PYROLYTIC SYNTHESES OF FUSED BRIDGEHEAD NITROGEN HETEROCYCLES.

BY

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Thesis presented for the degree of DOCTOR OF PHILOSOPHY

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DECLARATION.

I declare that this thesis is my own composition, that the work which is described has been carried out by myself, unless otherwise stated, and that it has not been submitted in any previous application for a higher degree.

This thesis describes the results of research carried out in the Department of Chemistry, University of Edinburgh, under the supervision of Dr. Hamish McNab, since January 1 1994, the date of my admission as a research student.
DEDICATION.

I should like to dedicate this thesis to all the people who have given me support and encouragement over the years.
ACKNOWLEDGEMENTS.

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I should also like to thank Professor Ramage for permitting me to undertake a part-time PhD.

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Aspects and Applications of NMR spectroscopy - Dr. I. H. Sadler (5 lectures)

Heterocyclic Chemistry - Dr. J. Sharp (8 lectures)
There are two distinct areas of work in this thesis, both involving pyrolytic syntheses of nitrogen heterocycles. The first area of work extends a previous synthesis of 1H-azepin-3(2H)-ones to examples with a fused ring in the 1,2-position. The synthetic strategy for such azepinones involved preparation of enaminals incorporating cyclic amines with different ring sizes, then condensation of the enaminals with Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione). Flash Vacuum Pyrolysis (FVP) of the Meldrum's acid derivative gave the fused azepinone with dicyclopentadienone formed by a competing reaction. As the size and nature of the nitrogen containing ring of the Meldrum's acid derivative was systematically altered, the amount of azepinone formed reached a maximum with six and seven membered rings.

The crystal structure of two typical enaminals were elucidated. The electron impact mass spectra of enaminals had not been previously studied and showed an unusual (M-17) breakdown peak due to loss of OH from the molecular ion and deuterium labelling studies were carried out to determine the mechanism of this breakdown. The hydrogen atom of the OH lost, was found to come from the aliphatic position α-to the nitrogen atom of the enaminal.

An alternative route to propargyl aldehyde (propynal), used in the synthesis of the enaminals, was established by a retro-ene rearrangement of dipropargyl ether.

The second area of work involved combining two known thermal rearrangements into one cascade reaction. The initial thermal process is the shift of
a pendant group from the nitrogen atom of a pyrrole or imidazole derivative to another ring position. This was further studied by pyrolysis of 1-, 2- and 3 phenylpyrroles, and 1-, 2- and 4-phenylimidazoles. Although there is interconversion between the 2- and 3-substituted pyrroles, movement of the pendant group from the nitrogen atom is irreversible.

The second stage of the cascade mechanism involves concerted loss of an alcohol molecule from 2-(2-alkoxycarbonylphenyl)pyrrole followed by the electrocyclic ring closure of the resulting ketene intermediate. These two thermal processes were combined by using readily available 1-substituted pyrroles, giving 5H-pyrrolo[2,1-a]isoindol-5-one in high yield. The chemical and physical properties of 5H-pyrrolo[2,1-a]isoindol-5-one were studied. The pyrolysis strategy was extended to include a number of derivatives structurally related to the original precursor, and in all cases the expected cyclised products were obtained. When the corresponding 1-(2-hydroxymethylphenyl)pyrrole was pyrolysed at 925 °C, 5H-pyrrolo[2,1-a]isoindole was only a minor product and benzofulvene and naphthalene were formed. The mechanism of formation of these hydrocarbons was studied by deuterium labelling.
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INTRODUCTION.

3H-Azepin-3-ones.
This introduction aims to review $3H$-azepin-3-ones in all the oxidation states which have been reported, examining preparation, reactions and spectroscopy.
Theoretically there are many more possible structures than actually have been studied. Of all the possible structures, only 1-4 are represented in the literature. Structure 2 for example has 5 isomers (2, 2a, 2b, 2c, 2d) but only 2 is reported. Structure 3 has 6 possible isomers and only one (3) is reported in the literature.

The depth to which each oxidation state is examined in this review is a reflection of the data available.

1. Synthesis.

(a) Hexahydro[3H]azepin-3-ones (azepan-3-ones).

\[
\begin{align*}
\text{O} \\
\text{N} \\
\text{H}
\end{align*}
\]

1

A variety of methods has been used to prepare the above compound (1). The first reference to the preparation of an azepan-3-one describes an extension of the application of the internal acetoacetic ester condensation (the Dieckmann reaction) to the synthesis of cyclic β-ketoesters. The Dieckmann reaction was then further applied to amines of the type \(\text{C}_2\text{H}_5\text{OOC(CH}_2)_m\text{N(CH}_3)(\text{CH}_2)_n\text{COOC}_2\text{H}_5\) (dicarbethoxydialkylmethylamines) to prepare cyclic amino ketones. When this reaction was applied to the ester (5) using sodium ethoxide as the condensing agent
and xylene as a solvent, the seven membered cyclic ketone 8 was isolated as the hydrochloride salt of the condensation product.

There are two possible condensation reactions as illustrated by intermediates 6 and 7 in Scheme 1. The condensation reaction, initiated by ionisation on the carbon α- to the nitrogen, occurred much more slowly, if at all, using sodium ethoxide. However, the reaction conditions required to produce 8 may have been sufficiently strenuous and prolonged to cause some condensation on the carbon α- to nitrogen, thus producing both of the possible isomeric β-keto esters. This was offered as an explanation as to why the hydrochloride salt of the esters, isolated directly from the reaction, could not be crystallised. The mixture of esters was hydrolysed and the hydrochloride salt of the ketone 8 was isolated.
This reaction was later used to obtain the amino ketones 9 and 10.\textsuperscript{2,3}

\[
\begin{align*}
\text{9} & \quad \text{H}_3\text{C} - \text{N} - \text{H}_5\text{C}_2 \quad \text{10} \\
& \quad \text{CH}_3 \\
& \quad \text{CH}_3
\end{align*}
\]

Two preparative methods involve ring expansions. Firstly, a diazoacetate ring expansion (Scheme 2) was applied to \textit{N}-methoxycarbonyl-3-piperidone 11 and yielded a mixture of azepane-3-keto 12 and 4-keto ester 13 from which the 4-keto was removed as a copper chelate 14 (Scheme 3).\textsuperscript{4}

\[
\begin{align*}
\text{O} & \quad \text{N} - \text{CH} - \text{COOEt, BF}_3, \text{O(Et)}_2 \\
\text{11} & \quad \text{Me} \\
\rightarrow & \quad \text{EtO} \quad \text{EtO} \\
\text{O} & \quad \text{N} - \text{CH} - \text{COOEt, BF}_3, \text{O(Et)}_2 \\
\text{12} & \quad \text{12} \\
\text{13} & \quad \text{13} \\
\text{HCl} & \quad \text{K}_2\text{CO}_3, \text{CH}_3\text{OCCl}
\end{align*}
\]

\textbf{Scheme 2}
Scheme 3

Around 25% of 13 existed in the enol form 16 whereas the enol form of 12 could hardly be detected.

After treatment of the mixture of 12 and 13 with copper (II) acetate, the copper (II) chelate 14 could be isolated. Thus there was reason to suppose that 12 and 13 might be separated via copper (II) salt formation of 14. The 3-keto ester was then hydrolysed to the amino ketone to give 15.

Secondly, ring expansion of the phenyl selenide 17 was achieved under free radical generating conditions, with tributyltinhydride and AIBN in refluxing benzene\(^5\). In this way the keto ester 18 was obtained in 71% yield (Scheme 4).
This ring expansion probably occurs firstly by formation of a primary radical, then attack by this radical on the carbonyl carbon. The resulting oxy radical then forces the internal cyclopropane ring bond to cleave. The radical centre is shifted to the carbon adjacent to the ester where it is stabilized through conjugation. The ester plays a critical role in the rearrangement. It appears to activate the ketone toward attack by the nucleophilic methylene radical and once the bond to the carbonyl carbon is formed, the ester provides the driving force for cyclopropane ring cleavage leading to the ring expansion product 18.

Intramolecular Friedel-Crafts cyclisation of N-tosylchloroalkenols was effected in 90% H$_2$SO$_4$ at -15° to 0° C providing ketones 19. This method utilises the chloro-2-enyl group as a useful 3-carbon synthon in the starting material 20 (Scheme 5).
This could best be cyclised by treatment with 90% sulphuric acid at 0 °C (30%) and may proceed by the mechanism shown in (Scheme 6).

Another ketone 21 could also be obtained (57%) from the corresponding secondary benzylic alcohol when R=CH₂CH₂CH(OH)Ph.
Iodide promoted Mannich cyclisation of 5-alkynylamine 22 provided convenient access to 3-alkylideneazepane 23 which, following ozonolysis, yielded the azepan-3-one 24.  

Another method for synthesising azepanes was by the electrochemical oxidation of α,β-unsaturated carbamates. Electrochemical oxidation of 25 in acetic acid, heating the products and subsequent hydrolysis gave 26 in 22% yield. Oxidation of 25 with \textit{m}-chloroperbenzoic acid (\textit{m}-CPBA) in toluene, followed by heating the
resulting solution in the presence of a catalytic amount of acid without isolation of the oxidation products also afforded 26 in 50% yield (Scheme 8).

\[
\begin{array}{c}
\text{Scheme 8}
\end{array}
\]

The treatment of aminodiazo-ketone substrate 27 with soluble Cu(II) catalysts yielded cyclic ylides which undergo a [2,3] shift to give the azepinone 28 (Scheme 9). The generation and rearrangement of these ylides has evolved as an important strategy in heterocyclic and carbocyclic synthesis. Examination of this reaction, which involves the use of Cu(acac)₂ resulting in the formation of azepinone in 58-61% yields suggests a remarkably efficient, and selective capture of the copper carbenoid by amine to give a medium sized ylide in preference to other carbenoid pathways.

\[
\begin{array}{c}
\text{Scheme 9}
\end{array}
\]
Also, the Rh$_2$(OAc)$_4$ catalyzed cyclisation of the α-diazo ketone 27 in benzene at reflux gave a 56% yield of azepinone 28.

![Scheme 10](image)

Micro-organisms can synthesize azepanes by oxygenation of N-substituted azepines. In a study which provided new methods for inserting oxygen functions at positions in heterocyclic compounds which are less accessible by chemical means, the micro-organism *Sporotrichum sulphurescens* converted N-benzoylazepine 29 into several products including the azepan-3-one 30 and also the 4-keto isomer 31 and corresponding alcohol 32. The overall conversion to ketones was improved by adding chromium trioxide to the crude bioconversion product (Scheme 11).

![Scheme 11](image)
When molinate 33 (a herbicide) came into contact with a micro-organism of the *Fusarium* species, 12 3-ketomolinate 34 was detected, and an even more highly oxygenated product 35 was detected when molinate was metabolized by organisms presents in Kazakstan rice paddies. 13

![Chemical structures](attachment:image.png)

A study of urinary metabolites of *N*-nitroso-azepane 36 showed that hydroxy and ketone 37 derivatives were formed. This observation was part of a study into the carcinogenic nature of *N*-nitroso compounds. The *N*-nitroso-azepane was found to induce oesophageal and liver tumours. 14

![Scheme 12](attachment:scheme.png)
(b) 1,2,6,7-Tetrahydro[3H]azepin-3-ones.

Only one example of this series (2) appears in the literature.\textsuperscript{15} It was isolated as a by-product in the preparation of azabicyclic compounds by [2+2] cycloadditions (Scheme 13).

These azabicyclic compounds were prepared from unsaturated $N$-tosylaminoamides 38 which were treated with triflic anhydride in dichloromethane.
followed by slow addition of collidene (2,4,6-trimethylpyridine). This yielded a solution of an iminium salt which was then heated at 90 °C for 90 minutes. Hydrolysis yielded ketonic products which were purified by chromatography on silica gel. The [2+2] cycloadduct 39 is the major product (71%), but 6% of the azepinone 40 was also isolated. This was thought to be the result of an intramolecular Friedel-Crafts type acylation of the alkene.

(c) 1,2-Dihydro[3H]azepin-3-ones (1H-Azepin-3(2H)-ones).

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{H}
\end{array}
\]

3

The almost exclusive method for the preparation of the 1,2-dihydro[3H]azepin-3-ones involves the flash vacuum pyrolysis (FVP) of certain dienamine derivatives of Meldrum’s acid.\textsuperscript{16,17} These Meldrum’s acid compounds lose acetone and carbon dioxide during FVP and rearrange \textit{via} a stable methyleneketene intermediate to give the azepinone 43 by electrocyclisation or to a bicyclic intermediate by cycloaddition across the carbonyl component of the ketone. Further collapse of the bicyclic compound leads to cyclopentadienone 44 and an imine. The pyrolytic cyclisation can take place at \textit{N}-methyl groups, \textit{N}-methylene groups and or \textit{N}-methine groups, leading to 1-substituted, 1,2-disubstituted and 1,2,2-trisubstituted
derivatives respectively. In a case of competitive substituents, e.g. $R^1 = H$, $R^2 = Pr'$, pyrolysis takes place with little regioselectivity.

![Scheme 14]
An azepinone, synthesised from the Meldrum’s acid derivative 45 using FVP, resulted in NMe₂ substitution in the 7 position of the product 46. The net result was an azepinone 46 in which the electron distribution was substantially modified (Scheme 15).

Another method for the preparation of a very specific 1H-azepin-3(2H)-one was given by Katritzky et al involving a ring expansion using LDA (lithium di-isopropylamide). 1-(α-Methylbenzyl)-4,6-diphenyl-2-pyridone 47 reacted with LDA in THF at -78 °C to give the anion 48. This anion rapidly rearranged and on quenching with H₂O, azepin-3-one 49 was formed (Scheme 16).
Two methods have been reported for the preparation of these fully unsaturated compounds. The first method involves the reaction of tin chloride with cyclobutane imidic esters followed by dehydrogenation of the resulting imidic ester.
The dehydrogenation of the 6-ethoxy and 6-unsubstituted derivatives was completed within 1-2 minutes at room temperature (Scheme 17).

![Scheme 17]

Alternatively, methylation of the azatropolone with diazomethane gave a mixture of the 3-0-methyl and 2-O-methyl azatropolone in around a 1:1 ratio (Scheme 18).  

![Scheme 18]
2. Reactions.

(a) Azepan-3-ones.

Very little work has been done on the reactions of azepan-3-ones. Reaction with \( \text{NaBH}_4/\text{C}_2\text{H}_5\text{OH} \) appears to proceed normally to give a 3-hydroxyazepane \( \text{50} \).  

\[
\text{Scheme 19}
\]

Clemmensen reduction of bases such \( \text{51} \) or \( \text{52} \) as gave rearranged products \( \text{53} \) and \( \text{54} \) respectively.  

This type of ring contraction is well known for other cyclic aminoketones of different ring sizes (Scheme 20).  

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The mechanism for the Clemmensen reaction has not been elucidated, but it is fairly certain that the corresponding alcohol is not an intermediate since alcohols prepared in other ways fail to give the desired product.

Wolff-Kishner reduction produces azepanes but also alkenes. These were observed when examining the crude product of the Wolff-Kishner reduction of 55.

As shown in Scheme 21, the azepane 56 was isolated as a high melting picrate 57 from the crude distillate of the reaction. The distillate furnished no low melting...
isomeric picrate but the presence of a secondary amine 58 was detected and confirmed by Infra Red spectroscopy with an absorption maximum at 3280 cm\(^{-1}\). The presence of unsaturation was indicated by peaks at 1655 and 966 cm\(^{-1}\). A quantitative catalytic hydrogenation of the distillate mixture provided an estimate that approximately 44% of the total Wolff-Kishner product consisted of unsaturated isomers, of which 58 is representative. The picrate of 56 was isolated from the catalytic hydrogenation mixture, and the presence of \(N\)-methylheptylamine was shown by the formation of its \(\alpha\)-naphthylthiourea derivative, thus revealing the \(N\)-methylheptenylamines 58 to be precursors for this final reduction.

Although unstable, azepan-3-ones have been successfully employed to annelate further rings to their structure to generate zwitterionic compounds.\(^{24,25}\) Thus the keto ester was reacted with hydroxylamine followed by deprotection with hydrogen chloride and basic work-up to give the zwitterionic compound 59 as shown in (Scheme 22).
These, and related zwitterions, have been used in the study of mammalian glycine antagonists. Other examples can be found in the patent literature.

Photochemical transformation of 60 led to the formation of 61.\textsuperscript{26}
Irradiation of the 7-membered substrate to give 61 (33%) was 20 times slower than the rate of formation of the corresponding 8-membered ring. The longer irradiation time that is required for the photocyclization of 60 could be responsible for the lower yield in this reaction, as the pyrrole product undergoes substantial decomposition on prolonged irradiation. A mechanism consistent with these results was outlined.

Scheme 24

Excitation of the vinylogous amide chromophore leads to bond homolysis to form the stabilized diradical, 62 which can then undergo ring closure to regenerate the starting material or, via cyclization at the other terminus of the aza-allylic radical, to the ring expanded ketoimine 63. The imine can then undergo a ground state transannular cyclization to give, after dehydration, the observed pyrrole product 61.
Also, the azepinone 64 was reacted with 2-(hexyloxy)-3-lithiopyrazine to give 65. This compound is used in a strategy to develop therapies for dementia.  

![Scheme 25](image_url)

**(b) 1,2-Dihydro[3H] azepin-3-ones.**

The geometry of this compound (3) has significant implications for the subsequent reactions it undergoes. X-ray crystallographic studies of the N-phenyl azepinone 66 show that it is an almost planar dienaminone system bridged by a methylene group (although the system is non-planar as a whole). 17 This electron rich system is potentially active towards electrophiles at carbon and oxygen centres as shown in Figure 2. 28
Analysis of $^1$H and $^{13}$C N.M.R. spectra show that $O$-protonation using trifluoroacetic acid (Scheme 26) takes place. Exchange at the 4-position was found to be considerably more rapid than that at the 6- and 2- positions.$^{28,29}$

Scheme 26
O-Alkylation using triethylxonium tetrafluoroborate takes place to give 67

Sequential deuterium exchange at the 4-, 6- and 2-positions of the methyl substituted azepinone occurs via the free base to give 68.

The potential acidic properties of the 2-methylene group of the azepin-3-ones are profoundly influenced by the counter Hückel (8π electron) character of the resulting anion. Thus deuterium exchange does not occur at all under mild basic conditions e.g. sodium methoxide in CD₃OD. A quantitative ring contraction to o-aminophenol derivatives 69 takes place (Scheme 27).

Treatment of 70 and 66 with N-halogenosuccinimides gives 4-halogeno 71 and 4,6-dihalogeno products 72.$^{29}$

The X-ray crystal structure of the 4-chloro derivative 73 shows that the halogen substituent has little effect on the geometry of the ring.$^{28}$
The relative reactivity of the ring positions in the deuterium exchange and halogenation reactions \([4>6(>2)]\) is parallel to that of electronically related sites in open chain dienaminones and pyridin-2-ones.\(^{29}\)

The reactivity of the diene unit of the azepin-3-one is demonstrated by cycloaddition and electrocyclisation reactions. Compound 66 reacts with maleic anhydride in two hours at room temperature to give 74.\(^{30}\)

Reaction with acetylenic dienophiles is accompanied by cleavage of the bridge at room temperature to give benzene derivatives in high yield (Scheme 28). The
reaction is thought to proceed via an intermediate 75, which can then undergo loss of
two stable fragments (CO and imine) to yield the aromatic product 76.

\[
\begin{align*}
\text{Me} & \quad \text{CO}_2R^2 \\
\text{R}^1 \\
\end{align*}
\]

Scheme 28

Photolysis of the azepinone 66 gives the bicyclic compound 77, but attempted
recrystallisation or distillation led only to recovery of the azepinone. This behaviour is
known for related bicyclic photoproducts some of which can only be detected at low
temperatures although concerted disrotatory thermal ring opening is formally
disallowed.\(^{31}\)

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

77
The synthesis of 46 as previously mentioned, which incorporates a strong electron-donating group at the 7-position, substantially modified the electron distribution in the conjugated system of these heterocycles.

![Chemical structure of 46](image)

The effect of the dimethylamino substituent on the stereoelectronic properties of the azepinone ring is reflected in a substantial increase in the free energy of activation for ring inversion by comparison with simple derivatives. The effect of the electronic interaction with the dienaminone conjugated system is shown by restricted rotation of the dimethylamino group.

![Scheme 29](image)
The reactivity towards electrophiles is affected, resulting in both O and C protonation. The presence of an amidinium unit, which can effectively delocalise the positive charge, is the rationale for the enhanced stability of this species.

In contrast with unactivated azepinones, 46 is sufficiently reactive to give a substitution product 78 with methoxymethylene Meldrum’s acid under mild conditions.

The dimethylamino compound reacted with two equivalents of methyl propiolate to give a single product identified as the 1,3,4-trisubstituted pyrrole 79.
This mechanism shown in Scheme 30 is given further support by the reaction of 46 with dimethyl acetylenedicarboxylate from which the related enamine 80 can be isolated in 35% yield. In this instance the electron density in the enamine system is insufficient to promote cyclisation under such mild conditions.
Only one reaction is reported for this type of compound. This was a benzilic type rearrangement (Scheme 31) where the base attacked the imine moiety of 81 resulting in ring contraction to give the product 82.
Scheme 31

A solution of 81 in benzene was absorbed on a silicon dioxide column and allowed to stand overnight at room temperature. Elution with benzene gave 82.

(a) $^1$H and $^{13}$C NMR Spectra.

(i) Azepan-3-ones.

\[
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{O} \\
\text{C} \\
\text{N} \\
\text{O} \\
\text{C} \\
\text{N} \\
\text{O} \\
\text{C} \\
\text{N} \\
\end{array}
\]

There is limited $^1$H NMR data available on these compounds and they generally tend to be poorly assigned and have overlapping multiplets. From the data available, we were able to make direct comparisons with the signal at position 2 in the N-1, C-2, C-3 unit (Figure 3):

\[
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{O} \\
\text{C} \\
\text{N} \\
\text{O} \\
\text{C} \\
\text{N} \\
\text{O} \\
\text{C} \\
\text{N} \\
\end{array}
\]

Figure 3

If we first compare the chemical shift of the protons on C-2 with different nitrogen substituents we find that $\delta_H$ (in ppm) varies as shown below for 83, 84 and 85:

\[
\begin{array}{ccc}
\text{EtOOC} & \text{N} & \text{O} \\
\text{83} & \text{Ph} & \text{H} \\
\delta_H 3.10, 3.35 \\

\text{N} & \text{H} & \text{O} \\
\text{84} & \text{Tosyl} & \text{H} \\
\delta_H 3.81 \\

\text{N} & \text{H} & \text{O} \\
\text{85} & \text{MeO} & \text{C=O} \\
\delta_H 4.16
\end{array}
\]
The H-2 protons are distinguishable from the protons at position 7 both in terms of chemical shift and multiplicity. In 85, the H-2 resonances occur as a broad peak due either to restricted rotation of the carbamate moiety or due to ring inversion in the NMR timescale. In contrast, the 2-H signals of 83 occur as two mutually coupled resonances at $\delta_h$ 3.10 and $\delta_h$ 3.35 owing to the dissymmetry caused by the ester substituent. The fact that little line broadening is reported suggests that the substituent hinders the ring inversion or that carbamate rotation may be the reason for the broad signals in 85 (Figure 4).

![Figure 4](image)

(ii) 1,2-Dihydro[3H]azepin-3-ones.

![3](image)

The 1H-azepin-3-ones have been thoroughly investigated and their spectra well documented. These compounds are characterised by their $^1$H NMR spectra.
which show two pairs of doublets and two pairs of double doublets in the region (δ_H 5-7).^{17,32}

Protons at the electron rich sites (H-4) and (H-6) are shielded relative to H-5 and H-7. The H-4 proton signal is always shifted to higher frequency than the H-6 proton probably due to the deshielding effect of the adjacent carbonyl group. The relative positions of H-5 and H-7 are variable and dependent on the nitrogen substituent.

The chemical shifts of all the ring protons indicate that competitive delocalisation takes place with aryl substitution on the nitrogen as in compound 66, even although the azepinone and phenyl rings are at an angle of ~50° with respect to each other in the solid state. When this angle is increased, for example with dimethyl substitution at the 2-position (86), the effect of competitive delocalisation of the lone pair of nitrogen is almost negligible. These alkyl groups at the 2-position have very little effect on the chemical shifts of the remaining protons in the molecule.

The proton-proton coupling constant \( ^3J_{4,5} \) of 11.0-11.5 Hz is to be expected for a Z-olefinic coupling in a 7-membered ring system. The other alkene unit shows a much smaller value \( ^3J_{6,7} \) 7.2-8.5 Hz; because the bond angles of the ring are smaller than expected for a regular 7-membered ring, this will tend to increase the angle.
between the appropriate hydrogen atom and the double bond giving rise to reduced coupling.

The remaining vicinal coupling constant is similar in size or slightly larger than $^3J_{6,7}$ even although it is across a formal single bond.

The spectrum of the 2-substituted compound 87 showed good resolution and a full analysis of long range coupling constants was possible.

At room temperature, the 2-substituent signals appeared as sharp singlets owing to rapid ring inversion in solution. At lower temperatures, the H-2 resonance of the N-phenyl derivative 66 showed considerable broadening. In $[^2\text{H}_6]$ acetone at 360 MHz, coalescence had not been reached even at -105 °C. However in the 2,2-dimethyl compound 86, partial separation of the pseudo axial/equatorial substituents was successfully achieved at -104 °C : $[^2\text{H}_2]$methylene dichloride solvent, 360 MHz.
In the $^{13}$C NMR spectra, the electron deficient sites (C-5 and C-7) occur at higher frequency ($\delta_C$ 137-147 ppm) than C-4 or C-6 at ($\delta_C$ 99-126 ppm). The signals due to electron rich 4- and 6- positions are well separated (usually > 20ppm) with the C-6 resonance at particularly low frequency ($\delta_C$~100). The carbonyl carbon C-3, resonates at $\delta_C$ 180-185 ppm. The C-7 resonance is shielded by 10 ppm in the 2,2-dimethyl-1-isopropyl derivative 88 with respect to the N-methyl derivative 89.

A similar effect is not shown by 2,2-disubstitution in the N-aryl series, so it may be possible that the change in N-alkyl substitution is contributing.

The pattern of proton-carbon one bond coupling constants is similar to that of an open chain dienaminone model compound. Analysis of long-range couplings is shown for compound 66.
(iii) \([3H]\text{Azepin-3-ones.}\)

The \([3H]\)-azepin-3-ones have all been prepared as highly substituted compounds. However, from the reported \(^1\text{H}\) NMR spectra it was possible to note how the proton signal at C-5 was affected by different substituents on C-6 when C-4 had a COOEt substituent.\(^{20}\)
Table 1. $^1$H NMR spectra of [3H]-azepin-3-one derivatives.

<table>
<thead>
<tr>
<th>R</th>
<th>$\delta_H$ at H-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>8.17</td>
</tr>
<tr>
<td>OEt</td>
<td>8.00</td>
</tr>
<tr>
<td>H</td>
<td>8.03</td>
</tr>
<tr>
<td>OAc</td>
<td>7.88</td>
</tr>
</tbody>
</table>

$\delta_H$ quoted in ppm

There is little difference in the chemical shift of $\delta_H$ at H-5 between the substituents Ph, OEt, and H as the effect is transmitted across a single bond between C-5 and R.

It was also possible to make a further comparison of the effect on the proton signal at C-5 when the COOEt substituent was on C-6 as illustrated in Table 2.
Table 2. $^1$H NMR spectra of [3H]-azepin-3-one derivatives.

<table>
<thead>
<tr>
<th>R</th>
<th>$\delta_H$ at H-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>7.80</td>
</tr>
<tr>
<td>OEt</td>
<td>7.28</td>
</tr>
</tbody>
</table>

$\delta_H$ quoted in ppm.

In this case the effect of the R group is transmitted across a double bond and the effect is greater.

(b) **Comparison of $^{13}$C NMR spectra.**

Finally, interesting comparisons can be drawn between the C=O carbon signal of all the azepinones reviewed here and that of cycloheptanone (90) and O-methyltropolone (91) itself (Figure 5).
Both saturated compounds have carbonyl signals at $\approx \delta_c 211$ ppm. For the 1,2-dihyro[3H]azepin-3-ones, $\delta_c$ is considerably lower at 180-186 ppm. The [3H]azepin-3-ones have the lowest value at $\delta_c 172$ ppm which is the same as the carbonyl signal of O-methyl tropolone itself, indicating extensive conjugation around the ring system resulting in reduction of the double bond character of the carbonyl.
Infra-red.

Infra-red analysis of the azepan-3-ones revealed that the C=O absorption varied between 1705 and 1715 cm\(^{-1}\), for all of the azepan-3-ones mentioned in the previous sections.

Mass Spectrometry.

The mass spectra of azepan-3-ones show significant molecular ions, then loss of the \(N\)-substituent to give a fragment of \(m/z\) 112. Further breakdown involves loss of 14 amu to give \(m/z\) 98.\(^{12}\)

The mass spectra of 1H-azepin-3(2H)-ones show a strong molecular ion then loss of CO and aromatisation to give a pyridinium species found in the spectra of the corresponding Meldrum’s acid derivatives. Alternatively, \(N\)-aryl examples generate an iminium radical cation from the \(N-(1)-C-(2)\) fragment \(\text{PhN}=\text{CH}_2.\)^{17}

Only accurate mass data is available for the very highly substituted 3H-azepin-3-ones.

In conclusion, the azepin-3-ones have been synthesised by a variety of methods and studied to varying depths. One example only appeared as the by-product in the synthesis of another compound, with no spectroscopic data available at all. The 1,2-dihydro compounds have been most extensively studied, and the presence of the dienaminone system allows scope for a variety of reactions to be carried out.
In the next section, the synthetic method involving pyrolysis of Meldrum's acid derivatives to form 1,2-dihydroazepinones has been extended to include azepinones with fused rings in the 1,2-position.
RESULTS AND DISCUSSION.
1. **Introduction.**

The aim of this section of work was to synthesise bicyclic azepin-3(2H)-ones, by Flash Vacuum Pyrolysis of Meldrum's acid derivatives as described in the introduction. Four examples of azepin-3(2H)-ones, with different sized fused rings were studied, i.e. five, six, seven and eight membered rings. This enabled a study of the effect of changing ring size of the fused ring on the formation of, and spectroscopic properties of the azepinones. In addition, the effect of adding a fused benzene ring in two different positions of the six membered ring species was also investigated.

The technique of Flash Vacuum Pyrolysis (FVP) uses the apparatus illustrated in Figure 6.
The technique involves subliming the precursor through a hot tube under vacuum and condensing the products in a trap cooled by liquid nitrogen. The object of the procedure is to raise the molecules rapidly to their reaction temperature, whilst keeping them as much as possible in isolation, and then to condense the molecules under conditions such that further reaction is limited. The relatively short contact time ($10^{-3}$-$10^{-1}$ sec) ensures that most functional groups can survive unchanged under typical conditions. There are no other reactants, no reagents and no solvents involved, so intramolecular reactions are favoured.35

Flash Vacuum Pyrolysis (FVP) of vinylogous aminomethylene derivatives of Meldrum's acid 92 gives successful formation of azepinones.

This work has been developed from the successful formation of pyrrolones by FVP. Gas phase pyrolysis of aminomethylene derivatives of the Meldrum's acid derivative 93 had yielded 1H-pyrrol-3(2H)ones 94 and has given access to exceptionally stable methyleneketenes. It was shown by spectroscopic studies i.e. matrix isolation of the methyleneketene 36 that the reaction involved the stepwise
elimination of acetone and carbon dioxide to give the methyleneketene derivative 95 (Scheme 32).\textsuperscript{37}

\begin{align*}
\text{O} & \quad \text{FVP} \quad \text{O} \\
\begin{array}{c}
\text{N} \\
\text{CH(R^2)_2}
\end{array} & \rightarrow \\
\begin{array}{c}
\text{N} \\
\text{CH(R^2)_2}
\end{array}
\end{align*}

\text{Scheme 32}

Evidence was also presented for the existence of the intermediate 96 on the reaction pathway, \textit{en route} from the methyleneketene to the pyrrolone.\textsuperscript{37} The transformation requires intramolecular hydrogen transfer from, and ring closure to, a site adjacent to the nitrogen atom of the methyleneketene.

In order to study this mechanism further, a pyrolysis was carried out on the mono-deuteriated Meldrum’s acid derivative 97.\textsuperscript{38}
Investigation of the product by $^1$H NMR and $^2$H NMR spectroscopy reveals that the transferred deuterium atom is located exclusively at C-4 and as expected, some unchanged deuterium remains at the 1-position of the N-cyclohexyl ring. The mass spectrum of this compound shows the absence of dideuteriated and non-deuteriated products which strongly suggest the reaction is intramolecular. This conclusion was confirmed by a co-pyrolysis of 97 and 98; no cross-over deuteriation was detected by $^1$H NMR spectroscopy of the products.

Employing the use of chiral centres at the site of H-transfer provided a detailed probe of the stereochemical changes during the course of the reaction. Pyrolysis of 99 and 100 resulted in partial loss of chirality in the products. Pyrolysis of 99 gave a 75:25 mixture of the enantiomeric pyrrolones 101 and 102 whereas pyrolysis of 100 gave the reverse ratio (Scheme 33).
Since there is at least partial loss of chirality from the above examples, the ring formation from the methyleneketene cannot be concerted and must involve an
intermediate with sufficient lifetime to allow racemisation after the hydrogen transfer step.

The pyrolysis method was also pursued as a route to thiophen-3(2H)-ones which are often very unstable, air sensitive and acid sensitive compounds which decompose easily. Pyrolysis of the Meldrum’s acid derivative 103 proceeded cleanly and efficiently via the dipolar intermediate 104 to thiophenone 105, which is in equilibrium with its hydroxy tautomer 106 (Scheme 34).  

![Scheme 34](image)

The same strategy was used for the synthesis of bicyclic pyrrolones. This involved the pyrolysis of aminomethylene Meldrum’s acid derivatives where R¹ and R² are part of the same ring 107 (Scheme 35) resulting in fused pyrrolones e.g. 108 109.
Pyrolysis of 107 yielded a 52 : 48 mixture of diastereoisomers, 108 and 109, which could be separated by chromatography.
Synthesis of 1H-azepin-3-(2H)-ones.

The first step in the route to azepinones was to synthesise suitable enaminals from the reaction of amines with propargyl aldehyde generated in situ. The enaminals were then reacted with Meldrum's acid and the Meldrum's acid derivative pyrolysed to give the azepinone (Scheme 36).

Scheme 36
2. **Enaminals.**

(a) **Preparation.**

The enaminals which were prepared were 110-115.

These were all prepared by the reaction of the appropriate amine with propargyl alcohol in benzene in the presence of an excess of activated manganese dioxide. Thus the propargyl alcohol is oxidised to the aldehyde and then reacts with the amine by conjugate addition to give the enaminal. The manganese dioxide is filtered off, washed with methylene chloride and the filtrate is evaporated and the product purified by Kugelrohr distillation or recrystallised from ethanol. The enaminal is obtained in yields of 18-40%.
(b) $^1$H and $^{13}$C NMR spectroscopy.

These compounds are characterised by three distinctive signals in their $^1$H NMR spectra. These are at 8.7-9.4 ppm (doublet) corresponding to the aldehydic proton H-1, 6.8-7.8 ppm (doublet) corresponding to the proton adjacent to the nitrogen atom. H-3 and at 5.0-5.6 ppm (doublet of doublets) corresponding to H-2 see (Figure 7).

![Figure 7](image)

Table 3. $\delta_H$ NMR data for enaminals.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\delta_H^1$</th>
<th>$\delta_H^2$</th>
<th>$\delta_H^3$</th>
<th>$^3J_{1,2}$</th>
<th>$^3J_{2,3}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>110</td>
<td>8.99</td>
<td>5.04</td>
<td>7.22</td>
<td>8.5</td>
<td>12.7</td>
</tr>
<tr>
<td>111</td>
<td>8.92</td>
<td>5.06</td>
<td>6.87</td>
<td>8.3</td>
<td>12.6</td>
</tr>
<tr>
<td>112</td>
<td>8.92</td>
<td>5.03</td>
<td>7.00</td>
<td>8.5</td>
<td>12.7</td>
</tr>
<tr>
<td>113</td>
<td>8.77</td>
<td>4.89</td>
<td>6.84</td>
<td>8.5</td>
<td>12.9</td>
</tr>
<tr>
<td>114</td>
<td>9.04</td>
<td>5.19</td>
<td></td>
<td>8.2</td>
<td>12.8</td>
</tr>
<tr>
<td>115</td>
<td>9.32</td>
<td>5.53</td>
<td>7.77</td>
<td>8.0</td>
<td>13.1</td>
</tr>
</tbody>
</table>

$\delta_H$ values are quoted in ppm.

$J$ values are quoted in Hz.

The following conclusions follow from the data:

(1) H-1 generally lies in the range $\delta_H$ 8.7-9.1 except for 115 (9.32)
(2) H-2 generally lies in the range $\delta_H$ 5.0-5.2 except for 115 (5.53)

(3) H-3 proton is more variable $\delta_H$ 6.87-7.77

(4) the coupling constant of $^3J_{1,2}$ is 8.0-8.5 and $^3J_{2,3}$ is 12.6-13.1Hz

The signal at the 1-, 2- and 3-positions varies most in 115 and shows a shift to higher frequency in all cases. This may be due to delocalisation of the lone pair of the nitrogen atom into the benzene ring, which reduces electron density at C-2. There is also the possibility of deshielding due to the ring current from the benzene ring. Of the two possible conformations (115a and 115b) only 115b is consistent with the large deshielding effect at H-3.

Thus the chemical shift of H-3 is shifted by 0.9 ppm to high frequency relative to compound 111. This can only be due to ring current deshielding caused by an adjacent aryl group.
The results of the $^{13}$C N.M.R. spectra of the enaminals are tabulated below.

### Table 4. $^{13}$C NMR data for enaminals.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\delta$C1</th>
<th>$\delta$C2</th>
<th>$\delta$C3</th>
</tr>
</thead>
<tbody>
<tr>
<td>110</td>
<td>189.18</td>
<td>100.17</td>
<td>159.03</td>
</tr>
<tr>
<td>111</td>
<td>188.57</td>
<td>101.77</td>
<td>159.76</td>
</tr>
<tr>
<td>112</td>
<td>188.80</td>
<td>100.30</td>
<td>159.62</td>
</tr>
<tr>
<td>113</td>
<td>188.59</td>
<td>100.96</td>
<td>159.33</td>
</tr>
<tr>
<td>114</td>
<td>189.00</td>
<td>100.85</td>
<td>159.00</td>
</tr>
<tr>
<td>115</td>
<td>190.43</td>
<td>105.60</td>
<td>152.95</td>
</tr>
</tbody>
</table>

$\delta$C values quoted in ppm.

With the exception of 115 there is very little variation in chemical shift across the series.

(c) X-Ray Crystallography.

The enaminal structural unit is a classic example of a push-pull substituted alkene, $^{42}$ 116a and b, yet surprisingly little crystallographic data is available for simple derivatives of this conjugated system.
The only published structure of a C-unsubstituted derivative is that of the β-naphthyl compound 117 but full details of this are not readily available.

Crystal structure data were obtained on \( N,N \)-diisopropylprop-2-enal 118 and 3-(1,2,3,4-tetrahydro-1-quinolinyl)prop-2-enal 115. These are both solid compounds and \( N,N \)-disubstitution precludes possible complications due to hydrogen bonding.

The crystal structure for 118 is shown in Figure 8 and the relevant data is in Table 5. Corresponding information for 115 is in Figure 9 and Table 6 respectively.
Table 5. Bond lengths [Å] and angles [deg]

<table>
<thead>
<tr>
<th>Bond Sequence</th>
<th>Bond Length [Å]</th>
<th>Angle [deg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(1) - C(1)</td>
<td>1.235(2)</td>
<td></td>
</tr>
<tr>
<td>C(1) - C(2)</td>
<td>1.412(2)</td>
<td></td>
</tr>
<tr>
<td>C(2) - C(3)</td>
<td>1.363(3)</td>
<td></td>
</tr>
<tr>
<td>C(3) - N(4)</td>
<td>1.334(2)</td>
<td></td>
</tr>
<tr>
<td>N(4) - C(6)</td>
<td>1.475(2)</td>
<td></td>
</tr>
<tr>
<td>N(4) - C(5)</td>
<td>1.480(2)</td>
<td></td>
</tr>
<tr>
<td>C(5) - C(52)</td>
<td>1.518(3)</td>
<td></td>
</tr>
<tr>
<td>C(5) - C(51)</td>
<td>1.521(3)</td>
<td></td>
</tr>
<tr>
<td>C(6) - C(62)</td>
<td>1.515(3)</td>
<td></td>
</tr>
<tr>
<td>C(6) - C(61)</td>
<td>1.527(3)</td>
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<tr>
<td>O(1') - C(1')</td>
<td>1.231(3)</td>
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<tr>
<td>C(1') - C(2')</td>
<td>1.413(3)</td>
<td></td>
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<td>C(2') - C(3')</td>
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<td></td>
</tr>
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<td>C(3') - N(4')</td>
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<tr>
<td>N(4') - C(6'')</td>
<td>1.193(5)</td>
<td></td>
</tr>
<tr>
<td>N(4') - C(5'')</td>
<td>1.369(3)</td>
<td></td>
</tr>
<tr>
<td>N(4') - C(6'')</td>
<td>1.616(4)</td>
<td></td>
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<tr>
<td>N(4') - C(5'')</td>
<td>1.816(7)</td>
<td></td>
</tr>
<tr>
<td>C(5') - C(52')</td>
<td>1.523(5)</td>
<td></td>
</tr>
<tr>
<td>C(5') - C(51')</td>
<td>1.575(4)</td>
<td></td>
</tr>
<tr>
<td>C(5') - C(52'')</td>
<td>1.527(10)</td>
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</tr>
<tr>
<td>C(6'') - C(61')</td>
<td>1.512(4)</td>
<td></td>
</tr>
<tr>
<td>C(6'') - C(62')</td>
<td>1.525(4)</td>
<td></td>
</tr>
<tr>
<td>C(6'') - C(62'')</td>
<td>1.530(8)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bond Sequence</th>
<th>Bond Length [Å]</th>
<th>Angle [deg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(1) - C(1) - C(2)</td>
<td>126.8(2)</td>
<td></td>
</tr>
<tr>
<td>C(3) - C(2) - C(1)</td>
<td>117.8(2)</td>
<td></td>
</tr>
<tr>
<td>N(4) - C(3) - C(2)</td>
<td>129.6(2)</td>
<td></td>
</tr>
<tr>
<td>C(3) - N(4) - C(6)</td>
<td>121.6(2)</td>
<td></td>
</tr>
<tr>
<td>C(3) - N(4) - C(5)</td>
<td>119.30(14)</td>
<td></td>
</tr>
<tr>
<td>C(6) - N(4) - C(5)</td>
<td>118.91(14)</td>
<td></td>
</tr>
<tr>
<td>N(4) - C(5) - C(52)</td>
<td>111.1(2)</td>
<td></td>
</tr>
<tr>
<td>N(4) - C(5) - C(51)</td>
<td>111.8(2)</td>
<td></td>
</tr>
<tr>
<td>C(52) - C(5) - C(51)</td>
<td>111.3(2)</td>
<td></td>
</tr>
<tr>
<td>N(4) - C(6) - C(62)</td>
<td>111.8(2)</td>
<td></td>
</tr>
<tr>
<td>N(4) - C(6) - C(61)</td>
<td>110.4(2)</td>
<td></td>
</tr>
<tr>
<td>C(62) - C(6) - C(61)</td>
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<td></td>
</tr>
<tr>
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<td>126.4(2)</td>
<td></td>
</tr>
<tr>
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<td></td>
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<tr>
<td>N(4') - C(3') - C(2')</td>
<td>128.4(2)</td>
<td></td>
</tr>
<tr>
<td>C(6'') - N(4') - C(3')</td>
<td>144.1(3)</td>
<td></td>
</tr>
<tr>
<td>C(3') - N(4') - C(5')</td>
<td>128.6(2)</td>
<td></td>
</tr>
<tr>
<td>C(3') - N(4') - C(6')</td>
<td>115.4(2)</td>
<td></td>
</tr>
<tr>
<td>C(3') - N(4') - C(5'')</td>
<td>101.9(2)</td>
<td></td>
</tr>
<tr>
<td>N(4') - C(5') - C(52')</td>
<td>108.4(3)</td>
<td></td>
</tr>
<tr>
<td>N(4') - C(5') - C(51')</td>
<td>114.5(3)</td>
<td></td>
</tr>
<tr>
<td>C(52) - C(5') - C(51')</td>
<td>109.5(3)</td>
<td></td>
</tr>
<tr>
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<td>106.5(5)</td>
<td></td>
</tr>
<tr>
<td>C(61') - C(6'') - C(62')</td>
<td>116.4(2)</td>
<td></td>
</tr>
<tr>
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<td>104.6(2)</td>
<td></td>
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<tr>
<td>C(62') - C(6'') - N(4')</td>
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<td></td>
</tr>
<tr>
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<td></td>
</tr>
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<td>Length [Å]</td>
<td>Bond</td>
</tr>
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<td>------</td>
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<td>------</td>
</tr>
<tr>
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<td>1.231(2)</td>
<td>C(1)-C(13)</td>
</tr>
<tr>
<td>C(1)-C(2)</td>
<td>1.420(2)</td>
<td>C(2)-C(3)</td>
</tr>
<tr>
<td>C(2)-N(4)</td>
<td>1.354(2)</td>
<td>N(4)-C(13)</td>
</tr>
<tr>
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<td>1.477(2)</td>
<td>C(5)-C(6)</td>
</tr>
<tr>
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<td>1.513(2)</td>
<td>C(7)-C(8)</td>
</tr>
<tr>
<td>C(8)-C(9)</td>
<td>1.391(2)</td>
<td>C(8)-C(13)</td>
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</tr>
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<td>C(11)-C(12)</td>
<td>1.384(2)</td>
<td>C(12)-C(13)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Angle</th>
<th>Value [deg]</th>
<th>Angle</th>
<th>Value [deg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(1)-C(1)-C(2)</td>
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<td>C(1)-C(13)-N(4)</td>
<td>119.00(12)</td>
</tr>
<tr>
<td>C(3)-C(2)-C(1)</td>
<td>118.48(14)</td>
<td>C(2)-C(13)-N(4)</td>
<td>121.36(12)</td>
</tr>
<tr>
<td>N(4)-C(3)-C(2)</td>
<td>127.04(14)</td>
<td>C(3)-C(13)-N(4)</td>
<td>121.36(12)</td>
</tr>
<tr>
<td>C(3)-N(4)-C(13)</td>
<td>122.04(12)</td>
<td>C(3)-N(4)-C(5)</td>
<td>120.99(11)</td>
</tr>
<tr>
<td>C(3)-N(4)-C(5)</td>
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<td>N(4)-C(5)-C(6)</td>
<td>113.11(12)</td>
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<tr>
<td>C(13)-N(4)-C(5)</td>
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<td>C(5)-C(6)-C(7)</td>
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<td>N(4)-C(5)-C(6)</td>
<td>113.11(12)</td>
<td>C(6)-C(7)-C(8)</td>
<td>109.12(13)</td>
</tr>
<tr>
<td>C(7)-C(6)-C(5)</td>
<td>109.12(13)</td>
<td>C(7)-C(8)-C(9)</td>
<td>108.72(12)</td>
</tr>
<tr>
<td>C(8)-C(7)-C(6)</td>
<td>108.72(12)</td>
<td>C(8)-C(9)-C(10)</td>
<td>112.79(14)</td>
</tr>
<tr>
<td>C(9)-C(8)-C(7)</td>
<td>112.79(14)</td>
<td>C(9)-C(10)-C(11)</td>
<td>119.17(14)</td>
</tr>
<tr>
<td>C(10)-C(9)-C(8)</td>
<td>119.17(14)</td>
<td>C(10)-C(11)-C(12)</td>
<td>120.5(2)</td>
</tr>
<tr>
<td>C(11)-C(10)-C(12)</td>
<td>120.5(2)</td>
<td>C(11)-C(12)-C(13)</td>
<td>120.37(14)</td>
</tr>
<tr>
<td>C(12)-C(11)-C(10)</td>
<td>120.37(14)</td>
<td>C(12)-C(13)-N(4)</td>
<td>119.63(13)</td>
</tr>
<tr>
<td>C(13)-C(12)-C(11)</td>
<td>119.63(13)</td>
<td>C(13)-C(12)-C(13)</td>
<td>121.36(12)</td>
</tr>
<tr>
<td>C(8)-C(13)-N(4)</td>
<td>119.00(12)</td>
<td>C(8)-C(13)-N(4)</td>
<td>119.00(12)</td>
</tr>
</tbody>
</table>
Interestingly, one of the two independent molecules of 118 in the asymmetric unit was found to be affected by disorder of the isopropyl groups. However there were no significant differences in their enaminal functions, but the values quoted refer to the ordered system.

The enaminal system of both compounds is approximately planar and adopts an E-s-E configuration. In the N-aryl system, the aryl ring adopts an s-E configuration with respect to the enaminal system. As discussed above, the compound 115 probably also adopts this configuration in solution.

The bond lengths of the conjugated portions of both 118 and 115 reflect the effect of electron delocalisation as predicted by the influence of the resonance structure 116b. The C1-C2 single bond is thus shorter than one would expect in $\alpha,\beta$-unsaturated carbonyl compounds, though the corresponding lengthening of the C2=C3 double bond is smaller in magnitude. In both compounds 118 and 115, the C1=O1 bond distance is relatively unaffected by the enamine system, and shows only marginal lengthening with respect to the average $\alpha,\beta$-unsaturated carbonyl value.

A consequence of the aryl ring in 115 removing electron density from the enaminal π-system, is a significant increase in the C3 to N4 bond length from 1.334(2) Å in 118 to 1.354 (2) Å in 115, though this is not reflected in the bonds further along the chain which remains substantially unchanged.

In both compounds 118 and 115 the C1-C2-C3 bond angle is significantly less than 120° [117.8(2) and 118.48(14)°] respectively whereas both the O1-C1-C2 [(126.8)(2) and 126.6(2)°] and C2-C3-N4 angles [129.6(2) and 127.04 (14)°] respectively are much greater than 120°. Similar trends are found in compound 117 and other E-s-E enaminals. The C2-C3-N4 angles are significantly different in
compounds 118 and 115. The larger angle in 118 possibly minimizes non-bonded contacts between the H6 and H2 atoms. These atoms are almost co-planar and lie only 2.03(3) Å apart, whereas the corresponding H atoms in 115 are staggered. In agreement with this interpretation, particularly large C2-C3-N4 angles (>130°) are found in enaminals containing substituents at the 2-position.46-48

The N-atom in both compounds is planar, the angles around N4 total 359.8(2)° for the ordered component of 118 and 360.0(3) for 115. The individual angles around N4 in compounds 117, 118 and 115 can deviate significantly by up to 3° from 120° but although no consistent pattern emerges, the constraints of the ring in 115 are certainly an important factor.

The entire enaminal system (O1-C1-C2-C3-N4) is approximately planar in both compounds 118 and 115. With more electron density available for delocalisation in the dialkyl example 118, it is not surprising that the r.m.s deviation from the best plane (0.006 Å) is almost an order of magnitude smaller than in the aryl example. In both cases, the unit is bowed with negative deviations at the terminii (O1 and N4). The C1 atom lies closest to the best plane in both molecules.

(d) Mass Spectrometry.

The mass spectra of the enaminals show a molecular ion peak of around 75% intensity and they all show loss from the molecular ion of m/z 17 and m/z 29. The mass spectra of several of the enaminals was studied in greater detail because there is very little in the literature on this subject.49 The enaminals selected were 110, 113, 115 and 119.
Mass spectrometry data was obtained for the above compounds and shown in Table 7. In each example there are characteristic fragments corresponding to M-17 and M-29.

Table 7. Mass spectrometry data of selected enaminals.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Parent Intensity</th>
<th>M-17 Intensity</th>
<th>M-29 Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>110</td>
<td>125 62%</td>
<td>108 14%</td>
<td>96 27%</td>
</tr>
<tr>
<td>113</td>
<td>167 100%</td>
<td>150 42%</td>
<td>138 38%</td>
</tr>
<tr>
<td>115</td>
<td>187 84%</td>
<td>170 76%</td>
<td>158 32%</td>
</tr>
<tr>
<td>119</td>
<td>235 83%</td>
<td>218 14%</td>
<td>206 31%</td>
</tr>
</tbody>
</table>

Accurate mass data was acquired for each of the above compounds. This was studied in order to determine the likely breakdown peaks in the spectrum. For example, compound 110:
Table 8. Mass spectrometry data for compound 110.

<table>
<thead>
<tr>
<th>m/z (Found)</th>
<th>Intensity</th>
<th>Formula</th>
<th>m/z (Requires)</th>
<th>Fragment</th>
</tr>
</thead>
<tbody>
<tr>
<td>125.08331</td>
<td>62%</td>
<td>C₇H₁₁NO</td>
<td>125.0840</td>
<td>M⁺</td>
</tr>
<tr>
<td>108.08092</td>
<td>14%</td>
<td>C₇H₁₀N</td>
<td>108.0813</td>
<td>M-17 (OH)</td>
</tr>
<tr>
<td>96.08098</td>
<td>27%</td>
<td>C₆H₁₀N</td>
<td>96.0813</td>
<td>M-29 (CHO)</td>
</tr>
</tbody>
</table>

From the results of the accurate mass data of 110, it appears that the fragments at m/z 108 and m/z 96 are unlikely to be due to consecutive breakdowns and might derive directly from the parent ion at m/z 125.

The next step was to confirm that the fragments M-17 and M-29 did indeed derive from the parent ion peak in each case. This was done by using a double focussing mass spectrometer (MS50TC) which employs both an electric sector and a magnetic sector for mass determination.

In order to obtain daughter ion peaks from the parent ion (i.e. only the fragment peaks which directly derive from the parent peak) an experiment was conducted on the mass spectrometer where the magnetic sector field strength B and the electric sector field strength E are scanned simultaneously, holding the accelerating voltage V constant so as to maintain the ratio B/E at a constant value. The constant value is determined by the ratio of the two field strengths required to transmit the parent ion. The fragmentation reactions occur in a field free region traversed before the two sectors are scanned in this way and the fragments recorded are directly related to the parent ion. This experiment is conducted at constant
accelerating voltage which helps to preserve focussing at the ion source. The results obtained confirmed that the peaks corresponding to loss of M-17 and loss of M-29 mass units derived directly from the parent ion peak.

Table 9. Daughter ion scans from parent peaks.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Parent</th>
<th>M-17</th>
<th>M-29</th>
</tr>
</thead>
<tbody>
<tr>
<td>110</td>
<td>125</td>
<td>18 %</td>
<td>18 %</td>
</tr>
<tr>
<td>113</td>
<td>167</td>
<td>34 %</td>
<td>32 %</td>
</tr>
<tr>
<td>115</td>
<td>187</td>
<td>98 %</td>
<td>89 %</td>
</tr>
<tr>
<td>119</td>
<td>235</td>
<td>65 %</td>
<td>76 %</td>
</tr>
</tbody>
</table>

These results confirm that the M-17 and the M-29 peaks are indeed daughter ions formed directly from the parent ion.

Comparisons of the above results can be made with typical α,β-unsaturated aldehydes 120 and 121 in the literature.

Table 10. Mass spectrometry data for aldehydes 120 and 121.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Parent</th>
<th>Intensity</th>
<th>m/z</th>
<th>Intensity</th>
<th>m/z</th>
<th>Intensity</th>
<th>m/z</th>
<th>Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>120</td>
<td>132</td>
<td>85%</td>
<td>131</td>
<td>100%</td>
<td>103</td>
<td>69%</td>
<td>77</td>
<td>56%</td>
</tr>
<tr>
<td>121</td>
<td>70</td>
<td>100%</td>
<td>69</td>
<td>48%</td>
<td>41</td>
<td>88%</td>
<td>29</td>
<td>15%</td>
</tr>
</tbody>
</table>
Typical $\alpha,\beta$-unsaturated aldehydes thus show loss of $H$ and $CHO$, but not loss of $OH$.

The M-29 fragment found in both $\alpha,\beta$-unsaturated aldehyde and enaminal spectra appears to be inductive $\alpha$-cleavage of $H-C\equiv O$.

This suggests that ionisation of the enaminal takes place at the carbonyl group.

$$\text{Scheme 37}$$

In contrast, the enaminals do not show a strong M-1 peak but they do show a strong M-17 peak which must involve cleavage of three bonds. To examine the mass spectra of enaminals in detail a series of specifically deuteriated substrates was synthesised to determine the source of the hydrogen atom in $OH$. Since this loss of $OH$ does not happen with other aldehydes, H-1 is unlikely to be the source of the hydrogen atom.

In order to study this loss of 17 mass units, compound 115 was selected as it has a large M-17 peak in the mass spectrum. The extent of deuteriation was confirmed by $^1H$ NMR spectroscopy. As previously mentioned, the $^1H$ NMR spectrum of 115 has a distinctive set of signals at H-1 $\delta_H$ 9.32 (d), H-2 $\delta_H$ 5.53 (dd), H-3 $\delta_H$ 7.7 (d).
A plausible mechanism for the loss of H-2 in OH as shown in Scheme 38.

Deuteriation at the 2-position of the enaminal unit was achieved by firstly dissolving 115 in deuteriated trifluoroacetic acid. The reaction was monitored by $^1$H NMR spectroscopy for the disappearance of the H-2 $\delta_H$ 5.53 (dd). There was little difference in the NMR spectra between one and two hours reaction time. The signal
at δ_H 5.53 ppm was no longer present, inferring deuterium exchange had taken place at the 2-position.

![Chemical Structure](image)

122

The mass spectrum of 122 showed molecular ion peaks at 188 and 187 indicating that the 2 position was not fully deuteriated. Back exchange of D/H was taking place and may have occurred in the sampling process, or in the mass spectrometer itself.

Figure 10. Mass spectrum of 122.
Breakdown peaks at 171 and 170 indicated loss of \( OH \) hence the \( H \) does not come from the 2-position in the enaminal. Loss of \( D(H) \) from the 2-position would result in a breakdown peak of \( m/z \) 170 only (Figure 10).

Having eliminated the possibility of the \( H \) coming from the 2-position of the enaminal unit, the possibility of the \( H \) coming from the 3-position was explored. A mechanism consistent with this breakdown can be drawn (Scheme 39).

![Scheme 39](image-url)
Experimentally, the simplest method to incorporate deuterium into the 3-position involves the 2,3-dideuteriation of the enaminal unit. However, having shown the source of $H$ is not from the 2-position, the di-deuterated species provides useful data.

An experiment was carried out to deuteriate the 2- and 3-positions in the enaminal unit.\textsuperscript{52} The first stage of the synthesis involved deuteriation of propargyl alcohol. Using flame-dried glassware throughout the experiment, propargyl alcohol was dissolved in $D_2O$ containing $NaOD$. The reaction was monitored by NMR spectroscopy for the disappearance of the proton signal at $\delta_H 2.5$ ppm in propargyl alcohol. The solution was extracted with benzene and the extract dried with magnesium sulphate. Tetrahydroquinoline was shaken with $D_2O$, extracted with benzene and dried with magnesium sulphate. The solutions were combined and reaction with manganese dioxide was carried out as previously described. After filtering off the manganese dioxide, the solvent was removed using a rotary pump (Scheme 40).

\[
\begin{align*}
  H\text{-}C≡C\text{-}CH_2OH & \xrightarrow{D_2O, NaOD} D\text{-}C≡C\text{-}CH_2OD & \xrightarrow{D_2O, MnO_2} D\text{-}C≡C\text{-}CHO \\
  \text{Scheme 40}
\end{align*}
\]
NMR spectroscopy revealed a single peak at $\delta_H 9.21$ and a partial doublet at $\delta_H 5.42$, indicating the structure 123.

When the mass spectrum of this compound was obtained, peaks at 189, 188 and a smaller peak at 187 were observed which implies molecular ions with two deuterium atoms, one deuterium atom and no incorporation of deuterium (Figures 11 and 12).

The breakdown peaks resulting from these parent ions were at $m/z$ 172, 171 and 170 with very similar relative intensity pattern to the parent ions. The only explanation for the peak at $m/z$ 172 is loss of 17 mass units and we have previously
disregarded the loss of the aldehyde proton as an explanation for loss of 17 mass units.

**Figure 12. Mass spectrum of 123.**

These results show that the enaminal system itself is not the source of the H-atom giving rise to the M-$OH$ peak in the enaminal spectra. Hence, an enaminal was synthesised (124) which had deuterium atoms on the position $\alpha$- to the nitrogen atom. A possible scheme for loss of this proton is shown in **Scheme 41**.
Scheme 41

Compound 124 was synthesised with the position α- to nitrogen doubly deuterated.
In order to synthesise 124, 3,4-dihydroquinolin-2-one (125) was reduced with LiAlD₄. The resulting compound was then reacted with propargyl alcohol and manganese dioxide to give the enaminal 124 (Scheme 42).

When the mass spectrum of this compound was obtained, the parent ion 189 showed loss of 18 mass units indicating the deuterium in the M-OH peak must indeed have originated from the position α- to nitrogen as in the proposed mechanism.
In conclusion, the $H$-atom shift occurs via a 7-membered transition state as shown in Scheme 41. The driving force behind the mechanism outlined for loss of $H(D)$, from the ring position $\alpha$- to nitrogen is the formation of a push-pull conjugated system after $H$-atom transfer, and also a radical stabilized by an adjacent lone pair.$^{53}$

Having established the source of the fragments in the M-17 peak, it was of interest to determine if there was an isotope effect occurring. An enaminal 126, where there would be competitive abstraction between $H$ and $D$ was synthesised. This compound was prepared by reaction of cyclohexylamine and cyclohexanone in toluene containing $p$-toluenesulphonic acid. The water formed was removed during the reaction by using a Dean and Stark apparatus. The imine formed was reduced with LiAlD$_4$ then the resulting deuteriated amine was reacted with propargyl alcohol
The mass spectrum obtained from 126 showed a parent ion at $m/z$ 236, with breakdown peaks at $m/z$ 219 and 218 in a ratio of $\sim 2.5 : 1$. However, because of the clusters of peaks, absolutely precise ratios were not obtained. However, if equal loss of $OH$ and $OD$ had taken place, the ratio of these peaks would have been $1\cdot1$. We conclude that the $H$-shift is rate determining; and that the kinetic isotope effect for this process $k_H / k_D \sim 2.5$.

### 3. Synthesis of propynal.

A novel spin-off from the enaminal project was an alternative synthesis of propynal 127.\textsuperscript{54}
Because the yields of enaminals from the one pot oxidation and reaction with amine synthesis were, on the whole quite low (18-40%), different methods for synthesising enaminals were explored. Another option was to synthesise the propynal (propargyl aldehyde) first, and then react it with the amine. Propynal can be made on a large scale by an Organic Synthesis route involving chromium trioxide oxidation of prop-2-ynol (propargyl) alcohol. However, this is a low yielding method with inconvenient work-up due, in part to the low boiling point (54-57 °C) of the product. Another method produces a solution of the aldehyde but this poses its own problems owing to the difficulty of separating the product from the mixture of solvents employed.

The possibility of using FVP to synthesise propynal in a one step route from commercially available diprop-2-ynyl ether 128 based on the retro-ene reaction, was successfully explored.

\[(\text{HC}≡\text{C}−\text{CH}_2)_2\text{O}\]

128

This reaction had been studied previously, but the details were not readily available. An analogous procedure has been used to generate propynethiol from diprop-2-ynyl sulphide for in situ photoelectron spectroscopic determination. The participation of prop-2-ynyl groups in retro-ene reactions has been widely investigated kinetically, and shown to be concerted, and consistently faster than the reaction of the corresponding allyl derivative. FVP of silylated prop-2-ynyl ethers has been used as a preparative route to silylallenones.
Small scale pyrolyses of diprop-2-ynyl ether were successful at 750 °C, generating essentially quantitative yields of propynal under those conditions (Scheme 44). The propynal was identified by characteristic peaks at δ_H 9.16 (1H, s) and 3.51 (1H, s). Significant amounts of starting material were recovered at lower pyrolysis temperatures. Allene 129, the only co-product, was identified by its characteristic singlet at δ_H 4.62 ppm in the ¹H NMR spectrum of the crude pyrolysate.

\[
\text{(HC≡C—CH}_2\text{)O} \quad \xrightarrow{\text{FVP}} \quad \text{\begin{tikzpicture} [scale=0.5]
\tikzstyle{every node}=[font=\small]
\node (o) at (0,0) [circle, draw, inner sep=2pt, fill=white] {$\text{O}$};
\node (h) at (0,1) [circle, draw, inner sep=2pt, fill=white] {$\text{H}$};
\draw (0,0) -- (0,1);
\end{tikzpicture}}\text{CHO} + \text{129}
\]

Scheme 44

The reaction could then be scaled up to gram scale using a specially modified trap with a wider vertical collection tube (2.5 cm diameter c.f. 2 cm). The wider tube was necessary to prevent the product solidifying and blocking the trap, which would adversely affect the contact time in the furnace tube. When these precautions were taken, the scale-up of the reaction did not affect the yields obtained (around 80%).

The prop-2-ynal obtained was then used to synthesise the enaminal 110. The amine was dissolved in chloroform and a solution of propynal in chloroform was added dropwise with the aid of a mechanical syringe pump. A yield of 46% enaminal was obtained. This gave an improvement of overall yield of the enaminal of 16% so improvement of the enaminal synthesis had been effected.
We were able to utilise this novel synthetic method in the preparation of benzaldehyde 130, from the unsymmetrical prop-2-ynyl ether, benzyl prop-2-ynyl ether 131.  

\[ \text{PhCHO} + \text{130} \rightarrow \text{PhCH}_2\text{CH} = \text{CH}_2 \]

Scheme 45
4. **Meldrum’s acid derivatives.**

(a) **Preparation.**

The Meldrum's acid derivatives prepared were 132-137.
The Meldrum's acid derivatives were all prepared by reacting the appropriate enaminal with an equimolar amount of Meldrum's acid in pyridine and allowing the reaction to stir overnight at room temperature. The pyridine was removed on a high vacuum rotary evaporator and the Meldrum's acid derivative was purified by recrystallisation from methanol. The products were obtained in yields of 21-50%.

The pyridine is present to base catalyse the reaction. The Meldrum's acid loses an acidic proton and a Knoevenagel reaction takes place.

Scheme 46
(b) $^1\text{H}$ and $^{13}\text{C}$ NMR spectroscopy.

These compounds are characterised by three signals in their $^1\text{H}$ NMR spectra. These are at $\delta_\text{H} 7.25-7.92$ (doublet) corresponding to H-1, $\delta_\text{H} 7.89-8.13$ (doublet of doublet) corresponding to H-2 and $6.79-6.97$ (doublet) corresponding to H-3 (Figure 14).

Table 11. $^1\text{H}$ NMR data for Meldrum's acid derivatives.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\delta_\text{H1}$</th>
<th>$\delta_\text{H2}$</th>
<th>$\delta_\text{H3}$</th>
<th>$^3J_{1,2}$</th>
<th>$^3J_{2,3}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>132</td>
<td>7.49</td>
<td>6.79</td>
<td>7.89</td>
<td>11.9</td>
<td>13.4</td>
</tr>
<tr>
<td>133</td>
<td>7.25</td>
<td>6.97</td>
<td>7.93</td>
<td>12.1</td>
<td>13.2</td>
</tr>
<tr>
<td>134</td>
<td>7.33</td>
<td>6.89</td>
<td>7.91</td>
<td>12.1</td>
<td>13.3</td>
</tr>
<tr>
<td>135</td>
<td>7.32</td>
<td>6.93</td>
<td>7.91</td>
<td>12.3</td>
<td>13.2</td>
</tr>
<tr>
<td>136</td>
<td>7.48</td>
<td>8.00</td>
<td>12.2</td>
<td>13.1</td>
<td></td>
</tr>
<tr>
<td>137</td>
<td>7.92</td>
<td>8.13</td>
<td>12.4</td>
<td>12.9</td>
<td></td>
</tr>
</tbody>
</table>

$\delta_\text{H}$ values are quoted in ppm.

$J$ values are quoted in Hz.
The H-1 proton in 137 varies most due to an increased effect from ring current deshielding and delocalisation of the nitrogen lone pair which reduces electron density in the conjugated system. There is more variation in the signal due to H-1 than the signals for H-2 and H-3 due to the different rings in the vicinity of this C-1.

Table 12. $^{13}$C NMR of Meldrum's acid derivatives.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\delta_C1$</th>
<th>$\delta_C2$</th>
<th>$\delta_C3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>132</td>
<td>157.8</td>
<td>103.2</td>
<td>158.7</td>
</tr>
<tr>
<td>133</td>
<td>161.3</td>
<td>102.9</td>
<td>158.6</td>
</tr>
<tr>
<td>134</td>
<td>162.7</td>
<td>101.8</td>
<td>158.5</td>
</tr>
<tr>
<td>135</td>
<td>162.4</td>
<td>102.5</td>
<td>158.5</td>
</tr>
<tr>
<td>136</td>
<td>161.2</td>
<td>101.6</td>
<td>158.7</td>
</tr>
<tr>
<td>137</td>
<td>155.3</td>
<td>104.3</td>
<td>159.2</td>
</tr>
</tbody>
</table>

$\delta_C$ values are quoted in ppm.

Similarly, $^{13}$C NMR spectra of the Meldrum's acid derivatives show the most variation in the signal for C-1.

Using the proton assignments shown in Table 11, it was possible to establish conclusively the carbon signals at C-1 and C-3 by means of a proton-carbon correlation on 134.

In this example, the C-3 signal is at $\delta_C 158.5$ ppm. The wider variation in the signal at C-1 across the series of compounds, is probably due to the different rings attached to the nitrogen atom adjacent to the carbon.
Also, the unsymmetrical Meldrum's acid derivatives 136 and 137 show extra signals in the $^{13}$C spectra which could be due to the presence of two rotamers.

(c) **Mass spectrometry.**

The mass spectra all show a strong parent ion of intensity 50-77% with breakdown peaks at M-57 followed by further loss of 29 mass units.
5. Reactions leading to fused azepinones.

(a) Pyrolysis of Meldrum’s acid derivatives.

The aim of pyrolysing the series of Meldrum’s acid derivatives, described in the previous section, was to determine the effect on the course of the reaction of changing the ring size and type fused to the azepinone product.

All the pyrolysies were carried out at 550 °C, as this was the temperature used in previous work \[16\] where maximum conversion of starting material to products was realised. All of the azepinone products sublimed well to form yellow liquid products, with little residue left in the inlet of the FVP apparatus.

The azepinones prepared were 138-143.

\[\begin{align*}
138 & \quad \text{Pyrazolone} \\
139 & \quad \text{Azepinone} \\
140 & \quad \text{Azepinone} \\
141 & \quad \text{Azepinone} \\
142 & \quad \text{Pyrazolone} \\
143 & \quad \text{Azepinone}
\end{align*}\]
The pyrolysis of the appropriate Meldrum's acid derivative was carried out at 550 °C and around 10^3 Torr. The inlet temperature ranged from 100-160 °C. During the pyrolysis, a bright yellow compound would appear in the trap indicating the presence of azepinone 147. Yields of the total pyrolysates were in the range 59-62%, and in all cases azepinone was obtained though in varying amounts. The other major component, identifiable in the crude pyrolysate, was cyclopentadienone dimer (150).

![Chemical structure diagram](image-url)

Scheme 47
On pyrolysis of the vinylogous Meldrum's acid derivative 144, a methyleneketene intermediate 145 is formed which undergoes hydrogen transfer leading to a dipolar intermediate 146. At this stage in the mechanism, the dipolar intermediate can either undergo electrocyclisation to give the fused azepinone 147 or undergo cycloaddition across the carbonyl component of the ketene, to give a tricyclic intermediate 148. Further collapse of 148 gives cyclopentadienone 149 which dimerizes to give the cyclopentadienone dimer 150, and the imine 151 (Scheme 47).

From the $^1$H NMR spectrum of the crude pyrolysate, the differing ratios of azepinone:cyclopentadienone can be determined. This was achieved by measuring the integral of the single proton in the cyclopentadienone dimer spectrum at $\delta_{H} \ 7.38$ ppm and the integral of the single proton appearing around $\delta_{H} \ 5.3-5.6$ ppm in the azepinone spectrum.

![Diagram of molecules 150 and 147]

The formula: azepinone / ( azepinone + 2 x cyclopentadienone dimer )
gives the desired ratio which was used to tabulate the results.
Table 13. % of Azepinone and cyclopentadienone in crude pyrolysate.

<table>
<thead>
<tr>
<th>Compound</th>
<th>% azepinone</th>
<th>% CPDO</th>
</tr>
</thead>
<tbody>
<tr>
<td>138</td>
<td>29</td>
<td>71</td>
</tr>
<tr>
<td>139</td>
<td>41</td>
<td>59</td>
</tr>
<tr>
<td>140</td>
<td>57</td>
<td>43</td>
</tr>
<tr>
<td>141</td>
<td>18</td>
<td>82</td>
</tr>
<tr>
<td>142</td>
<td>16</td>
<td>84</td>
</tr>
<tr>
<td>143</td>
<td>65</td>
<td>35</td>
</tr>
</tbody>
</table>

CPDO = cyclopentadienone.

In the series of azepinones with fused rings of 5-, 6-, 7- and 8-membered rings, the percentage of dimer formed decreased with increasing ring size except in the case of the 8-membered ring. This could be due to decomposition of the azepinone, which is known to happen\textsuperscript{65} although the temperature for the experiment was selected to minimise this. Or, from the results, distribution between the electrocyclisation / cycloaddition pathway appears to be proportional to ring size, \textit{i.e.} amount of cyclopentadienone dimer decreases as ring size increases (except for the eight-membered ring case.)
As the ring size increases, the intermediate formed *en route* to the cyclopentadienone becomes more crowded sterically and thus the favoured route is electrocyclisation to give the azepinone, except in the case of the 8-membered ring. In this case, there could be steric crowding, this time in the azepinone between the carbonyl of the azepinone ring and the fused 8-membered ring 141 (notwithstanding the non-planar nature of eight-membered rings).

![Diagram 141](image)

In the pyrolysis of 136, only a small amount of azepinone 142 was formed as there was very little steric hindrance in the intermediate formed *en route* to the cyclopentadienone. However there is the possibility of steric hindrance *en route* to the formation of azepinone.

![Diagram 136](image)

In the examples where high percentages of cyclopentadienone dimer were formed, the co-product of the imine 151 should also be detectable. Indeed, this is
true of the pyrolysis of 136 where large signals due to the imine 152 at δ_H 2.74, 3.75 and 8.00 ppm were present. Small signals were tentatively identified as isoquinoline itself 153, formed by thermal dehydrogenation of the dihydro compound under FVP conditions.

![Scheme 48]

Similarly, the cyclopentadienone intermediate 154 formed on pyrolysis of 137 also exhibits steric crowding and therefore a greater yield of azepinone 143.

![137 and 154]

From our results, it appears that if there is steric crowding in the intermediate formed \textit{en route} to formation of cyclopentadienone, then a greater proportion of azepinone is formed. If however there is steric interaction in the azepinone product,
or more accurately, in the transition state formed *en route* to the azepinone product, the reaction will favour the formation of cyclopentadienone dimer.

In order to test this hypothesis, two experiments were designed. One experiment involved the previously synthesised Meldrum's acid derivative 155 which, on pyrolysis, would lead to substantial crowding in the intermediate formed *en route* to the cyclopentadienone dimer, and therefore a good proportion of azepinone product if our hypothesis is correct. The other experiment involved the synthesis and pyrolysis of the Meldrum's acid derivative 156. This would be used to test the hypothesis of crowding in the azepinone transition state. When 136 was pyrolysed, there was no crowding in the intermediate *en route* to the cyclopentadienone dimer but there may have been steric hindrance involved in the formation of azepinone. By removing the fused benzene ring and its consequent effect on azepinone formation, and pyrolysing the Meldrum's acid derivative 156 we may see increased formation of the fused azepinone product, (although there is still no steric hindrance to the formation of cyclopentadienone dimer). In the event, the results only gave partial support to the hypothesis.
The azepinone 157 was synthesised by the previously mentioned route to azepinones using the cis isomer of 2,6-dimethylpiperidine, viz formation of the enaminal from dimethylpiperidine; reaction with Meldrum's acid to give 155, followed by FVP to give the azepinone 157.66

\[
\begin{align*}
\text{O} & \quad \text{O} & \quad \text{O} \\
\text{CH}_3 & \quad \text{CH}_3 & \quad \text{CH}_3
\end{align*}
\]

Scheme 49

In agreement with our hypothesis, pyrolysis of the Meldrum's acid derivative 155, which would exhibit steric crowding in the intermediate 158 en route to the formation of the cyclopentadienone dimer gave increased azepinone formation (73% compared to the unsubstituted fused 6-membered ring (41%). In the intermediate 158 leading to cyclopentadienone in the pyrolysis of 155, there is substantial crowding between the methyl group and Hₐ disfavouring the cycloaddition pathway and leading to the electrocyclisation, therefore the azepinone product is favoured.
This hypothesis was further tested by the pyrolysis of the Meldrum's acid derivative 156 (Scheme 50).
The pyrolysis was carried out at 550 °C. This gave large amounts of cyclopentadienone dimer and very little azepinone (14%). When the temperature of the pyrolysis was lowered to 500 °C, or the pressure in the system was reduced to ~10^{-5} Torr, the proportion of azepinone did not increase relative to the cyclopentadienone. The steric hindrance hypothesis does not hold for this example, and it is possible that the product is particularly thermally unstable.

(b) \( ^1H \) and \( ^{13}C \) NMR Spectroscopy.

Column chromatography on alumina effected a good separation of the azepinones from other components, and the \( ^1H \) NMR spectra are tabulated below. The azepinone component was characterised by its signals at \( \delta_{^1H} 6.3, 6.7, 5.3 \) and 6.8 ppm (approx) due to H-4, 5, 6 and 7 respectively. (147).
Table 14. $^1$H NMR data for azepinones.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\delta_{H4}$</th>
<th>$\delta_{H5}$</th>
<th>$\delta_{H6}$</th>
<th>$\delta_{H7}$</th>
<th>$^3J_{4,5}$</th>
<th>$^3J_{5,6}$</th>
<th>$^3J_{6,7}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>138</td>
<td>6.22</td>
<td>6.81</td>
<td>5.23</td>
<td>6.89</td>
<td>11.3</td>
<td>8.9</td>
<td>7.1</td>
</tr>
<tr>
<td>139</td>
<td>6.23</td>
<td>6.83</td>
<td>5.25</td>
<td>6.7</td>
<td>10.9</td>
<td>8.9</td>
<td>6.7</td>
</tr>
<tr>
<td>140</td>
<td>6.21</td>
<td>6.81</td>
<td>5.23</td>
<td>6.83</td>
<td>10.9</td>
<td>9.0</td>
<td>8.0</td>
</tr>
<tr>
<td>141</td>
<td>6.10</td>
<td>6.72</td>
<td>5.13</td>
<td>6.77</td>
<td>11.2</td>
<td>8.9</td>
<td>8.0</td>
</tr>
<tr>
<td>142</td>
<td></td>
<td>5.29</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>143</td>
<td>6.32</td>
<td>6.89</td>
<td>5.59</td>
<td>6.81</td>
<td>11.3</td>
<td>8.5</td>
<td>7.6</td>
</tr>
</tbody>
</table>

$\delta_{H}$ quoted in ppm.

$J$ quoted in Hz.

The shielded signals at H-4 and H-6 and the deshielded signals at H-5 and H-7 can be distinguished by their splitting patterns. The resonances due to the central protons are doublets of doublets, or apparent triplets, while the outer protons (H-4 and H-7) are simple doublets. Thus the most shielded signal ($\delta_{H}$ 5.13-5.59 ppm) is identified as corresponding to H-6, the next most shielded signal ($\delta_{H}$ 6.10-6.32 ppm) corresponds to H-4, while the remaining two signals are fairly close ($\delta_{H}$ 6.70-6.89 ppm).

The three bond coupling constant $^3J_{4,5}$ across the double bond is particularly large (10.9-11.3 Hz). The corresponding $^3J_{5,6}$ across the single bond is of the order of 8.5-9.0 Hz and across the remaining double bond $^3J_{6,7}$ is 6.7-8.0 Hz. The vicinal coupling constant $^3J_{5,6}$ is similar in size to $^3J_{6,7}$, even though $^3J_{5,6}$ is across a formal
single bond: a very similar value (8 Hz) has been reported for the corresponding coupling, i.e. across the single bond of the conjugated system in cycloheptadienone.67

The $^{13}$C signals of the azepinone component were assigned and tabulated below.

**Table 15. $^{13}$C NMR data for azepinones.**

<table>
<thead>
<tr>
<th>Compound</th>
<th>C-2</th>
<th>C-3</th>
<th>C-4</th>
<th>C-5</th>
<th>C-6</th>
<th>C-7</th>
</tr>
</thead>
<tbody>
<tr>
<td>138</td>
<td>65.78</td>
<td>180.67</td>
<td>122.93</td>
<td>141.03</td>
<td>99.43</td>
<td>143.27</td>
</tr>
<tr>
<td>139</td>
<td>61.13</td>
<td>180.15</td>
<td>123.70</td>
<td>140.68</td>
<td>99.90</td>
<td>145.83</td>
</tr>
<tr>
<td>140</td>
<td>67.38</td>
<td>181.5</td>
<td>122.87</td>
<td>140.75</td>
<td>99.30</td>
<td>145.94</td>
</tr>
<tr>
<td>143</td>
<td>61.91</td>
<td>184.79</td>
<td>124.05</td>
<td>139.25</td>
<td>104.81</td>
<td>140.76</td>
</tr>
</tbody>
</table>

$\delta_c$ quoted in ppm.

Elucidation of the $^{13}$C signals from the fused 8-membered ring azepinone and the fused isoquinoline azepinone was not possible.

The quaternary signal corresponding to the carbonyl group is considerably shielded with respect to that in the corresponding 5-membered ring system. This may be consistent with the expectation of the shielding on increased delocalisation. However, in comparison the corresponding open-chain systems dimethylaminopentadienal and dimethylaminopropenal show shifts of $\delta_c$ 191 and 187 ppm, respectively. It therefore appears that the effect observed is due to the change in geometry enforced by the seven-membered ring; five-membered rings are known to give rise to more deshielded signals than either smaller or larger rings.68
The electron deficient sites of the azepinones (C-5 and C-7) occur at higher frequency ($\delta_c$ 140-146) than C-4 or C-6 ($\delta_c$ 99-124 ppm) but C-5 is considerably shielded relative to the corresponding resonances of the pyrrolones (C-5; $\delta_c$ 158-166 ppm). The signals due to the electron rich 4- and 6-positions are well separated (usually around 20 ppm).

The olefinic signals of both double bonds in the diene unit exhibit similar trends to those observed in enamiones; thus, the C-4 and C-6 signals are shielded by mesomeric donation of the nitrogen atom's lone pair of electrons, while the C-5 and C-7 positions have shifts which are influenced by the electron withdrawing nature of the carbonyl group and the dipolar resonance structures which it allows.

(c) **Structural elucidation of**

10a-H-1,2,3,4-Tetrahydro-4,10a-dimethylpyrido[1,2a]azepin-10-one.

When the Meldrum’s acid derivative 155 was pyrolysed at 550 °C, a good yield of the azepinone product was obtained and from the spectra, it appeared that only one isomer was formed *i.e.* either the cis dimethyl, or the trans.
This was in contrast to the results of the pyrolysis of 107 in which both the cis (108) and trans (109) isomers were obtained in roughly equal proportions.

![Chemical structure of 107, 108, and 109]

Scheme 35

In order to elucidate the structure of the azepinone 157, molecular models of the cis and trans isomers (Figures 15 and 16 respectively) were generated by molecular calculations (Chem 3D) performed by Dr. A.N Hulme. Then further NMR experiments were conducted and elucidated by Dr. D Reed.

1. The $^1$H NMR spectrum was examined and thirteen distinct $^1$H environments were identified, two of which arise from Me groups and two from deshielded aliphatic single protons. The spectrum was labelled A-N (I not used) Figure 17.

Signals K-N are from the alkenic H's.

Signal J can be identified as being $^1$H α-to nitrogen because of the multiplicity i.e. a quartet due to splitting by geminal Me group and deshielding due to its proximity to the nitrogen atom.

H is the other deshielded signal, likely to be in the plane of the carbonyl group.
Figure 17. $^1$H NMR spectrum of 157.
2. The HMQC experiment (\(^1\text{H} / ^{13}\text{C}\) correlation) confirms that signals C/F, D/G, E/H are geminal pairs.

3. The \(^1\text{H}\) COSY experiment shows couplings:

J/F, J/C, J/B, H/G, H/E, G/F, G/E or D, F/C, D/C. **Figure 18.**

This established the positions of the other protons around the ring.

**Figure 18.**
4. $^1$H NMR nOe results show that:

Irradiation of J enhances M, H, F, C, B.

H enhances J, E, G, A.

C enhances B, J, F, (possibly E).

B enhances J, E, C, A.

A enhances (K, L, M N), (J?), H, E (D), C, B.

Now if the A/B enhancements are genuine, then both methyl groups are cis with respect to the ring. The B/E enhancement confirms that B and E are on the same side of the ring. If B and E are above the ring, then J and H must be below the ring and there is reciprocal enhancement of J and H. Thus the structure of the compound formed appears to be that shown in Figure 15.

Having established the structure, it is evident that the piperidine ring has retained the configuration of the starting material i.e. cis dimethylpiperidine. This retention of configuration is consistent with two steps in the overall process but it is not clear why a single isomer is formed exclusively. Although the corresponding 5-membered system resulted in two isomers, this may be because the 5-membered ring is planar in contrast with the 7-membered ring case. Although the intermediate dipole leading to product 157 has a pseudo axial Me group in the 6-membered ring this is not substantially disfavoured in cyclohexene type systems. Alternatively, it may be that in
the 7-membered ring situation, the cis-isomer is thermodynamically favoured over the trans.

(d) **Mechanism of the H-transfer step in azepinone formation.**

The reaction pathway in the FVP of vinylogous Meldrum’s acid derivatives to give azepinones involves a hydrogen transfer step of the hydrogen atom attached to the carbon $\alpha$- to the nitrogen. An experiment was designed to study this hydrogen transfer and determine whether $k_H/k_D$ is a function of $T_f$ (furnace temperature of the FVP apparatus).

The strategy was to use a deuteriated substance in which $H/D$ competition was designed. Then by analysing the site at which labelling took place and the quantity of label incorporated, it would be possible to obtain a measure of $H$ transfer versus $D$ transfer, hence $k_H/k_D$. Hence there would be an indication of whether the H-transfer step was the rate determining step.

A series of pyrolysis experiments was carried out on the deuteriated Meldrum’s acid derivative synthesised from the enaminal 126. From the deuteriated enaminal 126 (synthesised as previously discussed) the deuteriated Meldrum’s acid derivative 159 was prepared and pyrolysed to give the azepinone 160 (Scheme 51).
Pyrolysis was carried out at temperatures of 550 °C, 600 °C, 650 °C and 700°C. By monitoring the $^1$H and $^2$H NMR spectra, it was thought that $k_H/k_D$ as a function of $T_f$ could be determined. It was found however that at temperatures above 550 °C, azepinone was present but there were too many impurities for accurate integration of NMR spectra.

The $^1$H NMR spectrum of the pyrolysis at 550 °C was relatively clean so the corresponding $^2$H NMR spectrum was obtained. Triangulation of the peaks corresponding to the sites of deuterium incorporation gave approximate integrals and a value of $k_H/k_D \approx 2.9$. This result can be compared to the 5-membered ring example which shows an isotope effect of $k_H/k_D \approx 1.9$. 38
The data obtained were not as clean as in the 5-membered case, but there was still evidence for the H-shift being the rate determining step.

(e) **Attempted synthesis of a 1,3-diazepin-6-one.**

To pursue this route for synthesising fused azepinones, and to further extend the study, pyrolysis of 161 was attempted. Preparation of this compound involved synthesis of methoxymethylene Meldrum's acid 162 by reacting Meldrum's acid with trimethyl orthoformate. This was then reacted with a stoichiometric quantity of tetramethylguanidine in acetonitrile to give 161 in 89% yield (Scheme 52).

![Scheme 52](image)
The resulting Meldrum's acid derivative $161$ was pyrolysed over a range of temperatures, $T = 500 \, ^\circ \text{C}$, $550 \, ^\circ \text{C}$ and $600 \, ^\circ \text{C}$.

\[
\begin{align*}
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\text{O}
\end{array}
\end{align*}
\]

$\text{FVP}$

\begin{center}
Figure 16
\end{center}

Pyrolysis of the corresponding Meldrum's acid derivative $45$ was successful and gave yields of $> 90\%$ of the azepinone $46$.\textsuperscript{18} The $^1\text{H NMR}$ spectrum of the crude pyrolysate from the pyrolysis of $161$ at $500 \, ^\circ \text{C}$ was dominated by a number of singlets in the aliphatic region $\delta_H \, 1.9-3.1$. In addition, small pairs of doublets were identified at $\delta_H \, 7.33 \,(J \, 8.4 \, \text{Hz})$ and $\delta_H \, 5.71 \,(J \, 8.4 \, \text{Hz})$ and also at $6.71 \,(J \, 1.4 \, \text{Hz})$, $\delta_H \, 6.60(J \, 1.4 \, \text{Hz})$ integrating to c.a. $1\%$ of the total aliphatics. The signals at $\delta_H \, 7.33$ and $5.71$ may be due to a trace of the 1,3-diazepin-6-one.

The $^1\text{H NMR}$ spectra of pyrolysis products above $500 \, ^\circ \text{C}$ showed no alkene protons in the spectrum. There is the possibility that the mechanism followed the cycloaddition pathway to give the cyclopentadienone dimer but there is little evidence from $^1\text{H NMR}$ to support this.

However, it was clear from this example that having a nitrogen atom in place of carbon in this type of system profoundly influences the reaction, and any azepinone formed at all was a very minor product.
Scheme 53
INTRODUCTION.

This introduction aims to examine the preparation, reactions and spectroscopy of $5H$-pyrrolo[2,1-$a$]isoindolone (165) and also its dihydro derivatives, of which there are potentially three, 166, 167 and 168.

1. **Synthesis.**

Few general synthetic routes to these compounds appear to have been developed. In some instances, these compounds appear to have been identified as incidental by-products in the preparation of other compounds. For example, this is observed in the coupling reactions of aromatic compounds with palladium acetate salts and in the study of rearrangements of phthalamide derivatives both photochemically and thermally.

The synthetic routes to $5H$-pyrrolo[2,1-$a$]isoindolones have been classified according to the variation of bond formation in the ring closure step (Figure 19).

The numbering scheme $5H$-pyrrolo[2,1-$a$]isoindolones is shown in 165.
In a study to explore the potential of arylation of pyrroles and indoles as an efficient method of synthesis of aryl pyrroles and indoles, it was found that instead of arylation, the ring closed products were formed under certain conditions. The method chosen for arylation involved the use of palladium (II) salts to catalyze the reaction of $N$-arylpypyroles with aromatic solvents (Scheme 54).\textsuperscript{72,73,74}

\[
\begin{align*}
\text{AcO} & \quad \text{OAc} \\
\text{Pd} & \\
C & \quad \text{N} \\
\text{AcO} & \quad \text{OAc}
\end{align*}
\]

Thus oxidation of 1-benzoylpyrrole 169 in acetic acid with 0.34 mole equivalent of palladium acetate gave the 2,2-bipyrole 171, whereas oxidation of 169
with 1 mole equivalent palladium acetate gave the ring closed product 165 (28% yield) as the main product along with some 170, 171 and 172.

One mole equivalent of palladium acetate is required for the cyclisations. When the experiment was carried out with 0.5 mole palladium acetate in the corresponding arylindole series yields did not exceed 50% suggesting the process is stoichiometric in palladium.

Furthermore, treatment of 169 with palladium acetate in acetic acid and p-xylene, or in acetic acid and p-dichlorobenzene, gave the ring closed products 173, 174 and 175, (in 20%, 15% and 28% yields respectively), but no other arylated compounds were obtained (Scheme 55).

\[
\begin{align*}
\text{169} & \quad \rightarrow \quad \text{173} \quad R = \text{C}_6\text{H}_6 \\
 & \quad \quad \quad \text{174} \quad R = 2,5\text{-}\text{Me}_2\text{C}_6\text{H}_3 \\
 & \quad \quad \quad \text{175} \quad R = 2,5\text{-}\text{Cl}_2\text{C}_6\text{H}_3
\end{align*}
\]

Scheme 55

The catalytic version of this process was explored. Grigg et al.\textsuperscript{75} had noted that 1-arylinindoles 169 undergo dehydrogenation to the ring closed product 165 in hot acetic acid in the presence of palladium acetate (Scheme 54). As previously stated, the reaction was observed to be stoichiometric in palladium.\textsuperscript{72} Using a catalyst system comprising 10 mole % Pd acetate, 20 mole % triphenylphosphine, tetraethylammonium chloride (1 mole) and potassium carbonate (2 mole), in boiling
acetonitrile, the pyrrole 176 cyclised in 80% yield to give the pyrroloisoindolone 165. This is the best synthetic route currently available to this ring system.

\[
\begin{align*}
\text{Scheme 56} \\
176 & \quad \rightarrow \quad 165
\end{align*}
\]

(b) 4-5 Bond formation.

Base treatment of the bromide 177a, 177b yielded 178, 179 and 180.\(^{76, 77}\) When 179 was treated with acetic anhydride or heat it gave the pyrroloisoindolone 181 in 69% yield (Scheme 57).
In order to prepare highly functionalised derivatives of pyrroloisoindolone, 
\(N\)-hydroxyphthalimide 182 was reacted with dimethyl acetylenedicarboxylate in the 
presence of triphenylphosphine, yielding a multi-functionalised pyrroloisoindole 
derivative 183 (Scheme 58).
The intention had been to prepare isoindoloisoxazoles using an intramolecular Wittig reaction, but the tri-substituted pyrroloisoindolone was formed in 50% yield (Scheme 58).

(d) 1-9b Bond formation.

Samarium iodide has been extensively used in organic synthesis, and as samarium iodide promoted cyclizations of \( N \)-(iodoalkyl)-substituted cyclic imides had not been reported, there was an opportunity to study the cyclization to construct pyrrolizidinone, indolizidinone and quinolizidinone ring systems.\(^79\) \( N \)-(Iodoalkyl)imide cyclisation substrates were prepared by alkylation of corresponding imides with appropriate dibromoalkane followed by a bromide-iodide exchange reaction. Phthalimide 184 was subjected to 3 equivalents of samarium iodide in the presence of an iron complex catalyst. The imide cyclized smoothly at 0 °C in 2-3 hours to give a mixture of alcohol 185 and dehydration product 186.

![Scheme 59](image-url)
On chromatographic separation, alcohol 185 slowly dehydrated to 186; however, heating with 4Å molecular sieves and catalytic amounts of p-TsOH in dichloromethane gave the dihydropyrroloisoindolone compound 186 in 95% yield (Scheme 59).

In a study of photochemical reactions of phthalimides with monoolefin substituents, it was found that dihydropyrroloisoindolones could be obtained from reactions of the products of the photolysis.

Scheme 60
For example, photolysis of 187 led to a mixture 188 and 189, which on dehydration using acetic anhydride in sodium acetate gave 190. Further reaction with HCl gave the pyrroloisoindolone 191 (Scheme 60).

These intramolecular photocyclisations may be explained by a mechanism, involving initial one electron transfer, which was elucidated in a mechanistic study to determine whether there is evidence supporting radical - radical coupling of a photochemically generated radical ion pair (path b, Scheme 61).81

\[
\begin{align*}
\text{ABH} + C \rightleftharpoons \text{CC} & \quad \text{(a)} \\
\text{AB} + \text{CCCH} \rightarrow \text{ABC} + \text{CCCH} & \quad \text{(b)}
\end{align*}
\]

Scheme 61

The following reaction scheme was proposed and examination of the photolysis reaction by HPLC showed that 192 was one of the major products. 193 was shown to arise from 192 presumably via acid-catalysed dehydration and demethanolysis (Scheme 62).
A photochemical study was carried out to explore the difference between the behaviour of the imides and thioimides. In N-substituted phthalimides the imide carbonyl undergoes the Norrish type II photocyclization leading to a variety of ring systems. (The Norrish II reaction is intramolecular hydrogen abstraction in excited carbonyl compounds).

The irradiation of a series of N-ω-phenyl, -thio or dithio-phthalimides resulted in the formation of products from the Norrish type II cyclisation initiated by δ or ε hydrogen abstraction (see Figure 20).
The photochemical behaviour of a series of $S$-substituted $N$-thioalkylphthalimides was studied. From 194, $\delta$-hydrogen transfer yielded 195. This shows that the $\gamma$ hydrogen which is definitely reactive in ketones, is inert in the thioimide system (Scheme 63).

Scheme 63

The photochemical approach to macrocycles requires a strong electron donating substituent (e.g. thioether, enamine) in the side chain of the $N$-alkylphthalimide. The phthalimide chromophore behaves as an electron accepting group, but a disadvantage of this method is that the electron donor is incorporated into the ring in all cases. An approach in which the formation of the O-C single bond is combined with extrusion of the electron donor would be promising.
A C-protected glutamic acid 196 derivative provides a mixture of diastereomeric benzopyrrolizidines of which one isomer 197 undergoes dehydration to form the enantiomerically pure enamide 198 when treated with trifluoroactic acid. The other diastereoisomer does not undergo dehydration (Scheme 64). 

![Scheme 64]

(e) **1-9b and 3-4 Bond formation.**

A novel method for synthesising both O and N heterocycles was explored using the application of allyl silanes in a [3+2] annulation approach.

---

124
The reaction pathway is believed to be as follows: regiospecific electrophilic substitution of the N-aryliminium ion derived from 199 at C-3 of the allenylsilane produces a vinyl cation stabilized by hyperconjugative interaction with the adjacent carbon silicon σ-bond. A 1,2-cationic silyl shift then occurs affording an isomeric vinyl cation, which is intercepted by the nucleophilic N atom to generate the new heterocyclic ring. It was realised that by increasing the steric shielding about silicon, an unwelcome desilylation pathway could be suppressed and thereby the reaction could be directed exclusively to the desired heterocyclic products 200 and 201 (Scheme 65).

(f) 4-9b Bond formation.

An extension of the search for new synthetic routes to the 3H pyrrole ring system in which a modified Paal-Knorr reaction between 2,2-disubstituted 1,4-diketones 202 and ammonia was invoked.85
Scheme 66

However, structures of the type 202 are generally not conveniently accessible, but having $R^2$ as an acyl group allows an extrusion of the modified Paal-Knorr reaction.

Scheme 67
This is the reaction of a triketone 203, which was treated with ammonium acetate in refluxing acetic acid to give the tricyclic product 204 in 42-52% yields depending on substituents (Scheme 67).

All of the compounds investigated have a substituent on the carbon atom in the position α to the carbonyl leaving group. This may be to prevent the removal of an acidic proton by the strong base required in the reaction.

This mechanism is echoed in a hydrazinolysis reaction of phthalimide 205,

![Scheme 68](image-url)
The mechanism proceeds via a carbinolamine intermediate 206 (as in the previous mechanism) to the product 207, which on treatment with acid gives 208.\textsuperscript{86}

(g) **3-4 Bond formation.**

The only synthesis involving FVP was one designed to give fused ring systems.\textsuperscript{87} The starting material was prepared by the reaction of 209 with 210 to give 211. The compound 211 was then pyrolysed at 650 °C to give 212, 213 and pyrroloisoindolone 165 in 9% yield (Scheme 69).

![Scheme 69](image)

2. **Reactions.**

Very few reactions have been carried out on pyrroloisoindolone itself.
Base hydrolysis of the diphenyl substituted derivative 214 resulted in the ring opened compound 215. Bromination of 214 in chloroform resulted in the bromo-derivative 216 whereas bromination in methanol gave the methoxy derivative 217 (Scheme 70).\textsuperscript{76}

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {214};
  \node (b) at (1.5,0) {215};
  \node (c) at (3,0) {216};
  \node (d) at (4.5,0) {217};

  \draw[->] (a) -- node[anchor=east] {Br$_2$ in CHCl$_3$} (c);
  \draw[->] (a) -- node[anchor=west] {Br$_2$ in CH$_3$OH} (d);
  \draw[->] (a) -- node[anchor=south] {OH$^-$} (b);

  \draw[->] (a) -- node[anchor=north] {Ph} (b);
  \draw[->] (a) -- node[anchor=north] {Ph} (c);
  \draw[->] (a) -- node[anchor=north] {Ph} (d);
  \draw[->] (b) -- node[anchor=north] {Ph} (c);
  \draw[->] (b) -- node[anchor=north] {Ph} (d);
  \draw[->] (c) -- node[anchor=north] {Ph} (d);

  \node at (0,-2.5) {Scheme 70};
\end{tikzpicture}
\end{center}


(a) \textsuperscript{1}H NMR spectroscopy.

See Figure 21 for numbering scheme referred to in Table 16. An electron donating group e.g Me has the effect of shielding the H-1 signal by 0.54 ppm compared to unsubstituted pyrrolisoindolone, whereas 2,5-Cl$_2$C$_6$H$_5$ has a deshielding effect of 0.13 ppm compared to unsubstituted pyrrolisoindolone. Methyl substitution in the 2-position has a shielding effect on both H-1 and H-3 of 0.10 pm
and 0.15 ppm respectively while methyl substitution in both H-1 and H-3 positions resulted in substantial deshielding in H-2 of 0.54 ppm compared to unsubstituted pyrroloisoindolone 165.

![Diagram of pyrroloisoindolone](image)

**Figure 21**

### Table 16. $^1$H NMR data for pyrroloisoindolones.

<table>
<thead>
<tr>
<th>$R_1$</th>
<th>$R_2$</th>
<th>$R_3$</th>
<th>$\delta_{H}$ H-1</th>
<th>$\delta_{H}$ H-2</th>
<th>$\delta_{H}$ H-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>6.15</td>
<td>6.15</td>
<td>6.90</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>2,5-Cl$_2$C$_6$H$_5$</td>
<td>6.28</td>
<td>6.28</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>2,5-Me$_2$C$_6$H$_5$</td>
<td>6.26</td>
<td>6.05</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>6.05</td>
<td>6.75</td>
<td></td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>Ph</td>
<td>6.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>4-BrC$_6$H$_4$</td>
<td>6.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>4-MeOC$_6$H$_4$</td>
<td>5.96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>4-NO$_2$C$_6$H$_4$</td>
<td>6.35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>5.61</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$\delta_{H}$ quoted in ppm.
(b) **Mass spectrometry.**

Pyrroloisoindolone shows an intense molecular ion peak of 100% intensity followed by loss of 29 mass units.

Substituted compounds show strong molecular ions 50-100%, (depending on substituents).

(c) **Infra-red spectroscopy.**

**Table 17. Infra-red data for pyrroloisoindolones.**

<table>
<thead>
<tr>
<th>$R_1$</th>
<th>$R_2$</th>
<th>$R_3$</th>
<th>$\text{C}=\text{O}/\text{cm}^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>1760</td>
</tr>
<tr>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>1740</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>C$_6$H$_5$</td>
<td>1740</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>2,5-Cl$_2$C$_6$H$_3$</td>
<td>1755</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>2,5-Me$_2$C$_6$H$_3$</td>
<td>1740</td>
</tr>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>H</td>
<td>1751</td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>Ph</td>
<td>1740</td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>4-BrC$_6$H$_4$</td>
<td>1750</td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>4-MeOC$_6$H$_4$</td>
<td>1750</td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>4-NO$_2$C$_6$H$_4$</td>
<td>1740</td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>1730</td>
</tr>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>Br</td>
<td>1748</td>
</tr>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>OMe</td>
<td>1748</td>
</tr>
</tbody>
</table>
The C=O absorbtions are at higher wave number than for typical amides, which are generally around 1680 cm\(^{-1}\). This indicates that there is considerable double bond character in the carbonyl group.
RESULTS AND DISCUSSION.
1. **Introduction.**

The aim of this work was to combine two known thermal arrangements to give a unique cascade process resulting in the formation of a fused tricyclic system, \(5\text{H-pyrrolo}[2,1-a]isoindol-5\text{-one} \ 165.\)

![Chemical structure](image)

As reported in the introduction (C) to this section of work, there are very few high yielding syntheses of pyrroloisoindolone. The most successful synthesis requires that the starting material be heated under reflux for 12 hours in the presence of a complex catalyst system.\(^75\)

(a) **Proposed cascade process.**

The proposed cascade reaction for synthesis of pyrroloisoindolone involves using FVP to combine two thermal processes. The thermal processes involved are the isomerization of 1-substituted pyrroles \(^89\) (Scheme 71) and the ring closure of 2-substituted pyrroles with elimination of \(\text{CH}_3\text{OH}\) to give a fused ring system (Scheme 72).\(^90\)

1-Substituted pyrroles undergo thermal isomerization to give 2-substituted pyrroles and to a lesser extent, 3-substituted pyrroles (Scheme 71).
Pyrroles with substituents in the 2-position are able to undergo elimination to give ring closed products (Scheme 72).
These thermal processes are well established and will subsequently be discussed in greater depth.

The strategy behind the proposed cascade mechanism was that an appropriate 1-substituted pyrrole would isomerize to the corresponding 2-substituted pyrrole under FVP conditions. Then, without intervention of other substrates or changes in reaction conditions, the 2-substituted pyrrole would undergo the ring closure reaction illustrated in Scheme 72. This would result in the formation of a fused ring product. Both of these thermal rearrangements have been reported in the literature but have not been previously been combined in one cascade process. The advantage of using a 1-substituted pyrrole as a starting material is that they are readily synthesised, unlike 2-substituted pyrroles.

2. **Thermal rearrangements of 1-substituted pyrroles.**

Thermal rearrangements of 1-substituted pyrroles have been reported as far back as 1885, when it was found that the 1-substituent migrated to 2-position. The migration from the 1→2-position was reported for 1-phenyl and 1-pyridylpyrrole. A more extensive study was carried out on 1-methylpyrroles and it was found that when distilled through a dull-glowing combustion tube, the products were 2-methylpyrrole and pyridine. Kinetic studies showed that the thermal isomerization of 1-alkyl pyrroles is a unimolecular homogeneous process in which the 2-isomer is irreversibly formed from the 1-isomer while the 3-isomer is reversibly formed from the 2-isomer.
The negative entropies of activation calculated from the kinetic data have been interpreted as requiring a cyclic activated complex consistent with a concerted mechanism.\textsuperscript{95}

(a) **Pyrolysis of 1-phenylpyrrole.**

As the starting material for the proposed synthesis of pyrroloisoindolone would be a 1-phenylpyrrole derivative, a temperature profile of the rearrangement of 1-phenylpyrrole under FVP conditions was obtained. 1-Phenylpyrrole was pyrolysed over a range of temperatures and the resulting \textsuperscript{1}H NMR spectra were analysed quantitatively from the integrals of the 1-, 2-, and 3-phenylpyrrole obtained.

The spectra were verified by comparison with authentic literature data.\textsuperscript{96}

1-Phenylpyrrole was identified from its triplet signals at $\delta_{\text{H}}$ 6.26 and 6.99 ppm.
2-phenylpyrrole had a doublet of doublets at $\delta_H 6.20$ ppm.

3-phenylpyrrole had a doublet of doublets at $\delta_H 6.92$ ppm.

The results are tabulated below and illustrated in a graph (Figure 22).

**Table 18. Pyrolysis of 1-phenylpyrrole.**

<table>
<thead>
<tr>
<th>Pyrolysis temperature</th>
<th>% of 1-phenylpyrrole</th>
<th>% of 2-phenylpyrrole</th>
<th>% of 3-phenylpyrrole</th>
</tr>
</thead>
<tbody>
<tr>
<td>775 °C</td>
<td>80</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>825 °C</td>
<td>42</td>
<td>39</td>
<td>19</td>
</tr>
<tr>
<td>875 °C</td>
<td>19</td>
<td>52</td>
<td>29</td>
</tr>
<tr>
<td>925 °C</td>
<td>10</td>
<td>53</td>
<td>37</td>
</tr>
</tbody>
</table>

The graph (Figure 22) shows a steady decrease in amount of 1-phenylpyrrole present, with increasing pyrolysis temperature. At the same time, amounts of 2- and 3-phenylpyrroles steadily increase with increasing pyrolysis temperature. Maximum conversion of 1-phenylpyrrole occurs at 925 °C.
(b) **Pyrolysis of 2- and 3-phenylpyrroles.**

The second stage of the proposed cascade mechanism requires rearrangement from the 2-position of the pyrrole. Therefore, interconversion from 2→3 and from 3→2-phenylpyrroles was examined. A preparative pyrolysis of 1-phenylpyrrole was carried out at 925 °C to give maximum yields of 2- and 3-phenylpyrroles for this
rearrangements in the gas phase. High yields of 2-substituted imidazoles were obtained in most cases, although some 4-substituted derivatives were formed.\textsuperscript{98}

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

Scheme 74

(a) Pyrolysis of 1-phenyl imidazole.

1-Phenylimidazoles were pyrolysed over a range of temperatures and the resulting $^1$H NMR spectra were analysed quantitatively from the integrals of the 1-, 2- and 4-phenylimidazoles obtained.

1-phenylimidazole was identified from its triplet signals at $\delta_H 7.78$ (2H) ppm.

2-phenylimidazole had a doublet of doublets $\delta_H 7.89-7.85$ (1H) ppm.

4-phenylimidazole had a $\delta_H 7.68-7.59$ (3H) ppm.

The imidazoles were identified from authentic samples of each of the isomers.

The results were tabulated and illustrated in a graph (Figure 23).
Table 19. Pyrolysis of 1-phenylimidazole.

<table>
<thead>
<tr>
<th>Pyrolysis temperature</th>
<th>% of 1-phenylimidazole</th>
<th>% of 2-phenylimidazole</th>
<th>% of 4-phenylimidazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>775 °C</td>
<td>37</td>
<td>49</td>
<td>14</td>
</tr>
<tr>
<td>825 °C</td>
<td>19</td>
<td>67</td>
<td>14</td>
</tr>
<tr>
<td>875 °C</td>
<td>12</td>
<td>73</td>
<td>15</td>
</tr>
<tr>
<td>925 °C</td>
<td>0</td>
<td>83</td>
<td>17</td>
</tr>
</tbody>
</table>

Figure 23.

Pyrolysis of 1-phenylimidazole

- % of 1-phenylimidazole
- % of 2-phenylimidazole
- % of 4-phenylimidazole

Temperature / °C
As the amount of 1-phenylimidazole decreased on increase of pyrolysis temperature, the amount of 2-phenylimidazole increased, and to a lesser extent the amount of 4-phenylimidazole.

(b) Pyrolysis of 2- and 4-phenylimidazoles.

When 2-phenylimidazole was pyrolysed, it did not interconvert to 1- or 4-phenylimidazole. Likewise, when 4-phenylimidazole was pyrolysed, it did not interconvert to 1- or 2-phenylimidazole. This is in marked contrast to the results obtained from pyrolysis of 2- and 3-phenylpyrroles, where it was clearly established that interconversion did take place from 2 $\rightarrow$ 3-phenylpyrroles and from 3$\rightarrow$ 2-phenylpyrroles.

It would appear that the migration of a pendant group can occur to and from a carbon atom in the pyrrole ring, but not to a nitrogen atom. The movement of a pendant group from nitrogen atom in both pyrrole and imidazole appears to be irreversible, although hydrogen does appear to be able to migrate to nitrogen atoms.

For the interconversion of the 2$\rightarrow$4-phenylimidazoles to occur, and vice versa, the pendant phenyl group would have to migrate through a nitrogen atom. This does not appear to happen.

In both the pyrolysis of 1-phenylpyrrole and 1-phenylimidazole, the optimum furnace temperature for maximum formation of 2-phenylpyrrole and 2-phenylimidazole appears to be 925 °C. As the pyrrole ring is symmetrical, migration of the pendant group to the ring position $\alpha$- to nitrogen can occur in either direction to give 2-phenylpyrrole. However, migration of the pendant group to the ring
position α- to nitrogen can occur in either direction to give 2-phenylpyrrole. However, migration of the pendant group to the ring position α- to nitrogen in imidazole results in either 2-phenylimidazole or 4-phenylimidazole being formed, with formation of 2-phenylimidazole occurring in greater yield.


The second stage of the proposed cascade reaction to give pyrroloisoindolone would invoke a thermal ring closure of 2-(2-alkoxycarbonylphenyl)pyrrole. This is an extension of the work developed by McNab et al.\textsuperscript{90} who pyrolysed 3-(pyrrol-2-yl)propenoate to give pyrrolizinone (Scheme 72b). It was found that pyrolysis of the (E)-propenoate ester at 850 °C resulted in 87% yield of the pyrrolizin-3-one.

\[ \text{Scheme 72b} \]

The reaction proceeds with concerted loss of methanol followed by electrocyclic ring closure of the resulting ketene intermediate to give pyrrolizinone.
The mechanism of the pyrolysis appears to require $E$ to $Z$ isomerization of the alkene (a process known to occur under FVP conditions).99

This method was also employed to synthesise pyrroloimidazol-5-ones (Scheme 75). Pyrolyses of the $E$ and $Z$ isomers of the imidazole analogue of the propenoate system (219) revealed that ring closure of the $Z$-isomer occurred at a substantially lower temperature ($\sim 650 ^\circ C$) than the $E$-isomer ($\sim 800 ^\circ C$).100

\[
\begin{align*}
\text{N} & \quad \text{CO}_2\text{Me} \\
\text{219} & \quad \text{FVP}
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{CO} \\
\text{MeOH} & \quad \text{-MeOH}
\end{align*}
\]

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

\[
\begin{align*}
\text{N} & \quad \text{CO} \\
\text{Z-} & \quad \text{isomer}
\end{align*}
\]

\[
\begin{align*}
\text{N} & \quad \text{CO} \\
\text{E-} & \quad \text{isomer}
\end{align*}
\]

**Scheme 75**

It follows that isomerisation of the $C=\text{C}$ bond is the rate controlling process for the synthesis of pyrrolizinones and related compounds by FVP of propenoates. Hence the $Z$-isomer should be used if low furnace temperatures are required.

(a) Preparation and pyrolysis of 1-(2-carbomethoxyphenyl)pyrrole.

The initial starting material for studying the proposed thermal cascade was 1-(2-carbomethoxyphenyl)pyrrole 220. This was prepared in good yield by reaction of methyl anthranilate with 2,5-dimethoxytetrahydrofuran in glacial acetic acid.$^{101}$
1-(2-Alkoxy carbonylphenyl)pyrrole was then pyrolysed over a range of temperatures. There were no intermediates observed, suggesting clean transfer to product. At 925°C, no starting material was detected (by 1H NMR spectroscopy) in the product trap, therefore complete conversion into products had occurred. The product was obtained in high yield (79%) with a small amount of insoluble polymeric material also formed. Incidentally, if the pyrolysis is carried out at 900°C, the small amount of unconverted starting material which is a liquid can be pipetted clear of the product which is not contaminated by decomposition products at that temperature.

The pyrolysis was then carried out on a preparative scale. A single yellow, crystalline solid was obtained and confirmed as pyrroloisoindolone (5H-pyrrolo[2,1-a]isoindol-5-one) by melting point, 1H NMR spectroscopy and X-ray crystal structure. The 1H NMR spectrum showed the expected two doublets and two doublets of doublets for the six membered aromatic ring. The pyrrole signals were identified as a two doublets and a triplet agreeing with the literature.75 (NMR spectroscopy of (5H-pyrrolo[2,1-a]isoindol-5-one) is studied later).

In particular, the isomeric structure 221, (9H-pyrrolo[1,2-a]indol-9-one)102 in which cyclisation takes place with the pendant group remaining on the 1-position of the pyrrole, (Scheme 77) could be excluded by comparison of the 1H NMR data for each structure.
The crystal structure (see later) confirmed that the cyclisation had taken place after the shift of the pendant group to the 2-position of the pyrrole (223), thus confirming the validity of the cascade mechanism (Scheme 78).
(b) **Study of cascade reaction.**

Comparing the optimum temperature of 925 °C for the formation of pyrroloisoindolone by the cascade mechanism with that of the pyrolysis of 1-phenylpyrrole again 925 °C, it is clear that the high temperature is required in both cases. From the high temperature required and the fact that no intermediate is detected, it appears that the shift of the pendant group (from the 1- to 2-position of the pyrrole), could be the rate determining step of the cascade process. Further information on this feature was obtained by independent pyrolysis of the 2-derivative 223. This was prepared by base-catalysed ring opening of pyrroloisoindolone.(see Reactions)

2-(2-Carbomethoxyphenyl)pyrrole 223 would be the product formed from the shift of the pendant group from the 1- to the 2-position of the pyrrole i.e. the product
of the first stage of the cascade mechanism. If the 2-arylpyrrole is pyrolysed, pyrroloisoindolone 165 should be obtained.

\[ \text{Scheme 79} \]

This reaction was carried out over a range of temperatures and pyrroloisoindolone was indeed formed as a result of the pyrolysis. The minimum temperature at which no starting material was present was found to be 800 °C. This was considerably lower than the temperature required to obtain the product from the 1-aryl isomer (925 °C), suggesting that it is the first stage of the cascade mechanism which requires the very high temperature of 925 °C. It also suggests that the 2-pyrrolo compound may be formed *en route* to the pyrroloisoindolone.

There is the possibility that the mechanism proceeds *via* the intermediate 224 which is formed during the process of the 1→2 shift of the pendant group.
But the desired product of pyrroloisoindolone was obtained from pyrolysis of the 2-arylpyrrole indicating it could be a viable step in the cascade mechanism.

However, the temperature of 800 °C, required for the elimination step of the cascade process, is higher than the temperature of 650 °C required to convert the Z-isomer of 225 to pyrrolozipinone.\textsuperscript{90} Scheme 81.
This suggests that the higher temperature is required to break the aromatic ring and form the o-quinonoid intermediate 226.

![Diagram of 226]

To study this aspect of the mechanism in greater detail, 227 was synthesised by the literature method by heating o-phenylenediamine and phthalic anhydride under reflux in HCl for 3 hours.

![Diagram of 227]

The product was initially pyrolysed at 925 °C, but there was incomplete conversion of starting material to product. The pyrolysis was repeated at 950 °C with the addition of short silica rods placed in the furnace tube. (Using silica rods in the furnace tube has the equivalent effect on the pyrolysis of raising the furnace temperature by ~ 50 °C ). So in effect, the pyrolysis of 227 was carried out at ~ 1000 °C. The cyclised product was formed in 72% yield with some insoluble polymeric material also being formed. The product was identified as 228 by comparison of ¹H NMR spectrum with the literature.
Even although the 2-aryl derivative was being pyrolysed and therefore no movement of the pendant group from the 1→2 position of the pyrrole ring was required, the temperature required for the pyrolysis was very high. This can be explained by the presence of two o-quinonoid systems in the intermediate 229.

As with pyrolysis of the 2-(2-carbomethoxyphenyl)pyrrole, the temperature required to complete the conversion to fused ring products is substantially higher than for the propenoate example, which suggests that destruction of the aromaticity in the system to form the o-quinonoid intermediate requires very high furnace temperatures.

So the cascade mechanism appears to be a viable route to the formation of 5H-pyrrolo[2,1-α]isoindol-5-one by pyrolysis of 1-(2-alkoxycarbonyl)pyrrole with good yield (79 %) of product formed. By studying separately each step of the cascade mechanism in detail, information on the temperatures required for each stage
in the mechanism has been acquired. This has contributed to the understanding of the process, providing evidence that the cascade mechanism is indeed a two stage process involving movement of a pendant group from the 1→2-position of a pyrrole ring followed by concerted elimination of a molecule of methanol and ring closure via an o-quinonoid intermediate. Although pyrolysis of 1-phenylpyrrole led to some 3-phenylpyrrole being formed, there was no evidence that a product had been formed from the 3-aryl derivative. The elimination of methanol is only possible from the 2-position, and reaction between the 2- and 3-aryl derivatives is reversible, so product is formed from the 2-position only.

6. Extension of cascade mechanism.

The cascade mechanism has proved to be a viable synthetic method for 5H-pyrrolo[2,1-α]isoindol-5-one. In order to study its effectiveness in synthesising other fused ring systems, various aspects of the starting material were changed systematically. The N-aryl group was changed to an N-heteroaryl group, pyrrole was replaced by imidazole and the N-aryl substituent was changed to N-alkenyl.

(a) Synthesis of thieno[2,1-b]pyrrolizin-4-one.

The pendant group attached to the nitrogen of the pyrrole, was changed to thiophene. This compound [methyl 3-(1-pyrrolo)thiophene-2-carboxylate] 230 was commercially available and was pyrolysed to give a 79% yield of the tricyclic compound 231.
The structure was identified by $^1$H and $^{13}$C NMR spectroscopy and accurate mass measurement. The pyrrole ring protons of the sulphur containing product appeared at $\delta_H$ 5.96, 5.98, and 6.90 ppm, compared with the pyrrole ring protons of pyrroloisoindolone at $\delta_H$ 6.13, 6.17 and 6.97 ppm.

The alternative structure 232 was not formed as indicated by the literature $^1$H NMR spectrum.$^{105}$

$^1$H NMR chemical shifts in ppm.

This result indicates that the cascade mechanism is viable for a pendant group with an electron rich aromatic ring system. An example of a pendant group with an electron deficient ring system 233 was also successfully pyrolysed to give the ring closed product 234 expected from the cascade mechanism.$^{106}$
Scheme 83

(b) Synthesis of imidazo[2,1a]isoindolone.

The pyrrole ring in the original precursor was replaced by imidazole. As studies had been carried out on the thermal behaviour of 1-phenylimidazoles and the observation had been made that, under FVP conditions, migration of the pendant group from the 1-position to the 2- and (to a lesser extent) 4-imidazole positions had occurred, the next step was to test the cascade mechanism on imidazole derivatives.

The starting material was therefore 235.

This compound was synthesized by two different methods, the latter being more successful. The first method involved the reaction of imidazole with methyl o-fluorobenzoate in a stirred mixture also containing anhydrous potassium carbonate.
and copper (II) oxide in pyridine. Yields of around 12% were obtained by this method (Scheme 84).

![Scheme 84]

The second method involved the reaction of imidazole with sodium hydride, then with a solution of methyl p-fluorobenzoate (Scheme 85). This method proved to be slightly more successful (15% yield).

![Scheme 85]

The pyrolysis was then carried out on the imidazole derivative at 925 °C because that was the optimum temperature for conversion of 1-phenylimidazole to 2-phenylimidazole, although at 925 °C a small amount of 4-phenylimidazole was also formed (17%). If the starting material 235 successfully undergoes the cascade reaction, there are two possible products 236 and 237, depending on whether the pendant group undergoes migration to the 2- or 4-position of the imidazole ring in the first stage of the cascade mechanism (Scheme 86).
The major product from the pyrolysis was identified as 236 by $^1$H NMR and $^{13}$C NMR spectroscopy and X-ray crystal structure analysis. In order to determine the structure of the major product, comparisons were made with the corresponding bicyclic ring systems 238 and 239.

The above structures were distinguished by the one bond couplings shown above.\textsuperscript{109}

In the case of the tricyclic system, firstly the imidazole protons were assigned by comparison with the bicyclic system. Then the corresponding carbon atoms were identified by $^1$H-$^{13}$C correlation and then unambiguous assignment of the product was
established by comparison of the one bond $^{1}J_{\text{CH}}$ couplings for the imidazole carbons with those of the corresponding bicyclic systems shown above. The one bond $^{1}J_{\text{CH}}$ coupling positively identified that the major product of the pyrolysis is 236, obtained in 78% yield.

![Diagram](image)

236

As previously mentioned, 1-phenylimidazole also rearranges to 4-phenylimidazole under pyrolysis conditions to give 17% of 4-phenylimidazole at 925°C. There was the possibility that the crude pyrolysis product may contain some of the other isomer, formed as a result of 1→4-migration of the pendant group. The $^1$H NMR spectrum of the crude pyrolysis product obtained from the pyrolysis of 235 contained small signals, which may correspond to the alternative product 237 being formed. These chemical shifts were compared with those of the corresponding bicyclic system 238.$^{109}$

![Diagram](image)

$^1$H NMR chemical shifts.
To determine the effect of the fused benzene ring on chemical shift, comparisons were made with $^1$H NMR spectra of pyrrolizin-3-one 240 and pyrroloisoindolone 165.

\[ \begin{align*}
\text{240} & : \quad H_a 6.84, \quad H_b 5.94 \\
\text{165} & : \quad H_a 6.97, \quad H_b 6.17
\end{align*} \]

$^1$H NMR chemical shifts in ppm.

So the approximate effect of the benzene ring on the chemical shift of $H_a$ is 0.13 ppm, and the approximate effect of the benzene ring on the chemical shift of $H_b$ is 0.23 ppm.

Therefore the expected $\delta_H H_a$ in 237 is $> 7.7$ ppm. So from the crude $^1$H NMR spectrum of the pyrolysis, it can only be the peak at 7.87 ppm, therefore from the integrals of the spectrum, the maximum level of isomer could be 11%.

(c) 7-phenylpyrrolo[1,2-a]imidazol-5-one.

Having established that the cascade mechanism gives the expected product for 1-arylimidazoles, the pendant group was further changed to an alkenyl group 241.

\[ \begin{align*}
\text{241a} & : \quad \text{Ph} - \text{CO}_2\text{Me} \\
\text{241b} & : \quad \text{Ph} - \text{H} - \text{CO}_2\text{Me}
\end{align*} \]
It was convenient to use the imidazole ring to test the cascade mechanism for the alkenyl system as the corresponding pyrrole compound is not well known.

The imidazole compound 241 had been synthesised by three different methods. The first method involved the reaction of \( N\)-(trimethylsilyl)imidazole with methyl (triphenylphosphorylidene) acetate in benzoyl chloride.\(^{110}\) In our hands, the required product was obtained but it proved difficult to separate from the triphenylphosphine oxide in the reaction mixture.

Other methods of synthesis were explored. The literature contained two examples of syntheses involving addition of bromine to methyl cinnamate. The first method involved reaction of the resulting product with imidazole and triethylamine.\(^{111,112}\) (Scheme 87)

\[
\begin{array}{c}
\text{MeO} \quad \text{Br} \\
\text{Br} \quad \text{Ph} \\
\end{array} \xrightarrow{\text{N-NH}} \\
\begin{array}{c}
\text{MeO} \\
\text{H} \quad \text{Ph} \\
\end{array}
\]

(Scheme 87)

The second method again involved addition of bromine to methyl cinnamate. The resulting solution was then added to a solution of imidazole which had been treated with sodium hydride\(^{113}\) (also Scheme 87)

In our hands, the more successful preparation was the one involving triethylamine as a base.

\[
\begin{array}{c}
\text{MeO} \quad \text{Br} \\
\text{Br} \quad \text{Ph} \\
\end{array} \xrightarrow{\text{NaH/DMF or Triethylamine}} \\
\begin{array}{c}
\text{MeO} \\
\text{H} \quad \text{Ph} \\
\end{array}
\]

Scheme 87
The product was obtained in 57 % yield, and \(^1\)H NMR confirmed that only one isomer was formed. To establish which isomer of 241 was formed, nOe experiments were conducted. The results are illustrated below.

\[
\begin{align*}
\text{241a} \\
\text{Ph} & \quad \text{H} \\
\text{1.5\%} & \quad \text{Ph} \\
\text{1.5\%} & \quad \text{N} \\
\text{CO}_2\text{Me} & \quad \text{CO}_2\text{Me} \\
\end{align*}
\]

Irradiation of the \(\sigma\)-protons of the phenyl substituent enhanced the imidazole proton indicated in 241a by 1.5%. Significantly, irradiation of the \(\sigma\)-protons of the phenyl substituent enhanced the alkenyl proton by 8%. This gives strong evidence to suggest that 241a was the only isomer formed.

The starting material was pyrolysed at 750 °C, 800 °C and 850 °C to establish the optimum temperature for complete conversion of starting material. This was found to be 800 °C, when the ester group of the starting material was no longer present in the \(^1\)H NMR spectrum of the pyrolysis product.

As with all the other examples of the cascade mechanism, two isomers were possible.
The major product was identified by comparison with 238 and 239.

Significantly, the long range coupling present in 239 was also identified in the $^1$H NMR spectrum of the major pyrolysis product 242.

$^1$H NMR coupling constants in ppm.

The alternative structure 243 could be eliminated as the major product because there would be no long range coupling as illustrated in 238 because of the phenyl substituent in the alternative product.
So the presence of the long range coupling in the $^1$H NMR spectrum of the crude pyrolysis product indicated that 242 was the major product formed in 82% yield.

However, there were other peaks present in the spectrum which could be the result of the alternative product being formed. Significantly, a signal at $\delta_{\text{H}}$ 6.06 ppm in the crude pyrolysis product spectrum shows no coupling, which is good evidence for the presence of this alternative product in ~9% yield.

The optimum temperature of the pyrolysis (800 °C) is considerably lower than that required for movement of a pendant aryl group in the cascade reaction (925°C). There is literature evidence to confirm that phenyl shifts are around 900 times slower than alkene shifts in [1,5]-sigmatropic rearrangements. This temperature of 800 °C is, however, higher than that required to give the cyclised product (pyrrolizinone) from the Z-isomer of a propenoate ester precursor. Hence, the higher temperature must be required to facilitate the shift of the pendant alkenyl group from the 1-position.
7. Spectroscopy.

(a) $^{1}$H and $^{13}$C NMR spectroscopy of pyrrolo[2,1-$\alpha$]isoindol-5-one.

In the $^{1}$H NMR spectrum of pyrrolo[2,1-$\alpha$]isoindol-5-one, the pyrrole ring protons and the protons of the benzene ring were easily identified by their coupling constants. The pyrrole ring protons appear as two pairs of doublets and a triplet and the benzene ring protons appear as two sets of doublets and two sets of triplets. However, in order to assign the $^{1}$H spectrum unambiguously, nOe experiments were conducted (Figure 24).

![Figure 24](image)

$^{1}$H NMR chemical shifts in ppm.

Irradiation of E enhanced G and vice versa, but no other enhancements were observed involving those protons. Significantly, irradiation of F in the pyrrole ring enhanced C (doublet) in the benzene ring, and irradiation of C also enhanced B (triplet) in the benzene ring which allowed unambiguous assignment of two of the benzene ring protons. To confirm identification of the remaining benzene ring protons, A (doublet) was irradiated and this was found to enhance D (triplet).

The $^{1}$H NMR coupling constants were also elucidated as shown in Figure 25.
The \textit{para} couplings in the fused benzene ring are greater that in benzene itself.

With the unambiguous assignment of the $^1$H NMR signals from the nOe experiments, a $^1$H - $^{13}$C correlation enabled us to assign the non-quaternary $^{13}$C signals.

$^{13}$C NMR chemical shifts in ppm.

A fully coupled $^{13}$C spectrum enabled the fused benzene carbon signals ($\delta_{C}$ 131.78, 136.19 ppm) and the bridgehead pyrrole carbon signal ($\delta_{C}$ 135.43 ppm).

(b) \textbf{Comparison of $^1$H NMR spectra.}

(All of the following comparisons of spectra have been made between solutions of the compounds in $[^2]$H chloroform).
Comparison of the $^1$H NMR spectrum of pyrrolo[2,1-α]isoindol-5-one with that of pyrrolizinone indicated that the pyrrole ring protons of pyrroloisoindolone have a higher chemical shift than those of pyrrolizinone, but the coupling constants are very similar.\(^\text{109}\)

Further comparisons can be drawn between the $^1$H NMR spectra of 236 and 239.

The chemical shifts are consistently higher than in the pyrrolo[1,2-α]imidal-5-one, probably due an electron-withdrawing deshielding effect of the benzene ring as a whole, relative to an alkene group. For the special case of H\(_b\) in 165, a ring current effect of the fused benzene ring may also contribute to the deshielding.
(c) **Mass spectrometry data.**

The mass spectrum of pyrrolo[2,1-α]isoindol-5-one shows a strong molecular ion at m/z 169 (100%) with loss of 29 mass units (CHO), followed by loss of 26 mass units (CN). By comparison, the mass spectrum of 231 compound shows m/z 175 (100%) with loss of 28 mass units (CO) followed by loss of 1 mass unit (H) followed by loss of 26 mass units (CN). The mass spectrum of the pyrroloimidazolone showed m/z 170 (100%) with loss of 26 mass units (CN) compared with the more common loss of 28 mass units (CO).

8. **Crystal structure data of pyrrolo[2,1-α]isoindol-5-one and imidazo[2,1α]isoindolone**

The crystal structure of pyrrolo[2,1-α]isoindol-5-one 165 confirms the molecule has a planar structure. There are large exocyclic bond angles at the ring junctions, for example bond angle C1-C9B-C9A of 145.56(12)°. Comparing this with the corresponding imidazole structure (236) N1-C9B-C9A, the corresponding bond angle is 140.5(3) °. The bond lengths of N4-C5 in 165 and 236 1.403(2) Å and 1.407(2) Å respectively are long for amide bonds [γ-lactams(1.347(14) Å)]115 possibly due to competitive delocalisation of the nitrogen atom lone pair into the pyrrole or imidazole as well as into the C=O. As expected, the fused imidazole structure 236 also shows differences in the bonds of N1-C9B and C2-N1 (1.306(4) Å and 1.405(4) Å) which are noticeably shorter than the corresponding bonds in the pyrroloisoindolone structure 165 N1-C9B and C2-C1 (1.360(2) Å and 1.434(2) Å) but the two structures are otherwise very similar.
Figure 26. Crystal structure of 165.
Table 20. Bond lengths [Å] and angles [deg]

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Symmetry transformations used to generate equivalent atoms:
Figure 27. Crystal structure of 236.
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<td>C(5A)-C(6)-C(7)</td>
<td>117.9(3)</td>
</tr>
<tr>
<td>C(6)-C(7)-C(8)</td>
<td>120.7(3)</td>
</tr>
<tr>
<td>C(9)-C(8)-C(7)</td>
<td>121.7(3)</td>
</tr>
<tr>
<td>C(8)-C(9)-C(9A)</td>
<td>118.3(3)</td>
</tr>
<tr>
<td>C(9)-C(9A)-C(5A)</td>
<td>119.6(3)</td>
</tr>
<tr>
<td>C(9)-C(9A)-C(9B)</td>
<td>133.8(3)</td>
</tr>
<tr>
<td>C(5A)-C(9A)-C(9B)</td>
<td>106.5(3)</td>
</tr>
<tr>
<td>N(1)-C(9B)-N(4)</td>
<td>112.0(3)</td>
</tr>
<tr>
<td>N(1)-C(9B)-C(9A)</td>
<td>140.5(3)</td>
</tr>
<tr>
<td>N(4)-C(9B)-C(9A)</td>
<td>107.5(2)</td>
</tr>
</tbody>
</table>

The reactions in this section were carried out with respect to the reactions carried out on pyrrolizinone by Dr. X.L.M. Despinoy.\textsuperscript{116} This work established that pyrrolizinone was susceptible to reaction by both hard and soft nucleophiles. The soft nucleophiles reacted solely at the 1-2 site, the hard nucleophiles reacted at the C=O carbon. The same reactions using hard nucleophiles were undertaken on pyrroloisoindolone, which has a benzene ring fused in the corresponding 1-2 position of the pyrrolizinone.

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

(a) Kinetic study of ring opening with methanol.

The reaction of methanol with pyrroloisoindolone resulted in ring opening. The reaction was catalysed by a 1:1 ratio of Hunig's base (diethylisopropylamine) to pyrroloisoindolone.

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

\textbf{Scheme 88}
The product 223 (obtained in 88% yield) was identified by the presence of \( \delta_\text{H} \) 10.37 ppm (NH) and \( \delta_\text{H} \) 3.88 ppm (OMe) in the \(^1\text{H}\) NMR spectrum, and also accurate mass measurement.

In conjunction with kinetic studies being carried out by Dr X.L.M. Despinoy on the ring opening of pyrrolizinone,\(^{116}\) comparisons were made with pyrroloisoindolone and thieno[2,1-b]pyrrolizin-4-one (231) to see what effect (if any) a fused benzene or thiophene ring would have on the rate of the ring opening compared to pyrrolizinine.

The reaction was carried out as pseudo first order by using a vast excess of OMe\(^-\). The reaction was monitored by ultra-violet spectroscopy using SFA-20 Rapid Kinetics Stopped - Flow Apparatus. The absolute rate constant \( k \) was calculated from the equation:

\[
k' = k \times [\text{Na OMe}] \quad \text{(where } k' \text{ is the pseudo first order rate constant)}.
\]

True second order rate constant \( k = k'/[\text{OMe}] \).

Table 22. Rate constant for ring openings.

<table>
<thead>
<tr>
<th>Compound</th>
<th>( k ) (s(^{-1}))</th>
<th>( k ) (s(^{-1}) dm(^3) mol(^{-1}))</th>
<th>( k/k_{241} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>241</td>
<td>1.39±0.02</td>
<td>29.7</td>
<td>1</td>
</tr>
<tr>
<td>165</td>
<td>1.83±0.01</td>
<td>39.4</td>
<td>1.3</td>
</tr>
<tr>
<td>231</td>
<td>1.95±0.01</td>
<td>42.1</td>
<td>1.4</td>
</tr>
</tbody>
</table>

The results show that the rate of ring opening is not affected by the addition of a fused benzene ring, or by the addition of an electron rich fused ring.
(b) Lithium aluminium hydride reduction of pyrroloisoindolone.

Reduction with lithium aluminium hydride gave 2-(2-hydroxymethylphenyl)pyrrole 244 in 69% yield (Scheme 89). This compound was characterised by the presence of the NH pyrrole proton (δ_H 10.43 ppm) and the CH_2 protons of the alcohol moiety (δ_H 4.69 ppm) in the ^1H NMR spectrum and also by accurate mass measurement. This compound was used for work described in a later section.

\[
\begin{align*}
\text{165} & \quad \text{LiAlH}_4 \quad \rightarrow \quad \text{H} \quad \text{244} \\
\text{H} & \quad \text{CH}_2\text{OH}
\end{align*}
\]

Scheme 89

(c) Hydrogenation of pyrroloisoindolone.

Previous work revealed that hydrogenation of pyrrolizinone was accomplished using a palladium/charcoal catalyst system at 3.5 atmospheres of hydrogen for 2 hours. The same conditions were used for the hydrogenation of pyrrolo[2,1-α]isoindol-5-one (Scheme 90).

\[
\begin{align*}
\text{165} & \quad \text{H}_2/\text{Pd} \quad \rightarrow \quad \text{245} \\
\text{O} & \quad \text{O}
\end{align*}
\]

Scheme 90
The product 245, obtained in 90% yield, was identified by $^1$H NMR and $^{13}$C NMR spectroscopy, in particular the presence of 3 x CH$_2$ signals and 1 aliphatic CH in the DEPT confirmed the success of the hydrogenation. Also, accurate mass measurement confirmed that 245 was the product formed. The low resolution mass spectrum shows clusters of peaks of lower intensity around the major breakdown peaks, indicating the presence of saturated bonds in the molecule.

10. **Pyrrolo[2,1-α]isoindole by the cascade mechanism.**

Previous work had shown that pyrolysis of allylic alcohols $^{17}$ of the pyrrole series 246 had proceeded in an analogous fashion to the allylic esters of the pyrrole series. The ester reaction proceeded by elimination of methanol and electrocyclisation to give pyrrolizinone as shown in Scheme 72. (As previously discussed, this reaction is the second stage in the cascade mechanism). The alcohol reaction proceeded by elimination of water and electrocyclisation to give the ring closed product pyrrolizine (Scheme 91).
The strategy was to synthesise pyrroloisoindole 247 by the cascade mechanism.

Only one previous synthesis of pyrroloisoindole had been reported and involved oxidative radical cyclization of 1-(bromobenzyl)-2-methylsulfonylpyrrole. This was followed by partial or complete reductive desulfonylation to pyrroloisoindole by an AIBN (azoisobutyronitrile) initiated reaction with tri-\textit{n} butyltin hydride. The work up involved removal of solvent, agitation in ethyl acetate
with saturated aqueous potassium fluoride for two hours, extraction with ether and chromatographic separation.\textsuperscript{117}

(a) \textbf{Pyrolysis of 1-(2-hydroxymethylphenyl)pyrrole.}

The starting material required to synthesise pyrroloisoindole by the cascade reaction was 1-(2-hydroxymethylphenyl)pyrrole 248. This was synthesised by lithium aluminium hydride reduction of 1-(2-carbomethoxyphenyl)pyrrole (Scheme 92).

\begin{center}
\begin{tikzpicture}
\node[draw,rectangle, rounded corners] (a) at (0,0) {\textbf{Pyrolysis of 1-(2-hydroxymethylphenyl)pyrrole.}};
\end{tikzpicture}
\end{center}

\texttt{\begin{verbatim}
Scheme 92
\end{verbatim}}

The compound 248 was pyrolysed at 925 °C with the expectation of obtaining pyrrolo[2,1-\textit{a}]isoindole by the cascade reaction. However, \textsuperscript{1}H NMR spectroscopy revealed that whilst a small amount of pyrroloisoindole was formed, (identified from its characteristic signal at \(\delta_H \) 4.89 ppm in the \textsuperscript{1}H NMR spectrum of the crude pyrolysate),\textsuperscript{117} the major product was naphthalene 249. This was identified by taking a small sample of the pyrolysis product and adding naphthalene to it. No extra signals were present in this spiked \textsuperscript{1}H NMR sample, but the signals identified as naphthalene had grown in intensity. Another compound present in the pyrolysis product mixture was found to be benzofulvene 250 which was identified by
comparison of the \textsuperscript{1}H NMR spectrum of the crude pyrolysate with the literature spectrum of benzofulvene.\textsuperscript{118}

![Structural formulas]

Both naphthalene and benzofulvene may be derived from pyrroloisoindole by loss of HCN. As pyrroloisoindolone and the other tricyclic systems previously synthesised by the cascade mechanism were stable at 925 °C, it was surprising that pyrroloisoindole was not stable at that temperature.

Pyrolysis of 1-(2-hydroxymethylphenyl)pyrrole was repeated over a range of furnace temperatures, the proportions of pyrroloisoindole, benzofulvene and naphthalene varied as illustrated in the graph (Figure 28). The graph shows that the starting material was increasingly converted to products as the pyrolysis temperature was increased. The amount of pyrroloisoindole was at a maximum at a temperature of 800 °C. Above that temperature, benzofulvene and naphthalene were formed in increasing amounts until, at 900 °C the amount of benzofulvene started to decrease but the amount of naphthalene steadily increased, suggesting that the known (high temperature) interconversion from benzofulvene to naphthalene was beginning to take place.\textsuperscript{119}
Figure 28.

Pyrolysis of 1-(2-hydroxymethylphenyl)pyrrole

- % of starting material
- % of pyrroloisoindole
- % of benzofulvene
- % of naphthalene

Temperature / °C

725 775 825 875 925

100 75 50 25 0
Pyrolysis of 2-(2-hydroxymethylphenyl)pyrrole.

It appears therefore that the cascade mechanism is not a viable route to pyrroloisoindole. As previously established, the high temperature involved in the cascade reaction appears to be at the first stage to ensure movement of the pendant group from the 1-position. The second stage of the cascade mechanism does not require such a high temperature and it may be possible to obtain pyrroloisoindole from the pyrolysis of 2-(2-hydroxymethylphenyl)pyrrole 244. This was prepared by lithium aluminium hydride reduction of pyrroloisoindolone (Scheme 89).

\[
\begin{array}{cc}
\text{Scheme 89} \\
\text{LiAlH}_4 & \text{Pyrroloisoindole}
\end{array}
\]

The temperature chosen for the pyrolysis was 700 °C, based on the evidence from previous experiments where the temperature required for pyrolysis of the 2-substituted pyrrole was 100-150 °C lower than the temperature required to obtain the expected products from the 1-substituted pyrrole. At 700°C, pyrolysis of 2-(2-hydroxymethylphenyl)pyrrole yielded pyrroloisoindole which was obtained in 95% yield directly from the product trap.

Mechanistic study of the formation of benzofulvene and naphthalene.

The mechanism of the high temperature pyrolysis of 1- and 2-(2-hydroxymethylphenyl)pyrrole, in which naphthalene and benzofulvene were formed, was studied further. The temperature profile at high temperature for the 2-isomer was the same as for the 1-isomer because of products derived from the secondary
breakdown of pyrroloisoindole. Formation of naphthalene and benzofulvene involves loss of \textit{HCN} from pyrroloisoindole and also involve \textit{H}-shifts. In order to study this mechanism, deuterium labelling studies were conducted. The compound chosen for deuterium labelling studies was \textit{245}, which was synthesised by lithium aluminium deuteride reduction of pyrroloisoindolone (\textbf{Scheme 93}).

\textbf{Scheme 93}

The pyrolysis was carried out on \textit{245} at 900 \textdegree C as this was the temperature at which there appeared to be little pyrroloisoindole. A deuterium NMR spectrum was obtained and shown in \textbf{Figure 29}.

\textbf{Figure 29}. Deuterium NMR spectrum of pyrolysis products.
The products formed from the pyrolysis were found to be 246, 247, 248 and 249 (Scheme 94).

![Scheme 94](image)

The sites of the label on benzofulvene and naphthalene were identified by comparison with literature assignments. The ratio of benzofulvene to the total naphthalenes was 1:1. The labelled naphthalenes 248 and 249 were present in a 1:1.7 ratio. The possibility of 250 could not be ruled out although it was not possible to draw a mechanism for its formation.
Benzofulvene was formed from a single mechanism as illustrated in Scheme 95.

The mechanism is thought to proceed as follows. Thermal ring opening of pyrroloisoindole is followed by loss of HCN. The resulting diradical intermediate undergoes hydrogen transfer to give a cumulene intermediate which reversibly rearranges to a benzocyclobutene intermediate. From the benzocyclobutene
intermediate, a carbene is formed followed by abstraction of a deuterium atom. There is literature precedence for the carbene mechanism (Scheme 96).\textsuperscript{120}

\[ \text{Scheme 96} \]

The minor deuteriated naphthalene product 248 can be explained by the following mechanism in Scheme 97.

\[ \text{Scheme 97} \]
The mechanism proceeds \textit{via} ring opening of deuteriated pyrroloisoindole, followed again by loss of \textit{HCN}. This is followed by a deuterium shift and ring closure of the diradical intermediate.

\begin{center}
\textbf{Scheme 98}
\end{center}

The other deuteriated naphthalene species 249 can be explained as being the result of interconversion from benzofulvene again using a carbene mechanism (\textit{Scheme 98}). This interconversion increased by around 5\% as the pyrolysis temperature was raised by 25 °C.

It has been established that pyrroloisoindole 247 is less thermally stable than pyrroloisoindolone 165. From the mechanism in \textit{Scheme 99}, for pyrroloisoindolone 165: the rate constant for ring closure is probably much greater than the rate constant for loss of \textit{HCN}; the rate constant for ring opening is probably small, because of the double bond character described in the crystal structure section. However, for
pyrroloisoindole 247 the difference between the rate constant of ring closure and that of loss of HCN is not so pronounced as in the pyrroloisoindolone case, and the rate constant of ring opening is probably larger for pyrroloisoindole.

Loss of HCN (which is irreversible) follows, resulting in formation of naphthalene and benzofulvene.

\[ \text{Scheme 99} \]
EXPERIMENTAL.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>$\delta_H$, $\delta_C$</td>
<td>chemical shift</td>
</tr>
<tr>
<td>p.p.m.</td>
<td>parts per million</td>
</tr>
<tr>
<td>FVP</td>
<td>flash vacuum pyrolysis</td>
</tr>
<tr>
<td>mol</td>
<td>moles</td>
</tr>
<tr>
<td>mmol</td>
<td>millimoles</td>
</tr>
<tr>
<td>M</td>
<td>molarity</td>
</tr>
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<td>s</td>
<td>singlet</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>dd</td>
<td>doublet of doublets</td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>q</td>
<td>quartet ($^1$H spectra) / quaternary ($^{13}$C spectra)</td>
</tr>
<tr>
<td>m</td>
<td>multiplet</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant</td>
</tr>
<tr>
<td>mp</td>
<td>melting point</td>
</tr>
<tr>
<td>bp</td>
<td>boiling point</td>
</tr>
<tr>
<td>m/z</td>
<td>mass to charge ratio</td>
</tr>
<tr>
<td>M$^+$</td>
<td>mass of molecular ion</td>
</tr>
<tr>
<td>h</td>
<td>hours</td>
</tr>
<tr>
<td>min</td>
<td>minutes</td>
</tr>
</tbody>
</table>
atm  atmospheres

p.s.i.  pounds per square inch
1. INSTRUMENTATION AND GENERAL TECHNIQUES.

(a) Nuclear Magnetic Resonance Spectroscopy.

$^1$H NMR spectra were recorded on Bruker WH360 (360 MHz), Bruker AC250 (250 MHz), Bruker AC200 (200 MHz), and Varian Gemini 200 (200 MHz) spectrometers.

$^{13}$C NMR spectra were obtained on Bruker WH360 (90 MHz), AC250 (63 MHz) and AC200 (50 MHz) instruments.

The Bruker WH360 was operated by Dr. D. Reed, the Bruker AC250 by Mr. J.R.A. Millar, the Bruker AC200 by Mr. W.G. Kerr and Dr. H. McNab and the Varian Gemini 200 by Miss E. Stevenson.

Spectra were recorded in [$^2$H] chloroform, unless otherwise stated. Chemical shifts ($\delta_H$ and $\delta_C$) are quoted in ppm relative to tetramethylsilane, and all coupling constants are given in Hertz (Hz).

(b) Mass Spectrometry.

Low resolution electron impact mass spectra were recorded by Miss E. Stevenson on Finnigan 4500 instrument and by Mr H.G. McKenzie on a Finnegan 4600...
instrument. High resolution and parent-daughter scans were obtained on a Kratos MS50TC instrument operated by Mr A.T. Taylor.

(c) Elemental Analysis.

Microanalyses were carried on a Perkin Elmer 240 CHN Elemental Analyser by Mrs. L. Eades, Mr. S. Franklin and Mr. D. Glass.

(d) Structure Determination.

X-Ray crystal structure data were obtained by Dr. A.J. Blake, Dr. R.O. Gould and Dr. S. Parsons on a Stoe STADI-4 four circle diffractometer, with graphite monochronator.

(e) Chromatography.

Thin-layer chromatography was carried out on precoated aluminium sheets (0.2 mm silica gel, Merck, grade 60) impregnated with an ultra violet indicator.

Dry flash chromatography was carried out on silica gel (Merck, grade 60, 230-400 mesh, 60 Å). The crude materials were generally preabsorbed onto silica gel and then loaded onto the column. Ethyl acetate and n-hexane were frequently used as the
solvent system with 10% increments in the polar component every two or three fractions.

(f) **Solvents.**

Diethyl ether was dried by distillation from sodium using benzophenone as an indicator. Other commercially available solvents were dried over molecular sieves or used without further purification.
2. FLASH VACUUM PYROLYSIS.

The technique of FVP involves the exposure of gaseous molecules to high temperatures for very short periods of time, typically $10^2$-$10^3$ seconds. The apparatus used in such experiments is illustrated in Figure 6 and is based on the design of W.D. Crow of the Australian National University. In principle the substrate is distilled or sublimed through an electrically heated tube which is connected to a cold trap and vacuum line.

Volatilisation of the substrate at temperatures lower than 300°C was achieved by a glass Buchi drying oven. The volatilised substrate was then drawn through a silica tube (30 x 2.5 cm) which was heated by a Stanton Redcroft laboratory tube furnace. The temperature within the furnace was monitored and controlled by a platinum/platinum 13% rhodium thermocouple. On exiting the furnace the
product(s) were collected in a trap cooled by a liquid nitrogen bath. For a small pyrolyses (up to 2 g of starting material) the U-shaped trap (Figure 6) suffices; for larger scale pyrolyses this trap can be replaced with a larger 'finger trap' in order to avoid blockages. The vacuum was maintained, typically at $10^{-2}$-$10^{-3}$ Torr by an Edwards Model ED100 high capacity oil pump.

The product(s) formed were normally sufficiently pure that they could be either scraped from the trap for analysis or washed through with a suitable solvent. For small scale pyrolyses (50-100 mg) the solvent of choice was frequently [2H]chloroform enabling immediate examination by $^1$H and $^{13}$C NMR spectroscopy.

Standard pyrolysis parameters used throughout this section are furnace temperature, inlet temperature, pressure, sublimation time and mass of substrate.
3. EXPERTIMENTAL for PART 1.

(a) Preparation of 3-(dialkylamino)propenal derivatives.

The appropriate amine (50 mmol) was added to a solution of propargyl alcohol (2.8 g, 50 mmol) in benzene (40 cm³). The mixture was cooled in ice while activated manganese dioxide (12 g, 138 mmol) was added over a period of 1 hour while being stirred continuously. The manganese dioxide was filtered off and washed with dichloromethane. The filtrate was evaporated and then distilled using a Kugelrohr apparatus.

The following compounds were prepared using this method:

3-(Pyrrolidin-1-yl)propenal.

\[
\text{\framebox(2cm)} \text{N} \quad \text{\framebox(2cm)} \quad \text{O}
\]

(1.89 g, 30%), mp 54-56 °C (lit.,\textsuperscript{121} 55-57 °C); \(\delta_H \) 9.00 (1H, d, \(^3J\overline{8.5})\), 7.21 (1H, d, \(^3J\overline{12.7})\), 5.04 (1H, dd, \(^3J\overline{8.5} \) and \(^3J\overline{12.7})\), 3.47 (2H, m, \(^3J\overline{6.5} \) and \(^3J\overline{6.1})\), 3.15 (2H, m, \(^3J\overline{6.3} \) and \(^3J\overline{6.8})\) and 1.95 (4H, m); \(\delta_C \) 188.56, 155.76, 101.77, 51.99, 46.77, 24.90 and 24.77; \(m/z\) 125 (M\(^+\), 100%), 108 (24), 96 (23), 82 (14), 69 (41), 68 (36) and 54 (21).

3-(Piperidin-1-yl)propenal.

(1.27 g, 18%), bp 120 °C (0.1 Torr) [lit.,\textsuperscript{122} 124 °C (0.1 Torr)]; \(\delta_H \) 8.92 (1H, d, \(^3J\overline{8.3})\), 6.87 (1H, d, \(^3J\overline{12.6})\), 5.06 (1H, dd, \(^3J\overline{8.3} \) and \(^3J\overline{12.6})\), 3.30 (4H, m) and 1.53 (6H, m);
δc 189.18, 159.02, 100.17, 54.58, 45.87, 25.98, 24.41 and 23.50; m/z 139 (M⁺, 100%), 122 (79), 110 (21), 96 (31), 82 (22) and 70 (47).

3-(Hexahydroazepin-1-yl)propenal.

![Chemical Structure](image)

112

(2.13 g, 27%), bp 120 °C (0.2 Torr); (Found: M⁺, 153.11526. C₉H₁₅NO requires M, 153.11536); δh 8.93 (1H, d, 3J 8.5), 6.97 (1H, d, 3J 12.7), 5.03 (1H, dd, 3J 8.5 and 12.7), 3.34 (2H, m), 3.13 (2H, m) and 1.64-1.47 (8H, m); δc 188.80, 159.62, 100.29, 55.62, 48.26, 29.56, 27.41, 26.13 and 24.91; m/z 153 (M⁺, 84%), 136 (100), 124 (32), 112 (13), 110 (19), 98 (25), 97 (12), 96 (14), 84 (18), 82 (24), 69 (26), 69 (13) and 68 (17).

3-(Octahydroazocin-1-yl)propenal.

![Chemical Structure](image)

113

(2.93 g, 35%), bp 160 °C (0.05 Torr); (Found: M⁺, 167.1315. C₁₀H₁₇NO requires M, 167.13101); δh 8.77 (1H, d, 3J 8.5), 6.84 (1H, d, 3J 12.9), 4.88 (1H, dd, 3J 8.5 and 3J 12.9), 3.18-3.03 (4H, m) and 1.50-1.26 (10H, m); δc 188.59, 159.33, 100.95, 56.86, 48.26, 26.56, 25.72, 25.35, 24.27 and 24.08; m/z 168 (M⁺, 100%), 167 (99), 166 (18), 150 (45), 138 (48), 124 (35), 122 (21), 110 (28), 98 (33), 97 (16), 96 (31), 84 (28), 83 (19), 82 (43), 80 (14), 70 (32), 69 (18), 68 (29), 67 (13), 57 (17), 56 (44), 55 (93), 54 (35) and 53 (13).
3-(1,2,3,4-Tetrahydroisoquinolin-2-yl)-propenal.

(2.68 g, 29%), bp 96 °C (0.1 Torr); δ_H 9.04 (1H, d, \(^{3}J 8.2\)), 7.18-6.89 (5 H, m), 5.19 (1H, dd, \(^{3}J 8.2\) and 12.8), 4.41-4.14 (2H, m), 3.88-3.35 (2H m) and 3.19-2.65 (2H, m); δ_C 188.99, 158.56, 134.27, 134.27 (q), 133.30 (q), 128.14, 126.57, 126.30, 100.85, 53.91, 50.30 and 47.59; m/z 187 (M\(^{+}\), 10%), 169 (45), 132 (97), 116 (16), 104 (100), 76 (19) and 50 (10). This product was characterised by its Meldrum's acid derivative 136.

3-(1,2,3,4-Tetrahydroquinolin-1-yl)-propenal.

(3.82 g, 41%), mp 78-80 °C (lit., mp 79-80 °C); δ_H 9.31 (1H, d, \(^{3}J 8.0\)), 7.76 (1H, d, \(^{3}J 13.1\)), 7.25-6.98 (4H, m), 5.52 (1H, dd, \(^{3}J 13.1\) and \(^{3}J 8.1\)), 3.52 (2H, t, \(^{3}J 6.4\)), 2.74 (2H, t, \(^{3}J 5.8\)) and 1.93 (2H, \(^{3}J 6.2\)). δ_C 190.42 (q), 152.95 (q), 139.47 (q), 128.93, 127.59, 123.38, 116.01, 105.59, 46.30, 27.07 and 22.14; m/z 187 (M\(^{+}\), 59%), 170 (100), 158 (42), 156 (10), 146 (15), 132 (100), 133 (81), 130 (82), 117 (54) and 91 (30).
3-(1,2,3,4-Tetrahydroquinolin-1-yl)-propanal (60 mg, 0.32 mmol) was added to DTFA (1 cm³). The \(^1\)H NMR spectrum was obtained after 10 minutes, 1 hour 10 minutes, 2 hours 10 minutes and 4 hours 10 minutes. The reaction was monitored by \(^1\)H NMR spectroscopy for the disappearance of the signal at \(\delta_{\text{H}} 6.07 \text{ ppm}\), corresponding to the doublet of doublets of the 2 position of the enaminal. After 1 hour and 10 minutes, the signal had almost disappeared. No further change was noted after 2, 3 or 4 hours. There was little change between the spectra recorded at 1 and 2 hours. Deuterium exchange had taken place at the 2-position. The solution was added dropwise to D\(_2\)O (2 cm³). A slight cloudiness was observed but no definite precipitate. A solution of Na (10 mg, 0.43 mmol) in D\(_2\)O (2 cm³) was added dropwise to basify the DTFA solution and the product was extracted 3 times using chloroform. The solution was evaporated using a rotary evaporator and the resultant product was re-examined by \(^1\)H NMR in CDCl\(_3\). Unfortunately, it appeared that the deuterium had back-exchanged from the 2-position, probably as a result of using the rotary evaporator. (This observation however, could be useful in later experiments for washing out the label from the 2-position to leave deuterium elsewhere). The experiment was repeated using the same work-up as described above with the exception of using a rotary oil pump to remove the chloroform at 1 Torr. The crude product was submitted directly for mass spectrometry analysis which was recorded
within 24 hours of preparation. \( m/z \) 188 (M\(^+\), 7%), 187 (12), 171 (5), 170 (11), 158 (17), 134 (70) and 132 (57).

\[ \text{[2,3-^2H]-3-(1,2,3,4-Tetrahydroquinolin-1-yl)-propenal.} \]

\[
\text{D} \quad \text{N} \quad \text{D} \quad \text{O}
\]

123

All glassware for this experiment was flame-dried. Propargyl alcohol (1 g, 18 mmol) was dissolved in D\(_2\)O (3 cm\(^3\)) containing NaOD from (Na, 10 mg, 0.43 mmol) dissolved in D\(_2\)O (3 cm\(^3\)). The experiment was monitored by \(^1\)H NMR spectroscopy for disappearance of the proton at \( \delta_H \) 2.5 ppm corresponding to the CH\(_2\) of the alcohol. Then the solution was extracted with benzene (5 x 5 cm\(^3\)). The extract was dried with magnesium sulphate. Tetrahydroquinoline (2.5 g, 13 mmol) was shaken with D\(_2\)O (5 cm\(^3\)). The compound was extracted into benzene (3 x 5 cm\(^3\)), and dried with magnesium sulphate. These solutions were combined and benzene (20 cm\(^3\)), then manganese dioxide (4.5 g, 50 mmol) was added slowly with stirring and cooling. The solution was stirred overnight then the manganese dioxide was filtered off and the solvent was evaporated using a rotary pump to give compound 123. \( m/z \) 189 (M\(^+\), 3%), 188 (19), 187 (31), 172 (11), 171 (15), 170 (32), 160 (6), 159 (7), 158 (17), 134 (50), 133 (15), 132 (100), 130 (50), 119 (14), 118 (7), 117 (39) and 115 (14).
[2,2-\textsuperscript{2}H]-3-(3,4-Dihydroquinolin-1-yl)-propenal.

\[
\text{H} \quad \text{H} \\
\text{N} \quad \text{H} \\
\text{D} \quad \text{D} \\
\text{H} \quad \text{CH} = \text{O}
\]

All glassware was flame-dried for this experiment. 3,4-Dihydroquinolin-2-one (2 g, 14 mmol) was dissolved in sodium dried tetrahydrofuran (20 cm\textsuperscript{3}) and added slowly, dropwise with stirring to lithium aluminium deuteride (0.5 g, 12 mmol) dissolved in dry tetrahydrofuran (20 cm\textsuperscript{3}). The mixture was then heated under reflux for 2 hours. The mixture was cooled, then wet ether (20 cm\textsuperscript{3}) was added, followed by water (20 cm\textsuperscript{3}). Then a solution of potassium sodium tartrate (20\%, 30 cm\textsuperscript{3}) was added and the solid was filtered off through celite. The solute was evaporated and the crude product was then reacted with propargyl alcohol (1 g, 18 mmol) and manganese dioxide (4 g, 46 mmol) in benzene (15 cm\textsuperscript{3}). (The manganese dioxide had been shaken with D\textsubscript{2}O to minimise any back exchange of deuterium, and dried on a rotary oil pump). The preparation of the enaminal was then carried out in the usual manner. It had \textit{m/z} 189 (M\textsuperscript{+}, 90\%), 188 (10), 172 (15), 171 (86), 160 (53), 159 (8), 158 (13), 148 (45), 130 (81), 103 (42) and 78 (100).

\textit{N-[1-\textsuperscript{2}H]-Cyclohexylcyclohexylamine enaminal.}

The above compound was prepared in 3 stages:

(i) Preparation of \textit{N-cyclohexylidenecyclohexylamine}.\textsuperscript{38}
A mixture of cyclohexylamine (10 g, 0.1 mol) and cyclohexanone (10 g, 0.1 mol) in toluene (100 cm$^3$), containing p-toluenesulphonic acid (0.4 g) was heated under reflux for three hours, using a Dean and Stark apparatus to remove water. The solvent was evaporated using a rotary evaporator, and the product was distilled under vacuum. (16g, 58%), bp 128 °C, (1 Torr) [lit., 38 135-137 °C (20 Torr)]; δC 170.04 (q), 57.39, 39.77, 33.70, 28.55, 27.42, 27.12, 25.75, 25.21 and 24.59.

(ii) N-[$^1$H]-Cyclohexylcyclohexylamine.

A solution of the above imine (5 g, 28 mmol) in dry ether (50 cm$^3$) was added under dry nitrogen to a suspension of lithium aluminium deuteride (1.0 g, 24 mmol) in dry ether (150 cm$^3$). The mixture was heated under reflux for 35 minutes, cooled, and the excess of hydride was carefully decomposed with wet ether (20 cm$^3$) and water (30 cm$^3$). After the successive addition of aqueous potassium sodium tartrate (20%; 80 cm$^3$) and aqueous sodium hydroxide (10%; 30 cm$^3$), the organic layer was separated and the aqueous layer was extracted with ether (2 x 100 cm$^3$). The combined organic layers were dried (MgSO$_4$), concentrated and distilled (Kugelrohr) to give the title labelled amine (3.78 g, 74%), bp 141-145 °C (30 Torr), [lit., 38 136-138 °C (26 Torr) for undeuteriated compound].

(iii) Preparation of enaminal.
A solution of N-[1-$^2$H]-Cyclohexylcyclohexylamine (3 g, 16 mmol) in benzene (40 cm$^3$) was then reacted with propargyl alcohol (1 g, 18 mmol) and manganese dioxide (4.2 g, 48 mmol) in the usual manner, to obtain the enaminal 126. (1.4g, 36%); $m/z$ 236 (M$^+$, 100%), 219 (42), 207 (59), 193 (56), 179 (46), 165 (22), 152 (81), 124 (62), 111 (72) and 97 (56).

(b) Preparation of propynal and related experiments.

Propynal.

\[
\text{HO}==\text{CCHO}
\]

Diprop-2-ynyl ether (2.0 g, 21 mmol) was weighed into a round-bottomed flask and connected \textit{via} a right-angled adapter to an empty silica furnace tube which was maintained at 750 °C by an electrically heated furnace. The exit end of the furnace tube was connected to a U-tube trap of 1.9 cm diameter, which was cooled in liquid nitrogen. The inlet flask was cooled in ice, and the whole system was evacuated to $10^{-2}$-$10^{-3}$ Torr. The ether distilled through the furnace as the ice melted over a period of 40-60 minutes. If necessary, the evaporation can be completed by warming the flask in warm water (c.a. 60 °C). If the products blocked the trap, the liquid nitrogen
level at the trap was lowered to allow the products to melt and flow down the vertical
tube of the trap and resolidify. The product which remained in the trap after it was
warmed to room temperature was almost pure propynal. 54 (0.92 g, 80%); δH 9.16
(1H, s) and 3.51 (1H, s); m/z 54 (33%) and 53 (100).

**Preparation of enaminal 110 using the prop-2-ynal (127) prepared above.**

Prop-2-ynal 127 (32 mg, 0.6 mmol) dissolved in chloroform (5 cm³) was added
dropwise to pyrrolidine (41 mg, 0.6 mmol) in chloroform (15 cm³) using a
mechanical syringe pump at setting 5 (12 cm³ per hour). The mixture was stirred
continuously for 12 hours, the solvent was removed and the product purified using
silica column chromatography. (34.5 mg, 46%), mp 60 °C (lit., 121 55-57 °C); δH 9.00
(1H, d, 3J 8.5), 7.21 (1H, d, 3J 12.7), 5.04 (1H, dd, 3J 8.5 and 12.7), 3.47 (2H, m, 3J
6.5 and 6.1), 3.15 (2H, m, 3J 6.3 and 6.8) and 1.95 (4H, m); δC 188.56, 155.76,
101.77, 51.99, 46.77, 24.90 and 24.77; m/z 125 (M⁺, 100%), 108 (24), 96 (23), 82
(14), 69 (41), 68 (36) and 70 (21).

**Benzyl prop-2-ynyl ether.**

\[
\begin{align*}
\text{H} & \\
\text{H} - \text{C} & - \text{O} - \text{CH₂C=CH} \\
\text{Ph} & 
\end{align*}
\]

131

Propargyl alcohol (3.55 cm³, 0.06 mol) was added to a well stirred mixture of ground
potassium hydroxide (3.36 g, 0.06 mol) and hexadecyltributylphosphonium bromide
(0.46 g, 9 mmol) in toluene (18 cm³). Stirring was continued for fifteen minutes at
room temperature, then the mixture was heated to 70°C using an oil bath and
temperature controller. A solution of benzyl chloride (6.9 cm³, 0.06 mol) in toluene
(20 cm³) was slowly added over 1 hour. The mixture was stirred at 70 °C for an additional three hours then cooled to room temperature. Anhydrous sodium sulphate (1.1 g, 0.008 mol) was added with vigorous stirring. The solid was filtered on a sintered glass funnel and washed with toluene (3 x 2 cm³). The product was purified by distillation and collected at 100-102 °C. After collection, more solid precipitated out of solution so the product was filtered a second time and redistilled. (7.0 g, 80%), bp 100-102 °C [lit., 64 100-101°C (24 Torr)]; δH 7.40 (5H, s), 4.60 (2H, s), 4.15 (2H, d,d 4J 2.5) and 2.40 (1H, t, 4J 2.5).

**Benzaldehyde.**

PhCHO

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Benzyl prop-2-ynyl ether (0.5 g) was distilled at 10⁻¹ Torr (under similar conditions to those described above for prop-2-ynal) into the furnace which was maintained at 750 °C. The sole product in the trap after evaporation of allene was benzaldehyde, (0.23 g, 63%); δH 10.02 (1H, s), 7.88 (2H, m) and 7.65-7.45 (3H, m).

(c) **Preparation of Meldrum's acid derivatives.**

The enaminone (10 mmol) was added to a solution of Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) (10 mmol) in pyridine (4 cm³) and stirred overnight. The solution became very dark red in colour. The pyridine was removed by high vacuum rotary evaporator. The residue was triturated with ethanol which caused slow crystallisation of the product. The product was stored at -20 °C overnight, filtered
and washed with ethanol. The filtrate was concentrated and returned to the freezer to
give a second crop of product.

The following compounds were prepared using this method:

5-[3-(Pyrrolidin-1-yl)propenylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione.

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

(1.27 g, 50%), mp 244-246 °C; (Found: C, 62.15; H, 6.75; N, 5.60. C\text{_{13}}H\text{_{17}}NO\text{_{4}} requires C, 62.3; H, 6.8; N, 5.55 %); \(\delta^H\) 7.89 (1H, d, \(^3J\) 13.4), 7.49 (1H, d, \(^3J\) 11.9)
6.79 (1H, dd, \(^3J\) 11.9 and 13.4) 3.69-3.44 (4H, m), 2.25-1.96 (4H, m) and 1.65 (6H, s); \(\delta^C\) 165.41 (q), 163.31 (q), 158.70, 157.85, 103.24, 102.93 (q), 93.85 (q), 53.45, 48.30, 26.85, 24.90 and 24.81; \(m/z\) 251 (M\(^+\), 49%), 194 (13), 125 (10), 121 (12), 126 (73), 93 (100) and 70 (12).

5-[3-(Piperidin-1-yl)propenylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione.

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

133
(1.67 g, 63%), mp 167-169 °C; (Found: C, 62.7; H, 7.2; N, 5.1. C_{14}H_{19}NO_4 requires C, 62.55; H, 7.25; N, 5.2%); δ_H 7.93 (1H, d, ^3J 13.2), 7.25 (1H, d, ^3J 12.1), 6.97 (1H, dd, ^3J 13.2 and 12.1), 3.57-3.49 (4H, m), 1.72 (6H, s) and 1.69 (6H, s); δ_C 165.37 (q), 163.48 (q), 161.26, 158.62, 102.96 (q), 101.23, 93.67 (q), 56.42, 47.56, 26.86, 26.55, 25.18 and 23.50; m/z 265 (M^+, 67%), 208 (23), 134 (74), 122 (13), 106 (43), 93 (15), 83 (22) and 79 (100).

5-[3-(Hexahydroazepin-1-yl)propenylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione.

5-[3-(Octahydroazocin-1-yl)propenylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione.

(1.15 g, 41%), mp 171-173 °C; (Found: C, 64.5; H, 7.6; N, 5.0. C_{15}H_{21}NO_4 requires C, 64.6; H, 7.6; N, 5.1%); δ_H 7.91 (1H, d, ^3J 13.3), 7.33 (1H, d, ^3J 12.1), 6.89 (1H, dd, ^3J 13.3, and 12.1), 3.57-3.51 (4H, m), 1.80-1.78 (6H, m), 1.65 (6H, s) and 1.60-1.59 (2H, m); δ_C 165.35 (q), 163.29 (q), 162.65, 158.49, 102.90 (q), 101.78, 93.82 (q), 57.18, 49.75, 29.44, 27.43, 26.86, 26.30 and 25.51; m/z 279 (M^+, 77%), 222 (23), 148 (26), 120 (48), 106 (100), 107 (29), 97 (11), 96 (11), 93 (67), 80 (19), 79 (15), 68 (20) and 55 (19).
(1.31 g, 44%), mp 183-184.5 °C; (Found: \( M^+ \), 293.1632. \( \text{C}_{16} \text{H}_{23} \text{NO}_{4} \) requires \( M \), 293.1627); \( \delta^H \) 7.91 (1H, d, \( ^3J \) 13.1), 7.32 (1H, d, \( ^3J \) 12.3), 6.93 (1H, dd, \( ^3J \) 13.1, and 12.3), 3.59-3.47 (4H, m), 1.84-1.76 (4H, m), 1.66 (6H, s) and 1.60-1.57 (6H, m); \( \delta^C \) 165.42 (q), 163.29 (q), 162.39, 158.46, 102.95 (q) 102.48, 93.86 (q), 58.09, 49.66, 29.50, 26.88, 26.69, 25.66, 24.84 and 24.52; \( m/z \) 293 (\( M^+ \), 94%), 294 (18), 236 (36), 207 (13), 191 (15), 163 (25), 162 (65), 150 (36), 148 (20), 134 (52), 120 (100), 106 (84), 107 (56), 93 (48), 94 (27), 83 (42), 79 (67), 80 (63), 68 (42) and 55 (60).

5-[3-(1,2,3,4-Tetrahydroisoquinolin-2-yl)propenylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione.

(1.31g, 42%), mp 239-240°C; (Found: \( M^+ \), 313.1316. \( \text{C}_{18} \text{H}_{19} \text{NO}_{4} \) requires \( M \), 313.1314); \( \delta^H \) 8.00 (1H, d, \( ^3J \) 13.1), 7.47 (1H, d, \( ^3J \) 12.2), 7.28-6.94 (5H, m), 4.69
(2H, s), 3.81-3.74 (2H, m), 3.05-2.97 (2H, m) and 1.67 (6H, s); δc 165.16 (q), 163.22 (q), 161.23, 158.67, 132.75 (q), 129.61 (q), 128.49, 127.27, 103.09 (q), 101.57, 95.16 (q), 55.54, 52.07, 48.06, 44.77, 29.22, 27.64 and 26.87; m/z 313 (M⁺, 25 %), 182 (97), 167 (10), 131 (13), 130 (15), 129 (10), 117 (32), 116 (12), 115 (17), 104 (100), 91(10) and 84 (14).

5-[3-(1,2,3,4-Tetrahydroquinolin-1-yl)propenylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione.

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\text{O}
\end{array}
\]

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(1.62g, 52%), mp 242-244 °C; (Found: M⁺, 313.1330. C₁₈H₁₉NO₄ requires M, 313.13297); δH 8.13 (1H, d, \(^3\)J 12.9), 7.92 (1H, d, \(^3\)J 12.4), 7.31-7.12 (5H, m), 3.82 (2H, t, \(^3\)J 6.3 and \(^3\)J 6.4) 2.79 (2H, t, \(^3\)J 5.9 and \(^3\)J 6.4), 2.07 (2H, m) and 1.69 (6H, s); δc 164.83 (q), 162.84 (q), 159.20 (q), 155.32 (q), 138.56 (q), 129.90 (q), 129.30, 127.94, 125.35, 116.94, 104.28, 103.42, 98.27, 47.12, 27.06, 26.80 and 22.03; m/z 313 (M⁺, 62%), 256 (11), 182 (100), 170 (17), 167 (11), 154 (24), 132 (54), 123 (36) and 91 (8).
Preparation of azepinones by FVP.

The following azepinones were prepared by the flash vacuum pyrolysis of propenylidene-2,2-dimethyl-1,3-dioxane-4,6-dione derivatives. Pyrolysis conditions are reported in the form: precursor (quantity), furnace temperature ($T_f$), inlet temperature ($T_i$), pressure ($P$) and pyrolysis time (t). The bright yellow product formed was dissolved in CDCl$_3$, removed from the trap and analysed by $^1$H NMR spectroscopy. The products were then separated on a wet-flash column using alumina. The products from the column were identified as azepinone and cyclopentadienone dimer. From the $^1$H NMR of the crude pyrolysate, the differing ratios of azepinone:cyclopentadienone could be determined. This was achieved by measuring the integral of the single proton signal due to the cyclopentadienone dimer at $\delta_H$ 7.39 ppm, and the integral of the single proton (doublet of doublets) appearing around $\delta_H$ 5.3-5.6 ppm due to the azepinone.

1,2,3,9a-Tetrahydropyrrolo[1,2-a]azepin-9-one.

Pyrolysis of 5-[3-(Pyrrolidin-1-yl)propenylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione; 120 mg, 0.48 mmol, $T_f$ 550 °C, $T_i$ 100-250 °C, $P$ 0.01 Torr; t 20 minutes (20.7 mg, 29%), bp 143-145 °C (0.5 Torr); (Found: M$^+$, 149.08480. C$_9$H$_{11}$NO$_4$ requires M, 149.0841); $\delta_H$ 6.89 (1H, $^3$J 7.1), 6.81 (1H, dd, $^3$J 11.3 and 8.9), 6.23 (1H,d, $^3$J 11.3) and 5.22 (1H, dd, $^3$J 8.9 and 7.1) 3.70-3.48 (2H, m) 3.37-3.33 (1H, m), 2.98-2.91
(1H, m), 2.02-1.88 (2H, m) and 1.68 (1H, m); $\delta_c$ 180.67 (q), 143.27, 141.03, 122.93, 99.43, 65.78, 53.26, 24.92 and 24.84; $m/z$ 149 ($M^+$, 48%), 132 (29), 131 (34), 120 (68), 104 (25), 103 (21), 93 (100), 78 (38) and 77 (25).

10a-$H$-1,2,3,4-Tetrahydropyrido[1,2-$a$]azepin-10-one.

Pyrolysis of 5-[3-(Piperidin-1-yl)propenylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione

120 mg, 0.45 mmol; $T_r$ 550 °C, $T_i$ 100-160 °C, $P$ 0.05 Torr; t 20 minutes, (30 mg , 41%) bp 82 °C (0.3 Torr); (Found: $M^+$, 163.0991. $C_{10}H_{13}N0_4$ requires $M$, 163.0997); $\delta_h$ 6.85 (1H, dd, $^3J$ 10.9 and 8.9), 6.76 (1H, d, $^3J$ 6.8), 6.23 (1H, d, $^3J$ 10.9), 5.25 (1H, dd, $^3J$ 6.8 and 8.9), 3.43-3.32 (1H, m), 3.14-3.00 (2H, m), 2.54-2.44 (1H, m) and 1.98-1.56 (5H, m); $\delta_c$ 180.15 (q), 145.83, 140.68, 123.70, 99.90, 61.13, 49.06, 24.56, 22.44 and 19.45; $m/z$ 163 ($M^+$, 53%), 132 (72), 131 (100), 107 (21), 106 (28), 105 (12), 104 (50), 103 (41), 79 (85), 78 (78), 77 (27) and 53 (33).

7,8,9,10,11,11a-Hexahydroazepino[1,2-$a$]azepin-1-one.

Pyrolysis of 5-[3-(hexahydroazepin-1-yl)propenylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione; 120 mg, 43 mmol; $T_r$ 550 °C, $T_i$ 100-150 °C, $P$ 0.01 Torr, t 25 minutes;
(68 mg, 57%), bp 170-172 °C (0.4 Torr). (Found M⁺, 177.1157. C₁₄H₁₃NO requires M, 177.1154); δH 6.84 (1H, dd, 3J 10.8 and 9.1), 6.81 (1H, d 3J 8.1), 6.21 (1H, d, 3J 10.8) and 5.23 (1H, dd, 3J 9.1 and 8.1), 3.51-2.87 (4H, m) and 2.22-1.32 (7H, m); δC 193.55 (q), 145.94, 140.73, 122.87, 99.30, 67.38, 52.22, 31.03, 27.83, 25.79 and 25.59; m/z 177 (M⁺, 15%), 132 (20), 131 (23), 106 (16), 93 (19), 86 (45), 84 (100), 51 (20), 49 (30) and 47 (14).

7,8,9,10,11,12,12a-Heptahydroazepino[1,2-a]azocin-1-one..

![Structural formula](attachment:structure.png)

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Pyrolysis of 5-[3-(octahydroazocin-1-yl)propenylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione; 120 mg, 0.41mmol; Tf 550 °C, Ti 120-150 °C, P 0.001 Torr, t 25 minutes; (14 mg, 18%), bp 179-81 °C (0.4 Torr); (Found: M⁺, 191.1938. C₁₂H₁₇NO requires M, 191.1629); δH 6.78-6.66 (2H, m), 6.10 (1H, d, 3J 11.3), 5.13 (1H, d, 3J 11.3 and 8.5), 3.39-3.32 (2H, m) and 1.76-0.79 (11H, m). δC 185.35 (q), 144.13, 140.59, 120.75, 98.81, 68.43, 31.44, 27.03, 26.37, 25.84, 22.51 and 13.99.

Pyrolysis of 5-[3-(1,2,3,4-Tetrahydroisoquinolin-2-yl)propenylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione.

Pyrolysis of 5-[3-(1,2,3,4-Tetrahydroisoquinolin-2-yl)propenylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione; 120 mg, 0.57 mmol; Tf 550 °C, Ti 120-165 °C, P 0.001 Torr, t 25 minutes; (19 mg, 16%). Crude pyrolysate showed peaks at δH 7.39, 6.40-6.15, 3.6-2.8 ppm due to cyclopentadienone dimer₆₅ and at δH 8.32, 3.76 and 2.73 ppm due
to 3,4-dihydroisoquinoline, these were present in approximately a 1:1 ratio. There was also a trace of isoquinoline at $\delta_H 9.24$ and 8.50 ppm. A trace of double doublet signal at $\delta_H 5.27$ ppm may be due to the expected fused azepinone.

7a-H-5,6-Dihydroazepino[1,2-a]quinolin-7-one.

Pyrolysis of [3-(1,2,3,4-tetrahydroquinolin-1-yl)propenylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione; 120 mg, 0.57 mmol; $T_r 550 ^\circ C$, $T_i 100-150 ^\circ C$, $P 0.01$ Torr; t 35 minutes; (78 mg, 65%), bp 150-153 °C (0.5 Torr); (Found: $M^+$, 211.0978. C$_{14}$H$_{13}$NO requires $M$, 211.0971); $\delta_H 7.15-6.78$ (6H, m), 6.33 (1H, d, $^3J 11.3$), 5.56 (1H, dd, $^3J 8.5$ and 7.6), 3.73-3.70 (1H, m), 3.11-3.03 (1H, m), 2.77-2.62 (2H, m) and 2.26-2.12 (1H, m); $\delta_C$ 184.79 (q), 161.23 (q), 141.24 (q) 140.76, 139.25, 128.19, 127.23, 126.48, 124.05, 119.55, 104.81, 61.91, 24.66 and 21.94; $m/z$ 211 ($M^+$, 48%), 182 (100), 170 (15), 154 (11), 131 (62), 104 (22), 103 (22), 78 (23), 77 (22), 58 (38) and 51 (24).

4,10a-dimethyl-1,2,3-tetrahydropyrido[1,2-a]azepin-10-one.
This azepinone has previously been prepared and was obtained under the same conditions.\textsuperscript{66}

The Meldrum's acid derivative 5-[3-(2,6-dimethylpiperidin-1-yl)propenylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione (100 mg, 34 mmol) was pyrolysed using the following conditions; $T_f \, 550^\circ C$, $T_i \, 100-160^\circ C$, $P \, 0.001 \text{ Torr}$, $t \, 25$ minutes; bp 101 $^\circ C$ (0.3 Torr); $\delta_n$ 6.73-6.63 (2H, m), 6.15 (1H, d, $^3J \, 11.5$), 5.26 (1H, t, $^3J \, 8.4$), 3.56-3.44 (1H, m), 2.68-2.62 (1H, m), 1.94-1.53 (5H, m), 1.38 (3H, d) and 0.97 (3H, s). $\delta_c$ 161.34 (q), 140.74, 138.67, 121.90, 101.40, 63.39 (q), 54.45, 28.81, 28.34, 21.13, 19.72 and 15.05. The NMR spectrum is interpreted in detail in the Discussion section.

3-(1,2,3,6-Tetrahydropyridin-1-yl)propenal.

The enaminal was prepared by the usual method from 1,2,3,6-tetrahydropyridine (2.5 g, 30 mmol) which was added to propargyl alcohol (1.7 g, 30 mmol) in benzene (8 cm$^3$) and manganese dioxide (6 g, 69 mmol). The usual work-up gave the enaminal. (1.43 g, 35%), bp 118 $^\circ C$ (0.1 Torr); $\delta_n$ 9.02 (1H, d, $^3J \, 8.3$), 7.03 (1H, d, $^3J \, 12.5$), 5.87-5.82 (1H, m), 5.68-5.60 (1H, m), 5.17-5.09 (1H, m), 3.63 (2H, s), 3.40 (2H, s) and 2.21-2.19 (2H, m); $\delta_c$ 189.26, 159.04, 125.32, 122.17,
This product was characterised by its Meldrum's acid derivative 156.

5-[3-(1,2,3,6-Tetrahydropyridin-1-yl)propenylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione.

The Meldrum's acid derivative 156 was prepared from the enaminal described above. Enaminal (0.9 g, 7 mmol) was added to a solution of Meldrum's acid (1.0 g, 7 mmol) in pyridine (5 cm³) and stirred overnight. The pyridine was removed using a high-vacuum rotary evaporator and the solid was recrystallised from methanol to give 156 (1 g, 55%), mp 230 °C; (Found M⁺, 263.1152. C₁₄H₁₇NO₄ requires M 263.1157); δH 7.93 (1H, d, 3J 13.1), 6.93 (1H, d, 3J 13.1), 7.01-6.85 (1H, m), 5.94-5.88 (1H, m), 5.70-5.66 (1H, m), 4.04-4.00 (2H, m), 3.69-3.58 (2H, m), 2.30 (2H, m) and 1.62 (6H, s); ¹³C NMR showed rotamers in ratio 2.5:1. Major rotamer showed signals at δc 165.16 (q), 163.20 (q), 161.66, 158.54, 125.29, 121.61, 102.93 (q), 101.50, 94.45 (q), 51.34, 45.73, 26.81 and 25.15. The minor rotamer showed signals at 165.16 (q), 163.33 (q), 161.21, 158.78, 125.82, 122.55, 102.93 (q), 100.72, 93.97 (q), 53.44 and 43.73; m/z 263 (M⁺, 10%), 161 (11), 132 (100), 117 (16) and 79 (42).
Pyrolysis of 5-[3-(1,2,3,6-tetrahydropyridinyl)propenylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione.

5-[3-(1,2,3,6-Tetrahydropyridinyl)propenylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione (120 mg, 0.45mmol) was pyrolysed under the following conditions; \( T_f \) 550 °C, \( T_i \) 120-220 °C, \( P \) 0.05 Torr, t 40 minutes; The crude pyrolysate was dissolved in deuteriated solvent to remove the product from the FVP trap. Although an \(^1\)H NMR spectrum was obtained immediately, the sample turned brown and solid precipitated out. The \(^1\)H NMR spectrum showed signals corresponding to cyclopentadienone dimer, (e.g. \( \delta_H \) 7.37 ppm) and a doublet of doublets at \( \delta_H \) 5.30ppm which may correspond to a trace of the anticipated azepinone product. The \(^1\)H NMR spectrum also indicated that polymeric material was formed.

5-{3[N(1-\(^2\)H)Cyclohexylcyclohexylamino]propenylidene}-2,2-dimethyl-1,3-dioxane-4,6-dione 159.

[Diagram of compound 159]

The enaminal 126 (2.46 g, 10 mmol) was added to Meldrum's acid (1.44 g,10 mmol) and stirred overnight in pyridine (4 cm\(^3\)). The solution became very dark red in colour. After removing the solvent in vacuo, the material was triturated with ethanol and a solid slowly precipitated. The mixture was stored in the freezer, filtered and
washed with ethanol. The filtrate was returned to the freezer and more solid was recovered. (1.08 g, 37%); \( \delta_H \) 7.93 (1H, d, \( ^3J \) 13.1), 7.38 (1H, d, \( ^3J \) 12.2), 6.98 (1H, dd, \( ^3J \) 12.2 and 13.1), 3.82-3.73 (0.5H, m), 3.26-3.15 (0.5H, m) and 1.93-1.06 (26H, m); \( \delta_C \) 165.60 (q), 163.52 (q), 159.49, 158.79, 102.87 (q), 101.88, 92.74, 59.54, 57.87, 34.10, 34.01, 29.85, 29.74, 26.79, 25.00, 24.80; \( \delta_D \) 3.80, 3.30. \( m/z \) 362 (M\(^+\), 41%), 219 (20), 178 (10), 139 (20), 125 (13), 111 (15) and 97 (14).

1-Cyclohexyl-2,2-pentamethylene-1H-azepin-3-(2H)-one.

Pyrolyses were carried out on the deuteriated Meldrum's acid derivative 159 at furnace temperatures of \( T_f \) 550 \(^\circ\)C, \( T_f \) 600 \(^\circ\)C, \( T_f \) 650 \(^\circ\)C and \( T_f \) 700 \(^\circ\)C. The products were removed from the FVP trap by dissolving in CDCl\(_3\). It was found that at temperatures higher than 550 \(^\circ\)C, too many products other than azepinone were formed, which made accurate quantitative measurement of the proportion of azepinone unfeasible by NMR integration.

5-[3-(N-1\(^3\)H)Cyclohexylecyclohexylamino]propenylidene)propenylidene]-2,2-dimethyl-1,3-dioxane4,6-dione 159 (100mg, 0.4mmol) was pyrolysed under the following conditions; \( T_r \) 550 \(^\circ\)C, \( T_l \) 165-200 \(^\circ\)C, \( P \) 0.001 Torr t 40 minutes; The pyrolysate was dissolved in chloroform and analysed by \(^2\)H NMR spectroscopy. The \(^2\)H NMR spectrum showed peaks at \( \delta_D \) 6.24, 5.27, 4.53, 3.37 and 2.95 of which
those at $\delta_0$ 6.24 and 3.34 were due to the azepinone. Triangulation of these signals respectively gave a ratio of 1:2.9.

**Methoxymethylene Meldrum’s acid.**

![Methoxymethylene Meldrum’s acid](image)

Meldrum’s acid (43.2 g, 0.3 mol) was dissolved in trimethyl orthoformate (250 cm³) and stirred under reflux for 2.5 hours. The solution was initially pale yellow, then changed through yellow, orange and finally red. The solution was allowed to cool to room temperature, then placed in the freezer overnight to recrystallise. The mixture was filtered and hexane was used to wash the crystals. The crystals were dried for 20 minutes using a vacuum pump to remove any remaining solvent, weighed and $^1$H and $^{13}$C NMR spectra obtained. $^1$H 8.22 (1H, s), 4.34 (3H, s) and 1.78 (6H, s); $^{13}$C 174.93, 162.70 (q), 158.18 (q), 104.25 (q), 96.8 (q), 65.95 and 26.81.

**5-[3,3-Bis(dimethylamino)-2-azapropenylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione.**

![5-[3,3-Bis(dimethylamino)-2-azapropenylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione](image)
Methoxymethylene Meldrum's acid (1.9 g, 11 mmol) and tetramethylguanidine (1 g, 13 mmol) was added to acetonitrile (5 cm³). The solution was allowed to stand for 5 minutes and it turned red. The solvent was removed to give the product 161. δ_H 8.36 (1H, s), 2.92 (12H, s), and 1.63 (6H, s); δ_C 169.16 (q), 161.80 (q), 102.34 (q), 87.28 (q), 40.30, 39.55, 26.53.

Pyrolysis of 161.

The compound 161 (50 mg, 0.2 mmol) was pyrolysed using the following conditions:

T_p 500 °C, 550 °C, 600 °C, T_i 105 °C. P 0.05 Torr, t 25 minutes. During the pyrolyses, a yellow colour appeared in the trap, but this subsequently turned brown on reaching room temperature. The 1H NMR spectra of pyrolysis products T_p>500 °C only show signals in the aliphatic region. For T_p 500 °C the 1H NMR spectrum of the crude pyrolysate was dominated by a number of singlet resonances in the region δ_H 1.9-3.1. In addition, small pairs of doublets at δ_H 7.33 (J 8.4 Hz) and δ_H 5.71 (J 8.4 Hz) were identified and also at δ_H 6.71 (J 1.4) δ_H 6.60 (J 1.4), integrating to c.a. 1% of the total aliphatics. The signals at δ_H 7.33 and 5.71 ppm may be due to a trace of the 1,3-diazepin-6-one.
4. EXPERIMENTAL for PART 2.

Pyrolysis of 1-phenylpyrrole.

Pyrolysis was carried out on 1-phenylpyrrole (50 mg, 0.3 mmol) using the following conditions: $T_r$ 775, 825, 875, 925 °C, $T_i$ 60-80 °C, $P$ 0.001 Torr. The products were dissolved in deuteriated chloroform and removed from the product trap. The resulting amounts of 2- and 3-phenylpyrrole formed were quantitatively determined by measuring the integrals in the $^1$H NMR spectrum. (see Discussion Section D).

A preparative scale pyrolysis was carried out on 1-phenylpyrrole (500 mg, 3.5 mmol) at $T_r$ 925 °C, $T_i$ 60-80 °C, $P$ 0.001 Torr. The resulting pyrolysis products were dissolved in dichloromethane, removed from the product trap and separated by dry-flash column chromatography on silica. The product was successfully separated into 2-phenylpyrrole (0.2 g, 40%) and 3-phenylpyrrole (0.12 g, 24%).

Pyrolyses of 2- and 3-phenylpyrroles.

Pyrolysis was then carried out on 2-phenylpyrrole (50 mg, 0.3 mmol using the following conditions $T_r$ 775, 825, 875, 925 °C, $T_i$ 60-80 °C, $P$ 0.001 Torr. For each pyrolysis, the product was dissolved in deuteriated chloroform and a $^1$H NMR spectrum was obtained to determine the quantities of 2- and 3-phenylpyrrole formed. Another pyrolysis was carried out on 3-phenylpyrrole $T_r$ 925 °C (50 mg, 0.3 mmol) and the product was dissolved in deuteriated chloroform and a $^1$H NMR spectrum was obtained and the relative proportions of products (2- and 3-phenylpyrrole) were determined. (See Discussion Section D).
Pyrolysis of 1-phenylimidazole.

Pyrolysis was carried out on 1-phenylimidazole (50 mg, 0.35 mmol) using the following conditions: $T_f$ 775, 825, 875, 925 °C, $T_i$ 80-100 °C, $P \ 0.001 \ \text{Torr}$. The products were dissolved in deuteriated chloroform (to which 10 μl of deuteriated dimethyl sulphoxide was added), and removed from the product trap. The resulting amounts of 2- and 4-phenylimidazole formed were quantitatively determined by measurement of integrals in the $^1$H NMR spectrum and comparison with authentic samples. 

Pyrolysis of 2- and 4-phenylimidazoles.

Pyrolyses were carried out on 2-phenylimidazole (50 mg, 0.35 mmol) under the following conditions $T_f$ 775, 825, 875, 925 °C, $T_i$ 80-100 °C $P \ 0.001 \ \text{Torr}$. The products for each pyrolysis were dissolved in deuteriated chloroform (with 10 μl of deuteriated dimethyl sulphoxide added) and $^1$H NMR spectra were obtained. Only 2-phenylimidazole was obtained. Identification was achieved by comparison with authentic samples.

Pyrolyses were carried out on 4-phenylimidazole (50 mg, 0.35 mmol) under the following conditions $T_f$ 775, 825, 875, 925 °C, $T_i$ 80-100 °C $P \ 0.001 \ \text{Torr}$. The products for each pyrolysis were dissolved in deuteriated chloroform (with 10 μl of deuteriated dimethyl sulphoxide added) and $^1$H NMR spectra were obtained. Only 4-phenylimidazole was obtained. Again, identification was achieved by comparison with authentic samples.

1-(2-Carbomethoxyphenyl)pyrrole.
Methyl anthranilate (3.02 g, 20 mmol) was added to 2,5-dimethoxytetrahydrofuran (3.17 g, 24 mmol), glacial acetic acid (20 cm³) and dioxan (30 cm³) and heated under reflux for two hours. Volatiles were removed on a rotary evaporator, and the product was distilled using a Kugelrohr apparatus to give 220. (3.3 g, 83%), bp 109-111 °C (lit bp 110 °C). δH 7.83-7.78 (1H, m), 7.54-7.51 (1H, m) 7.42-7.35 (2H, m), 6.84-6.83 (2H, m), 6.35-6.33 (2H, m) and 3.72 (3H, s).


Pyrolysis was carried out on (1-(2-carbomethoxyphenyl)pyrrole) 220 (50 mg, 0.25 mmol) under the following conditions: Tf 800 °C, Tf 850 °C, Tf 900 °C, Tt 925 °C, Tt 120-180 °C, P 0.05 Torr; Optimum furnace temperature, under which no starting material was present in product trap, was Tf 925 °C. A preparative pyrolysis was carried out using the pyrrole 220 (0.50 g, 2 mmol) under the following conditions: Tf 925 °C, Tt 120 °C, P 0.01 Torr, t 30 minutes, to give a yellow coloured pyrolysate.
cm$^3$). Removal of the solvent gave 5H-pyrrolo[2,1-a]isoindol-5-one. (0.30 g, 79%), mp 86 °C. (lit., 72 86-86.5 °C); $\delta_H$ (360 MHz) 7.61 (1H, dt, $^3J$ 7.5, $^4J$, $^5J$ 1.0), 7.39 (1H, td, $^3J$ 7.5, $^4J$ 1.0), 7.24 (1H, dt, $^3J$ 7.5, $^4J$, $^5J$ 1.0), 7.14 (1H, td, $^3J$ 7.5, $^4J$ 1.0), 6.98 (1H, dd, $^3J$ 3.1, $^4J$ 0.9), 6.17 (1H, dd, $^3J$ 3.1, $^4J$ 0.9) and 6.14 (1H, t $^3J$ 3.1) $\delta_c$ 162.93 (q), 136.19 (q), 135.43 (q), 134.29, 131.78 (q), 126.94, 125.56, 119.34, 117.01, 116.44 and 107.21; m/z 169 (M$^+$, 100%), 140 (31), 114 (47), 113 (20), 88 (5), 87 (11), 63 (13) and 62 (10).

2-(2-Carbomethoxyphenyl)pyrrole.

\[ \text{Pyrroloisoindolone 165 (1.69 g, 10 mmol) was added to a solution of Hunig's base (diethylisopropylamine) (1.29 g, 10 mmol) in methanol (5 cm}^3\text{) and stirred for 10 minutes. The solvent was removed and the product 2-(2-carbomethoxyphenyl)pyrrole was obtained (1.79 g, 89%), bp 147-150°C (0.4 Torr); (Found: M$^+$, 201.0784, C$_{12}$H$_{11}$NO$_2$ requires M, 201.0790); $\delta_H$ 10.38-10.36 (1H, broad s), 7.77 (1H, d, $^3J$ 7.9), 7.69 (1H, d, $^3J$ 7.9), 7.48 (1H, t, $^3J$ 7.3), 7.25 (1H, t, $^3J$ 7.3), 6.91 (1H, m), 6.53 (1H, m), 6.31 (1H, m) and 3.88 (3H, s); $\delta_c$ 170.43 (q), 133.06 (q), 131.71, 130.46 (q), 130.39, 129.60, 127.71 (q), 125.54, 118.99, 109.59, 109.17 and 52.58; m/z 201 (M$^+$, 100%), 170 (30), 144 (72) and 132 (10).

Pyrolysis of 2-(2-carbomethoxyphenyl)pyrrole 223.

Pyrolysis was carried out on 2-(2-carbomethoxyphenyl)pyrrole 223 (50 mg, 0.2 mmol) under the following conditions $T_f$ 650 °C, 750 °C, 800 °C, $T_i$ 850 °C, $T_i$
120-180 °C, $P$ 0.05 Torr; Optimum furnace temperature, under which no starting material was present in product trap, was $T_f$ 800 °C, $T_i$ 130° C. $P$ 0.05 Torr; The exclusive product was the pyrroloisoindolone 165 (40 mg, 0.19 mmol) mp 86.5 °C. (lit., 86-86.5 °C) $\delta_H$ 7.62 (1H, d, $^{3}J$ 7.5), 7.42 (1H, t, $^{3}J$ 7.5), 7.27 (1H, d, $^{3}J$ 7.5), 7.14 (1H, dd, $^{3}J$ 7.5 and $^{3}J$ 7.5), 6.98 (1H, d, $^{3}J$ 3.1), 6.20-6.13 (2H, m). $m/z$ 169 (M+,100%), 140 (34), 114 (39), 113 (23), 88 (10), 87 (12), 63 (15) and 62 (11).

2-(1H-Benzimidazol-2-yl)-benzoic acid.

![227]

$\sigma$-Phenylenediamine (5.4 g, mmol) and phthalic anhydride (7.4 g, mmol) were stirred in water (50 cm$^3$) with concentrated hydrochloric acid (9 cm$^3$). The mixture was heated under reflux for 3 hours. After 2.5 hours, a grey mass was formed which proved difficult to stir. After 3 hours the reaction was stopped, and the product was cooled, filtered and washed with water. A grey powder was obtained which was insoluble in most readily available solvents and difficult to recrystallise. mp 270 °C (lit., 103 262-263 °C); other mps of 245, 270 and 271 °C have all been quoted.


![228]
Pyrolysis was carried out on [2-(1H-benzimidazol-2-yl)benzoic acid] 227, (120 mg, 0.5 mmol), \( T_f 950 \, ^\circ\text{C} \), \( T_i 200-270 \, ^\circ\text{C} \), \( P 0.01 \, \text{Torr} \), t 45 minutes. For this pyrolysis, silica tubes were placed in the furnace. This has the equivalent effect on the pyrolysis of raising the temperature by \(-50-100 \, ^\circ\text{C}\). The product, a yellow solid material, was removed from the product trap by dissolving it in dichloromethane (5 cm\(^3\)) (some insoluble material remained in the trap). After removal of solvent, the major product was identified as benz[4,5]imidazo[2,1-\(a\)]isoindol-11-one (79 mg, 72%), m.p 228-229 \, ^\circ\text{C} \) (lit., \( 225-227 \, ^\circ\text{C} \)).

\[
\begin{align*}
\delta_H &= 7.82 \, (3\text{H, m}), \ 7.68 \, (2\text{H, m}), \ 7.52 \, (1\text{H, t}), \ 7.31 \, (2\text{H, m}), \\
\delta_C &= 160.87 \, (q), \ 156.58 \, (q), \ 149.00 \, (q), \ 134.92 \, (q), \ 134.68, \ 132.05 \, (q), \ 131.57, \ 129.00 \, (q), \ 126.37, \ 125.81, \ 125.01, \ 122.25, \ 121.17 \text{ and } 112.62.
\end{align*}
\]

**Thieno[2,1-b]pyrrolizin-4-one.**

Methyl 3-(1-pyrrolo)thiophene-2-carboxylate (100 mg, 0.48 mmol) was pyrolysed under the following conditions. \( T_f 950 \, ^\circ\text{C} \), \( T_i 125-175 \, ^\circ\text{C} \), \( P 0.01 \, \text{Torr} \) to give the product as an orange solid. The product was removed from the pyrolysis trap by dissolving it in dichloromethane (5 cm\(^3\)) After removal of solvent, the product was found to be thieno[2,1-b]pyrrolizin-4-one. (66 mg, 79%) mp 91 \, ^\circ\text{C}. (Found: \( M^+ \), 175.0093. \( \text{C}_9\text{H}_7\text{NOS} \) requires \( M \), 175.0092); \( \delta_H \) 7.60 (1H, d, \( ^3J \ 4.7 \)), 6.92 (1H, d, \( ^3J \ 4.7 \)), 6.91 (1H, d, \( ^3J \ 3.1 \)), 5.98 (1H, d, \( ^3J \ 3.1 \)) and 5.96 (1H, t, \( ^3J \ 3.1 \)); \( \delta_C \) 158.13 (q),
148.78 (q), 140.95 (q), 138.40, 131.91 (q), 119.05, 118.91, 114.68 and 107.54; \( m/z \)
175 (M⁺, 100%), 148 (15), 147 (54), 146 (37), 121 (12), 120 (36), 103 (30), 94 (13),
93 (15) and 74 (16).

1-(2-Carbomethoxyphenyl)imidazole.

All glassware for this experiment was dried in an oven overnight, and the reaction was
carried out under an atmosphere of nitrogen. A solution of imidazole (1.1 g, 16
mmol) in dry DMSO (10 cm³) was added dropwise to a suspension of sodium hydride (0.65 g, 27 mmol) in dry DMSO. Then a solution of methyl o-
fluorobenzoate (2.5 g, 16 mmol) in DMSO (15 cm³) was added to the mixture while
stirring. The reaction mixture was heated to 100 °C for 18 hours while stirring
continued. Ethanol (5 cm³) was added to destroy the excess hydride, then the
mixture was treated with crushed ice and hydrochloric acid (10 cm³). After
extraction with diethyl ether (5 x 20 cm³), the organic layer was discarded and the
solution made alkaline by the addition of solid sodium hydrogen carbonate (2 g).
Extraction with ethyl acetate (5 x 20 cm³) followed by drying over magnesium
sulphate and evaporation of the solvent yielded a residue which was distilled using a
Kugelrohr apparatus to give 235.(0.5 g, 15%) b.p.122-125 °C; (Found: M⁺, 202.0739
C₁₁H₁₀N₂O₂ requires \( M \), 202.0742); \( \delta_H \) 7.89 (1H, d, \(^3J\) 7.7), 7.61-7.42 (2H, m), 7.30
(1H, d, \(^3J\) 7.6), 7.11-7.10 (1H, m), 7.02-7.01(1H, m) and 3.65 (3H, s); \( \delta_C \) 165.81 (q),
137.39, 136.34 (q), 132.53, 129.05, 128.48, 127.63 (q), 127.21, 120.53 and
52.24; m/z 202 (100%), 170 (23), 144 (28), 132 (13), 115 (20) and 89 (22).

**Imidazo[2,1-\(a\)]isoindol-5-one.**

![Structure of Imidazo[2,1-\(a\)]isoindol-5-one](image)

**Pyrolysis** was carried out on 1-(2-carbomethoxyphenyl)imidazole. **235** (120 mg, 0.6 mmol) under the following conditions: T\(_f\) 925 °C, T\(_i\) 100-250 °C, P 0.01 Torr, t 25 minutes. The crude pyrolysate, which was brown in colour, was removed from the product trap by dissolving the solid in dichloromethane (5 cm\(^3\)). Removal of the solvent yielded imidazo[2,1-\(a\)]isoindol-5-one **236** (79 mg, 78%), mp 90 °C; (Found: M\(^+\), 170.0471. C\(_{10}\)H\(_6\)N\(_2\)O requires M, 170.0480); \(\delta\)\(_H\) 7.71 (1H, d, \(^{3}J 7.5\)), 7.61 (1H, d, \(^{3}J 7.5\)), 7.54 (1H, t, \(^{3}J 7.5\)), 7.39 (1H, t, \(^{3}J 7.5\)), 7.15 (1H, d, \(^{3}J 1.7\)) and 7.03 (1H, d, \(^{3}J 1.7\)); \(\delta\)\(_C\) 160.96 (q), 153.91 (q), 135.57, 135.11, 135.50 (q), 133.24 (q), 129.83, 126.16, 120.54 and 113.24; m/z 170 (100%), 144 (70) and 129 (30). Other signals present in the \(^1\)H NMR spectrum of the crude pyrolysate (\(\delta\)\(_H\) 7.86, 7.00 ppm) could correspond to an alternative product **237** (see Discussion Part D).

**Methyl 3-(imidazol-1-yl)-3-phenylpropanoate.**

![Structure of Methyl 3-(imidazol-1-yl)-3-phenylpropanoate](image)
Methyl cinnamate (1.6 g, 10 mmol) was dissolved in dichloromethane (20 cm³). A solution of bromine (1.6 g, 10 mmol) in methylene chloride (20 cm³) was added dropwise with cooling. This was stirred for one hour, during which time the solution decolourised. The dichloromethane was evaporated at room temperature using a rotary evaporator. Then a solution of imidazole (0.95 g, 14 mmol) and triethylamine (5 g, 50 mmol) in toluene (40 cm³) was added and the solution was heated under reflux for twelve hours at 80 °C. The cooled solution was washed with water (50 cm³) and the residual solid dissolved in the water. The toluene layer was removed and the water layer extracted with dichloromethane (5 x 30 cm³). The organic layers were combined and the solution was concentrated. The product was purified by dry flash column chromatography using a 60% hexane: 40% ethyl acetate mixture. The identity of the product 241 (1.29 g, 57%) which was obtained from the column was confirmed by comparison with literature data. \(^{112}\)  

\[ \delta_H 7.50 (1H, s), 7.37-7.12 (5H, m), 7.04 (1H, s), 6.82 (1H, s), 6.14 (1H, s) and 3.57 (3H, s) \]  

\[ m/z \quad 228 (M^+, 56\%), 197 (38), 162 (86), 161 (89), 131 (100), 115 (17), 103 (58) \text{ and } 102 (62). \]

7-Phenylpyrrolo[1,2-\(\alpha\)]imidazol-5-one.

The compound 241 (50 mg, 0.2 mmol) was pyrolysed under the following conditions; 

\( T_f 750 °C, 800 °C, 850 °C, T_i 100-250 °C, P 0.01 \text{ Torr, t 15 minutes.} \) When pyrolysis was complete \( i.e. \) when no further starting material was present in the inlet,
the liquid nitrogen trap was removed whilst keeping the system under vacuum for a
further 10 minutes after the product trap had warmed to room temperature, thus
preventing any reaction between the desired product and the methanol formed as a
by-product. The optimum temperature for this pyrolysis was found to be 800 °C. At
this temperature, there was maximum conversion of starting material to products, and
minimum decomposition of product. The major product was found to be 7-
*phenylpyrrolo[1,2-a]imidazol-5-one* (32 mg, 82%), bp 143 °C (0.3 Torr); (Found:
M⁺, 196.0621. C₁₂H₈N₂O requires M, 196.0636); δ_H 8.09 (2H, d; J 8.0), 7.45-7.42
(3H, m), 7.09-7.08 (1H, m), 7.02-7.01 (1H, m) and 6.14 (1H, s); δ_C 162.77 (q),
154.78 (q), 148.99 (q), 134.15, 131.90, 128.80, 128.34, 127.25 (q), 116.58 and
113.86. There was also the possibility that a minor isomer 243 (see Discussion Part
D) was formed which could be identified from a singlet at δ_H 6.06 ppm in ~ 9% yield.

**Lithium aluminium hydride reduction of 5H-pyrrolo[2,1-a]isoindol-5-one.**

\[
\text{H} \quad \text{CH}_2\text{OH}
\]

A solution of 5H-pyrrolo[2,1-a]isoindol-5-one. 165 (2 g, 12 mmol) in dry ether (30
cm³) was added to a suspension of lithium aluminium hydride (0.5 g, 12 mmol) in
dry ether (30 cm³) under an atmosphere of nitrogen, at such a rate to produce a gentle
reflux. The mixture was heated under reflux for a further 40 minutes, then the flask
was cooled in ice. Wet ether (30 cm³) was added slowly, followed by water (30 cm³).
A solution of potassium tartrate (20%, 20 cm³) was added. After filtration through
celite, the ether layer was separated and the aqueous layer extracted with ether (3 x
The combined organic extracts were dried with sodium sulphate and the ether was removed using a rotary evaporator to give 2-(2-hydroxymethylphenyl)pyrrole 244 (1.4 g, 69%), bp 138 °C (0.1 Torr); (Found: M⁺, 173.0842. C₉H₁₁NO₄ requires M⁺, 173.0841); δ_H 10.43 (1H, s), 7.61 (1H, d, 3J 7.8), 7.38-7.17 (4H, m), 6.93-6.90 (1H, m), 6.49-6.46 (1H, m), 6.34-6.30 (1H, m) and 4.69 (2H, s); δ_C 134.35 (q), 130.68, 129.64 (q), 129.02, 128.90, 128.53 (q), 126.27, 119.15, 109.15, 107.79 and 65.48. m/z 173 (M⁺, 51%), 154 (100), 128 (16), 115 (21) and 91 (26).


A suspension of 5H-pyrrolo[2,1-a]isoindol-5-one 165 (0.02 g, 0.12 mmol), and Pd/C (10%, 16 mg) catalyst in hexane (30 cm³), was prepared in the hydrogenation reaction vessel. The system was carefully evacuated and then flushed twice with hydrogen. The vessel was then filled with hydrogen (3.5 atm/45 psi) and the compound was hydrogenated for 2 hours. The product flask was removed from the system and the Pd/C catalyst was removed by filtration through celite. Removal of the solvent gave the product 1,2,3,9b-tetrahydro-5H-pyrrolo[2,1-a]isoindol-5-one 245. (0.019 g, 90%), mp. 109 °C; (Found: M⁺, 173.0838. C₁₁H₁₃NO requires M⁺, 173.0840) δ_H 7.79 (1H, d, 3J 7.9), 7.55-7.39 (3H, m), 4.69-4.63 (1H, m), 3.73-3.68 (1H, m), 3.45-3.36 (1H, m), 2.39 -2.23 (3H, m) and 1.77 (1H, s); δ_C 171.53 (q), 170.15 (q), 134.35 (q), 130.68, 129.64 (q), 129.02, 128.90, 128.53 (q), 126.27, 119.15, 109.15, 107.79 and 65.48. m/z 173 (M⁺, 51%), 154 (100), 128 (16), 115 (21) and 91 (26).
147.88 (q), 146.29 (q), 133.54 (q), 131.45, 128.21, 123.85, 122.54, 64.57, 41.79 and 29.08; m/z 173 (M', 63%), 145 (100), 117 (57), 90 (35) and 57 (23).

1-(2-Hydroxymethylphenyl)pyrrole.

![Chemical structure of 1-(2-hydroxymethylphenyl)pyrrole]

A solution of 1-(2-carbomethoxyphenyl)pyrrole (2 g, 10 mmol) in dry ether (30 cm³) was added to a suspension of lithium aluminium hydride (0.4 g, 10 mmol) in dry ether (30 cm³) under an atmosphere of nitrogen, at such a rate to produce a gentle reflux. The mixture was heated under reflux for a further 40 minutes, then the flask was cooled in ice. Wet ether (30 cm³) was added slowly, followed by water (30 cm³). A solution of potassium tartrate (20%, 20 cm³) was added. After filtration through celite, the ether layer was separated and the aqueous layer extracted with ether (3 x 30 cm³). The combined extracts were dried with sodium sulphate and the ether removed using a rotary evaporator to give compound 248 (1.28 g, 74%), bp 124 °C (1.0 Torr). [lit.,²TÜRK bp 119-121 °C (1.0 Torr)]; δH 7.56-7.26 (4H, m), 6.80 (2H, t, 3J 2.1), 6.31 (2H, t 3J 2.1), 4.53 (2H, s) and 2.70 (1H, s)

Pyrolysis of 1-(2-hydroxymethylphenyl)pyrrole 248.

Pyrolyses were carried out on compound 248 (50 mg, 0.3 mmol) under the following conditions; Tf 700 °C, 750 °C, 800 °C, 850 °C, 900 °C, 925 °C, Ti 100-250 °C. P 0.01 Torr, The crude pyrolysate was dissolved in dichloromethane (5 cm³) and the solvent was removed to yield four compounds in varying proportions depending on
the furnace temperature (see Discussion Part D). The four compounds present in the crude pyrolysate were: starting material 248 δ_H 3.40 ppm, naphthalene, δ_H 7.87-7.83, 7.50-7.46 ppm, benzofulvene δ_H 7.75-7.45 (1H, m), 7.40-7.00 (3H, m), 6.88 (1H, d, \(^{3}J 5.5\)), 6.52 (1H, d, \(^{3}J 5.5\)), 6.06 (1H, m) and 5.72 (1H, s) pyrroloisoindole δ_H 7.61 (1H, d, \(^{3}J 6.9\)). These were identified by comparison with literature data.\(^{117,118,124,125}\)


![5H-Pyrrolo[2,1-a]isoindole](image)

A pyrolysis was carried out on 2-(2-hydroxymethylphenyl)pyrrole 244 (50 mg, 0.3 mmol) under the following conditions; \(T_f 700 \, ^{\circ}C, T_i 100-250 \, ^{\circ}C, \, P \, 0.01 \, \text{Torr}\). The resulting product was dissolved in deuteriated chloroform and a \(^{1}H\) NMR was obtained. The product was identified as 5H-pyrrolo[2,1-a]isoindole 247 (47 mg, 94%) δ_H 7.30 (2H, m), 7.17 (1H, t), 6.96 (1H, d), 6.38 (1H, t), 6.30 (1H, d) and 4.92 (2H, s). The \(^{1}H\) NMR spectrum was consistent with literature data.\(^{117}\)


![Lithium aluminium deuteride reduction of 5H-pyrrolo[2,1-a]isoindol-5-one.](image)

A solution of pyrroloisoindolone 165 (0.5 g, 3 mmol) in dry ether (20 cm\(^{3}\)) was added to a suspension of lithium aluminium deuteride (0.11 g, 3 mmol) in dry ether (20 cm\(^{3}\))
under an atmosphere of nitrogen, at such a rate to produce a gentle reflux. The mixture was heated under reflux for a further 40 minutes, then the flask was cooled in ice. Wet ether (20 cm$^3$) was added slowly, followed by water (20 cm$^3$). A solution of potassium tartrate (20%, 20 cm$^3$) was added. After filtration through celite, the ether layer was separated and the aqueous layer extracted with ether (3 x 30 cm$^3$). The combined extracts were dried with sodium sulphate and the ether removed using a rotary evaporator to give the compound 245 (0.35 g, 68%), b.p. 141 °C (0.1 Torr); (Found: $M^+$, 175.0823 C$_9$H$_9$NO$_4$D$_2$ requires $M^+$, 175.0831); $\delta_H$ 10.57 (1H, bs), 7.51 (1H, d), 7.28-7.05 (3H, m), 6.89-6.78 (1H, m), 6.40-6.36 (1H, m) and 6.24-6.19 (1H, m).

**Pyrolysis of 2-(2-^2$H_2$ hydroxymethyl)phenylpyrrole.**

The deuteriated compound 248 (100 mg, 0.6 mmol) was pyrolysed under the following conditions $T_f$ 900 °C, $T_i$ 100-150 °C, $P$ 0.01 Torr. The crude pyrolysate was dissolved in deuteriated chloroform and pipetted into an NMR tube. $^2$H NMR revealed peaks at $\delta_D$ 7.89, 7.53 ppm, corresponding to 1,4-dideuteriated and 1,2-dideuteriated naphthalene in 1:1.7 ratio, $\delta_D$ 6.94 ppm and $\delta_D$ 6.57 ppm corresponding to benzofulvene.
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68. See reference 33 p.139.


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   1994, 72, 15.

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   21, 2223.


   35, 3618.

   34.


PUBLICATIONS.
H atoms and isotropic displacement parameters for H atoms. All H atoms were included at calculated positions and refined using a riding model, each with an isotropic displacement parameter equal to 1.5 times that of the attached C or N atom.

Data collection: CAD-4 Software. Cell refinement: MoIST (Fair, 1990). Program(s) used to solve structure: SHELXS86 (Sheldrick, 1990). Program(s) used to refine structure: SHELXL93 (Sheldrick, 1993). Molecular graphics: PLATON (Spek, 1996a) and PLUTON (Spek, 1996b). Software used to prepare material for publication: SHELXL93.

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: AB 1390). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

References

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Two C-Unsubstituted Enaminals
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Abstract
In both 3-(N,N-diisopropylamino)-2-propanol, C3H12N0, (3), and 3-(1,2,3,4-tetrahydro-1-quinolinyl)-2-propanol, C12H13NO, (4), the entire enaminal system (O1—C1—C2—C3—N4) is approximately planar. The angles around the N atoms in (3) and (4) sum to values near 360°, indicating planarity in both molecules. One of the two crystallographically independent molecules of (3) exhibits disorder in its isopropyl groups.

Comment
The enamino structural unit (1) (Greenhill, 1977) is a classic example of a 'push-pull' substituted alkene, yet surprisingly little crystallographic information is available for simple derivatives of this conjugated system. Most enamino structures which have been reported involve derivatives which have substituents either in the 1- (Carugo, Castellani & Rizzi, 1990) or 2-position (Mague, De & Krogstad, 1995; Niederhauser, Sterchi & Neuenschwander, 1976). Structures of 1,2-disubstituted (Arriortua et al., 1992; Peralta et al., 1995) and 1,3-disubstituted (Emsley, Freeman, Parker, Kuroda & Overill, 1987) derivatives are known, as are those in which the system is incorporated in a heterocyclic ring (e.g. Hickson et al., 1986; Blake, McNab & Monahan, 1988). The only published crystal structure of a C-unsubstituted derivative, however, is that of the β-naphthyl compound (2) (Chunli, Zhongheng, Heng & Youqi, 1984), but full details of this determination are not readily available. We therefore report here the structures of a typical N,N-dialkyl enaminal and an N-alkyl N-aryl derivative; simple enamines are liquids, so for convenience we have selected the N,N-diisopropyl compound (3) and the tetrahydroquinoline structure (4). In order to avoid possible complications due to hydrogen bonding at this stage, we have specifically focused on N,N-diisubstituted examples for these determinations.
As described below, one of the two independent molecules of compound (3) in the asymmetric unit was found to be affected by disorder of the isopropyl groups. Although modelling of this was successful and there are no significant differences in their enaminoe functions, values quoted below refer to the ordered molecule (Fig. 1).

The enaminal system of both compounds (3) and (4) is approximately planar (see below) and adopts an E-s-E configuration. 1-Substituted (Carugo, Castellani & Rizzi, 1990) and 1,3-disubstituted (Emsley et al., 1987) derivatives, and also the related 1-substituted azaenaminones and enaminothiones (5) (Blake, McNab & Murray, 1989), in contrast, all adopt E-s-Z configurations. In both the N-aryl examples (2) and (4), the aryl ring adopts an s-E configuration with respect to the enaminoe system. There is good evidence from $^1$H NMR spectroscopy that compound (4) (Fig. 2) also adopts this configuration in solution. The chemical shift of H3 is thus shifted by 0.9 p.p.m. to high frequency relative to the model compound (6), which can only be due to ring-current deshielding caused by an adjacent aryl group.

The bond lengths of the conjugated portions of both compounds (3) and (4) show the effect of electron delocalization predicted by the influence of the resonance structure (1a). The C1—C2 single bond is thus shortened from an average value of 1.464 (18) Å found in $\alpha,\beta$-unsaturated carbonyl compounds (Allen et al., 1987) to 1.412 (2) and 1.420 (2) Å in compounds (3) and (4), respectively, though the corresponding lengthening of the C2==C3 double bond, from 1.340 (13) to 1.363 (3) and 1.355 (2) Å, respectively, is smaller in magnitude. The magnitude of the delocalization found in these enaminal systems is less than that found in the symmetrical iminium salt (7) (Matthews, Stenkamp & Colman.

Fig. 1. A view of the ordered molecule of compound (3) with the atom-numbering scheme. Displacement ellipsoids enclose 50% probability surfaces and H atoms are shown as spheres of arbitrary radii.

Fig. 2. A view of a molecule of (4) with the atom-numbering scheme. Displacement ellipsoids enclose 50% probability surfaces and H atoms are shown as spheres of arbitrary radii.
of the average 1.38 (3) Å in length. This is well within one e.s.d. of the average [1.39 (3) Å] of the C1—C2 and C2—C3 bond lengths in both compounds (3) and (4). The C3—N4 bond in the dialkyl compound (3) [1.334 (2) Å] is likewise shortened in comparison with average values for enamines with planar N atoms [1.355 (14) Å; Allen et al., 1987], although this effect is not found in the N-aryl examples (see below). In both compounds (3) and (4), the carbonyl C1—O1 bond distance [1.235 (2) and 1.231 (2) Å, respectively] is relatively unaffected by the enamine system and shows only marginal lengthening with respect to the average α,β-unsaturated carbonyl value [1.222 (10) Å; Allen et al., 1987].

A consequence of the aryl ring in (4) removing electron density from the enaminal π system is a significant increase in the C3—N4 bond length from 1.334 (2) Å in (3) to 1.354 (2) Å in (4), though this is not reflected in the bonds further along the chain which remain substantially unchanged. We reached exactly the same conclusions in the case of the cyclic enamines (8) (Hickson et al., 1986) and (9) (Blake, McNab & Monahan, 1988), and so this is likely to be a general effect of N-aryl substitution on the enaminal system. Bond lengths in the two N-aryl examples (2) (Chunli, Zhongheng, Heng & Youqi, 1984) and (4) do not differ significantly.

In both compounds (3) and (4), the C1—C2—C3 bond angle is significantly less than 120° [117.8 (2) and 118.48 (14)°, respectively], whereas both the O1—C1—C2 [126.8 (2) and 126.6 (2)°] and C2—C3—N4 angles [129.6 (2) and 127.04 (14)°] are much greater than 120°. Similar trends are found in compound (2) and in other E⋯E enamines. The C2—C3—N4 angles are significantly different in compounds (3) and (4). The larger angle in compound (3) possibly minimizes non-bonded contacts between the H6 and H2 atoms; these atoms are almost coplanar and lie only 2.03 (3) Å apart, whereas the corresponding H atoms in compound (4) are staggered. In agreement with this interpretation, particularly large C2—C3—N4 angles (>130°) are found in enamines containing substituents at the 2-position (Mague, De & Krogstad, 1995; Arriortua et al., 1992; Peralta et al., 1995). The N atom in both compounds (3) and (4) is planar; the angles around N4 total 359.8 (2)° for the ordered component of (3) and 360.0 (3)° for (4). The individual angles around N4 in compounds (2), (3) or (4) can deviate significantly (by up to 3°) from 120° but, although no consistent pattern emerges, the constraints of the ring in (4) are certainly an important factor.

The entire enaminal system (O1—C1—C2—C3—N4) is approximately planar in both compounds (3) and (4). With more electron density available for delocalization in the dialkyl example (3), it is not surprising that the r.m.s. deviation from the best plane (0.006 Å) is almost an order of magnitude smaller than in the aryl example (4) (0.044 Å). In both cases, the unit is bowed, with negative deviations at the termini (O1 and N4) and the major positive distortions at atoms C2 and C3. The C1 atom lies closest to the best plane in both molecules.

Intermolecular contacts are relatively weak and differ for compounds (3) and (4). In the dialkyl case (3), there are two contacts, but to different molecules; O1⋯O3A(1—x, —y, 1—z) 2.41 and O1⋯H6A(1—x, 1—y, 2—z) 2.47 Å. In contrast, each O atom of compound (4) participates in two O⋯H—C contacts to a single neighbouring molecule related by the symmetry operation (x—1/2, y, 1/2—z), viz. O1⋯H3 of 2.40 and O1⋯H12 of 2.53 Å. None of these contacts are likely to have any significant effect on molecular geometry.

**Experimental**

The title enaminals were synthesized by addition of the appropriate secondary amine to propynal, generated in situ by oxidation of propynol with activated MnO2. Crystals suitable for analysis were obtained from toluene solution.

**Compound (3)**

**Crystal data**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td>Chemical formula</td>
<td>C_{12}H_{15}NO</td>
</tr>
<tr>
<td>M, g/mol</td>
<td>211.27</td>
</tr>
<tr>
<td>Triclinic</td>
<td></td>
</tr>
<tr>
<td>a = 15.52 Å</td>
<td></td>
</tr>
<tr>
<td>b = 11.16 Å</td>
<td></td>
</tr>
<tr>
<td>c = 8.30 Å</td>
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</tr>
<tr>
<td>α = 98.93 (3)°</td>
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</tr>
<tr>
<td>β = 102.08 (3)°</td>
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<tr>
<td>γ = 109.48 (2)°</td>
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</tr>
<tr>
<td>V = 117.8 (2)°</td>
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<tr>
<td>Z = 4</td>
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<tr>
<td>D = 1.054 Mg m^{-3}</td>
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<tr>
<td>D_{c}, not measured</td>
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</tr>
</tbody>
</table>

**Data collection**

- Stoe Stadi-4 four-circle diffractometer
- ω-2θ scans
- Absorption correction: none
- 4905 measured reflections
- 4642 independent reflections
- 3392 observed reflections
- 1 > 2σ(1)

**Refinement**

- R(F) = 0.0659
- wR2(F^2) = 0.1844
- S = 0.984
- 4623 reflections
- 217 parameters

**Cell parameters from 53 reflections**

- a = 109.48 (2)°
- b = 11.16 (3) Å
- c = 8.30 (2) Å
- α = 98.93 (3)°
- β = 102.08 (3)°
- γ = 109.48 (2)°
- V = 117.8 (2)°
- Z = 4
- D = 1.054 Mg m^{-3}
- D_{c}, not measured

**X-ray data**

- Mo Kα radiation
- θ = 28.0°
- μ = 0.068 mm^{-1}
- T = 150.0 (2) K
- Cube
- Colourless
- Colourless

**Intensity decay:** none

**Refinement**

- R(F) = 0.0635
- wR2(F^2) = 0.1844
- S = 0.984
- 4623 reflections
- 217 parameters

**Extinction correction**

- SHELX93
- Extinction coefficient: 0.025 (6)
H atoms: see below


Table 1. Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²) for (3)

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<thead>
<tr>
<th>Atom</th>
<th>x</th>
<th>y</th>
<th>z</th>
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<td>0.3431(2)</td>
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<td>0.2971(2)</td>
<td>0.9807(2)</td>
<td>0.0328(4)</td>
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<tr>
<td>C2</td>
<td>0.6858(2)</td>
<td>0.3307(2)</td>
<td>0.8957(2)</td>
<td>0.0289(4)</td>
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<td>C3</td>
<td>0.4464(2)</td>
<td>0.3664(2)</td>
<td>0.7801(2)</td>
<td>0.0266(4)</td>
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<tr>
<td>N4</td>
<td>0.3671(2)</td>
<td>0.2836(15)</td>
<td>0.6799(9)</td>
<td>0.0303(3)</td>
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<td>C5</td>
<td>0.3626(3)</td>
<td>0.1989(2)</td>
<td>0.5630(2)</td>
<td>0.0336(4)</td>
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<td>C51</td>
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<td>0.5516(2)</td>
<td>0.0418(5)</td>
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<td>Cl</td>
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<td>0.2292(2)</td>
<td>0.5428(2)</td>
<td>0.0449(5)</td>
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<td>C6</td>
<td>0.2746(3)</td>
<td>0.3758(2)</td>
<td>0.6061(2)</td>
<td>0.0374(4)</td>
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</table>

Table 2. Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²) for (4)

<table>
<thead>
<tr>
<th>Atom</th>
<th>x</th>
<th>y</th>
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<tbody>
<tr>
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<td>1.3206(6)</td>
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<td>C1</td>
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<td>C2</td>
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<td>C3</td>
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<td>0.12704(7)</td>
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<td>0.10609(9)</td>
<td>1.01782(9)</td>
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<td>N4''</td>
<td>-0.2463(2)</td>
<td>0.17442(10)</td>
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</tr>
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<td>C7</td>
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<tr>
<td>C8</td>
<td>0.0407(2)</td>
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<td>0.89056(9)</td>
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<tr>
<td>C9</td>
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<td>0.17831(10)</td>
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<td>C10</td>
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<td>0.83222(10)</td>
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<td>C11</td>
<td>0.3277(2)</td>
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Table 3. Comparison of molecular geometry parameters (Å, °) for compounds (3) and (4)

<table>
<thead>
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<th>(3)</th>
<th>(4)</th>
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</thead>
<tbody>
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<td>Molecule 1</td>
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<td>O1-C1</td>
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<td>C2-C3</td>
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<td>C3-N4</td>
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<td>C5-C6</td>
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</tr>
<tr>
<td>O1-C1-C2</td>
<td>126.8(2)</td>
</tr>
<tr>
<td>C2-C1-C2</td>
<td>117.2(2)</td>
</tr>
<tr>
<td>C3-C2-C1</td>
<td>129.6(2)</td>
</tr>
<tr>
<td>C3-N4-C1</td>
<td>121.8(4)</td>
</tr>
<tr>
<td>C3-N4-C5</td>
<td>119.30(14)</td>
</tr>
<tr>
<td>C4-N4-C5</td>
<td>118.91(14)</td>
</tr>
<tr>
<td>C5-N4-C4</td>
<td>122.04(12)</td>
</tr>
<tr>
<td>C6-N4-C5</td>
<td>120.99(11)</td>
</tr>
<tr>
<td>O1-C1-C2-C3</td>
<td>179.9(9)</td>
</tr>
<tr>
<td>C1-C2-C3-N4</td>
<td>178.1(9)</td>
</tr>
<tr>
<td>C2-C3-N4-C5</td>
<td>173.7(2)</td>
</tr>
<tr>
<td>C2-C3-N4-C6</td>
<td>1.8(3)</td>
</tr>
</tbody>
</table>

Notes: (a) the actual atom labels of this disordered molecule are primed in Table 1; (b) C5—C6 in compound (4); (c) C2—C3—N4—C13 in (4); (d) C2—C3—N4—C5 in (4).

Disorder in the isopropyl groups of the second (primed) mol-
ecule of compound (3) was modelled in terms of a major (C5', C6', C6'' and C6''') orientation, the occupancies of which converged at 0.647 (4) and 0.353 (4), respectively. The C atoms of the major
component only were allowed anisotropic thermal motion. The long molecular axes of the ordered molecules of compound (3) lie along the z axis, while those of the disordered molecules are disposed approximately orthogonal to this direction, lying parallel to [110]. This non-crystallographic relationship, combined with the disorder, presumably results in a lower lattice energy than any arrangement with one molecule per asymmetric unit. For compound (3), H atoms were initially placed at calculated positions, with $U_{	ext{iso}} = 1.5U_{	ext{eq}}$ (for methyl groups) or $1.2U_{	ext{eq}}$ (for others) of their parent atom. The H atoms of the minor disorder component (primed molecule) were not included.

For both compounds, data collection: DIF4 (Stoe & Cie, 1992a); cell refinement: DIF4. Data reduction: REDU4 (Stoe & Cie, 1992b) for (3); X-RED (Stoe & Cie, 1995) for (4). Program(s) used to solve structures: SHELXTL/PC (Sheldrick, 1995) for (3); SHELX92 (Altomare et al., 1994) for (4). For both compounds, program(s) used to refine structures: SHELXL93 (Sheldrick, 1993); molecular graphics: SHELXTL/PC; software used to prepare material for publication: SHELXL93.

The authors are grateful to SERC for a Research Studentship (to LCM), a postdoctoral award (to SP) and for the provision of a four-circle diffractometer.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates, complete geometry and least-squares-planes data for compounds (3) and (4), and displacement ellipsoid plots of compounds (3) and (4), have been deposited with the IUCr (Reference: AR 1382). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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References


4-Methyl-1,2,4-triazole and 1-Methyltetrazole

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Abstract

The crystal structures of 4-methyl-4H-1,2,4-triazole, C$_4$H$_7$N$_3$, and 1-methyl-1H-tetrazole, C$_4$H$_7$N$_4$, are composed of layers of planar molecules with partially delocalized π systems. Differences in the bond lengths in these two closely related ring systems are ascribed to differing π-electron polarization effects, which are analysed with reference to ab initio calculations performed using a triple-zeta + polarization basis set at both the SCF and MP2 levels of theory.

Comment

The 1,2,4-triazole and tetrazole ring systems are typical planar π-electron partially aromatic systems. They possess an extensive chemistry (Temple, 1981; Benson, 1967) and we have in the past investigated the natures of the predominant tautomers of the parent molecules (1H-1,2,4-triazole and 2H-tetrazole) under gas-phase conditions by comparison of the UV-photoelectron spectra with those of the selectively prepared methyl derivatives (Palmer & Wheeler, 1981). After prolonged storage at room temperature, two of the methylated compounds formed crystals suitable for structure determination by X-ray crystallography and their structures are reported here. Other than the parent compounds, which are heavily hydrogen bonded (Goldschmidt, Ladell & Abowitz, 1969; van der Putten, Hedenrijk & Schenk, 1974), 4-methyl-1,2,4-triazole, (I), and 1-methyltetrazole, (II), are the simplest derivatives of their respective classes yet to be characterized structurally.

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A Short, Convenient Synthesis of Propynal†
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Propynyl (propargyl) aldehyde 1 is a useful three-carbon reagent which can be made on a large scale by an Organic Syntheses route involving chromium trioxide oxidation of prop-2-ynyl alcohol 2. However, this is a low-yielding method (35-41%) with inconvenient work-up due in part to the low boiling point (54-57 °C) of the product. The procedure is particularly awkward if only a small quantity of propynal 1 is required. A more recent variant may be useful for producing a solution of the aldehyde, but in our hands it proved impossible to separate the product from the mixture of solvents employed, using standard laboratory distillation apparatus. Here we report full experimental conditions for a convenient one-step flash vacuum pyrolysis (FVP) route to pure propynal 1 based on the retro-ene reaction of commercially available diprop-2-ynyl ether 3 (Scheme 1). This reaction has been studied previously, but details are not readily available. An analogous procedure has been used to generate propynethial from diprop-2-ynyl sulfide for in situ photoelectron spectroscopic determination. The participation of prop-2-ynyl groups in retro-ene reactions has been widely investigated kinetically and shown to be concerted and consistently faster than the reaction of the corresponding allyl derivative. FVP of silylated prop-2-ynyl ethers has been used as a preparative route to silylallenes.

Experimental

\[\text{FVP of silylated prop-2-ynyl ethers has been used as a preparative route to silylallenes.}\]

**References**


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*To receive any correspondence.
†This is a Short Paper as defined in the Instructions for Authors, Section 5.0 [see J. Chem. Research (S), 1997, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M).*