixture of 2-benzoyl-4,5-dimethoxystyrene (2.3g, 0.0086 mole) and toluene-p-sulphonylhydrazide (1.73g, 0.0093 mole) in methanol (12ml) containing conc. hydrochloric acid (0.1ml) was boiled under reflux for 2.5 hours. The solution was concentrated by evaporation of the solvent and the product which crystallised out on standing was recrystallised from benzene/petroleum ether (60-80°) to give 2-benzoyl-4,5-dimethoxystyrene toluene-p-sulphonylhydrazone (2.62g, 70%) m.p. 178-180° (decomp.). (Found: C, 66.1; H, 5.6; N, 6.3. C_{24}H_{24}N_{2}O_{4}S requires C, 66.0; H, 5.5; N, 6.4%).

I.r. (nujol): 3180cm^{-1} (N-H).

N.m.r. spectrum: See Appendix.

G. trans-2-Formylstilbene toluene-p-sulphonylhydrazone - A mixture of trans-2-formylstilbene (3.29g, 0.0158 mole), toluene-p-sulphonylhydrazide (2.94g, 0.015 mole) in methanol/...
methanol (20ml), containing concentrated hydrochloric acid (0.1ml), was boiled under reflux for 2 min. After standing overnight, the product was filtered off and recrystallised from ethanol to give 2-formylstilbene toluene- \( \beta \)-sulphonylhydrazone (3.6g, 60%). m.p. 145-146.5° (Found: C, 70.3; H, 5.5; N, 7.4. \( \text{C}_{22}\text{H}_{20}\text{N}_{2}\text{O}_{2}\text{S} \text{ requires } \text{C}, 70.2; \text{H}, 5.5; \text{N}, 7.4\%)

I.r. (nujol): 3210cm\(^{-1}\) (N-H).

N.m.r. spectrum: See Appendix.

H. 2-Formyl-5-ethoxy-\( \beta,\beta \)-dimethylstyrene toluene-\( \beta \)-sulphonylhydrazone - 2-Formyl-5-ethoxy-\( \beta,\beta \)-dimethylstyrene (1.04g, 0.0051 mole) in methanol (5ml) was added to a warm solution of toluene-\( \beta \)-sulphonylhydrazide (0.95g, 0.0051 mole) in methanol (6ml) containing concentrated hydrochloric acid (2 drops). The solution was heated to 60° for ca. 3 min and left to stand overnight in the dark. The solid deposited was filtered off and recrystallised from ethanol to give 2-formyl-5-ethoxy-\( \beta,\beta \)-dimethylstyrene toluene-\( \beta \)-sulphonylhydrazone (1.27g, 67%). m.p. 120-122° (decomp.). (Found: C, 64.8; H, 6.6; N, 7.8. \( \text{C}_{20}\text{H}_{24}\text{N}_{2}\text{SO}_{3} \text{ requires } \text{C}, 64.5; \text{H}, 6.5; \text{N}, 7.5\%)

I.r. (nujol): 3150cm\(^{-1}\) (N-H).

N.m.r. spectrum: See Appendix.
SYNTHESIS OF 1H-2,3-BENZODIAZEPINES FROM THE CYCLISATION OF THE CORRESPONDING TOLUENE-p-SULPHONYLHYDRAZONE SODIUM SALTS

In general, the sodium salts were prepared by the method described below for 2-formyl-4,5-dimethoxystyrene toluene-p-sulphonylhydrazone. All solvents used in salt preparation and cyclisation reaction were removed under high vacuum on a rotary evaporator, keeping the bath temperature below 40°C. Cyclisations were carried out in the dark to prevent photolysis of the reactants and products.

A. 7,8-Dimethoxy-1H-2,3-benzodiazepine - Sodium (0.16g, 0.00695 mole) was dissolved in super-dry ethanol (20ml) and 2-formyl-4,5-dimethoxystyrene toluene-p-sulphonylhydrazone (2.50g, 0.00695 mole) added. The mixture was stirred for ca. 10 min. in the dark. The ethanol was then removed using a rotary evaporator with the water bath at room temperature. The residual salt was dried overnight in the reaction flask, under high vacuum and over phosphorus pentoxide. Dry dimethoxyethane (90ml) was then added, and the mixture heated to reflux under nitrogen in the dark. After a few minutes a white precipitate of sodium p-toluenesulphinate was observed. The reaction was continued for twenty minutes until t.l.c. monitoring (alumina/1:1 benzene:ether) showed that all the starting material had been consumed. After cooling, the mixture was filtered through/...
through a dry, weighed funnel and the precipitate washed thoroughly with dimethoxyethane. The solvent was then removed on a rotary evaporator using minimum heat to give a yellow oil (1.38g) which solidified on standing. This was recrystallised from ethanol to give 7,8-dimethoxy-1H-2,3-benzodiazepine (0.99g, 70%). m.p. 89-91°. (Found: C, 64.6; H, 6.0; N, 13.4. C_{11}H_{12}N_{2}O_{2} requires C, 64.7; H, 5.9; N, 13.7%).

N.m.r. spectrum: See Appendix.
Mass spectrum: See Appendix.

B. 1-Phenyl-1H-2,3-benzodiazepine - The sodium salt was prepared from sodium (0.25g, 0.108 mole) in dry ethanol (40ml), and 2-benzoylstyrene toluene-γ-sulphonylhydrazone (4.10g, 0.108 mole). After drying the sodium salt under the usual conditions, dry dimethoxyethane (120ml) was added and the mixture heated to reflux under nitrogen in the dark for 30 min. by which time all starting material had been consumed (t.l.c. alumina/benzene: ether 1:1). After cooling and filtration, the solvent was evaporated giving a yellow oil (2.2g) which crystallised on standing. This was recrystallised from ethanol to give 1-phenyl-1H-2,3-benzodiazepine (1.49g, 62%). m.p. 101-102°. (Found: C, 81.8; H, 5.5; N, 12.9. C_{15}H_{12}N_{2} requires C, 81.8; H, 5.5; N, 12.7%).

N.m.r. spectrum: See Appendix
Mass spectrum: See Appendix
C. 1-Pheny1-7,8-dimethoxy-1H-2,3-benzodiazepine - The sodium salt was prepared from sodium (0.125g, 0.054 mole), dry ethanol (25ml) and 2-benzoyl-4,5-dimethoxystyrene toluene-p-sulphonylhydrazone (2.35g, 0.054 mole). After drying the sodium salt under the usual conditions, dry dimethoxyethane (80ml) was added and the mixture heated to reflux under nitrogen in the dark. T.l.c. monitoring (alumina/benzene:ether) showed that all starting material had been consumed after 30 min. After cooling and filtration, the solvent was evaporated giving a yellow solid (1.46g). This was recrystallised from ethanol to give 1-phenyl-7,8-dimethoxy-1H-2,3-benzodiazepine (1.25g, 84%). m.p. 112-113°. (Found: C, 72.8; H, 5.8; N, 10.0. \( \text{C}_{17}\text{H}_{16}\text{N}_{2}\text{O}_{2} \) requires C, 72.8; H, 5.75; N, 10.0%).

N.m.r. spectrum: See Appendix.
Mass spectrum: See Appendix.

D. 4-Phenyl-1H-2,3-benzodiazepine - The sodium salt was prepared from sodium (0.183g, 0.00795 mole), dry ethanol (25ml) and 2-formylstilbene toluene-p-sulphonylhydrazone (3.0g, 0.00795 mole). After drying the sodium salt in the usual manner, dry dimethoxyethane (120ml) was added and the mixture heated to reflux under nitrogen in the dark. T.l.c. monitoring (alumina/benzene:ether) showed all starting material had been consumed after 20 min. After cooling, filtration and evaporation of solvent, a yellow solid (1.65g) was obtained/...
obtained. This was recrystallised from ethanol to give 4-phenyl-1H-2,3-benzodiazepine (1.25g, 71%). m.p. 132-133°. (Found: C, 81.6; H, 5.6; N, 12.5. \( \text{C}_{15}\text{H}_{12}\text{N}_2 \) requires C, 81.8; H, 5.5; N, 12.7%).

N.m.r. spectrum: See Appendix.

Mass spectrum: See Appendix.

E. 1-Ethyl-1H-2,3-benzodiazepine - The sodium salt was prepared from sodium (0.23g, 0.01 mole), dry ethanol (25ml) and 2-propionylstyrene toluene-p-sulphonylhydrazone (3.28g, 0.01 mole). After drying the sodium salt in the usual manner, dry dimethoxyethane (120ml) was added and the mixture heated to reflux in the dark under nitrogen. T.l.c. monitoring (alumina/benzene:ether) showed that all starting material had been consumed after 2 h. After cooling and filtration, the solvent was evaporated giving a yellow oil (1.68g) which solidified on standing overnight. This was recrystallised from methanol with some difficulty to give 1-ethyl-1H-2,3-benzodiazepine (1.07g, 68%). m.p. 40-41°. (Found: C, 76.2; H, 7.2; N, 16.15. \( \text{C}_{11}\text{H}_{12}\text{N}_2 \) requires C, 76.7; H, 7.0; N, 16.3%).

N.m.r. spectrum: See Appendix

Mass spectrum: See Appendix

F. 1-Methyl-1H-2,3-benzodiazepine - The sodium salt was prepared from sodium (0.27g, 0.118 mole) in dry ethanol (30ml) and 2-acetylstyrene toluene-p-sulphonylhydrazone (3.72g 0.118 mole). After drying/...
drying in the usual manner, the sodium salt was heated under reflux for 2 h under nitrogen in the dark in dry dimethoxyethane (100ml). After cooling, filtering and removal of solvent, a yellow oil (1.78g) remained. This was dissolved in a little warm ethanol and left at -20° for several days giving crystals of pure 1-methyl-1H-2,3-benzodiazepine (0.96g, 64%). m.p. 47°. (Found: C, 75.7; H, 6.5; N, 17.8. C¹⁰H¹⁰N₂ requires C, 75.9; H, 6.4; N, 17.7%).

N.m.r. spectrum: See Appendix.
Mass spectrum: See Appendix.

G. 1-Methyl-7,8-dimethoxy-1H-2,3-benzodiazepine - The sodium salt was prepared from sodium (0.227g, 0.00985 mole) in dry ethanol (30ml) and 2-acetyl-4,5-dimethoxy-styrene toluene-p-sulphonylhydrazone (3.68g 0.00985 mole). After drying in the usual manner, dry cyclohexane (120ml) was added and the mixture boiled under reflux under nitrogen in the dark. T.l.c. (alumina/benzene:ether 1:1) showed that all of the starting material had been consumed after 8 h. After cooling, the reaction was filtered and the solvent evaporated, giving an orange solid (1.98g). This was recrystallised from ethanol giving 1-methyl-7,8-dimethoxy-1H-2,3-benzodiazepine (1.48g, 66%). m.p. 113-114°. (Found: C, 65.8; H, 6.6; N, 12.6. C¹²H¹₃N₂O₂ requires C,66.0; H, 6.5; N, 12.8%).

N.m.r. spectrum: See Appendix.
Mass spectrum: See Appendix.
A. 1-Phenyl-5H-2,3-benzodiazepine - This was prepared by two methods:

(a) The sodium salt of 2-benzoylstyrene toluene-p-sulphonylhydrazone (3.76g, 0.01 mole) was prepared in the usual way, but using ca. 5% excess sodium, and heated under reflux under nitrogen in dry toluene (120ml) for 12 h. The mixture was washed with water (2 x 50ml), and the organic layer dried over magnesium sulphate. After removal of the solvent under high vacuum, an orange solid (2.10g) was obtained. This was recrystallised from ethanol to give 1-phenyl-5H-2,3-benzodiazepine (1.50g, 69%) m.p. 152°-153°. (Found: C, 81.9; H, 5.6; N, 12.6. C_{15}H_{12}N_{2} requires: C, 81.8; H, 5.5; N, 12.7%).

(b) 1-Phenyl-1H-2,3-benzodiazepine (0.050g, 0.00023 mole) and anhydrous potassium acetate (0.050g) were heated under reflux under nitrogen in ethanol (20ml) in the dark for 6 days. The solvent was removed on a rotary evaporator and the product washed with water (10ml), and extracted into benzene (30ml). After drying over magnesium sulphate, the benzene was evaporated to give a pale solid (0.035g) which was recrystallised from ethanol to give 1-phenyl-5H-2,3-benzodiazepine (0.023g, 46%) m.p. 150-152°.

N.m.r. spectrum: See Appendix.
Mass spectrum: See Appendix.
B. 1-**Phenyl-7,8-dimethoxy-5H-2,3-benzodiazepine** - This was prepared by two methods:

(a) From 2-benzoyl-4,5-dimethoxy styrene toluene-\(\pi\)-sulphonylhydrazone (2.0g, 0.0046 mole) with a reaction time of 7 h, as described previously for 1-phenyl-5H-2,3-benzodiazepine. The crude product (1.2g) was recrystallised from ethanol to give the 5H-benzodiazepine (0.74g, 57%) m.p. 162-163\(^{0}\). (Found: C, 73.1; H, 5.9; N, 9.8. C\(_{17}\)H\(_{16}\)N\(_2\)O\(_2\) requires C, 72.8; H, 5.75; N, 10.0%).

(b) 1-Phenyl-7,8-dimethoxy-1H-2,3-benzodiazepine (0.20g, 0.00072 mole) was dissolved in dry ethanol (50ml) containing an equimolar amount of sodium ethoxide. The solution was boiled under reflux under nitrogen in the dark for 3 h. The solvent was removed on a rotary evaporator and benzene (60ml) added. The solution was washed with water (2 x 20ml), dried and evaporated to give a pale yellow solid (0.19g) which was recrystallised from ethanol/petroleum ether to give the 5H-benzodiazepine (0.165g, 82%) as colourless crystals, m.p. 162-163\(^{0}\).

N.m.r. spectrum: See Appendix.

Mass spectrum: See Appendix.

C. 1-p-**Tolyl-4-phenyl-5H-2,3-benzodiazepine** -

1-p-Tolyl-4-phenyl-1H-2,3-benzodiazepine\(^*\) (0.25g, 0.0008 mole) dissolved in dry ethanol (50ml) containing an equimolar amount of sodium ethoxide was boiled under reflux under nitrogen in the dark for 4 h. On cooling/...
cooling, colourless crystals were deposited (0.22g) m.p. 256-257°. These were recrystallised from benzene/ethanol to give the 5H-benzodiazepine (0.186g, 84%) m.p. 269-270°. (Found: C, 84.8; H, 5.9; N, 9.0.
C_{22}H_{18}N_{2} requires C, 85.1; H, 5.85; N, 9.0%). In a duplicate reaction carried out in the absence of base the 1H-benzodiazepine was unchanged.

**N.m.r. spectrum:** See Appendix.
**Mass spectrum:** See Appendix.

*This compound was prepared by Mr. P.B. Thorogood.

D. **1-Methyl-4-phenyl-5H-2,3-benzodiazepine** - 1-Methyl-4-phenyl-1H-2,3-benzodiazepine (0.25g, 0.0011 mole) was dissolved in n-propanol (25ml). The solution was boiled under reflux under nitrogen in the dark and monitored by t.l.c. (alumina/benzene) which showed the appearance of a second slow-moving spot. After a reaction time of 28 days, most of the 1H-diazepine had been consumed. The reaction was stopped, cooled and the solution concentrated by evaporation, resulting in crystallisation of a white solid (0.135g) m.p. 136-140°. On recrystallisation from ethanol, this afforded 1-methyl-4-phenyl-5H-2,3-benzodiazepine (0.12g, 48%) m.p. 136-140°. (Found: C, 82.1; H, 6.15; N, 12.1. C_{16}H_{14}N_{2} requires C, 82.0; H, 6.0; N, 12.0%).

**N.m.r. spectrum:** See Appendix.
**Mass spectrum:** See Appendix.
PHOTOLYSIS OF 1H-2,3-BENZODIAZEPINES

The general procedure for photolysis of the series of 1H-2,3-benzodiazepines was as follows:

A dilute solution of the 1H-benzodiazepine in dry dimethoxyethane or dry ether was irradiated at 0° in the Hanovia reaction vessel for 5-10 min. under nitrogen. The reaction was monitored by disappearance of the yellow 1H-benzodiazepine colour and by t.l.c. (alumina/benzene:ether 1:1). The products were usually isolated in an analytically pure state by low temperature evaporation of the solvent. Prolonged irradiation gave complex mixtures of products. Dry cyclohexane was also used as solvent in some cases, but many benzodiazepines proved to be only sparingly soluble in it.

A. 1-Methyl-7,8-dimethoxy-1H-2,3-benzodiazepine -

The diazepine (0.3g, 0.0014 mole) was dissolved in dry cyclohexane (150ml). The reaction was complete after 10 min. giving 4-methyl-6,7-dimethoxy-4H-[1,2]diazeto[3,2-a]isoindole. (0.3g, quantitative) as a white solid m.p. 116-119° (decomp.). (Found: C, 65.9; H, 6.5; N, 12.4. C_{12}H_{14}N_{2}O_{2} requires C, 66.0; H, 6.5; N, 12.8%). Attempted recrystallisation resulted in extensive decomposition. Examination of the product by t.l.c. showed only one spot.

I.r. (nujol): 1600cm⁻¹ (C=N).

N.m.r. spectrum: See Appendix.

Mass spectrum: See Appendix.
**B. 7,8-Dimethoxy-1H-2,3-benzodiazepine** - The reaction was carried out using the benzodiazepine (0.8g, 0.0039 mole) dissolved in dry dimethoxyethane (200ml) and was complete after 10 min giving 6,7-dimethoxy-4H-1,2]diazeto[3,2-a]isoindole. (0.76g, 95%) m.p. 119-122°.

(Found: C, 64.7; H, 5.7; N, 13.5. \(C_{11}H_{12}N_2O_2\) requires C, 64.7; H, 5.9; N, 13.7%). The compound, a grey solid darkened rapidly on standing at room temperature.

I.r. (nujol): 1600cm\(^{-1}\) (C=N).

N.m.r. spectrum: See Appendix.

Mass spectrum: See Appendix.

**C. 1-Phenyl-1H-2,3-benzodiazepine** - The reaction was carried out using the benzodiazepine (0.20g, 0.0009 mole) dissolved in dry dimethoxyethane (100ml) and was complete after 10 min giving 4-phenyl-4H-1,2]diazeto[3,2-a]isoindole (0.184g, 92%) m.p. 94-97° (decomp.). (Found: C, 82.1; H, 5.6; N, 12.4. \(C_{15}H_{12}N_2\) requires C, 81.8; H, 5.5; N, 12.7%).

N.m.r. spectrum: See Appendix.

Mass spectrum: See Appendix.

**D. 1-Methyl-1H-2,3-benzodiazepine** - The reaction was carried out using the benzodiazepine (0.1g, 0.00063 mole) dissolved in dry ether (150ml). The reaction was complete in 5 min giving 4-methyl-4H-1,2]diazeto[3,2-a]isoindole (0.093g, 93%) m.p. 77-81° (decomp.). (Found: C, 76.1; H, 6.7; N, 17.6. \(C_{10}H_{10}N_2\) requires C, 75.9; H, 6.4; N, 17.7%).
B. 1-Methyl-4-phenyl-1H-2,3-benzodiazepine - The reaction was carried out using the benzodiazepine (0.5g, 0.0021 mole) dissolved in dry dimethoxyethane (120ml) and was complete after 10 min giving 1-phenyl-4-methyl-4H-[1,2]diazeto[3,2-a]isoindole (0.5g, quantitative) m.p. 97-100\(^\circ\) (decomp.) as a white solid. (Found: C, 82.0; H, 6.0; N, 12.0. \(\text{C}_{16}\text{H}_{14}\text{N}_{2}\) requires C, 82.0; H, 5.8; N, 11.7%).

N.m.r. spectrum: See Appendix.
Mass spectrum: See Appendix.

F. 4-Phenyl-1H-2,3-benzodiazepine - The reaction was carried out using the diazepine (0.4g, 0.0018 mole) dissolved in dry dimethoxyethane (200ml) and was complete after 10 min giving 1-phenyl-4H-[1,2]diazeto[3,2-a]isoindole. (0.38g, 95%) m.p. 77-83\(^\circ\) (decomp.) as a colourless solid. (Found: C, 81.7; H, 5.7; N, 12.3. \(\text{C}_{15}\text{H}_{12}\text{N}_{2}\) requires C, 81.8; H, 5.45; N, 12.7%).

N.m.r. spectrum: See Appendix.
Mass spectrum: See Appendix.
PHOTOLYSIS OF 5H-2,3-BENZODIAZEPINES

A. 1-Phenyl-5H-2,3-benzodiazepine - The 5H-diazepine (0.264g, 0.00012 mole) was dissolved in dry ether (150ml) and irradiated at 0° for 15 min under dry nitrogen. T.l.c. (alumina/benzene) showed that starting material was still present along with a fast moving spot Rf ~ 0.9. The reaction was continued for 2 h when t.l.c. showed that all of the diazepine had been consumed giving a single product spot. The solvent was removed in vacuo giving a yellow oil (0.241g). This was redistilled giving a colourless liquid (0.151g, 72%) b.p. 122-123° at 0.7mm Hg. This had i.r. and n.m.r. spectra identical to authentic 3-phenylindene.

N.m.r. (CDCl₃): \( \gamma 2.3-2.95 \) (m,9H), 3.5 (t,1H) and 6.6 (d,2H).

Mass spectrum: \( m^+ 192 \).
ATTEMPTED CYCLISATION OF 2-FORMYL-5-ETHOXY-PP-DIMETHYLSTYRENE TOLUENE-p-SULPHONYLHYDRAZONE SODIUM SALT

A. Decomposition in dimethoxyethane - The sodium salt was prepared from sodium (0.23g, 0.01 mole) in ethanol (25ml) and 2-formyl-5-ethoxy-PP,PP-dimethylstyrene toluene-p-sulphonylhydrazone (3.72g, 0.01 mole). After drying in the usual manner, dry dimethoxyethane (100ml) was added and the mixture boiled under reflux under nitrogen. After 5 min, white solid began to precipitate and a red colouration developed. This began to fade after 0.5 h, and had disappeared after 3 h. The reaction was worked up in the normal manner and a yellow oil (1.74g) was obtained. T.l.c. benzene/alumina indicated three major products. These were separated by chromatography on a 24" x 1" alumina column eluting with benzene.

Fraction I - This was a colourless solid (0.252g) m.p. 65-68°. Recrystallisation from petroleum ether (40-60°) gave colourless crystals (0.185g) m.p. 84-85°. This was assigned the structure bis-(2-PP,PP-dimethylvinyl-4-ethoxy) trans-stilbene on n.m.r., mass spectral and analytical data. (Found: C, 82.6; H, 8.75; C_{26}H_{30}O_{2} requires C, 82.9; H, 8.6%).

N.m.r. spectrum: See Appendix.
Mass spectrum: See Appendix.

Fraction II - This was a yellow solid (0.457g) m.p. 133-135°. Recrystallisation from ethanol afforded (0.40g) m.p. 141°. This was assigned the structure
bis-(2-\(\beta\),\(\beta\)-dimethylvinyl-4-ethoxybenzaldehyde)azine on n.m.r., mass spectral and analytical data. (Found: C, 76.8; H, 8.2; N, 6.9. \(\text{C}_{26}\text{H}_{32}\text{N}_{2}\text{O}_{2}\) requires C, 77.2; H, 8.0; N, 6.9%).

N.m.r. spectrum: See Appendix.
Mass spectrum: See Appendix.

**Fraction III** - This was a colourless semi-solid (0.561g) which on further purification by column chromatography gave colourless crystals (0.47g) m.p. 98-102°. These were recrystallised from ethanol to give needles (0.32g) m.p. 117-118°. This was assigned the structure \(\text{N}-(2-\(\beta\),\(\beta\)-dimethylvinyl-4-ethoxy)benzyl-2-formyl-5-ethoxy-\(\beta\),\(\beta\)-dimethylstyrene toluene-\(p\)-sulphonylhydrazone on n.m.r., mass spectral and analytical data*.* (Found: C, 70.8; H, 7.3; N, 5.0. \(\text{C}_{33}\text{H}_{40}\text{N}_{2}\text{SO}_{4}\) requires C, 70.7; H, 7.2; N, 5.0%).

N.m.r. spectrum: See Appendix.
Mass Spectrum: See Appendix.

*The compound gave a positive Lassaigne's test for sulphur.

The residue (0.357g) contained mainly unseparable material along with a little of the azine and the toluene-\(p\)-sulphonylhydrazone mentioned above, as detected by n.m.r. No cyclisation product was obtained from the reaction.
ATTEMPTED THERMAL CYCLISATION OF trans-STILBENE-2-AZIDE

A. Decomposition in dimethoxyethane - trans-Stilbene-2-azide (0.2g, 0.0009 mole) was dissolved in dry dimethoxyethane (25ml) and heated to reflux under nitrogen. Examination by t.l.c. (alumina/benzene) at intervals from 15 min to 20 h did not reveal any compound other than starting material.

B. Decomposition in toluene - trans-Stilbene-2-azide (2.0g, 0.009 mole) was dissolved in dry toluene (150ml) and heated to reflux under nitrogen. After 16 h, t.l.c. (alumina/benzene) showed a second spot $R_f = 0.6$. At the same time a duplicate thermolysis was run in ethylene glycol following Sundberg's$^{107}$ method and 2-phenylindole, which is the thermolysis product in this case was found to correspond to the second spot on t.l.c. Confirmation was obtained by leaving the azide to decompose completely over 21 days in toluene. T.l.c. at no time showed any other spots to be present. The toluene was evaporated and the solid obtained recrystallised twice from ethanol, giving 2-phenylindole (1.6g, 92%) m.p. 187° (lit. $^{107}$, 187-188°).

I.r. (nujol): 3430cm$^{-1}$ (N-H).

N.m.r. (CDCl$_3$): $\gamma$ 1.85 (bs,1H), 2.4-3.0 (m,9H) and 2.28 (d,1H).
THERMOLYSIS STUDIES

I. 1-Phenyl-1H-2,3-benzodiazepine.

A. Decomposition in toluene - 1-Phenyl-1H-2,3-benzodiazepine (0.2g, 0.0009 mole) was dissolved in dry toluene and boiled under reflux under nitrogen in the dark for ca. 2 days. T.l.c. (alumina/benzene:ether 1:1) showed that all of the diazepine had been consumed. The solvent was removed on a rotary evaporator giving a dark brown oil (170mg). Distillation of this afforded a yellow oil (84mg), b.p. 120-122° at 0.5mm Hg.

N.m.r. (CDCl₃): \( \gamma \) 2.3-2.95 (m,9H), 3.5 (t,1H) and 6.55 (d,2H).

Mass spectrum: Parent ion had mass 192.093715. \( \text{C}_{15}\text{H}_{12} \) requires 192.093896.

From this evidence, the compound was deduced to be 3-phenylindene (lit.\(^{109}\) b.p. 117-119° at 0.49mm Hg). The n.m.r. spectrum is identical to that reported\(^{109}\) for 3-phenylindene.

B. Kinetics of decomposition in diphenyl ether - The rate of decomposition in diphenyl ether (b.p. 258-259° at 760mm Hg) was determined by n.m.r. spectroscopy by measuring the rate of disappearance of the singlet at \( \gamma 6.1 \) (1H) and the appearance of the doublet at \( \gamma 6.6 \) (2H), all integrations being done in triplicate. 2,6-dichlorotoluene (b.p. 198° at 760mm Hg) provided a convenient internal standard giving a singlet at \( \gamma 7.7 \).
It was distilled and dried over calcium chloride before use.

Experimental procedure - The diazepine (ca. 30mg) was accurately weighed into an n.m.r. tube and a standard solution of 2,6-dichlorotoluene in diphenyl ether added. The integrals at zero time were then taken. The tube was then placed in a thermostatically controlled oil-bath (temperature variation ± 0.15°) and the clock started. The tube was equipped with a plastic cap which allowed escape of nitrogen produced in the reaction while preventing entry of moisture or dust. At fixed time intervals, the tube was removed, the reaction quenched by plunging it into ice-water, and the n.m.r. spectrum taken. Due to the small scale of the reaction, warming up and cooling down was rapid. Each run was carried out in duplicate and results were calculated as shown in the tables. Disappearance of the diazepine with time was found to give a straight line for a first order plot (Fig. XXVII). The experiment was repeated at a higher temperature giving two rate constants from which the activation energy for the reaction could be calculated. (See results section).

The yield of 3-phenylindene was calculated to be ca. 87% using the infinity readings.
Fig XXVII

$T = 383.7^\circ K$
### TABLE I - KINETIC DATA FOR 1-PHENYL-1H-2,3-BENZODIAZEPINE THERMOLYSIS

\[ T = 383.7^\circ K \]

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<th>IND. (2H)</th>
<th>MAR.</th>
<th>DIAZ. MAR.</th>
<th>IND. MAR.</th>
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TABLE II - KINETIC DATA FOR 1-PHENYL-1H-2,3-BENZODIAZEPINE THERMOLYSIS

\[ T = 383.7^\circ K \]

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\[ \log \frac{A_o}{A_t} \]

\[ T = 393.3^\circ K \]
TABLE III - KINETIC DATA FOR 1-PHENYL-1H-2,3-BENZODIAZEPINE THERMOLYSIS

\[ T = 393.3^\circ K \]

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TABLE IV - KINETIC DATA FOR 1-PHENYL-1H-2,3-BENZODIAZEPINE THERMOLYSIS

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<td>.4803</td>
<td>.7193</td>
<td>.8399</td>
<td>1.823</td>
<td>.2608</td>
</tr>
<tr>
<td>191</td>
<td>17.0</td>
<td>43.7</td>
<td>44.2</td>
<td>.3846</td>
<td>.9887</td>
<td>.8789</td>
<td>2.277</td>
<td>.3573</td>
</tr>
<tr>
<td>243</td>
<td>12.2</td>
<td>47.8</td>
<td>42.0</td>
<td>.2905</td>
<td>1.1381</td>
<td>.8596</td>
<td>3.014</td>
<td>.4792</td>
</tr>
<tr>
<td>283</td>
<td>9.5</td>
<td>51.5</td>
<td>39.5</td>
<td>.2405</td>
<td>1.3038</td>
<td>.8914</td>
<td>3.641</td>
<td>.5612</td>
</tr>
</tbody>
</table>
RESULTS

<table>
<thead>
<tr>
<th>$k_1$ min$^{-1}$</th>
<th>Temp. °K</th>
<th>Run 1</th>
<th>Run 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>383.7</td>
<td>1.64x10$^{-3}$</td>
<td>1.56x10$^{-3}$</td>
<td></td>
</tr>
<tr>
<td>393.3</td>
<td>4.48x10$^{-3}$</td>
<td>4.58x10$^{-3}$</td>
<td></td>
</tr>
</tbody>
</table>

Error in $k$ is ± 5%. (from extreme gradient in graph).

Using the mean $k$ values obtained above:

$k_1 = 1.60x10^{-3}$ min$^{-1}$

$k_2 = 4.53x10^{-3}$ min$^{-1}$

Plotting log $k$ against inverse temperature gives a gradient of $-E_a/2.303R$ ($R =$ gas constant)

This gives $E_a = 137.5 \pm 13$ k J mole$^{-1}$

$(32.7 \pm 3$ k cal mole$^{-1}$)

From this value of $E_a$ it is possible to calculate the enthalpy $\Delta H^\pm$ and the entropy $\Delta S^\pm$ of the reaction by means of the following equations.

\[ E = H + RT \quad (1.) \]

\[ \Delta S^\pm/4.576 = \log k - 10.753 - \log T + E/4.576T \quad (2.) \]

where $k =$ rate constant in sec$^{-1}$.

Thus $\Delta H^\pm = 140.7 \pm 12.6$ k J mole$^{-1}$

$(33.5 \pm 3$ k cal mole$^{-1}$)

$\Delta S^\pm = + 14.66 \pm 0.28$ J deg$^{-1}$ mole$^{-1}$

$(+ 3.49 \pm 0.1$ cal deg$^{-1}$ mole$^{-1}$)
Sources of error

By far the largest source of error is in the measurement of n.m.r. integration values ($\pm 0.5$ squares). This error becomes more significant as the concentration of reactant diminishes. Errors in timing and temperature are small in comparison and can be disregarded.
B. 4-Phenyl-4H-[1,2]diazeto[3,2-a]isoindole - This compound was prepared by photolysis of 1-phenyl-1H-2,3-benzodiazepine. The sample (0.10g, 0.00045 mole) was placed in a boat in the heating inlet of a pyrolysis apparatus and the apparatus evacuated to 0.005mm Hg. The furnace was heated to 500°, and the inlet very gently heated to 60°. After 2 days a white solid had collected outside the liquid nitrogen cold trap. On dissolving the solid in ether, a fluorescent blue solution was obtained from which the white solid could not be reisolated. A small sample of the solid had a parent ion mass 193.089285. $C_{14}H_{11}N$ requires 193.089145. N.m.r. (CDCl$_3$) on the total product showed peaks at $\gamma3.4$ (t, 1H) and 6.5 (d, 2H) indicating the presence of 3-phenylindene in the reaction mixture. An attempt to trap any 1-phenylisoindole in the product by mixing the reaction solution with a slight excess of tetra-cyanoethylene was unsuccessful.

C. 1-Phenyl-4H-[1,2]diazeto[3,2-a]isoindole - A sample (30mg) was dissolved in diphenyl ether (0.5ml) in an n.m.r. tube and heated to 200° for several minutes until all of the starting material decomposed. The reaction mixture was analysed by g.l.c. (2% CAR 90°). Benzonitrile was found to be present in the reaction mixture, and this was confirmed using a g.l.c. coupled to a mass spectrometer with an injection heater temperature of 240°. The component corresponding to benzonitrile gave a mass spectrum identical with that of authentic benzonitrile.
D. 1-Phenyl-4-methyl-4H[1,2]diazeto[3,2-a]isoindole-

Quantitative measure of benzonitrile extrusion from thermolysis in diphenyl ether - The sample (0.0700g, 0.0003 mole) in diphenyl ether (10ml) was sealed in a glass tube and left in an oven at 190° for 20 h. Standard solutions for a calibration graph were then made up using benzonitrile and naphthalene as an internal standard.

<table>
<thead>
<tr>
<th>Naphthalene (g)</th>
<th>Benzonitrile (g)</th>
<th>Diphenyl ether (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>.1920</td>
<td>.1560</td>
<td>25</td>
</tr>
<tr>
<td>.1094</td>
<td>.1433</td>
<td>25</td>
</tr>
<tr>
<td>.2102</td>
<td>.0796</td>
<td>25</td>
</tr>
</tbody>
</table>

These were analysed on a PYE 104 g.l.c. (5% CAR 122°) using an integrator. A plot of area standard/area marker against weight standard/weight marker was a straight line.

After cooling, the tube was opened and naphthalene (0.0327g) dissolved in the reaction solution. T.l.c. (alumina/benzene:ether 1:1) showed that all of the starting material had been used up. Several samples of the reaction mixture were then analysed by g.l.c. and the mean value of As/Am obtained. From the graph the yield of benzonitrile in the thermolysis experiment was found to be 31.4%
### APPENDIX I

**1H-2,3- Benzodiazepines**

**Mass Spectral Data**

<table>
<thead>
<tr>
<th>Compound</th>
<th>m/e (relative abundance %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X = H Y = H Z = OMe</td>
<td>39(43), 50(33), 51(47), 62(22), 63(58), 64(25), 77(44), 89(65), 90(100), 91(22), 102(29), 103(53), 105(75), 115(56), 118(93), 131(22), 133(83), 161(92), 162(14), 176(100), 177(17), 204(31).</td>
</tr>
<tr>
<td>X = H Y = Ph Z = H</td>
<td>114(15), 164(20), 189(24), 191(91), 192(100), 193(15), 220(4).</td>
</tr>
<tr>
<td>X = H Y = Ph Z = OMe</td>
<td>44(11), 115(15), 165(31), 178(14), 191(13), 194(12), 206(16), 209(10), 221(15), 237(37), 252(100), 280(5).</td>
</tr>
<tr>
<td>X = Ph Y = H Z = H</td>
<td>115(20), 164(20), 189(21), 191(80), 192(100), 193(16), 220(1).</td>
</tr>
<tr>
<td>X = H Y = CH₃CH₂ Z = H</td>
<td>115(37), 127(12), 128(37), 129(100), 130(12), 144(29), 172(19).</td>
</tr>
<tr>
<td>X = H Y = CH₃ Z = H</td>
<td>39(12), 51(24), 63(18), 64(25), 77(12), 89(10), 115(100), 116(22), 128(25), 129(89), 130(84), 131(15), 158(42).</td>
</tr>
<tr>
<td>X = H Y = CH₃ Z = OMe</td>
<td>51(40), 63(33), 77(40), 89(20), 91(46), 103(40), 104(37), 107(26), 115(53), 117(33), 131(32), 132(57), 133(17), 147(53), 175(46), 176(33), 189(40), 190(100), 191(33), 204(32), 218(23).</td>
</tr>
</tbody>
</table>
## APPENDIX II

**5H-2,3- Benzodiazepines**

### Mass Spectral Data

<table>
<thead>
<tr>
<th>Compound</th>
<th>m/e (relative abundance %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$X = \text{H} \quad Y = \text{Ph} \quad Z = \text{H}$</td>
<td>51(17), 77(28), 89(26), 90(23), 91(13), 115(13), 116(17), 165(32), 179(19), 191(36), 192(55), 193(68), 194(36), 219(34), 220(100).</td>
</tr>
<tr>
<td>$X = \text{H} \quad Y = \text{Ph} \quad Z = \text{OMe}$</td>
<td>51(12), 77(21), 165(15), 237(12), 238(14), 249(10), 252(19), 253(16), 280(100).</td>
</tr>
<tr>
<td>$X = \text{Ph} \quad Y = \text{p-Tolyl} \quad Z = \text{H}$</td>
<td>91(24), 120(20), 121(23), 165(12), 206(22), 207(53), 208(11), 282(20), 310(100).</td>
</tr>
<tr>
<td>$X = \text{Ph} \quad Y = \text{CH}_3 \quad Z = \text{H}$</td>
<td>89(20), 90(11), 103(11), 116(35), 130(50), 131(37), 234(100).</td>
</tr>
</tbody>
</table>
### APPENDIX III

**1H-2,3-Benzodiazepines**

**1H N.m.r. Spectral Data**  
Solvent: CDCl$_3$

<table>
<thead>
<tr>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>$\gamma_A$ (Hz)</th>
<th>$\gamma_b$ (Hz)</th>
<th>$\gamma_Y$ (Hz)</th>
<th>$\gamma_Z$</th>
<th>Aromatic Protons</th>
<th>Temp</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>OMe</td>
<td>3.40, 1H</td>
<td>1.91, 1H</td>
<td>7.24, 1H</td>
<td>3.72, 1H</td>
<td>9</td>
<td>6.14bs, 6H</td>
</tr>
<tr>
<td>H</td>
<td>CH$_3$</td>
<td>H</td>
<td>3.34, 1H</td>
<td>1.90, 1H</td>
<td>7.19, 1H</td>
<td>7.70, 3H</td>
<td>6</td>
<td>2.3-2.8m, 4H</td>
</tr>
<tr>
<td>H</td>
<td>CH$_3$CH$_2$</td>
<td>H</td>
<td>3.36, 1H</td>
<td>1.90, 1H</td>
<td>6.7-7.1m, 1H</td>
<td>8.77t, CH$_3$</td>
<td>7.2-7.4m, CH$_2$</td>
<td>2.3-2.8m, 4H</td>
</tr>
<tr>
<td>H</td>
<td>Ph</td>
<td>H</td>
<td>3.19, 1H</td>
<td>1.75, 1H</td>
<td>6.11s, 1H</td>
<td>2.0-3.1m, 9H</td>
<td>28°C</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>Ph</td>
<td>OMe</td>
<td>3.30, 1H</td>
<td>1.84, 1H</td>
<td>6.29, 1H</td>
<td>6.14s, 3H</td>
<td>2.1-2.7m, 5H; 6.40s, 3H</td>
<td>28°C</td>
</tr>
<tr>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>3.05s, 1H</td>
<td>6.95, 1H</td>
<td>3.60, 1H</td>
<td>6.15s, 3H</td>
<td>3.16s, 1H; 6.24s, 3H</td>
<td>28°C</td>
</tr>
<tr>
<td>H</td>
<td>CH$_3$</td>
<td>OMe</td>
<td>3.60, 1H</td>
<td>2.08, 1H</td>
<td>7.52, 1H</td>
<td>7.78, 3H</td>
<td>6</td>
<td>3.16s, 1H; 3.27s, 1H</td>
</tr>
</tbody>
</table>

* Spectrum run in CC1$_4$
### APPENDIX IV

**5H-2,3- Benzodiazepines**

\(^1\text{H N.m.r. Spectral Data (28}°\text{)}\

Solvent: CDCl\(_3\)

<table>
<thead>
<tr>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>(\gamma_X)</th>
<th>(\gamma_Y)</th>
<th>(\gamma_Z)</th>
<th>Aromatic Protons</th>
<th>(\gamma_{CH_2})</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Ph</td>
<td>H</td>
<td>In aromatic multiplet</td>
<td></td>
<td>2.2-2.8m, 1CH</td>
<td>AB part of ABX; (\gamma_A = 6.58), (\gamma_B = 6.98) J(<em>{AB} = 12.5\text{Hz}); J(</em>{AX} = J_{BX} = 5\text{Hz})</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ph</td>
<td>OMe</td>
<td>In aromatic multiplet</td>
<td>6.09s, 3H</td>
<td>2.2-3.3m, 8H</td>
<td>AB part of ABX; (\gamma_A = 6.65), (\gamma_B = 7.05) J(<em>{AB} = 12.5\text{Hz}); J(</em>{AX} = J_{BX} = 5\text{Hz})</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CH(_3)</td>
<td>H</td>
<td>7.43s, 3H</td>
<td></td>
<td>2.0-2.8m, 9H</td>
<td>AB : (\gamma_A = 5.97), (\gamma_B = 6.87) J(_{AB} = 12.5\text{Hz})</td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>–Tolyl</td>
<td>H</td>
<td>7.62s, 3H+ aromatics</td>
<td></td>
<td>2.0-2.8m, 13H</td>
<td>AB : (\gamma_A = 5.87), (\gamma_B = 6.75) J(_{AB} = 12.5\text{Hz})</td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX V

4H-\([1,2]\) Diazo\([3,2-a]\) isoindoles

Mass Spectral Data

<table>
<thead>
<tr>
<th>Compound</th>
<th>(m/e) (relative abundance %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(X = H\ Y = CH_3\ Z = OMe)</td>
<td>51(33), 77(42), 78(22), 89(22), 90(16), 91(27), 103(24), 104(27), 105(18), 107(33), 132(25), 133(42), 147(35), 148(40), 175(40), 176(78), 177(24), 190(42), 191(100), 203(12), 218(22).</td>
</tr>
<tr>
<td>(X = H\ Y = H\ Z = OMe)</td>
<td>45(53), 63(18), 64(13), 77(11), 89(12), 90(15), 91(13), 119(16), 132(12), 133(15), 134(26), 161(15), 162(18), 177(100), 204(28).</td>
</tr>
<tr>
<td>(X = H\ Y = Ph\ Z = H)</td>
<td>89(10) 90(15), 165(27), 191(20), 192(20), 193(100), 220(22).</td>
</tr>
<tr>
<td>(X = Ph\ Y = CH_3\ Z = H)</td>
<td>51(18) 77(20), 89(21), 90(28), 103(24), 116(85), 130(88), 131(100), 234(29).</td>
</tr>
<tr>
<td>(X = Ph\ Y = H\ Z = H)</td>
<td>89(30), 90(100), 91(13), 103(97), 115(10), 116(10), 117(85), 118(27), 165(16), 191(25), 192(26), 220(83).</td>
</tr>
<tr>
<td>(X = H\ Y = CH_3\ Z = H)</td>
<td>89(11), 90(16), 115(20), 116(19), 129(18), 130(60), 131(100), 143(10), 158(26).</td>
</tr>
</tbody>
</table>
APPENDIX VI
4H- [1,2] Diazeto [3,2-a] isoindo1es

$^1$H N.m.r. Spectral Data at 28°

<table>
<thead>
<tr>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>$\gamma_A$ (Hz)</th>
<th>$\gamma_B$ (endo) (Hz)</th>
<th>$J_{AB}$ (Hz)</th>
<th>$\gamma_Y$ (exo) (Hz)</th>
<th>$J_{BY}$ (Hz)</th>
<th>$\gamma_Z$ (Hz)</th>
<th>Aromatic Protons</th>
<th>Solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>OMe</td>
<td>4.45bs, 1H</td>
<td>2.26d, 1H</td>
<td>1</td>
<td>5.50d, 1H</td>
<td>15</td>
<td>6.61s, 3H</td>
<td>3.71s, 1H</td>
<td>C$_6$D$_6$</td>
</tr>
<tr>
<td>H</td>
<td>CH$_3$</td>
<td>OMe</td>
<td>4.03d, 1H</td>
<td>1.79s, 1H</td>
<td>2</td>
<td>8.63d, 3H</td>
<td>7</td>
<td>6.14s, 6H</td>
<td>3.25s, 1H</td>
<td>CDC$_3$</td>
</tr>
<tr>
<td>H</td>
<td>Ph</td>
<td>H</td>
<td>3.81d, 1H</td>
<td>1.76s, 1H</td>
<td>2</td>
<td></td>
<td></td>
<td>2.6-3.0m, 9H</td>
<td></td>
<td>CDC$_3$</td>
</tr>
<tr>
<td>Ph</td>
<td>CH$_3$</td>
<td>H</td>
<td>3.66bs, 1H</td>
<td>5.28q, 1H</td>
<td>2</td>
<td>8.53d, 1H</td>
<td>7</td>
<td>2.2-2.95m, 9H</td>
<td></td>
<td>C$_6$D$_6$</td>
</tr>
<tr>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>4.02bs, 1H</td>
<td>5.66d, 1H</td>
<td>1</td>
<td>5.39d, 1H</td>
<td>15</td>
<td>2.3-3.3m, 9H</td>
<td></td>
<td>C$_6$D$_6$</td>
</tr>
<tr>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>3.67bs, 1H</td>
<td>5.44bs, 1H</td>
<td></td>
<td></td>
<td></td>
<td>2.2-2.95m, 9H</td>
<td></td>
<td>CDC$_3$</td>
</tr>
<tr>
<td>H</td>
<td>CH$_3$</td>
<td>H</td>
<td>3.95d, 1H</td>
<td>1.81s, 1H</td>
<td>2</td>
<td>8.61d, 3H</td>
<td>7</td>
<td>2.5-2.9m, 4H</td>
<td></td>
<td>CDC$_3$</td>
</tr>
</tbody>
</table>
### APPENDIX VII

#### 2- Acylstylene toluene-p-sulphonylhydrazones

<table>
<thead>
<tr>
<th>$\gamma$ values</th>
<th>$Y = H$ $Z = \text{OMe}$</th>
<th>$Y = \text{CH}_3$ $Z = H$</th>
<th>$Y = \text{CH}_3$ $Z = \text{OMe}$</th>
<th>$Y = \text{Ph}$ $Z = H$</th>
<th>$Y = \text{Ph}$ $Z = \text{OMe}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N$-H</td>
<td>1.37s, 1H</td>
<td>1.62bs, 1H</td>
<td>ca. 1.7bs, 1H</td>
<td>1.60bs, 1H</td>
<td>unresolved</td>
</tr>
<tr>
<td>Ar</td>
<td>2.14d, 2H</td>
<td>2.11d, 2H</td>
<td>2.20d, 2H</td>
<td>2.13d, 2H</td>
<td>2.19d, 2H</td>
</tr>
<tr>
<td></td>
<td>2.76d, 2H</td>
<td>2.48-3.00m, 6H</td>
<td>2.05-2.90m, 6H</td>
<td>2.74d, 2H</td>
<td>2.3-3.2m, 12H</td>
</tr>
<tr>
<td></td>
<td>2.74s, 1H</td>
<td>2.07s, 1H</td>
<td></td>
<td>2.98s, 1H</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.16s, 1H</td>
<td></td>
<td></td>
<td>3.07s, 1H</td>
<td></td>
</tr>
<tr>
<td>$H$-A</td>
<td>2.92-3.28m, 1H</td>
<td>3.22-3.62m, 1H</td>
<td>3.68-4.04m, 1H</td>
<td>3.28-3.62m, 1H</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.54-4.80m, 1H</td>
<td>4.33-4.67m, 1H</td>
<td>4.24-4.52m, 1H</td>
<td>4.35-4.54m, 1H</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.54-4.70m, 1H</td>
<td></td>
<td>4.54-4.70m, 1H</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$H$-c</td>
<td>4.78-4.98m, 1H</td>
<td>4.84-5.06m, 1H</td>
<td>4.81-5.03m, 1H</td>
<td>4.88-5.14m, 1H</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.94-5.13m, 1H</td>
<td>5.02-5.24m, 1H</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$M$-e</td>
<td>7.62s, 3H</td>
<td>7.60s, 3H</td>
<td>7.57s, 3H</td>
<td>7.62s, 3H</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.62s, 3H</td>
<td></td>
<td>7.62s, 3H</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$Y$</td>
<td>1.92s, 1H</td>
<td>7.91s, 3H</td>
<td>7.58q, 2H</td>
<td>7.87(s, 3H</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8.98t, 3H</td>
<td></td>
<td>7.89t, 3H</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$Z$</td>
<td>6.14s, 2X $\text{OMe}$</td>
<td></td>
<td>6.15s, 3H</td>
<td>6.06s, 3H</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6.24s, 3H</td>
<td>6.26s, 3H</td>
<td></td>
</tr>
</tbody>
</table>

Syn and anti forms present

$\text{J}ab = 18\text{Hz}$ $\text{J}ac = 11\text{Hz}$ $\text{J}bc = 1.5\text{Hz}$
APPENDIX VIII

Substituted 2-acylstyrene toluene-p-sulphonylhydrazones

$^1$H N.m.r. Spectral Data  Solvent : CDCl$_3$

<table>
<thead>
<tr>
<th>$^1$H N.m.r. Values</th>
<th>$X_1 = \text{H}$</th>
<th>$X_1 = \text{CH}_3$</th>
<th>$X_2 = \text{Ph}$</th>
<th>$X_2 = \text{CH}_3$</th>
<th>$Z = \text{H}$</th>
<th>$Y = \text{H}$</th>
<th>$Z = \text{OEt}$</th>
<th>$Y = \text{H}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-H</td>
<td>1.34bs, 1H</td>
<td></td>
<td></td>
<td>1.70bs, 1H</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ar</td>
<td>2.18d, 2H</td>
<td>2.78d, 2H; 3.20-3.55m, 2H</td>
<td>2.28-2.97m, 2H</td>
<td>2.05-2.38m, 4H</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ha</td>
<td>Unresolved</td>
<td></td>
<td></td>
<td>2.84bs, 1H</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$X_1$</td>
<td>3.17d, 1H</td>
<td>8.18d, 3H</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$X_2$</td>
<td></td>
<td>8.51d, 3H</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Me</td>
<td>7.72s, 3H</td>
<td>7.66s, 3H</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>1.89s, 1H</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unresolved</td>
<td></td>
</tr>
<tr>
<td>Z</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8.65t, 3H; 6.02q, 2H</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$J_{X_1 Ha} = 16$Hz
APPENDIX IX

2-Formyl-5-ethoxy-\(\beta,\beta\)-dimethylstyrene toluene-p-sulphonylhydrazone sodium salt: Thermal decomposition products

1. -

![Chemical Structure]

a) \(^1^H\) N.m.r. Spectral Data. Solvent: CDCl\(_3\)

Aromatics \((\tau)\)

<table>
<thead>
<tr>
<th>Aromatics</th>
<th>(\tau)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ha</td>
<td>3.02 (s, 1H)</td>
</tr>
<tr>
<td>Hb</td>
<td>3.70 (bs, 1H)</td>
</tr>
<tr>
<td>EtO</td>
<td>5.98 (q, 2H), 8.62 (t, 3H)</td>
</tr>
<tr>
<td>Me(_2)</td>
<td>8.04 (d, 3H) (J = 1)Hz</td>
</tr>
<tr>
<td>Me(_1)</td>
<td>8.26 (d, 3H) (J = 1)Hz</td>
</tr>
</tbody>
</table>

b) Mass Spectrum (\(m/e\) relative abundance %)

160(10), 187(10), 188(25), 317(10), 318(12), 332(16), 360(9), 375(100), 376(32).
APPENDIX IX (continued)

2. -

\[
\begin{align*}
\text{EtO} & \quad \text{Me}\_2 \\
\text{Hb} & \quad \text{Me}\_1 \\
\text{Ha} & \quad \text{Me}\_1 \\
\text{Me}\_2 & \quad \text{Hb}
\end{align*}
\]

a) \textsuperscript{1}H N.m.r. Spectral Data. Solvent : CDC\textsubscript{3}

Aromatics \((\delta)\)

- 1.92(d,1H), 3.06-3.40(m,2H).
- 1.24(s,1H).
- 5.61(bs,1H).
- 5.95(q,2H), 8.60(t,3H).
- 8.08(d,3H). \(J = 1\text{Hz}\).
- 8.36(d,3H). \(J = 1\text{Hz}\).

b) Mass Spectrum \((m/e \text{ relative abundance } \%\))

174(40), 188(39), 189(55), 202(10), 390(27), 389(100), 404(23).
APPENDIX IX (continued)

3. -

\[
\begin{align*}
\text{EtO} & \quad \text{Me}, \\
\text{H} & \quad (\text{NS} \ 0 \ 2\text{CH}_3 \\
\text{CH} & \quad \text{Me}, \\
\text{O} & \quad \text{A})
\end{align*}
\]

\[\begin{align*}
\text{Ha} & \quad 2.14 (d, 2H), 2.25 (d, 1H), 2.60-2.86 (m, 3H), \\
\text{Hb} & \quad 3.18-3.40 (m, 3H), 3.51 (d, 1H). \\
\text{Hc} & \quad 6.01 (q, 4H), 8.63 (t, 6H). \\
\text{Me} & \quad 7.58 (s, 3H). \\
\text{Me} & \quad 8.13 (d, 3H). J = 1Hz. \\
\text{Me} & \quad 8.35 (s, 6H). \\
\text{Me} & \quad 8.70 (s, 3H). \\
\end{align*}\]

a) \[^1\text{H} \text{N.m.r. Spectral Data. Solvent: CDCl}_3\]

<table>
<thead>
<tr>
<th>Compound</th>
<th>Signal Type</th>
<th>Chemical Shift (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>\text{Aromatics}</td>
<td>(\gamma)</td>
<td>2.14 (d, 2H), 2.25 (d, 1H), 2.60-2.86 (m, 3H), 3.18-3.40 (m, 3H), 3.51 (d, 1H).</td>
</tr>
<tr>
<td>\text{Ha}</td>
<td>s</td>
<td>2.48 (s, 1H).</td>
</tr>
<tr>
<td>\text{Hb}</td>
<td>bs</td>
<td>3.78 (bs, 1H).</td>
</tr>
<tr>
<td>\text{Hc}</td>
<td>bs</td>
<td>4.12 (bs, 1H).</td>
</tr>
<tr>
<td>\text{EtO}</td>
<td>q</td>
<td>6.01 (q, 4H), 8.63 (t, 6H).</td>
</tr>
<tr>
<td>\text{CH}</td>
<td>s</td>
<td>5.44 (s, 2H).</td>
</tr>
<tr>
<td>\text{CH}</td>
<td>s</td>
<td>7.58 (s, 3H).</td>
</tr>
<tr>
<td>\text{Me}</td>
<td>s</td>
<td>8.13 (d, 3H). J = 1Hz.</td>
</tr>
<tr>
<td>\text{Me} and \text{Me}</td>
<td>s</td>
<td>8.35 (s, 6H).</td>
</tr>
<tr>
<td>\text{Me}</td>
<td>s</td>
<td>8.70 (s, 3H).</td>
</tr>
</tbody>
</table>

b) Mass Spectrum (\(^m/e\) relative abundance %)

160(40), 188(100), 189(36), 404(9), 545(44), 546(16), 560(9).
INDEX TO DISCUSSION

PREAMBLE 118

I 2,3-BENZODIAZEPINES 123

A. SYNTHESIS 123

1. 1H-2,3-benzodiazepines 123
2. 5H-2,3-benzodiazepines 138

B. REACTIONS 142

1. Photolysis of 1H- and 5H-2,3-benzodiazepines 142
2. Thermolysis of 1H-2,3-benzodiazepines 153

II POSSIBLE EXTENSIONS OF THE CYCLISATION REACTION 163

A. Attempted cyclisation of trans-stilbene-2-azide 163

B. Attempted cyclisation of 2-formyl-5-ethoxy-ββ-dimethylstyrene toluene-p-sulphonylhydrazone 165
DISCUSSION

PREAMBLE - The toluene-\(p\)-sulphonylhydrazones of \(\alpha,\beta\) - unsaturated carbonyl compounds were shown in some instances to cyclise in the presence of base to give pyrazoles and/or products formed from carbenic intermediates (see Introduction pages 20-25). Closs and Boll\(^{32}\) were able to obtain 3\(H\)-pyrazoles (1) by the thermal cyclisation of the sodium salts of the toluene-\(p\)-sulphonylhydrazones of some open chain and cyclic ketones (2).

Closs and Boll\(^{64}\) later showed that irradiation of the 3\(H\)-pyrazole (3) in methylene chloride at -60\(^\circ\) gave the photoisomer (4) which reverted to the pyrazole on warming to 0\(^\circ\).

\[
\begin{align*}
R_1 & \quad R_2 \\
C & \quad C \\
\hat{C} & \quad N = N \\
\rightarrow & \quad \text{carbene} \\
\rightarrow & \quad \text{pdt}s
\end{align*}
\]
Fig 1
Irradiation of (3) in pentane at \(-60^\circ\) however, resulted in loss of nitrogen with subsequent cyclopropene formation. Brewbaker and Hart\(^{34}\) have examined the mechanism of pyrazole formation and concluded that ring closure occurs via an intramolecular 1,3-dipolar cycloaddition.

Sharp and Thorogood\(^{35}\) extended this electrocyclic ring closure to the formation of seven membered rings by making pyrazole formation sterically or energetically unfavourable, resulting in the synthesis of 1,2-benzo-diazepines (6) from (5).

\[
\begin{array}{c}
\text{(5)} \\
\begin{array}{c}
\text{Ph} \\
\text{Ph}
\end{array}
\end{array}
\xrightarrow{\Delta}
\begin{array}{c}
\text{(6)} \\
\begin{array}{c}
\text{Ph} \\
\text{N=N}
\end{array}
\end{array}
\]

(See Introduction pages 24-25). In this work the conjugation of (2) was extended\(^{36}\) by one double bond to give a system in which there are several possible modes of electrocyclic ring closure (Fig. 1). In studies on a number of such systems it was observed that mode (a) was generally preferred to mode (c) unless some constraint existed on pyrazole formation. This condition was fulfilled when \(R_4\) and \(R_5\) were parts of a benzene ring or \(R_3\) and \(R_4\) were parts of the same cyclopentane ring. Thus the toluene-\(p\)-sulphonylhydrazone sodium salts of \(\alpha\)-(\(\alpha\)-alkenylaryl)diazoalkanes cyclised to/...
to give 1H-2,3-benzodiazepines (7) in good yield (Fig. 2).

The mechanism proposed was electrocyclic ring closure of the diazoalkene to give a non-aromatic intermediate which aromatises via a [1,5] sigmatropic hydrogen migration.

Although diazoalkanes with \( \alpha, \beta \)-olefinic unsaturation generally cyclise readily to pyrazoles, those with \( \alpha, \beta \)-aromatic unsaturation do not likewise give indazoles (8) (Fig. 3).
Instead, reaction occurs principally via loss of nitrogen to give carbene derived products such as azines and/or stibenes\textsuperscript{2}.

In cases where the aromatic 'double bonds' are more localised e.g. in (2-naphthyl) - and (9-phenanthryl) - diazomethanes (9) some cyclisation does occur to give benzindazoles (10) in useful yields. (ca. 10\% and 35\% respectively\textsuperscript{110}) (Fig. 4).

\[
\begin{align*}
\text{(9)} & \rightarrow \begin{array}{c}
\text{[}\ \text{benzindazole]}\text{]} \\
\text{(10)}
\end{array} \\
\text{Fig 4}
\end{align*}
\]

The object of the research undertaken was:

(a) To further develop the cyclisation reaction of $\alpha$-(o-alkenylaryl) diazoalkenes (11) by varying the substituents $R$, 

\[
\begin{align*}
\text{(11)}
\end{align*}
\]
thus extending the scope of the diazepine synthesis. In the case where \( R_1 \) and \( R_2 \) were groups other than hydrogen, it was thought possible that alternative symmetry allowed sigmatropic migrations might take place.

(b) To undertake photochemical and thermal studies on the 1H-2,3-benzodiazepines produced in the cyclisation reaction.

(c) To extend the electrocyclic ring closure to 1,3-dipoles other than \(-C=N=\bar{N}\).

The synthesis of 1H-2,3-benzodiazepines led to the discovery of a new series of 5H-2,3-benzodiazepines which in turn led to studies of ring inversion by n.m.r. of both 1H- and 5H-2,3-benzodiazepines. A brief thermolysis study of the photoproducts of the 1H-2,3-benzodiazepines was also carried out.
Fig 5

1. YCOCl \cdot (YCO)_2O
2. P_2O_5/POCl_3
3. Me_2SO_4/ OH^-
I - 2,3-BENZODIAZEPINES

A. SYNTHESIS

1. 1H-2,3-benzodiazepines

This series of compounds (7) was prepared by cyclisation of the diazoalkenes generated by the thermal decomposition of the sodium salts of the toluene-\(p\)-sulphonylhydrazones (Fig. 2) of a series of \(p\)-acylstyrenes and in one case an \(o\)-acylstilbene.

The \(o\)-acylstyrenes (12) were obtained by the reaction sequence shown in Fig. 5. The \(p\)-substituted phenylethylamine was treated with the appropriate acid chloride or acid anhydride to form the amide which was then cyclodehydrated by phosphorus pentoxide and phosphorus oxychloride to the \(1\)-substituted-3,4-dihydroisoquinoline. This was in turn ring opened to the \(o\)-acylstyrene (12) by dimethyl sulphate in aqueous alkali.

The \(o\)-acylstilbene, stilbene-2-aldehyde (13) was prepared by the reduction of stilbene-2-carboxylic acid (14) in four stages by the method of Natelson and Gottfried\(^{103}\) as shown in Fig. 6.

The toluene-\(p\)-sulphonylhydrazones were generally prepared by the acid catalysed condensation of the \(o\)-acylstyrene (12) or -stilbene (13) with toluene-\(p\)-sulphonylhydrazide in methanol or ethanol. When (12) or (13) were aldehydes (\(Y=H\)), the toluene-\(p\)-sulphonylhydrazone was obtained by mixing warm solutions of the...
Fig 6
the reactants and leaving the mixture to stand at room temperature. With ketones on the other hand, where \( Y = \text{alkyl} \), the reaction solution was heated to \( \text{ca. } 60^\circ \)C for 5 min from which the toluene-\( p \)-sulphonylhydrazone precipitated on cooling. In the case of ketones with \( Y = \text{Ph} \) reactions were slow, possibly due to steric and conjugative effects of the phenyl group, and here the competition of polymerisation reactions became significant, often resulting in low yields of toluene-\( p \)-sulphonylhydrazone.

Some of the toluene-\( p \)-sulphonylhydrazones crystallised as mixtures of \( \text{syn} \) and \( \text{anti} \) isomers. This caused no problems other than a complication of the i.r. and n.m.r. spectra.

The decomposition of the toluene-\( p \)-sulphonylhydrazone salts was generally carried out in boiling cyclohexane or dimethoxyethane for the minimum time required to consume all of the starting material. The majority of these reactions gave only a single cyclised product as shown by n.m.r. of the crude product which was a \( 1H \)-2,3-benzodiazepine (7) as shown in Fig. 2. These products were isolated by filtering off the sodium-\( p \)-toluenesulphinate precipitated during the reaction, and then removing the reaction solvent under reduced pressure, giving an oil or solid from which the pure benzodiazepine was obtained by crystallisation. The \( 1H \)-2,3-benzodiazepines (7) prepared along with their percentage yields are shown in Table 1.
Table 1

<table>
<thead>
<tr>
<th>Compound</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>(7a) 7,8-dimethoxy-1H-2,3-benzodiazepine</td>
<td>70</td>
</tr>
<tr>
<td>(b) 1-phenyl-1H-2,3-benzodiazepine</td>
<td>62</td>
</tr>
<tr>
<td>(c) 1-phenyl-7,8-dimethoxy-1H-2,3-benzodiazepine</td>
<td>84</td>
</tr>
<tr>
<td>(d) 4-phenyl-1H-2,3-benzodiazepine</td>
<td>71</td>
</tr>
<tr>
<td>(e) 1-ethyl-1H-2,3-benzodiazepine</td>
<td>68</td>
</tr>
<tr>
<td>(f) 1-methyl-1H-2,3-benzodiazepine</td>
<td>64</td>
</tr>
<tr>
<td>(g) 1-methyl-7,8-dimethoxy-1H-2,3-benzodiazepine</td>
<td>66</td>
</tr>
</tbody>
</table>

In the preparation of 1-methyl-1H-2,3-benzodiazepine (7f), difficulty was encountered in the purification of starting materials. This was caused by the formation of 2-propionystyrene (ca. 12%) in the preparation of 2-acetylstyrene from the ring opening of 1-methyl-3,4-dihydroisoquinoline (Fig. 5). Distillation of the mixture gave no appreciable separation, and considerable loss of the product due to polymerisation. It also proved impossible to fractionally crystallise the toluene-\(p\)-sulphonylhydrazones formed from the mixture. However, on cyclisation of the toluene-\(p\)-sulphonylhydrazone mixture, two benzodiazepines (7e) and (7f) were produced in 1:8 ratio as shown by g.l.c. (5% CAR. 150\(^\circ\)) and h.s.l.c. A solution of this diazepine mixture in methanol/...
Fig 7
methanol gave crystals of pure (7f), (64%) on standing at -20°. Compound (7e) was identified by g.l.c. analysis and comparison of an n.m.r. spectrum of the mixture with authentic material. It would appear that during or after the ring opening of the isoquinoline (Fig. 5), the dimethyl sulphate and base combination is also effecting methylation on carbon. In the case of 2-acylstyrenes (12) where Y=H or Ph no C-methylation can take place and only one product is formed. In the attempted preparation of 2-phenylacetylstyrene (12: Y=CH₂Ph, Z=H) from the ring opening of 1-benzyl-3,4-dihydroisoquinoline, using Genslers⁹⁹ method, 2-phenylacetylstyrene accounted for only 55% of the crude product. The n.m.r. spectrum indicated the possible presence of 2-(2-phenylpropanoyl)styrene (15) (τ8.5d,3H and 5.6q,1H) and 2-(2-phenylisopropyl)styrene (16) (τ7.4s and 7.8,s).

Thus it would appear that Gensler⁹⁹ has overlooked this side reaction in the preparation of 2-acylstyrenes (12). The mechanism of this C-methylation probably involves attack on the initially formed 2-acylstyrene as shown in Fig. 7. As can be seen, when R=Ph the intermediate/...
intermediate (17) will be stabilised by conjugation, thus facilitating its formation. When R=CH₃, (17) will be destabilised and therefore less likely to be formed. This may account for the fact that no side products were observed in the synthesis of 2-propionylstyrene (12: Y=Et, Z=H) from the ring opening of 1-ethyl-3,4-dihydroisoquinoline (Fig. 5).
Structure of the cyclisation products - Elemental analysis and mass spectra of the products indicate that they are isomeric with their diazoalkene precursors. A large number of structures having this composition are possible products of the reaction (Fig. 1) and the isomers derived from them.

For example, if the cyclisation of o-diazomethylstyrene (18) occurred by route (c) in Fig. 1 to give (19) as a primary product, then the isolated product could be (19), (20), (21) or (22) or the diazanorcaradienes (23) derived from them by ring contraction.
Fig 8
There are also a number of other possible products which could be derived from (23) and its analogues by sequential $[1,5]$ sigmatropic migrations of the methylene group and electrocyclic ring expansion and contraction$^{111,112}$. e.g. Berson and Willcott$^{112}$ have observed a remarkable series of isomerisations of methyl-substituted cycloheptatrienes. Their results (Fig. 8) are consistent with a sequence of $[1,5]$ sigmatropic rearrangements and electrocyclic reactions.

The possibility of formulating the products as compounds of type (23) had to be carefully considered in view of recent structural work on analogous 1,2-diazepines not annelated to benzene rings$^{113-116,91}$. The structures of products of the reactions of tetrazines and cyclopropenes were thought to depend on the substitution pattern. e.g. (25a)/(26a) was reported to exist as the monocyclic form (25a) and (25b)/(26b) as the bicyclic form (26b) at room temperature and the monocyclic form (25b) at high temperature$^{114}$.
However, it has recently been shown by X-ray structural analysis\textsuperscript{116} and by n.m.r. study\textsuperscript{115, 116, 91} that compounds of this type exist entirely in the bicyclic diazanorcaradiene form, and that the monocyclic diazepine form could not be detected at any temperature. It was suggested\textsuperscript{91} that the higher stability of the diazanorcaradiene structure (26) was due to the much lower bond energy of nitrogen-nitrogen double bonds than carbon-carbon or carbon-nitrogen double bonds. It is interesting to note that compound (26a) gave a mass spectrum\textsuperscript{114} which showed a base peak corresponding to loss of a PhCN fragment from the parent ion rather than a base peak corresponding to loss of N\textsubscript{2} which might have been expected from the monocyclic structure (25a).

The mass spectra of all the cyclisation products (7) showed only a small peak due to the parent ion and a larger peak due to a (P-28) ion. This facile loss of twenty-eight mass units (N\textsubscript{2}) from the parent ion is typical of cyclic azocompounds and supports formulations containing an -N=N- group. e.g. (19), (20) or (24) rather than structures such as (21), (22), or (23); and although it would of course be possible for ring expansion in compounds like (23) to precede fragmentation, this was not observed for (26) as noted previously.

Following the synthesis of the 1H-2,3-benzodiazepines reported in this thesis, the parent system, 1H-2,3-benzodiazepine (20) has recently been prepared in this laboratory\textsuperscript{117}. Its mass spectrum also shows that the indene/...
Fig 9

Hα
Hb
Hα
Hc

MeO
MeO

-50°

(7a)
indene fragment ion formed by loss of N₂ readily loses H from the parent ion of indene itself (m/e 116:115 = 100%: 73%). The mass spectra of the 1H-2,3-benzodiazepines reported are tabulated in Appendix I.

More definitive information on the structure of the cyclisation products was obtained from their n.m.r. spectra; that of (7a) is shown in Fig. 9 and that of (7d) in Fig. 10.

All of the others are tabulated in Appendix III.

The low temperature spectrum of (7a) shows four doublets each integrating for one proton; decoupling experiments showed coupling between the (a)/(b) pair and the (c)/(d) pair. An examination of the temperature dependence of the spectrum showed that the (c) and (d) doublets broadened with increasing temperature, and eventually coalesced to a singlet. On cooling, the original spectrum was restored, providing that the compound was not held at the high temperature long enough for extensive/...
extensive thermolysis to occur. This temperature
dependence will be discussed in more detail later. Of
all possible formulations, this spectrum fits a structure
of type (20) best, and thus the peaks are assigned as
shown in Fig. 9. These assignments are based on the
effects of group substitution on the spectrum, on the
chemical shifts and on the variable temperature study.
An unexpected feature of compounds having a methylene at
C-1 (7, Y=H) is the very large chemical shift difference
between the methylene protons (ca. 3.4 p.p.m.). The
azo-group is well known to have a strong deshielding effect
on the protons attached to α-carbon atoms.

\[
\begin{align*}
\text{Ph} & \quad \text{H} \\
\text{N} & \quad \text{N} \\
\text{H} & \quad \text{Ph}
\end{align*}
\]

(27)

e.g. the methine proton in (27) absorbs at 5.06 and
experimental data has shown that protons in positions
in the -C-N=N- plane are deshielded relative to those in
positions above or below this plane. The physical
mechanism for this effect is not fully understood, but it
is thought that it does not derive solely from magnetic
anisotropy.

A Dreiding stereomodel of (7a) shows that the Hd proton
is located almost in the plane of the azo-group, and
should/...
should therefore be more deshielded than Hc which lies well above the plane. Hd also lies virtually in the plane of the benzene ring at ca. 3.4 Å from its centre and will therefore also be deshielded by 0.6-0.7 p.p.m. due to ring current effects. Hc will also experience some deshielding from the same source. The Hc proton lying out of the plane of the azo-group would be expected to absorb at higher field and will additionally be subject to a shielding effect from the C4-C5 double bond, although since it is ca. 2.1 Å above the plane of the bond and ca. 2.5 Å from the bond axis, this effect would be expected to be small. On the basis of existing data, it would therefore be predicted that Hd would absorb at lower field than Hc (Fig. 9), however the magnitude of the separation is surprising. Ha absorbing at 1.93γ is also strongly deshielded by the azo-group. These assignments are supported by the variable temperature study (see later) in which the spectrum of compounds with methylene at C-1 exhibit temperature dependence which is consistent with inversion of the diazepine ring. Similar temperature dependence has been found in the spectra of 4H-1,2-diazepines. The spectrum of (7d) (Fig. 10) shows two doublets (Hc and Hd) and a singlet for Hb, each integrating for one proton. A similar chemical shift difference for Hc and Hd of 3.5 p.p.m. is observed, while the spectrum also exhibits temperature dependence. It is interesting to note that the n.m.r. spectra/...
Fig 11
spectra of compounds in which one of the C-1 hydrogens is substituted by an alkyl or aryl group show no temperature dependence e.g. (7f) showed no temperature dependence on warming to ca. 180°. This indicates that they are locked in one conformation, probably the least hindered one with the bulky substituent in the exo-position.

The n.m.r. spectrum (Fig. 9) might be fitted to a structure of type (23) with the assignments shown, and the temperature dependence of the spectrum explained by diastereotopomerisation via structure (20). This formulation is ruled out however by consideration of the chemical shift of the (d) proton which occurs at much lower field than would be predicted for (23) and on the coupling constant Jcd, which at 9Hz is much higher than would be expected for the gem-coupling constant of an aziridine ring\textsuperscript{121}.

Therefore, on the basis of mass and n.m.r. spectral data the reaction products are formulated as 1H-2,3-benzodiazepines (7). This structure has been confirmed\textsuperscript{122} by an X-ray structure determination on 1-methyl-4-phenyl-1H-2,3-benzodiazepine as shown in Fig. 11. This also confirms that the preferred conformation of this molecule has the methyl group in the exo- rather than the endo-position, which is in agreement with predictions from n.m.r. data.

The series of compounds (7) exist entirely as diazepines and not as the diazanorcaradiene tautomers as was mentioned in the case of compounds (25) and (26). Apparently, in this case, the loss of aromatic stabilisation energy which/...
which would be involved in the transformation of e.g. (20) to (23) outweighs the gain in stability which would result from the absence of the nitrogen-nitrogen double bond in the latter form.

The 1H-2,3-benzodiazepines were all yellow crystalline solids, the colour of the compounds being due to \(-\text{N}=\text{N}\)-conjugation with other chromophores. The general stability of the compounds increased with substitution in the seven membered ring. All were moderately soluble in the common organic solvents, but solutions in halogen containing solvents tended to darken on standing at room temperature.

Brewbaker and Hart\textsuperscript{34}, having studied the mechanism of 3-diazoalkene cyclisations to pyrazoles concluded that the relative insensitivity of the reaction rate to substituents indicated that the reaction was an intramolecular 1,3-dipolar cycloaddition. Thus it would seem reasonable to postulate the same type of mechanism for benzodiazepine synthesis from a related system. This mechanism involves electrocyclic ring closure of the diazoalkene to an intermediate (Fig. 12) which is destabilised by virtue of being non aromatic and containing an \(-\text{N}=\text{N}\)\. It seems likely that the driving force behind the 1H-benzodiazepine synthesis is therefore the subsequent \([1,5]\) sigmatropic hydrogen migration which restores the aromaticity of the system. This is in accordance with the Woodward-Hoffmann rules for conservation/...
conservation of orbital symmetry\textsuperscript{58}. There are two distinct ways of effecting a sigmatropic migration (Fig. 13).

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{fig13}
\caption{Fig 13}
\end{figure}

(a) a suprafacial process in which the migrating hydrogen is at all times associated with the same face of the \pi-system. The transition state thus possesses a plane of symmetry and due to the spherical 1s symmetry of the hydrogen atom, only a \textsuperscript{[1,5]} suprafacial migration is allowed thermally.

(b) an antarafacial process in which the migrating hydrogen passes from the top face of one carbon terminus to the bottom face of the other through a transition state possessing a two-fold axis of symmetry. From Fig. 13 it is seen that for hydrogen, symmetry allowed antarafacial thermal migrations are \textsuperscript{[1,3]} and \textsuperscript{[1,7]}. Antarafacial processes are not observed in small and medium sized rings for steric reasons. Thermally induced hydrogen migrations have been studied in cyclopentadienes and cycloheptatrienes\textsuperscript{124} in which only specific/...
specific $[1,5]$ migrations have occurred with no evidence of $[1,3]$ or $[1,7]$ shifts.

If we now consider the intermediate in the cyclisation reaction (Fig. 12), the possible products of the symmetry allowed hydrogen migrations would be as shown in Fig. 13. As already mentioned, the product corresponding to the $[1,5]$ migration is the only one isolated, even although a $[1,7]$ shift would result in the formation of the more thermodynamically stable 5H-isomer or the as yet unknown 8π-electron N-H isomer (Fig. 12). This product formation appears to be kinetically controlled as would be expected if the 1H-isomer is formed via an 'allowed' migration of low activation energy, whereas 5H-formation would require an antarafacial migration with a sterically impossible transition state.

The inference that diazocompounds are involved in the cyclisation step, rather than their precursors, the toluene-p-sulphonylhydrazone salts is drawn from the deep red colouration observed in the early stages of several of the cyclisations, and from the trapping of the diazoalkene in a related reaction^4.
2. 5H-2,3-benzodiazepines (28)

While attempting to synthesise 1-phenyl-1H-2,3-benzodiazepine (7b) from the cyclisation of its diazoalkene precursor in toluene, it was observed that t.l.c. of the reaction solution showed 2 spots. The reaction was continued until only one spot remained. The product isolated from the reaction was not (7b), but was shown to be isomeric with (7b) from elemental analysis and mass spectral data. The structure of the isomer was deduced from n.m.r. and mass spectral data to be 1-phenyl-5H-2,3-benzodiazepine (28a). The formation of (28a) as a primary product in the cyclisation was rejected on the grounds that it would involve a [1,7] hydrogen migration from the intermediate (Fig. 14), and as already mentioned this would involve a sterically impossible transition state:

![Chemical structure diagram]

Fig 14
It seemed more likely that (28a) was formed as a secondary product from (7b) by:

(a) a second \([1,5]\) sigmatropic migration in (7b).
(b) the base catalysed isomerisation of (7b) (Fig. 14).

In a repeat experiment with careful monitoring only the 1H-compound (7b) was isolated with no sign of the 5H- showing that (7b) was indeed the primary product of cyclisation. Mechanism (a) was rejected on the grounds that thermolysis of a sample of (7b) at the reaction temperature gave no isomerisation, the products being hydrocarbons formed by nitrogen loss. On the other hand, (7b) was found to isomerise in basic media to give good yields of (28a) which is in accordance with mechanism (b).

Due to the tiny amounts of sodium used in small scale cyclisation reactions, it is easy to inadvertently add a slight excess of base, thus leading to isolation of the 5H- isomer.

The 5H-benzodiazepines reported in this thesis are shown in Table 2.

Table 2

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>(28a) 1-phenyl-5H-2,3-benzodiazepine</td>
<td>69%</td>
</tr>
<tr>
<td>(28b) 1-phenyl-7,8-dimethoxy-5H-2,3-benzodiazepine</td>
<td>82%</td>
</tr>
<tr>
<td>(28c) 1-methyl-4-phenyl-5H-2,3-benzodiazepine</td>
<td>48%</td>
</tr>
<tr>
<td>(28d) 1-p-toly1-4-phenyl-5H-2,3-benzodiazepine</td>
<td>84%</td>
</tr>
</tbody>
</table>
In the case of (28d), an 84% yield was obtained by boiling the 1H-compound under reflux for 4h with an equimolar amount of sodium ethoxide in ethanol, while a blank reaction in the absence of base left the 1H-compound unchanged.

It is interesting to note however that (28c) was also formed thermally from the 1H-compound by boiling it under reflux in n-propanol for ca. 28 days showing that a second [1,5] sigmatropic hydrogen migration does occur slowly, giving the more thermodynamically stable 5H-isomer. This isomerisation was not observed in cases where loss of nitrogen is a much faster decomposition route e.g. (7b) \( \rightarrow \) (28a).

Structure of the 5H-benzodiazepines - The structure of these compounds follow from their mass and n.m.r. spectral data (See Appendices II and IV). The mass spectrum of 1-methyl-4-phenyl-5H-2,3-benzodiazepine (28c) (Fig. 15) shows the parent ion as the base peak, fragmenting via loss of PhCN from the molecular ion to give an isoindole fragment which loses H to give the peak at m/e 130 or CH\(_3\) to give the m/e 116 peak. The 4H-1,2-diazepines (29) also give large peaks corresponding to loss of PhCN from the molecular ion.

![Structure of 5H-benzodiazepines](image-url)
ABX splitting

(28a)

(28b) expanded

Fig 16
The mass spectrum of 1-\(p\)-tolyl-4-phenyl-5H-2,3-benzodiazepine (28d) similarly showed loss of PhCN from the parent ion as the major fragmentation path. This also showed a loss of twenty-eight mass units to give a peak at m/e 282 which may reflect some isomerisation to the corresponding 1H- isomer either of the molecular ion, or of the compound itself prior to ionisation. The mass spectra of compounds (28a, 28b) showed loss of HCN as a decomposition path.

The n.m.r. spectra of the 5H-benzodiazepines prepared, showed temperature dependence due to the methylene at C-5. The spectra of the compounds (28a, 28b) gave an eight line pattern for the methylene group, which constituted the AB part of an ABX system (Fig. 16).

\[ J_{AB} = 12.5 \text{ Hz} \quad J_{AX} = J_{BX} = 5 \text{Hz} \]

On the other hand the spectra of (28c, 28d) gave a pair of doublets for the methylene \( J_{AB} = 12.5 \text{ Hz} \) (See Appendix IV).

In contrast to the 1H-2,3-benzodiazepines, the 5H-compounds were colourless. They were also higher melting and generally much less soluble in organic solvents than their 1H-counterparts.
1. **Photolysis of 1H-2,3-benzodiazepines** - The irradiation of dilute solutions of 1H-2,3-benzodiazepines (7) using a medium pressure Hanovia lamp, in dry dimethoxyethane or dry ether, afforded complete conversion to isomeric products in 5-10 min, as indicated by mass spectral and analytical data (See Appendices V and VI). The disappearance of the benzodiazepine was monitored by the gradual fading of its characteristic colour, and by t.l.c. (alumina/benzene:ether 1:1) which showed only one product spot in each case. Irradiation of the solutions for longer periods gave complex mixtures of products. Analytically pure samples were obtained by low temperature evaporation of the solvent. Attempts to recrystallise the compounds resulted in extensive decomposition, especially in the case of the less substituted examples. On the basis of chemical and spectroscopic evidence these products were formulated as $4H-\left[1,2\right]$diazeto$\left[3,2-a\right]$isindoles (30); a new heterocyclic system.

![Chemical structure](image)

**(7)** \(\rightarrow\) **(30)**
Fig 17

s symmetric
a antisymmetric

(7)

(30)

(31)
These compounds (30) were predicted as possible photo-products of (7) on the basis of orbital symmetry arguments. Consider the following possible photochemical and thermal transformations in a 1,3-butadiene system. The symmetry allowed modes of reaction are shown in Fig. 17. As can be seen, the configuration and structure of the products are dependent on the mode of reaction. Extending this to the 1,2-diazabutadiene system present in the 1H-2,3-benzodiazepines, there are two probable concerted pathways as shown in Fig. 17.

1. An S+S combination of the two Π-orbitals. 
2. An a+a combination of the two Π-orbitals.

It would also be possible for the reactant to lose nitrogen by a non-concerted mechanism as observed in the photolysis of 1,2-benzodiazepines,65 and many other cyclic and acyclic azo-compounds. Since elemental analysis indicated that isomerisation had taken place, only modes 1 and 2 need be considered (Fig. 17). The primary product of a \[Π^2a + Π^2a\] ring closure might be expected to ring open to a less strained product e.g. (31).

All the products gave mass spectra with the (M⁺ - XCN) ion as the base peak (See Appendix V), a fragmentation pattern which could be expected from either structure (30) or (31).

The photoprodut of 7,8-dimethoxy-1H-2,3-benzodiazepine (7a) gave a 28° n.m.r. spectrum (Fig. 18) in C₆D₆, the peaks/...
peaks of which could be assigned to either (30) or (31) where X=H, Y=H, Z=OMe. However, in this case the spectrum of compound (31) would be expected to undergo temperature dependent ring inversion as in the case of the corresponding 1H-2,3-benzodiazepine (7a) in which the methylene shows two broad doublets constituting an AB system which rapidly coalesce at ca. 80°. The spectrum of the photoproduct showed no tendency to coalesce at 80° in C_6D_6, and in fact, sharpening of the AB system was observed. The pair of doublets moved slightly closer together, consistent with decrease in solvation due to rise in temperature. This points to (30a) as the structure of the photoproduct, since the five membered ring is locked in one conformation and is thus unable to undergo ring inversion. Further variable temperature n.m.r. studies on compound (30c) in diphenyl ether again showed sharpening of the AB system with no sign of coalescence at 200°, at which temperature decomposition began to set in.

![Diagram of compound (30c)](image)

An interesting point is that H_B and H_C give only a broad singlet in CDCl_3 at 28° which could be interpreted as/...
as indicative of fast ring inversion e.g. in (31). However, since this remained unchanged on cooling to -60°, it would appear that the chemical shifts of $H_B$ and $H_C$ are nearly identical in this solvent. A comparison of the n.m.r. spectra of (30a) in CDCl$_3$ and C$_6$D$_6$ is shown in Fig. 18. All peaks are shifted upfield in C$_6$D$_6$ which also shows $H_C$ and $H_B$ as a well defined AB system and also separates the methoxy groups.

Thus the n.m.r. spectral evidence supports the formulation of the photoproducts as 4H-[1,2]diazeto [3,2-a]isoindoles (30). The photoproducts reported are shown in Table 3.

<table>
<thead>
<tr>
<th>Compound</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>X Y Z</td>
<td></td>
</tr>
<tr>
<td>(30a)</td>
<td>H H OMe</td>
</tr>
<tr>
<td></td>
<td>95</td>
</tr>
<tr>
<td>(30b)</td>
<td>H Ph H</td>
</tr>
<tr>
<td></td>
<td>92</td>
</tr>
<tr>
<td>(30c)</td>
<td>Ph H H</td>
</tr>
<tr>
<td></td>
<td>95</td>
</tr>
<tr>
<td>(30d)</td>
<td>H Me H</td>
</tr>
<tr>
<td></td>
<td>93</td>
</tr>
<tr>
<td>(30e)</td>
<td>H Me OMe</td>
</tr>
<tr>
<td></td>
<td>100</td>
</tr>
<tr>
<td>(30f)</td>
<td>Ph Me H</td>
</tr>
<tr>
<td></td>
<td>100</td>
</tr>
</tbody>
</table>

The $^1$H n.m.r. spectra of the photoproducts generally showed no coupling between $H_A$ and $H_D$ in structures such/...
such as (30a) (Fig. 18). Since models indicate that the dihedral angle involved is ca. 65°, coupling would be expected to be small. A similar type of zero coupling has been observed in related systems e.g. Paquette and Barret\(^6^0\) found that in system (32) \(J_{bc} = 0\).

\[\text{(32)}\]

Similarly, Wiberg and Nist\(^{12^5}\) have studied the n.m.r. spectra of cyclobutenes and found zero coupling between the olefinic and allyl protons. Very recently, Streith and co-workers\(^{12^6}\) have found that in systems such as (33) \(J_{ad} = 0\) and \(J_{bd} = 0-0.6\) Hz. They concluded that the mechanism of the allylic spin coupling in this case is more complex than the dependence on the dihedral angle. The factors causing this are unknown. Thus \(J_{AD} = 0\) in (30a) is not surprising in view of this evidence.

Other points of note in the n.m.r. spectrum of (30a) are \(J_{AB} \text{ (trans) ca. } 2\text{Hz}\) and \(J_{AC} \text{ (cis) ca. } 1\text{Hz}\). In compounds containing the aldiminic proton \(H_D\), this was found to come in the range \(\gamma 1.81-2.26\) due to deshielding by \(\text{CH} = \text{N} - \text{N}\). \(H_A\) is also deshielded by \(-\text{C} = \text{N}\), the aromatic ring and the adjacent \(-\text{N}\) and is found in the range \(\gamma 3.66-4.45\).
In compounds of structure (30) where Y = CH₃ or Ph, n.m.r. spectra showed the presence of only the least hindered isomer with the substituent in the exo-position indicating steric control over the mode of disrotatory cyclisation. This was deduced by comparing the chemical shift of the hydrogen atom at C-4 with the spectra of compounds containing a methylene group at C-4.

In a very recent paper by Zimmerman it was shown that direct photolysis of 7,7-dimethyl-2,5-diphenyl-3,4-diazanorcaradiene (34) gave 4,4-dimethyl-3,7-diphenyl-1,2-diazepine (35).

When shorter wavelength light was employed, a secondary electrocyclic closure occurred to give the bicyclic product (36). This thermally reverted to (35) at 151°.

Thus the photoisomerisation of 1H-2,3-benzodiazepines (7) follows the general scheme of \([\pi 2s + \pi 2s]\) photochemical reactions, like the butadiene unit in cycloheptatriene and its heterocyclic analogues to which reference has already been made. (See Introduction/...
Introduction, pages 32-37). The only other example known of this type of reaction involving a 1,2-diazabutadiene, and indeed of this ring system, is the unstable photoproduct (4) formed by Closs\textsuperscript{64} by low temperature irradiation of the 3H-pyrazole (3).

This process must be very facile with respect to nitrogen elimination and is very fast compared with some of Paquette's\textsuperscript{60} reactions involving azepines and oxepines, probably again due to the presence of a -N=N- double bond in the reactant. Therefore there is a high tendency for an allowed reaction which eliminates this -N=N-.

In 1972, Neiman\textsuperscript{128} carried out molecular orbital calculations for 2-azabutadiene and aza- and diaza-hexatrienes. These results indicated that the introduction of nitrogen atoms into butadiene and hexatriene should not cause any important perturbation in the course of electrocyclic reactions. Thus, 2-azabutadiene should react conrotatorily in a thermal reaction and disrotatorily upon photochemical excitation. This is in accordance with the results obtained for the photolysis of the 1,2-diazabutadiene unit in 1H-2,3-benzodiazepines.
Thermolysis of the photoproducts - This was initially carried out to obtain further structural evidence for the photoproducts (30). As mentioned in the Introduction (page 34), Paquette\textsuperscript{60} observed thermal reversion and Snieckus\textsuperscript{63} observed loss of phenylacetylene from analogous compounds. Therefore, it might be expected in the case of (30) that, (a) reversion to the diazepine would occur, which could then isomerise and/or decompose via loss of nitrogen (see later), (b) loss of XCN would occur, leaving an isoindole (37). The latter are relatively unstable, but can be trapped by dimethylacetylene dicarboxylate (DMADC) or tetracyanoethylene (TCE) (Fig. 19).

Substituted isoindoines of type (38) have been successfully trapped by Vernon\textsuperscript{129} giving 1:1 and 2:1 adducts.
1-Phenyl-4H-[1,2]diazeto[3,2-a]isoindole - A solution of this compound in diphenyl ether was thermolysed at 200⁰ until complete decomposition had taken place. Samples were analysed by g.l.c. (2 p.c. CAR, 100⁰) using a benzonitrile standard. Benzonitrile was found to be present by a comparison of retention times, and was confirmed by analysis on a g.l.c. coupled to a mass spectrometer which gave a spectrum with M⁺ 103 for the g.l.c. peak corresponding to benzonitrile. This spectrum was identical to that of authentic benzonitrile.

1-Phenyl-4-methyl-4H-[1,2]diazeto[3,2-a]isoindole (30f) - A solution of this compound in diphenyl ether was thermolysed at 200⁰ for 20h in a sealed tube. Benzonitrile extrusion was measured quantitatively by g.l.c. analysis using naphthalene as the internal standard. This indicated that ca. 31% benzonitrile extrusion was occurring.

4-Phenyl-4H-[1,2]diazeto[3,2-a]isoindole (30b) - Gas phase pyrolysis of this compound at 500⁰ gave a white solid which was fluorescent blue in ether solution. T.l.c. (alumina/benzene) showed no residual starting material. This solid could not be reisolated from solution, but exact mass measurement of the solid gave a molecular formula C₁₄H₁₁N which fits 1-phenylisoindole (37, Y = Ph). Attempts to form adducts with DMADC and TCE were unsuccessful, resulting in tars. An n.m.r. spectrum of the products collected in the cold trap also indicated/...
indicated the presence of 3-phenylindene (39). This can be explained by thermal reversion of the photoproduct to diazepine which then undergoes thermolysis with nitrogen loss (Fig. 20) (see later).

The limited availability of starting material prevented quantitative measurements being carried out. However, it would appear that thermal reversion is competing with HCN extrusion.
Photolysis of 5H-2,3-benzodiazepines - In contrast to 1H-2,3-benzodiazepines, the irradiation of a dilute solution of 1-phenyl-5H-2,3-benzodiazepine (28a) in dry ether at 0°C did not give an isomeric product, but resulted in the isolation of 3-phenylindene (39) (72%). N.m.r. indicated that this was the sole product of the reaction. The yield was lowered by polymerisation of the indene during distillation. Considering the mechanism proposed for the photolysis of 1H-2,3-benzodiazepines (27) it is likely that this reaction also proceeds via a \[\Pi 2s + \Pi 2s\] cycloaddition giving the tricyclic intermediate (40), which undergoes nitrogen loss due to the relief of ring strain and the energetically favourable formation of N₂.

\[\text{(28a)} \xrightarrow{\text{hν}} \text{(40)} \xrightarrow{-\text{N}_2} \text{(39)}\]

It would be interesting to find out if this intermediate (40) is stable at low temperature as in the case of the low temperature photolysis of the 3H-pyrazole as reported by Closs⁶⁴ (see Introduction page 37).
2. Thermolysis of 1H-2,3-benzodiazepines - As has already been shown, thermolysis of 1H-2,3-benzodiazepines in certain cases can lead to isomerisation via a [1,5] sigmatropic shift, affording the corresponding 5H-isomer e.g. formation of (28c) and/or products derived from nitrogen loss e.g. 1-methyl-4-phenyl-1H-2,3-benzodiazepine (41) gives the corresponding 5H-isomer (28c) in 48% yield on thermolysis at 90° for 28 days.

The ratio of products obtained on thermolysis depends on the stability of the individual diazepine. Thus in the case of (7b), thermolysis in toluene or diphenyl ether gives 3-phenylindene (39) in high yield with no trace of isomeric products.

![Chemical structure](image)

Recent investigations carried out in this laboratory on the thermolysis of (41) in chlorobenzene at ca. 130° indicate that at least four products are formed as shown below (Fig. 21).
Factors such as acidity and concentration of reactants were found to markedly affect the product ratios. The results reported here are concerned with the thermolysis of (7b) to give (39).

Having found that 3 phenylindene (39) was the sole product of the thermolysis of (7b) in toluene, the kinetics of the reaction were then investigated. The reasons for this study were:

(1) to attempt to elucidate the mechanism in view of the current interest in azo-compound thermolysis.

(2) 3-phenylindene was not an expected product in the thermolysis reaction since its rate of formation from 1-phenylindene is slow\textsuperscript{109}.

(see later in this section). The chemical shifts of the reactant and product peaks were suitable as to allow the reaction to be followed by n.m.r. spectroscopy. Thus a suitable, inert, high boiling solvent was chosen (diphenyl ether) containing an inert internal standard (2,6-dichlorotoluene). The reaction was carried out in duplicate/
route (a)

\[ \text{route (b)} \]

\[ \text{route (b)} \]
duplicate using a thermostatically controlled oil bath, first at $110^\circ$ then at $120^\circ$ as described in the Experimental Section page 97. This disappearance of diazepine with time was found to follow a first order process in both cases. An Arrhenius plot of the rate constants at the two temperatures gave a value of $137.5 \pm 13 \text{ kJ mole}^{-1}$ for loss of nitrogen. This comes within the range of values reported for decomposition of azo-compounds, some of which are shown in Fig. 22. It is interesting to note the very low value obtained for compound (f) in Fig. 22 due to its decomposition via a concerted mechanism\textsuperscript{73,74}. Calculation\textsuperscript{134} of the enthalpy and entropy of activation for the thermolysis of (7b) using the above activation energy gave $\Delta H^\ddagger = 141 \text{ kJ mole}^{-1}$ and $\Delta S^\ddagger = +14.66 \text{ J deg mole}^{-1}$ (+ 3.5 e.u.).

**Mechanism of the thermolysis** - The decomposition of azo-compounds generally takes place via a non-concerted mechanism involving one or two bond scission or more rarely by a concerted mechanism. In view of the points mentioned earlier (see Introduction pages 41-45), and the value obtained for the free energy of activation, decomposition via a concerted process is ruled out.

The most plausible mechanisms are

(a) a two stage loss of nitrogen takes place with formation of (42). This diradical which is stabilised at one end would be expected to undergo an intramolecular combination/...
Fig 22

Ea Values
K J Mole^-1

Ref 133

Ref 132

Ref 131

Ref 130-143

Ref 73

Ref 62.5

Ref 188

Ref 164

Ref 139

Ref 6N

Ref 125

Ref 154
combination resulting in the formation of 1-phenylindene (43).

(b) a ring opening of the diazepine by the reverse mechanism of ring closure to give the diazoalkene, which decomposes via loss of nitrogen to the carbene. One of the most likely products resulting from this mechanism would again be 1-phenylindene (43) by a C-H insertion of the carbene. If mechanism (b) is operating, it would be reasonable to expect the rate determining step to consist of a \([1,5]\) sigmatropic hydrogen migration, in reverse to 1H-diazepine formation, which would have a negative \(\Delta S^\ddagger\) value. McLean and Haynes\(^{135}\) have previously reported \(\Delta S^\ddagger = -10\) e.u. for the \([1,5]\) hydrogen rearrangement of 1-methylcyclopentadiene, while Roth reported\(^{136}\) \(\Delta S^\ddagger = -12\) e.u. for 5H-perdeuteriocyclopentadiene. The \(\Delta S^\ddagger\) obtained for the thermolysis of (7b); +3.5 ± 0.1 e.u. tends to indicate that (b) is at least not the major decomposition pathway. Values of \(\Delta S^\ddagger\) ranging from +7 to +15 e.u. have been calculated from the kinetics of thermolysis of acyclic azo-compounds\(^{71,137}\), e.g.

\[
\text{Ar—CH—N=N—CH—Ar} \\
\text{Me} \quad \text{Me}
\]

A value of \(\Delta S^\ddagger = +3.2\) e.u. has been obtained by Bergman\(^{138}\) for thermolysis of the bicyclic pyrazoline.
At no point in the thermolysis of (7b) did n.m.r. indicate the presence of 1-phenylindene (43). Thus, if the latter is formed as a primary product in the thermolysis it must be isomerised very quickly to the more thermodynamically stable 3-phenylindene.

Miller and Boyer have studied sigmatropic phenyl and hydrogen migrations in the thermolysis of substituted indenes, and found that the rate constant for isomerisation of the phenylindenes mentioned above was $k = 1 \times 10^{-4}$ min$^{-1}$ at 150$^\circ$. Since the rate constant found for diazepine (7b) thermolysis was $k = 4.5 \times 10^{-3}$ min$^{-1}$ at 120$^\circ$, then this apparently seems to rule out 1-phenylindene as an intermediate, as according to this data its concentration should build up, and then very slowly diminish during the reaction.

Kende and Bogard, prepared 1-phenylindene (43) for the first time in 1967, by the dehydration of alcohol (44) with a catalytic amount of toluene-$p$-sulphonic acid in boiling chloroform.

![Diagram](image)

These workers reported that 1-phenylindene (43) was kinetically stable in the presence of acid, but addition of one drop of a base such as triethylamine gave a very rapid and complete conversion to 3-phenylindene (39). If/...
If (43) is an intermediate in the thermolysis of (7b), then it must therefore have a very short lifetime and, must be rapidly isomerised by a non-thermal route. In view of this work it seemed just possible that the isomerisation of any 1-phenylindene might be catalysed by the unreacted diazepine, even though azo-compounds of this type are normally of very low basicity e.g. pKa azo-benzene is ca. -2.5 whereas the pKa of triethylamine is ca. 11. To investigate this possibility, 1-phenylindene (41) was synthesised by the method of Miller and Boyer 109, and two solutions of 1-phenylindene were made up in diphenyl ether, one of which contained 10% by weight of the diazepine (7b). After being kept for 95 min. at 110⁰, an n.m.r. spectrum of the blank tube showed no measurable isomerisation, whereas the tube containing 10% diazepine showed complete conversion of the 1-phenylindene to 3-phenylindene. The experiment was repeated using resublimed 1-phenylindene with 5% by weight of the diazepine (7b), and a similar result was obtained. Thus, 1-phenylindene cannot be ruled out as an intermediate in the thermolysis of (7b), although it is not detected.

An attempt was made to look for the presence of radical intermediates by means of a C.I.D.N.P. study on the thermolysis in diphenyl ether at 130⁰. This proved inconclusive however, as no peak enhancement or negative peaks were observed.

Thus none of the evidence points against diradical cleavage/...
cleavage whereas the $\Delta S^\pm$ obtained is against the carbene mechanism.
Fig 23

170°

120°

110°

28°
3. Ring inversion studies on 2,3-benzodiazepines -
As already briefly discussed, the 1H-2,3-benzodiazepines with a methylene group at C-1, and the 5H-2,3-benzodiazepines reported in this thesis, show temperature dependent n.m.r. spectra consistent with inversion of the seven membered ring. The $28^\circ$ spectrum of 1-phenyl-5H-2,3-benzodiazepine (Fig. 23) shows an ABX system for $H_A$ and $H_B$. As these are non equivalent, this results in a pair of doubly split doublets giving an 8 line spectrum. Fig. 23 shows the effect of raising the temperature. The 8 lines gradually collapse with coalescence at $120^\circ$. Above this temperature, a doublet gradually appears which is fairly sharp at $170^\circ$. Inversion is now so fast that $H_A$ and $H_B$ are chemically equivalent.

The coalescence temperatures along with the free energies of activation ($\Delta G^\ddagger$) for the compounds studied are shown in Table 4.
Table 4

Ring inversions of 1H- and 5H-2,3-benzodiazepines

<table>
<thead>
<tr>
<th>Compound</th>
<th>T (°C)</th>
<th>ΔG° (kJ mole⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1H-</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>X</td>
<td>Y</td>
</tr>
<tr>
<td>(7d)</td>
<td>Ph</td>
<td>H</td>
</tr>
<tr>
<td></td>
<td>100 + 15 (ODCB)</td>
<td>72 + 4.5</td>
</tr>
<tr>
<td>(7a)</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td></td>
<td>80 + 20 (d₈-T)</td>
<td>67 + 5</td>
</tr>
<tr>
<td></td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td></td>
<td>60 + 20 (d₈-T)</td>
<td>63 + 5</td>
</tr>
<tr>
<td>5H-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(28a)</td>
<td>H</td>
<td>Ph</td>
</tr>
<tr>
<td></td>
<td>120 + 5 (ODCB)</td>
<td>82 + 1.5</td>
</tr>
<tr>
<td>(28b)</td>
<td>H</td>
<td>Ph</td>
</tr>
<tr>
<td></td>
<td>110 + 5 (ODCB)</td>
<td>80 + 1.5</td>
</tr>
<tr>
<td>(28c)</td>
<td>Ph</td>
<td>CH₃</td>
</tr>
<tr>
<td></td>
<td>137 + 5 (DPE)</td>
<td>83.5 + 1.5</td>
</tr>
<tr>
<td>(28d)</td>
<td>Ph</td>
<td>p-tolyl</td>
</tr>
<tr>
<td></td>
<td>180 + 5 (N)</td>
<td>93 + 1.5</td>
</tr>
</tbody>
</table>

In the variable temperature experiments the probe temperature was determined accurately from the chemical shift difference between the methylene and hydroxy protons of ethylene glycol. As seen from the table, the energy barriers are similar to those recorded for the monocyclic diazepines\textsuperscript{90} (ca. 84 k J mole\textsuperscript{-1}). Increasing the bulk of the substituents X and Y increases $\Delta G^\ddagger$, most probably due to increased steric interaction in the transition state between the methylene group and X, and between Y and the peri-hydrogen on the aromatic ring. The values obtained for (7a) and the parent compound are higher than that of the substituted benzocycloheptatriene (46).

![Diagram](image)

(46)

by 12 and 16 k J mole\textsuperscript{-1} respectively\textsuperscript{140}, presumably due to the effect of two nitrogen atoms on inversion. Buchardt\textsuperscript{89} also found higher energy barriers for monocyclic diazepines in comparison to cycloheptatrienes.
II - POSSIBLE EXTENSIONS OF THE CYCLISATION REACTION

A. Attempted cyclisation of trans-stilbene-2-azide.

The synthesis of 1H-2,3-benzodiazepines (7) involved an intramolecular electrocyclic reaction of a diazoalkene. This can be represented in the general case as shown below where \( -a=b=-c \) is the dipole concerned.

\[
\begin{align*}
\text{a} & = \text{b} = \text{c} \\
\text{N} & \quad \text{H}
\end{align*}
\]

Therefore, it might be possible for the azide group \((-N=\overline{N}=\overline{N})\) to give a triazepine. However, Sundberg\(^{107}\) has already shown that the high temperature pyrolysis of azides gives indoles (48) (Fig. 24). In view of the fact that the 1H-2,3-benzodiazepine (7b) was shown to give indene (39) on thermolysis, it was thought possible that a 1,2,3-benzotriazepine intermediate might be involved in Sundberg's\(^{107}\) reaction (Fig. 24).

Consequently, stilbene-2-azide was synthesised, and its low temperature decomposition studied in an attempt to...
Fig 25

\[
\text{CHO} + \begin{array}{c}
\text{Ph} \\
\text{NO}_2
\end{array}
\begin{array}{c}
\text{Ph} \\
\text{NO}_2
\end{array} \xrightarrow{\text{Fe/HCl}} \text{NH}_2
\]

\[
\text{CHO} + \begin{array}{c}
\text{Ph} \\
\text{NO}_2
\end{array} \xrightarrow{\text{Ph}} \begin{array}{c}
\text{Ph} \\
\text{NH}_2
\end{array}
\]

(47)
to isolate a possible triazepine intermediate.

Trans-Stilbene-2-azide was prepared by the reaction scheme depicted in Fig. 25. O-Nitrobenzaldehyde undergoes a Wittig reaction with benzyltriphenylphosphonium chloride to give a mixture of cis- and trans-2-nitrostilbenes which was isomerised to the trans-isomer by boiling under reflux in nitrobenzene with a crystal of iodine. The nitrocompound was then reduced to the amine by Fe/HCl, which in turn was diazotised and treated with sodium azide to give trans-stilbene-2-azide (47).

Decomposition of stilbene-2-azide - The azide showed no sign of decomposition in dimethoxyethane on boiling under reflux under nitrogen for 20 h. In toluene, decomposition was also slow, as the appearance of a second product occurred after 16 h boiling under reflux. After 21 days, the decomposition was complete, and the single isolated product was identified as 2-phenylindole (48, R = Ph) from m.p. and spectral data. Since this was the product isolated by Sundberg, there is apparently no tendency for ring closure to occur in this system, loss of nitrogen being the preferred pathway.
B. Attempted cyclisation of 2-formyl-5-ethoxy-β,β-
dimethylstyrene toluene-p-sulphonylhydrazone.

The mechanism suggested in Section I A. for the
cyclisation of the diazoalkene in the synthesis of
1H-2,3-benzodiazepines is as shown below.

\[
\text{DIAZOALKENE} \xleftrightarrow{(a)} \text{RING CLOSED} \xleftrightarrow{(b)} \text{DIAZEPINE}
\]

The reaction is driven to the right by step (b) which
involves a [1,5] hydrogen migration restoring the
aromaticity of the system (Fig. 2).

It was therefore of interest to replace hydrogen by other
groups to see:

1. if the ring closed product was isolable.
2. if other migrations took place in the second stage (b).
3. if the reaction followed a carbenic path since a
   facile hydrogen migration was no longer possible.
By using p orbitals, groups such as methyl and phenyl can undergo suprafacial migrations forbidden to hydrogen atoms which only possess a 1s orbital. Thus [1,3] and [1,7] suprafacial migrations are symmetry allowed in addition to [1,5] (Fig. 26).

Miller and Boyer\textsuperscript{109} have recently studied sigmatropic migrations in the thermolysis of substituted indenes. Their kinetic and product studies demonstrate that hydrogen migrates to the exclusion of phenyl which is in turn much preferred to methyl. Thus in 7,7-dimethyl-cycloheptatriene, thermolysis does not proceed via a sigmatropic methyl migration\textsuperscript{141}, but by an alternative rearrangement pathway.

2-Formyl-5-ethoxy-β,β-dimethylstyrene (49) was prepared by the ring opening of 3,3-dimethyl-6-ethoxy-3,4-dihydroisoquinoline with dimethyl sulphate. The toluene-\textsubscript{p}-sulphonylhydrazone (50) was then easily prepared by condensation of (49) with toluene-\textsubscript{p}-sulphonylhydrazine.

\begin{center}
\includegraphics[width=\textwidth]{image.png}
\end{center}

Decomposition in dimethoxyethane - The sodium salt of (50) was completely decomposed in 3 h. in boiling dimethoxyethane, giving three major products which were/...
Fig 27
were separated by column chromatography. No trace of any cyclisation product was found, all of the major products being carbene derived. The structures of the products were assigned on the basis of n.m.r. and mass spectral data (see Appendix IX).

The first product, a white crystalline solid, was identified as the dimer of carbene (51) (Fig. 27), which is derived by nitrogen loss from the corresponding diazoalkene. It was assigned the structure bis-\((2-\beta,\beta\text{-dimethylvinyl-4-ethoxy})\text{trans-stilbene}\) (52) (13.5%). As carbene dimerisations are statistically unlikely\(^7\), it is probably formed by attack of carbene (51) on the diazoalkene precursor which then loses nitrogen.

The second product (24.5%) also resulted from carbene (51) attack on the diazoalkene without nitrogen loss giving the azine. The structure assigned was bis-\((2-\beta,\beta\text{-dimethylvinyl-4-ethoxy-benzaldehyde})\text{azine}\) (53), and was a yellow crystalline solid.

The third major product in the reaction, and perhaps the most surprising was assigned the structure \(N-\text{benzyl-2-formy1-5-ethoxy-\(\beta,\beta\text{-dimethylstyrene toluene-}\(\beta\text{-sulphonylhydrazone}\)}\) (54).
This would appear to be formed by an N-H insertion reaction of the carbene (51) on the toluene-$p$-sulphonylhydrazone (50). However, at the start of the reaction, all of (50) should have been present in the salt form. The formation of (54) is probably caused by the presence of ethanol of crystallisation in the sodium salt, a frequent observation for 1,2-benzodiazepine precursors$^{142}$. Thus (54) can be formed by the following mechanism (Fig. 28).

The diazoalkene is protonated by ethanol giving a diazonium cation which reacts with the sodium salt giving (54) with loss of nitrogen. The residue of the reaction contained/...
contained a little of products (53) and (54) along with polymeric material.

It is concluded therefore, that no group migration occurs from the ring closed product, which reverts to the diazoalkene and decomposes via a carbenic mechanism. This result supports the proposed mechanism in that the reaction is driven to the right by a facile hydrogen migration. It would be interesting to see if any cyclised product is produced from a structure such as (55) where only a phenyl migration is possible.

\[ \text{(55)} \]
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