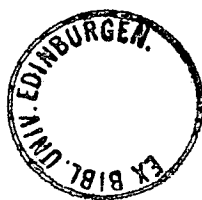


THE SYNTHESIS AND PROPERTIES OF
SIMPLE PYRROL-3-ONES AND AZEPIN-3-ONES

By

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Thesis presented for the degree of
Doctor of Philosophy,
University of Edinburgh,
November, 1986



DECLARATION

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

This thesis describes the results of research carried out in the Department of Chemistry, University of Edinburgh, under the supervision of Dr. H. McNab, since October 1st, 1983, the date of my admission as a research student.

Signed

Date

1/12/86

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LECTURE COURSES

The following courses have been attended during the period of research:

Organic Research Seminars, Edinburgh University,
Chemistry Department (3 years attendance).

Current Topics in Organic Chemistry (15 lectures, 3 years attendance).

Organo-Silicon Compounds: Preparation, Properties and
Utility in Synthesis - Dr. E. Colvin (Glasgow University,
5 lectures).

Strategy of Synthesis - Dr. I. Gosney (5 lectures).

Multipulse N.M.R. Spectroscopy - Dr. I.H. Sadler (5 lectures).

Industrial Topics in Organic Chemistry, I.C.I. Pharmaceutical
and Organic Divisions, and Beecham's Pharmaceuticals
(5 lectures).

ABSTRACT

This thesis presents an account of the study of a novel hydrogen-transfer reaction, which occurs under flash vacuum pyrolysis conditions, and its use in synthesis.

Pyrolysis of aminomethylidene Meldrum's Acid derivatives gives 1,2-dihydro-3H-pyrrol-3-ones in good yields, thus providing the first viable synthesis of simple examples of this ring system. The mechanism was investigated using chiral precursors and competitive experiments. The reactivity of the system towards acid, base, electrophiles, nucleophiles and radicals was examined and various substituted examples have been prepared.

The electrophilic reactivity of methoxymethylidene Meldrum's Acid has been investigated and used to prepare novel derivatives, suitable for further elaboration to heterocyclic systems.

This led to the extension of the hydrogen transfer, mentioned above, to vinylogous systems which gave the first synthesis of simple examples of 1,2-dihydro-3H-azepin-3-ones. The reactivity of this new system was studied in a similar manner to the five-membered ring and its involvement in electrocyclic processes was examined.

In addition, crystal structures of simple examples of both systems were obtained and detailed n.m.r. spectroscopic studies of a number of examples were carried out.

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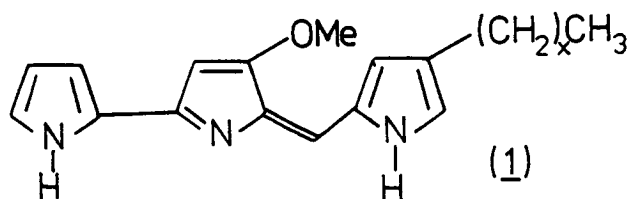
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INTRODUCTION

A. 1,2-DIHYDRO-3H-PYRROL-3-ONES (3-HYDROXYPYRROLES)

Pyrroles are one of the widely studied groups of simple heteroaromatics. However, a cursory examination of basic texts¹ or pyrrole monographs² reveals comparatively little information on examples with electron donating substituents and, in particular, those with oxygen functionality in β -positions. The knowledge which has been accumulated can be divided into three main areas. The first results from interest in the antibiotic prodigiosin (1)³ and involves consideration of synthetic routes to suitably substituted examples of the ring system and its reactions which may allow further elaboration.



The second area concerns a number of theoretical and experimental studies on the keto-enol tautomerism shown in Figure 1. Throughout this thesis, structure A will be referred to as 3-hydroxypyrrole, structure B will be named 1,2-dihydro-3H-pyrrol-3-one and structure C, 3-hydroxy-2H-pyrrole.

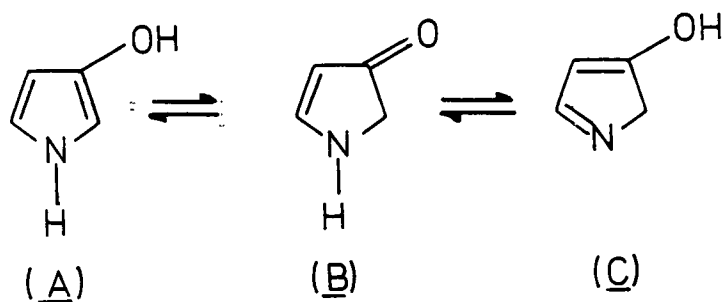
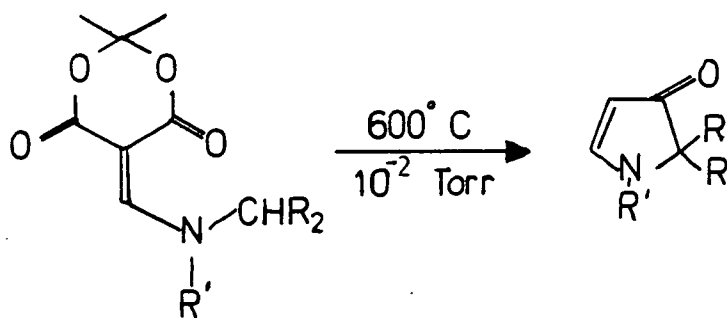


Figure 1

Finally, a range of reactions are considered which lead to isolated examples of substituted 3-hydroxypyrroles in varying yields from predicted and unexpected pathways.

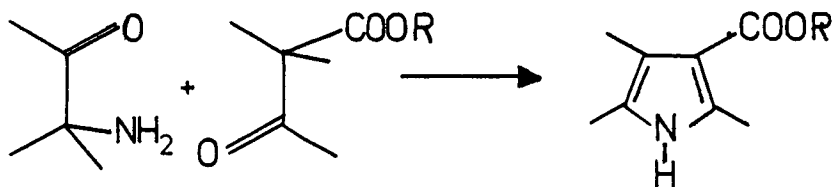
This review will attempt to (i) show the various approaches to synthesis and indicate their generality, (ii) draw some overall conclusions on the tautomerism and (iii) discuss the reactivity of the system. This will provide background for a major part of this thesis which is concerned with the generation of the ring system⁴ (Scheme 1) and an investigation of its properties.



Scheme 1

SYNTHESES

The most widely used route in pyrrole syntheses involves reaction of an α -amino ketone with carbonyl compounds containing an α -methylene group and preferably further electron-withdrawing substitution. This Knorr pyrrole synthesis is illustrated in Scheme 2. In most

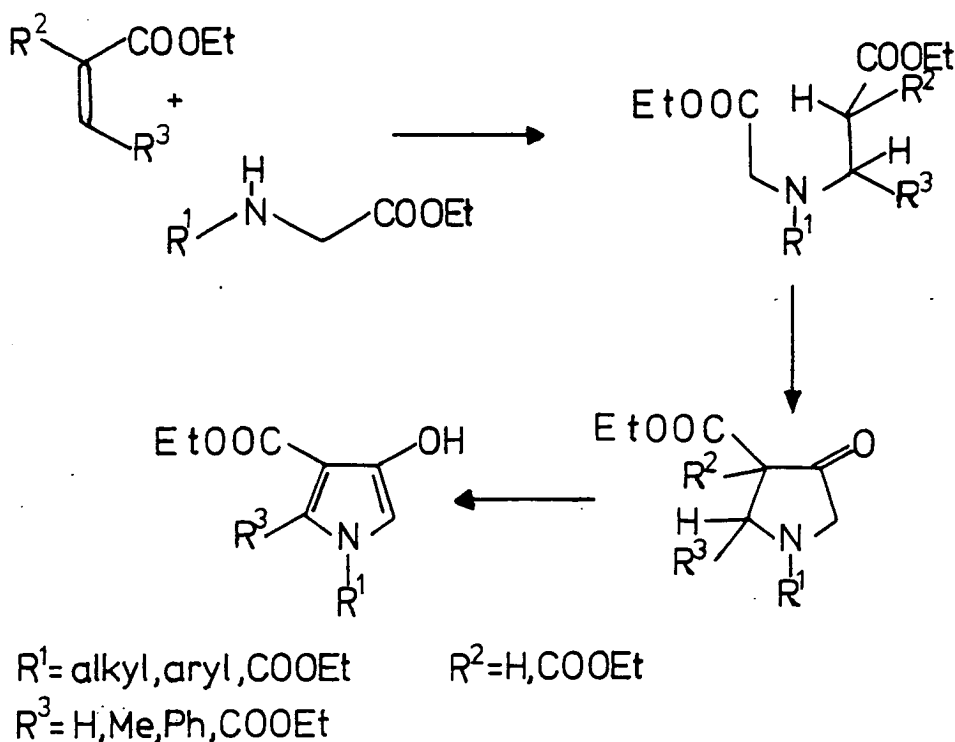


Scheme 2

cases the intermediate open chain compound resulting from one bond formation is not isolated as the cyclisation reaction occurs rapidly in situ. Replacement of the aminoketones by aminoesters allows introduction of a carbonyl group to the ring, while a range of different substrates have been used to supply the remaining two-carbon fragment. This strategy has been used in a number of syntheses of 3-hydroxypyrroles [1,2-dihydro-3H-pyrrol-3-ones] but the need for electron withdrawing groups to activate sites towards bond formation results in additional substitution of the ring system. Where α - β -unsaturated carbonyl compounds provide the two-carbon fragment, the heterocycle formed may not undergo elimination reactions

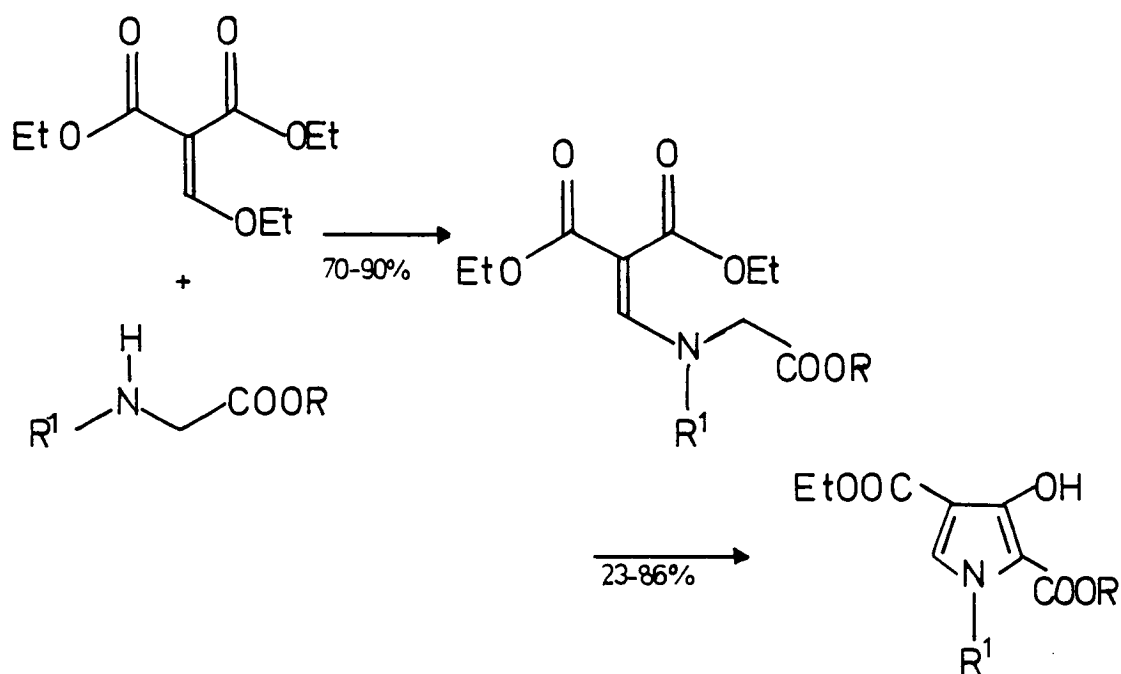
spontaneously and further modification of the saturated system may be required.

Thus, glycine esters have been condensed with substituted acrylic acid derivatives to give pyrrolidines (Scheme 3). Kuhn and Osswald⁵ originally proposed that the cyclisation occurred to the methylene group α - to nitrogen giving rise to ester substitution in the 2-position. However, the use of glycine esters with carbon-13 labelled carbonyl groups disproved this⁶ since the label was retained on hydrolysis and decarboxylation and was therefore supplying the ring carbonyl function. Hence the synthesis leads to 4-substitution. Oxidation under a variety of conditions leads to aromatisation.⁷

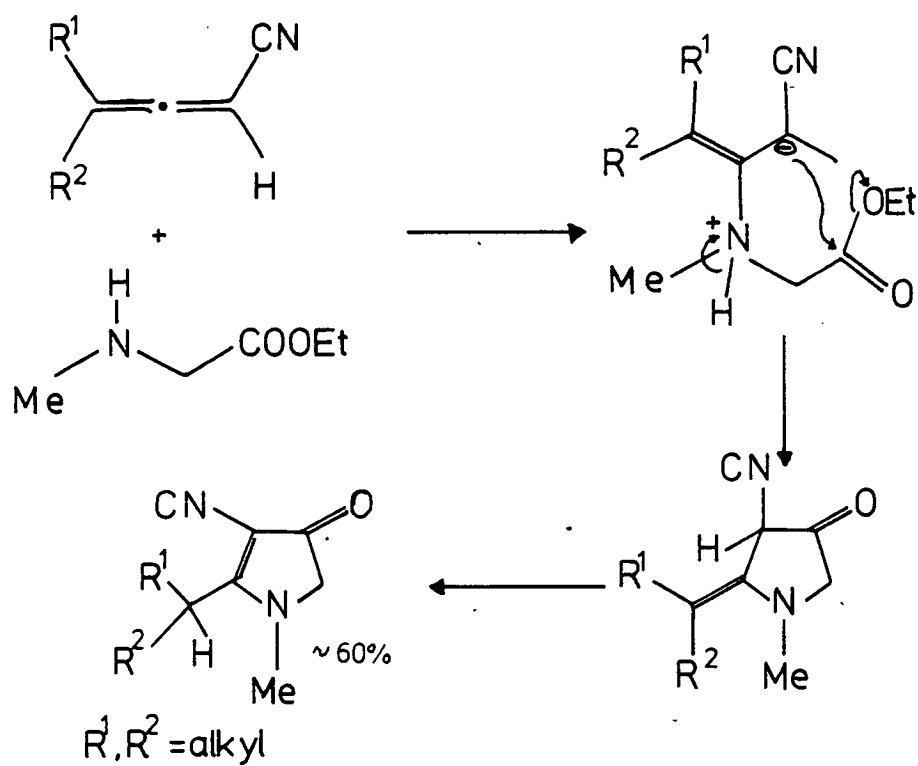


Scheme 3

The most efficient method of oxidation uses one equivalent of N-bromosuccinimide in dioxane. Recently, Margaretha has isolated a 4,4-dibromo compound obtained on treatment of methyl 2,2-dimethyl-3-oxo-pyrrolidine 1-carboxylate with bromine in CCl_4 . Dehydrobromination leads to the monobromo unsaturated heterocycle in good yield and the 1-carbomethoxy group is removed on chromatography. Further, the monobromo saturated heterocycle can be obtained by initial formation of the silyl enol ether⁸. Alternatively, treatment of the saturated heterocycle with dimethylsulphite gives the 3-dimethyl ketal and thermal elimination of methanol followed by dehydrogenation leads to the alkoxypyrroles in poor yield.^{5,6} Direct dehydrogenation of the ketal gives the unsaturated heterocycle in better yield.⁶ When R^3 , in Scheme 3, is a $\text{CH}_2\text{CO}_2\text{Et}$ group the unsaturated hydroxypyrrole is formed directly on cyclisation⁹ by elimination of $\text{CH}_3\text{CO}_2\text{Et}$ without a subsequent oxidation step. By using ethoxymethylene-diethylmalonate as the olefin ($\text{R}^2 = \text{CO}_2\text{Et}$, $\text{R}^3 = \text{OEt}$), the unsaturated heterocycle is again obtained, this time by elimination of ethanol^{10,11}, before cyclisation. However, ring closure of the unsaturated open-chain compound formed must occur α to nitrogen and the 2,4-disubstituted 3-hydroxypyrrole is therefore formed (Scheme 4).

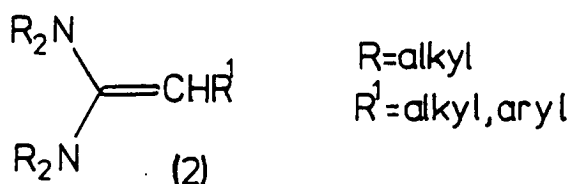


Scheme 4



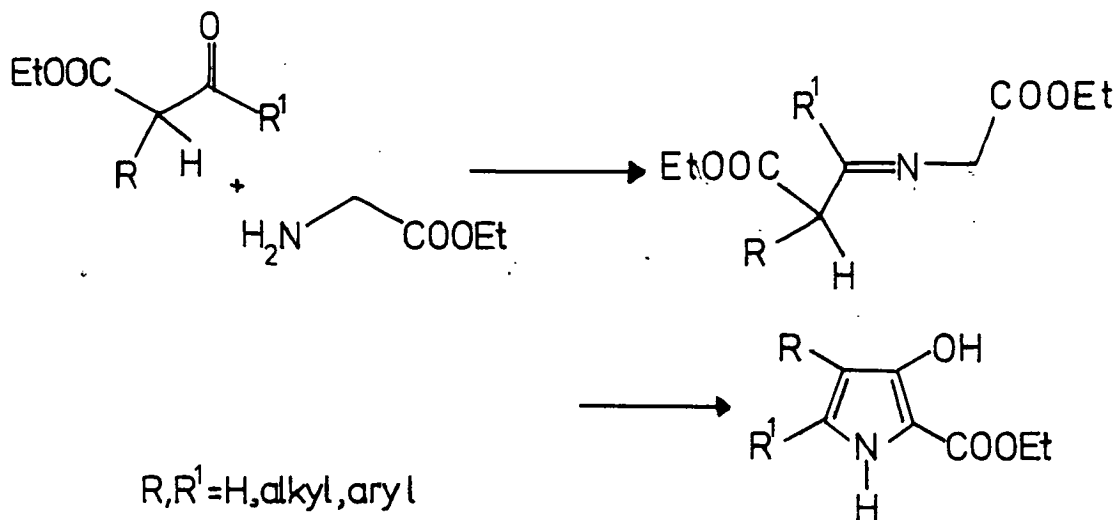
Scheme 5

Other olefins can also lead directly to the unsaturated heterocycles. For example, addition of glycine esters to allenes leads to an exo double bond which can isomerise into the ring.¹² This requires attack by nitrogen at the central carbon of the allene followed by concerted cyclisation and elimination of an ethoxy group (Scheme 5). However, primary glycine esters add to the 3,4-bond and the resulting enamine could not be cyclised. The cyano or similar electron withdrawing group is presumably necessary to promote the required attack. Ketene aminals (2)¹³ have also been utilised as the vinyl fragment.



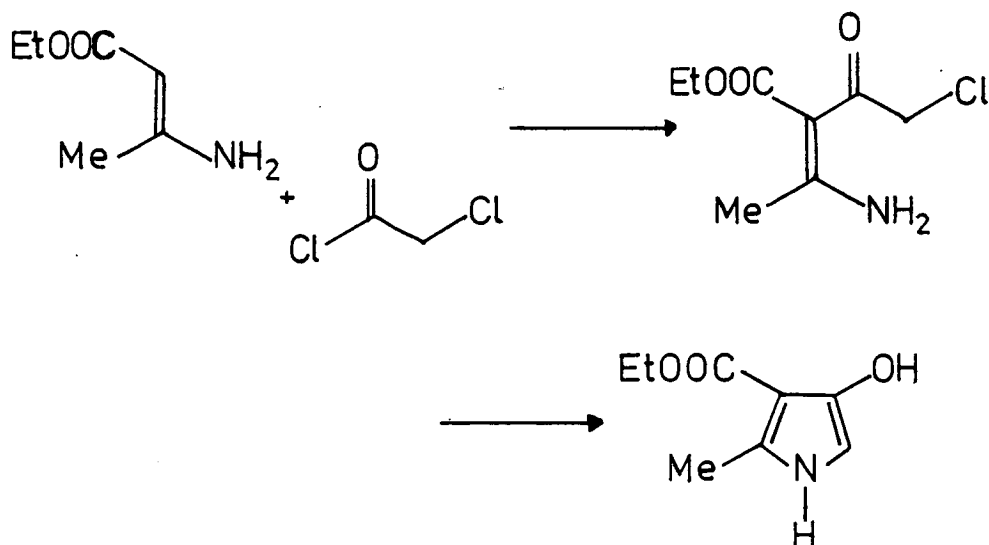
Addition of glycine esters to this double bond results in gem-dialkylamino substitution of the saturated heterocycle and elimination of an amine gives the 5-amino heteroaromatic product in 45-60% yields. Amino-alkynes give the same products in better yields (65-80%).

β -Ketoesters react with primary glycine esters to give imines^{14,15} and subsequent ring closure yields the 3-hydroxypyrrole-2-carboxylic esters (Scheme 6). Cyclisation also occurs with the corresponding enamines.¹⁶



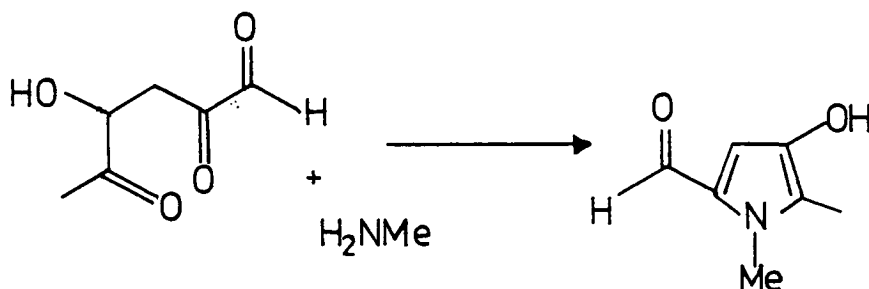
Scheme 6

α -Chlorocarbonyl compounds can also be used to effect ring closure in acid solution. Thus, the acyclic compound formed by reaction of aminocrotonic ester with chloroacetylchloride cyclises to give the 3-hydroxy-pyrrole-4-carboxylic esters¹⁷ (Scheme 7). The 4-cyano compounds have also been prepared.¹⁸ The substitution of the α -positions can be varied,¹⁸ but reactions with secondary nitrogen are unsatisfactory.



Scheme 7

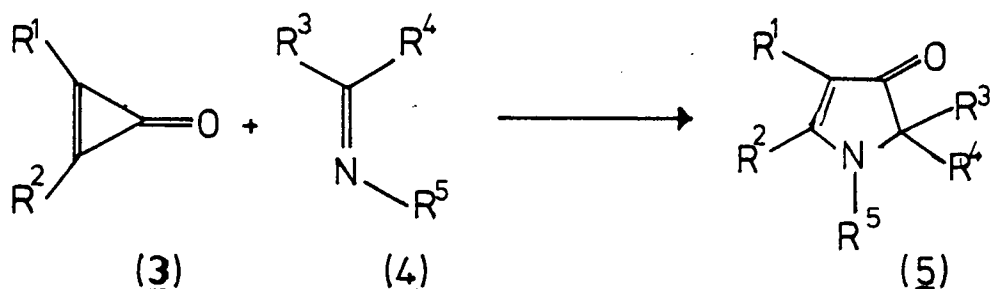
Another typical route to pyrroles - the Paul-Knorr Synthesis - involves the condensation of amines with 1,4-dicarbonyl compounds and it has also been adapted to give 3-hydroxypyrroles. Thus heating aniline with 3-hydroxyhexane-2,5-dione¹⁹ gave the 2,5-dimethyl-1-phenyl-3-hydroxypyrrole in 66% yield. The corresponding hexanal reacted with methylamine to give the 5-formyl-3-hydroxypyrrole²⁰ (Scheme 8) but in only 1% yield so this does not appear to have general application.



Scheme 8

Although these methods generally produce ester substitution, hydrolysis and subsequent decarboxylation can provide a synthetic route to examples without this additional substitution. Benzyl ester groups have been removed by hydrogenation^{11,19} while t-butyl ester groups have been removed by acid cleavage.¹¹ Momose et al¹¹ have succeeded in producing examples with only mono-substitution either on nitrogen or in the 5-position by these methods. No yields are recorded for the final deprotection step and they have not been able to isolate the parent compound. Failures to remove ester groups from particular examples have also been reported.^{21,22}

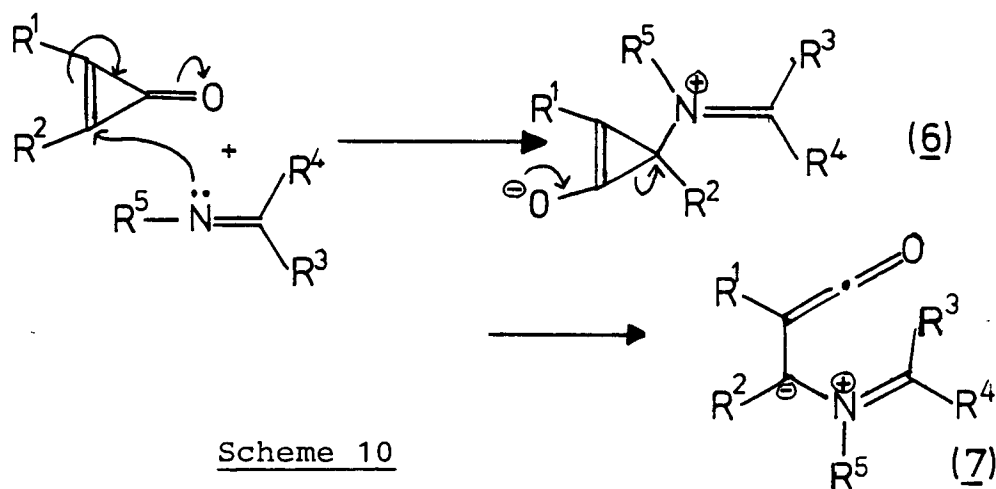
A number of substituted pyrrolones have been formed by reaction of compounds containing an imino bond with cyclopropenone, a reaction which has been studied by Eicher and his co-workers and by two Japanese groups. The general reaction is illustrated in Scheme 9.



Scheme 9

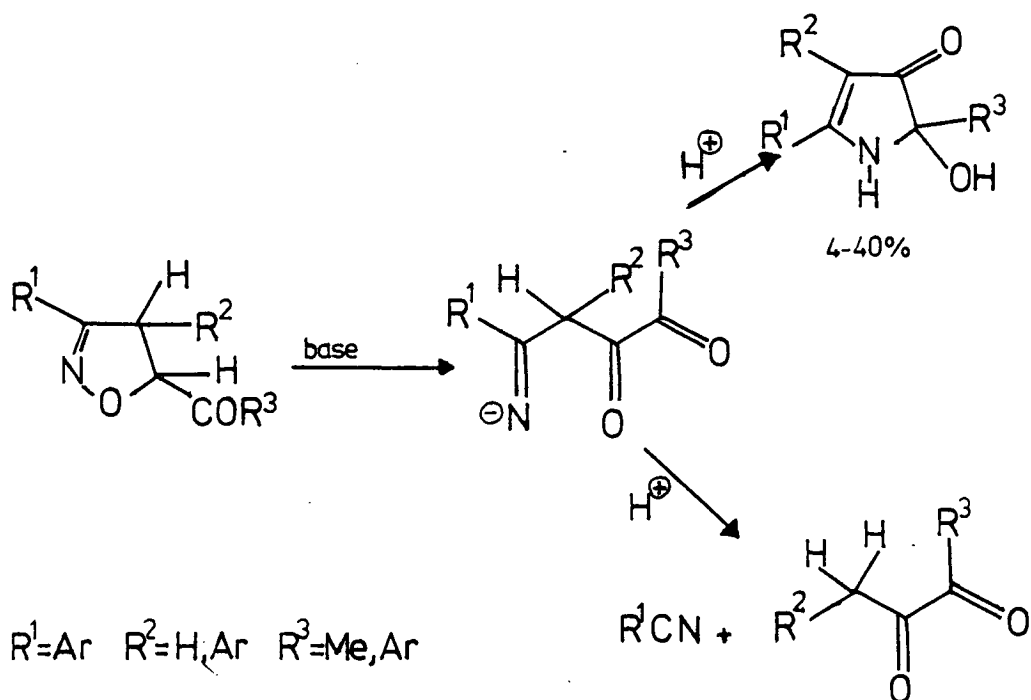
The reaction is limited by the availability of cyclopropenones (3) and most examples in the literature involve 4,5-diphenyl substitution. Simple aryl or alkyl substituted imines give 2,2-disubstituted 1,2-dihydro-3H-pyrrol-3-ones (5; R^3, R^4, R^5 = alkyl, aryl) in 70-90% yields²³, while the aldimines (4; R^3 or R^4 = H) give 2-monosubstituted examples in ~90% yield²⁴ provided atmospheric oxygen is excluded; oxidation of this type of compound will be discussed later. Diazines (4; R^5 = -N = CHR) eliminate nitriles to give -NH compounds.²⁵ Guanidines (4; R^3 = R^4 = NR_2) and benzamidines (4; R^3 = Ph, R^4 = NR_2) lead to 2-amino substitution (~90%)²⁶ while 1,4-diazabutadienes (4; R^3 or R^4 = -C=N-Ar) lead to 2-imino substitution (30-80%).²⁷ N-Imidoysulphoximes (4; R^3 = R^5 = alkyl, aryl, R^4 = N(SO) R_2) give 2-sulphoximes in up to 80% yields²⁸

and these can be modified to give oxygen, nitrogen and sulphur substituted products.²⁹ Similar products can also be obtained directly by using suitably substituted imines (4; $R^3 = R^5 = \text{aryl, alkyl}$, $R^4 = \text{OR, NR}_2, \text{SR}$).³⁰ Takahashi *et al*²⁷ have proposed a mechanism for this reaction involving nucleophilic attack by nitrogen on the cyclopropene ring to give the dipole (6) which rearranges to give a ketene dipole (7) which collapses to the 5-membered ring (Scheme 10).



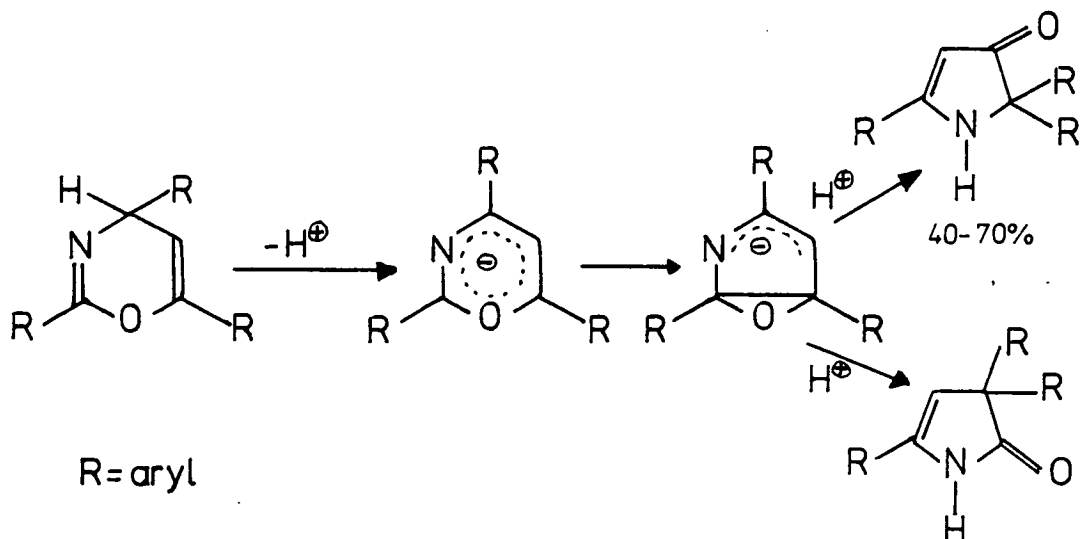
No evidence is provided for this mechanism apart from the observation of decreased reactivity when R^5 contained electron-withdrawing substitution.²⁸

Some preparations have involved the rearrangement or modification of other heterocycles. Thus 2-methylene-furan-3(2H)-ones³¹ and 2-methoxyfuran-3(2H)-ones³² react with primary amines to give 2-hydroxy-1,2-dihydro-3H-pyrrol-3-ones in reasonable yields while isoxazolines³³ also produce 2-hydroxy compounds as well as α -diketones on reaction with base (Scheme 11).



Scheme 11

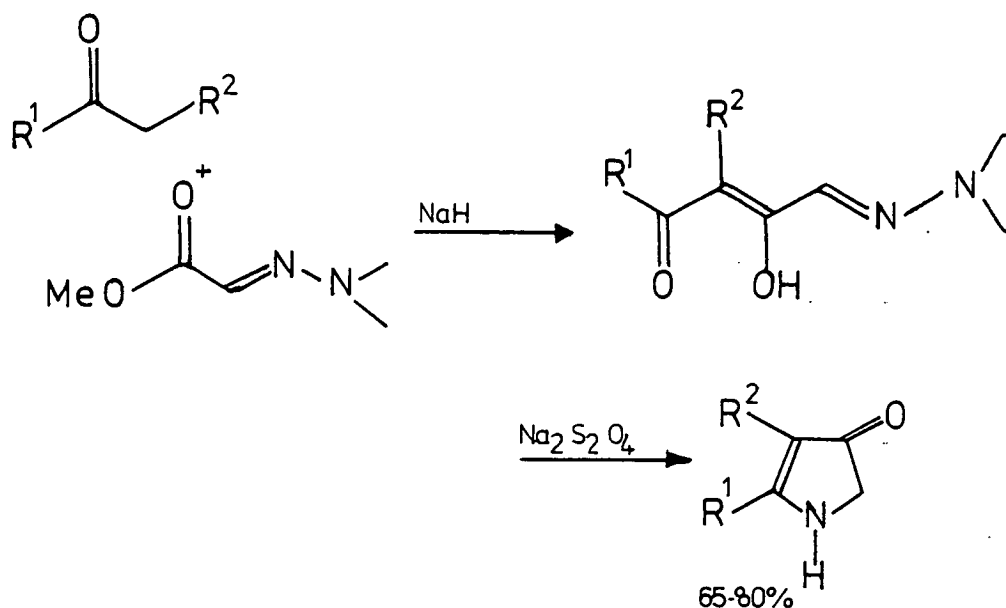
1,3-Oxazines can be prepared in reasonable yields from α -keto-chloroimines and arylacetylenes. The corresponding anions are electronically destabilised, heterocyclic 8- π systems which isomerise at low temperatures to 1,2-dihydro-3H-pyrrol-3-ones with triaryl substitution³⁴ (Scheme 12).



Scheme 12

Another approach is the modification of an existing pyrrole nucleus and this has been used in the photolytic oxidation of 2,3,5-trimethyl pyrrole to 2-methoxy-1,2-dihydro-3H-pyrrol-3-one.³⁵ However, this is one of six products and is isolated in only 9% yield. Pyrrolone-1-oxides have been reduced to 3-hydroxypyrroles under precise conditions³⁶ although other reduction conditions have led to a dimeric structure.³⁷

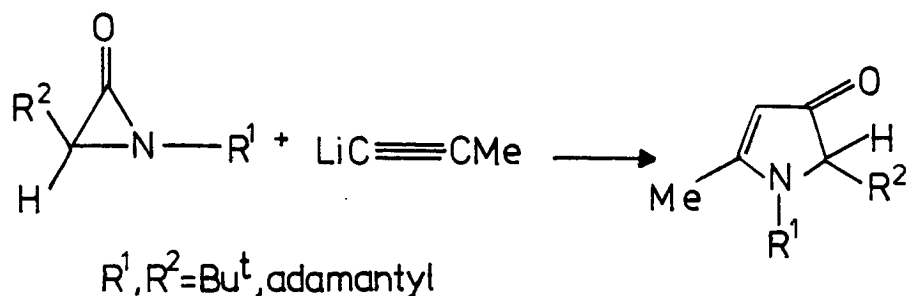
A number of other routes of limited generality lead to 3-hydroxypyrroles or 1,2-dihydro-3H-pyrrol-3-ones. Thus ketones with an active methylene group react with the monohydrazone of methyl glyoxylate³⁸ to give hydrazono-ethylidene derivatives which can be reduced to pyrroles (Scheme 13). The examples without substitution in the



Scheme 13

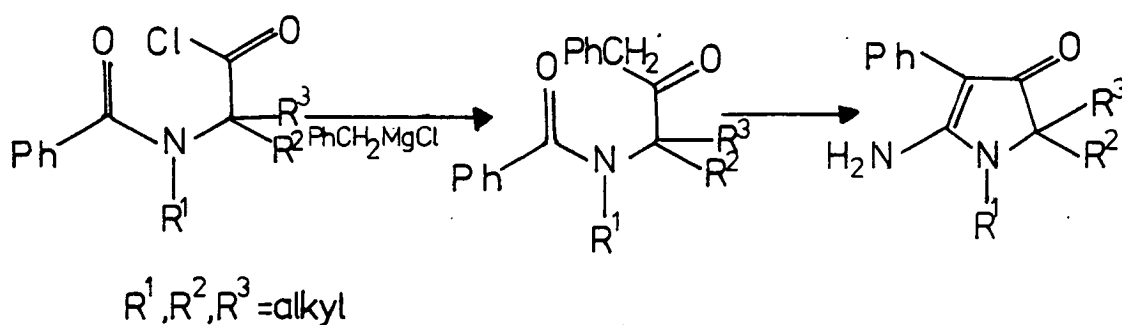
4-position could only be characterised as their 2-benzylidene derivatives.

Reaction of α -lactams with alkynyl lithium reagents has produced examples of 1,2-dihydro-3H-pyrrol-3-ones with bulky substituents (Scheme 14).³⁹



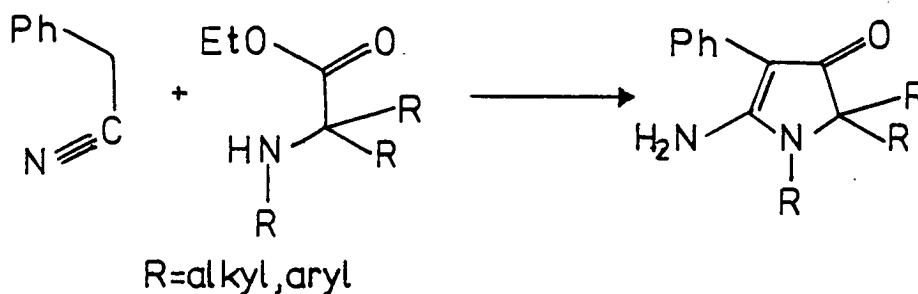
Scheme 14

Eicher synthesised a 4,5-diphenyl example by condensation of an appropriate open chain compound to verify his results from the cyclopropenone synthesis (Scheme 9).^{23,24} Thus, a β -ketoamide was cyclised to give 2,2-dimethyl-4,5-diphenyl-1,2-dihydro-3H-pyrrol-3-one (Scheme 15).



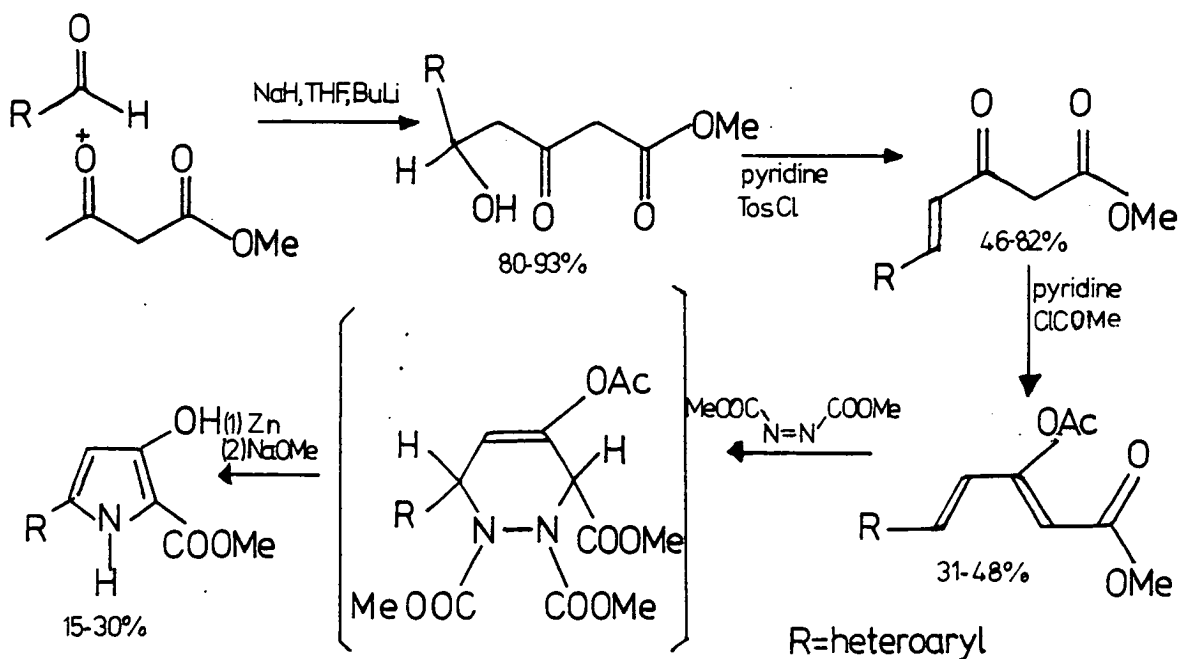
Scheme 15

A Russian group has produced examples with 5-amino substitution by two routes.⁴⁰ One involves the condensation of a primary amine with 1-chloro-3-cyanopropan-2-ones; the nitrile gives rise to the C5-N portion. The other uses benzyl nitriles to provide the C4-C5 portion by reaction with α -amino-esters (Scheme 16).



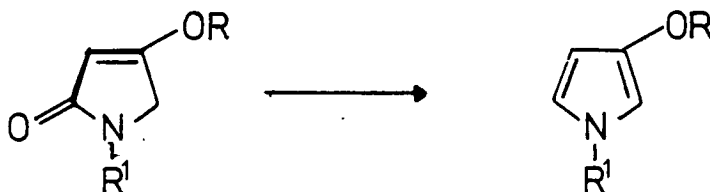
Scheme 16

A route involving a 4+2 cycloaddition and ring contraction leads to 3-hydroxypyrroles with heteroaromatic substitution in the 5-position (Scheme 17).⁴¹



Scheme 17

Finally, two routes which lead directly to 3-alkoxypyrroles have been published.⁴² Reduction of 4-alkoxy-2,5-dihydro-1H-pyrrol-2-ones with di-iso-butylaluminium hydride gives 1-substituted-3-alkoxypyrroles in up to 80% yield (Scheme 18).



Scheme 18

4-Nitro-3-alkoxypyrroles can be prepared by nucleophilic attack on 3,4-dinitropyrroles by alkoxide. The dinitropyrroles, however, are available only in rather poor yield.

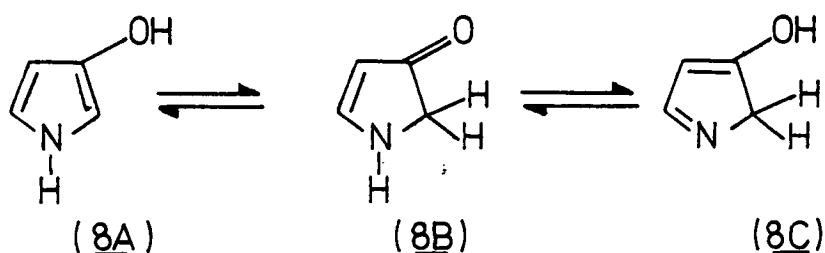
These reactions can be divided into three groups of synthetically useful methods: (a) those producing electron withdrawing substitution. Of these, the method illustrated in Scheme 4 provides the best route to examples with 2,4-disubstitution and after hydrolysis and decarboxylation the 2-substituted compounds.¹¹ The yields vary with N-substitution, the methyl example gives 65% overall for the monoester while the NH compound is produced in only 15% yield. The method of Scheme 3 provides the best route to 4-monosubstituted examples, with a yield of 74% from the glycine ester for the otherwise unsubstituted compound;⁶ (b) those producing

only alkyl or aryl substitution. The methods of Bauer and Severin depicted in Schemes 6 and 13 respectively, both produce reasonable yields of 4,5-disubstituted examples and must produce unsubstituted nitrogen. The cyclopropenone route (Scheme 9) gives 2,4,5-substituted compounds with a variety of nitrogen substitution in good yields but the 4,5-positions are limited by the availability of the required cyclopropenone; (c) those which produce hetero-atom substitution. The cyclopropenone method gives numerous 2-substituted examples in good yields with the limitations mentioned above. The general method of Scheme 3 has been adapted to give 5-amino substituted examples.¹³

TAUTOMERISM

The keto-enol tautomerism illustrated in Figure 1 has been the subject of two theoretical studies. The first⁴³ uses a semi-empirical π -electron method and considers the 3-hydroxypyrroles only briefly in connection with a number of other five- and six-membered heterocycles. The results predict that the parent exists preferentially as the ketonic tautomer as do the other five-membered ring systems investigated. The second study⁴⁴ is more specialised and uses the all valence electron MINDO method. It discusses equilibrium geometries for the various tautomers but draws no conclusions from the values obtained. It does, however, predict energies of formation

and hence reaction enthalpies for the different tautomerisms. These predictions imply that the parent compound exists principally as the 3-hydroxypyrrole (8A), although this is only slightly favoured over the 1,2-dihydro-3H-pyrrol-3-one (8B) and both are considerably more energetically favoured than the 3-hydroxy-2H-pyrrole (8C). The authors further suggest that methyl



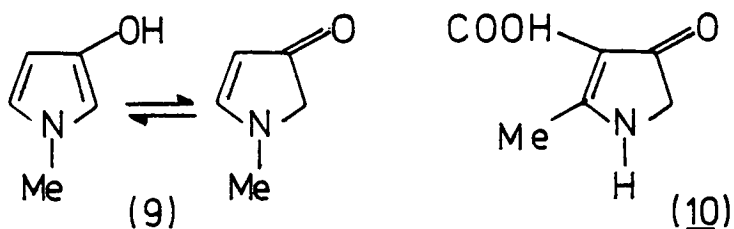
substitution in the 2-position increases the stability of the 3-hydroxypyrrole form. Work to be discussed later in this thesis shows that in the N-substituted series at least it is the keto form which is favoured. Further predictions of Schuster that calculated dipole moments imply the keto form will be increasingly favoured in more polar solutions are also certainly not true for N-substituted examples. It can be seen that a free NH could considerably influence the effect of solvents but the 4,5-dialkylpyrrol-3-one synthesised by Bauer exists in the keto form in dimethylsulphoxide.⁴⁵

Early workers attempted to determine the tautomeric form of examples prepared using chemical tests^{5,17}, but the results were inconclusive, which is not surprising in the light of later results which indicate that the tautomerism is largely solvent dependant. Ultra-violet and infra-red spectroscopy has been used for determination of structure in a number of cases. Davoll has compared the U.V. spectra of a series of compounds¹⁹ including those in which tautomerism was possible and examples where a particular form was fixed by further substitution. This showed that in ethanolic solution the keto form produced an absorption at 290-325 nm while the aromatic form absorbed at 250-285 nm. Although these regions of absorption almost overlap the majority of examples lie well within one range or the other. Davoll does not appear to have considered the 3-hydroxy-2H-pyrrole form, presumably because of good agreement between values for the N-H and N-substituted examples.¹⁹ Viehe, however, has recorded spectra for examples with amino substitution¹³ and claims this form (8C) absorbs around 290 nm. U.V. spectroscopy has also been used to study the kinetics of ketonisation of 3-hydroxypyrroles and other five-membered heterocycles.⁴⁶ The 3-hydroxypyrroles are found to undergo considerably more rapid tautomerism than furan, thiophene and benzo-analogues.

Infra-red spectra are, in general, complicated by additional ester absorptions in the carbonyl region and marked differences are observed between those recorded as KBr discs or nujol mulls and those in solution.^{15,19} In solution a number of bands are present in the NH and OH region because of H-bonding and concentration dependence is also observed.⁴⁷

More recently, nuclear magnetic resonance spectroscopy has been used to examine this tautomerism and the marked differences in both chemical shift and coupling constants for the keto and enol tautomers make it an extremely useful method. The aromatic enol form has signals for the ring protons at between $\delta 5.5$ and $\delta 7.0$ with 3- and 4-bond coupling constants of 2.5-3.0 Hz, while the keto form has a characteristic aliphatic signal around $\delta 3.0$ -4.5 and only very fine coupling (if any) is observed between the C2-H and C5-H signals. The solvent dependence of the equilibrium is clearly shown by proton n.m.r. where both forms can be observed. For example, both tautomers of 1-methyl-3-hydroxypyrrole (9) are observed in chloroform and methanol solutions with the amount of the enol form increasing markedly in methanol.^{11b} It has been claimed that the steric bulk of substituents strongly disfavors the enol form³⁹ but the keto tautomer would be predicted even for simpler examples under the solvent conditions used. The insolubility of the N-unsubstituted compounds in chloroform has led to problems in attempting to study

the tautomerism by this means; for instance, the n-octyl ester of 5-methyl-2,3-dihydro-3-oxo-1H-pyrrole-4-carboxylic acid (10) was required for solubility.⁴⁷ However, the spectra of some simpler N-unsubstituted



examples have been recorded in dimethylsulphoxide,⁴⁵ the 4,5-dimethyl-1,2-dihydro-3H-pyrrol-3-one apparently existing in the keto form.

The keto-enol tautomerism of the 3-hydroxy-pyrrole ring system will be discussed in detail later in this thesis on the basis of both proton and carbon-13 nuclear magnetic resonance studies, in chloroform and dimethylsulphoxide solution but the existing evidence allows a number of general conclusions on the preferred structure of these compounds to be made despite some rather insecure evidence for specific examples. This can be summarised as follows:-

- (i) Those examples with no polar functionality favour the keto form.
- (ii) A carboxyl, cyano or phenyl function in the 2-position favours the enol form because of the extended conjugation afforded by it and, in the carboxyl case, by the possibility of hydrogen bonding (Figure 2).^{11b,19,22}

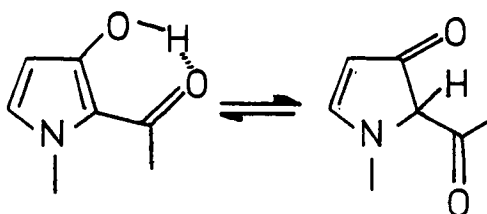


Figure 2

- (iii) Carboxyl functionality in the 4-position can also be involved in hydrogen bonding so again the enol form should be favoured. This is the case in some examples but by no means all, and certainly not when there is α -substitution on the ring. This can be explained by
 - (a) less double bond character in the 3,4- than the 2,3-bond, thus decreasing the importance of hydrogen-bonding since there is less contribution from the mesomeric form

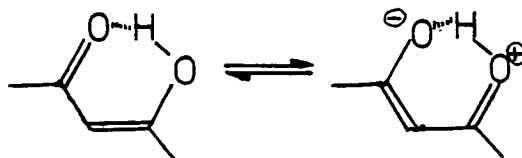
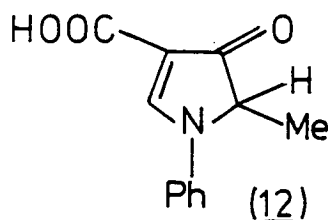
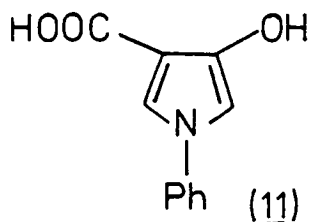


Figure 3

illustrated in Figure 3, (b) conjugation with the substituent is also possible in the keto form, and (c) steric interactions from 5-substituents precludes the required conformation for H-bonding between the enol and 4-carboxyl groups.^{11b}

Davoll suggested that interannular conjugation was important in promoting the enol form of the 1-phenyl-4-carboxylic acid (11) and was prevented by the methyl substitution in (12) forcing the rings out of co-planarity¹⁹ and therefore leading to the keto form. Momose et al,¹¹ however, regard this as unimportant since the simple 1-phenyl-1,2-dihydro-3H-pyrrol-3-one exists wholly in the keto form.



PROPERTIES

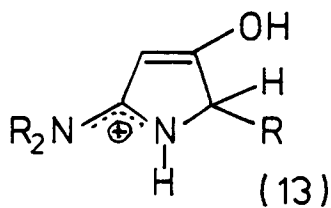
The 3-hydroxypyrrole nucleus is a potentially very reactive system. The highly electron rich centre may react in a manner reflecting enone, enamine, active methylene or aromatic character. To date, most work on the reactivity of the system has been limited by its accessibility and studies have involved examples with competing electron-withdrawing substitution or with a number of substituents blocking potentially reactive sites.

(a) Acidity and Basicity

The amphoteric nature of the 3-hydroxypyrrole system has been shown by spectroscopic methods^{15,47} although it seems that for 4-carboxylate substituted examples at least, the acidic and basic functions are weak - an acid strength of 3N in hydrochloric acid was required to produce a marked change in the ultra-violet spectrum.⁴⁷

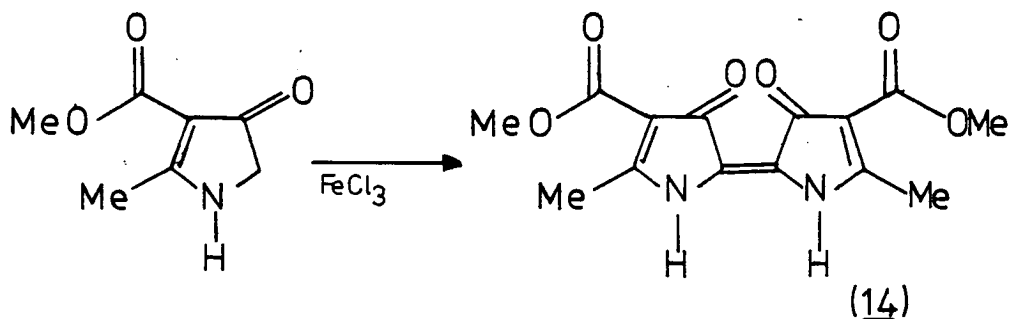
The protonation of the ring system and of the alkoxy analogues has been studied by U.V. spectroscopy and, in one instance, by n.m.r. spectroscopy. The ultra-violet spectra of the protonated species exhibit a maximum around 290 nm which corresponds to a shift to longer wavelength of 60-70 nm for the hydroxypyrrole form or the fixed alkoxy-pyrrole¹⁵ while the position of the pyrrolone absorbance is reduced by 15-20 nm.^{47,48} This shift is shown to be reversible by addition of dilute acid to

methanol solutions followed by addition of dilute alkali. These shifts provide evidence for O-protonation, since C-protonation would effectively remove the conjugation and therefore the absorption, while N-protonation is expected to give larger hypsochromic shifts.⁴⁹ O-protonation of 1,2-dihydro-3H-pyrrol-3-ones⁴⁷ is also indicated by proton n.m.r. spectroscopy which shows deshielding of the C2-H and of the NH (which retains an intensity of one proton). Spectra of the protonated species were obtained either by acidifying a chloroform solution with trifluoroacetic acid or by obtaining the spectra in trifluoroacetic acid as solvent. In aqueous sodium hydroxide solution the methyl 5-methyl-1,2-dihydro-3H-pyrrol-3-one-4-carboxylate gives rise to a methylene signal which is deshielded and split to a poorly defined quartet while the ring methyl appears a triplet.⁴⁷ This coupling indicates a 3-hydroxy-2H-pyrrole form for the anion rather than a pyrrolic structure, if the anion is formed. Bauer can find no evidence for the pyrrolic anion of an alkyl substituted example using ultra-violet spectroscopy.⁴⁸ Examples with α -amino substitution, which are thought to exist in the 3-hydroxy-2H-pyrrole form, protonate on nitrogen with (13) representing the major contribution to structure.¹³



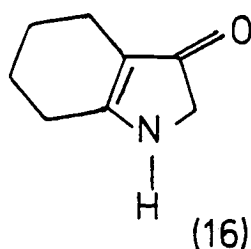
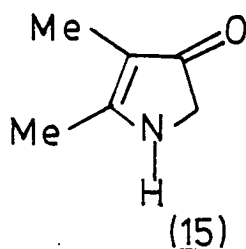
(b) Oxidation

The oxidation of 3-hydroxypyrroles proceeds by a number of routes dependant both on conditions and the particular substrate. The 2-unsubstituted examples undergo oxidative dimerisation in the presence of a number of one electron oxidising agents. Benary¹⁷ and later Atkinson and Bullock⁵⁰, found that methyl 5-methyl-2,3-dihydro-3-oxo-1H-pyrrol-4-carboxylate dimerised in aqueous ferric chloride solution to give an indigo-like product (Scheme 19).

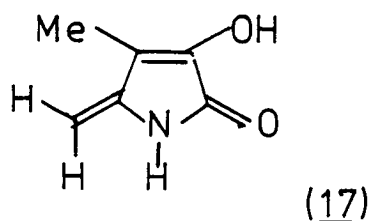


Scheme 19

The product (14) does not seem to have indigo-like properties, however, decomposing with acid and heat and forming no recognisable products on direct acetylation or on attempts to reduce the bridging double bond.⁵⁰ Bauer has reported corresponding products for both the 4,5-dimethyl-1,2-dihydro-3H-pyrrol-3-one (15)^{15,45} and tetrahydroindoxyl (16)^{48,51}, using either ferric chloride or potassium ferricyanide in aqueous solutions. These dimers can be

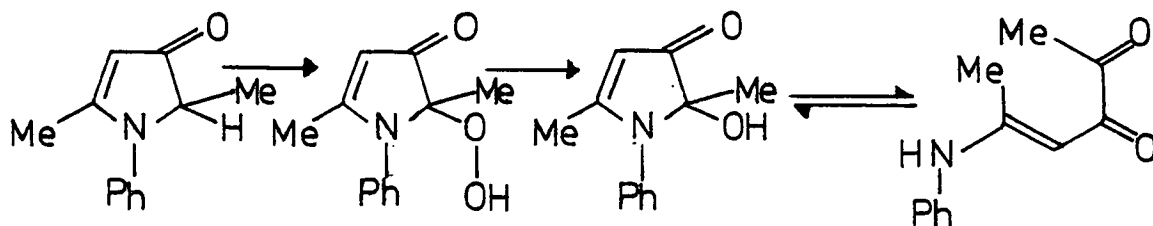


reduced by sodium dithionite, but the product was not isolated. Comparisons of their electronic spectra with that of the indigo system have been made.⁴⁸ Bauer also isolated a monomeric compound (17) on treatment of (15) with potassium ferricyanide and quenching with base after completion of reaction.⁵⁸ A similar product is formed on treating the tetrahydroindoxyl with selenium dioxide.⁴⁸



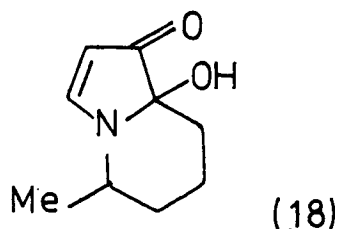
The oxidation of 2-mono-substituted compounds is complicated by the ease of further oxidation, the formation of dimers and the possibility of ring-chain tautomerism of the oxidised products. Davoll has found that 2,5-dimethyl-1-phenyl-1,2-dihydro-3H-pyrrol-3-one readily oxidises at the 2-position giving the α -hydroxy compound (Scheme 20)¹⁹ simply when exposed to air as a thin film or, in better

yield (46%), when treated with potassium ferricyanide in aqueous solution at room temperature. A number of tests



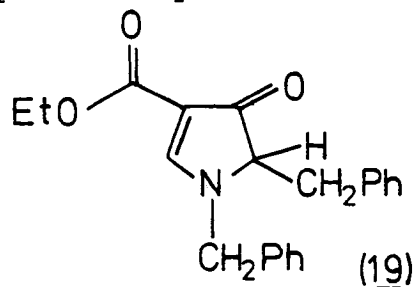
Scheme 20

carried out in attempts to identify the structure of the product show that the compound reacts both as the cyclic vinylogous amide and the α -dicarbonyl and this facile equilibrium has been found in the course of work described later in this thesis. Thus, the 2-methyl-1-phenyl-1,2-dihydro-3H-pyrrol-3-one readily oxidises to give a product exhibiting the cyclic form in dimethylsulphoxide solution but the open chain structure in chloroform. An example where the nitrogen- and 2-substituents are joined to form a ring has also been isolated (18).⁴ In this case the ring tautomer is locked in the bicyclic structure preventing formation of the α -diketo compound.

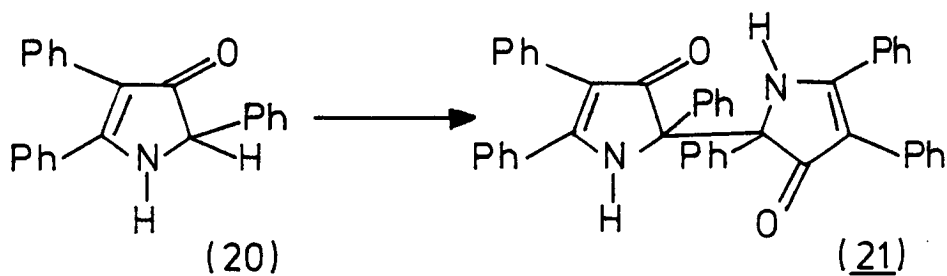


Gelin has shown the ester substituted example (19)³¹ can be similarly oxidised as a thin film giving the cyclic

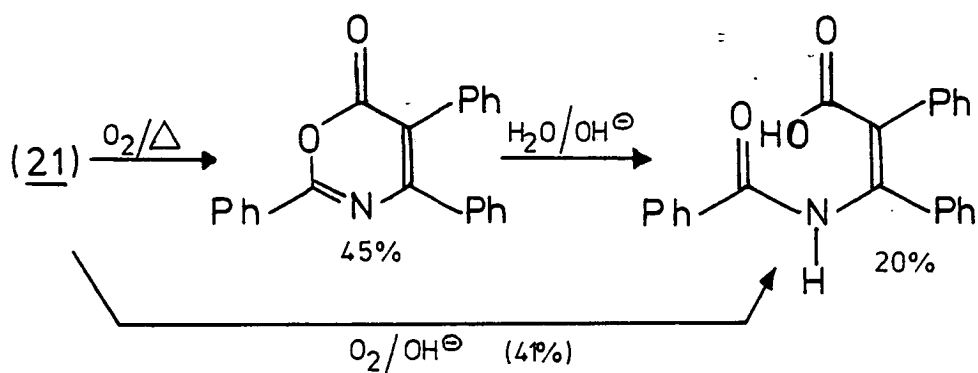
product as shown by the non-equivalence of the N-benzylmethylene group in the proton n.m.r. spectrum in chloroform.



Freeman has found that the 2,4,5-triphenyl-1,2-dihydro-3H-pyrrol-3-one (20) dimerises in an aerated chloroform solution over a period of a week while treatment with alcoholic base gives immediate dimerisation. The dimer formed (21) has the properties previously attributed to the monomer (20) by Jones⁵² and Takahashi.⁵⁴



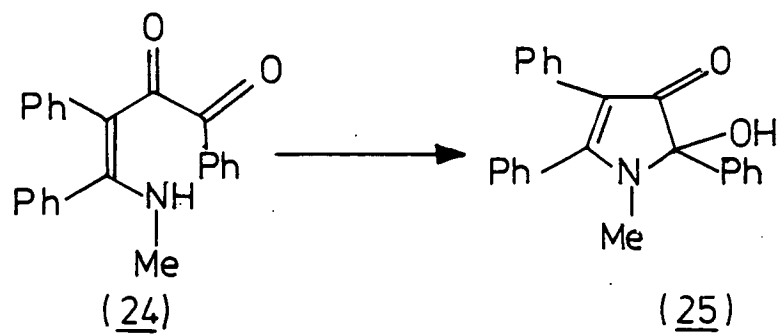
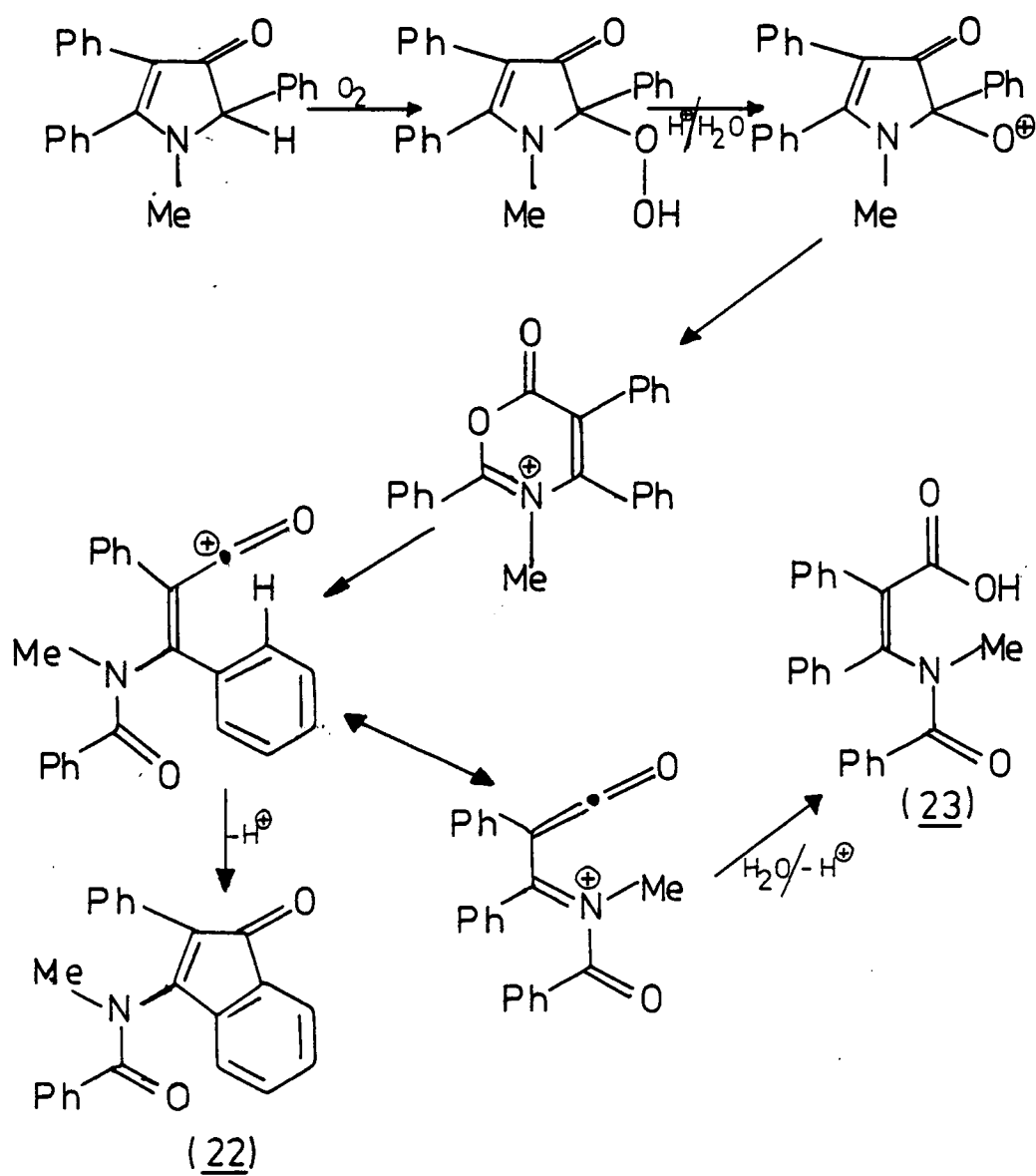
Takahashi found that treatment of this compound with a stream of oxygen in a pyridine solution at reflux gave an oxazinone which could be further oxidised to 3-benzylamino-2,3-diphenylacrylic acid (Scheme 21).



Scheme 21

The acrylic acid could also be obtained directly by treating (21) with an aqueous pyridine solution containing potassium hydroxide. Eicher has proposed the oxazolinone structure as an intermediate in the oxidation of the N-methyl derivative of (20)²⁴ and it explains neatly the indenone (22) which is formed in addition to the acrylic acid (23) (Scheme 22).

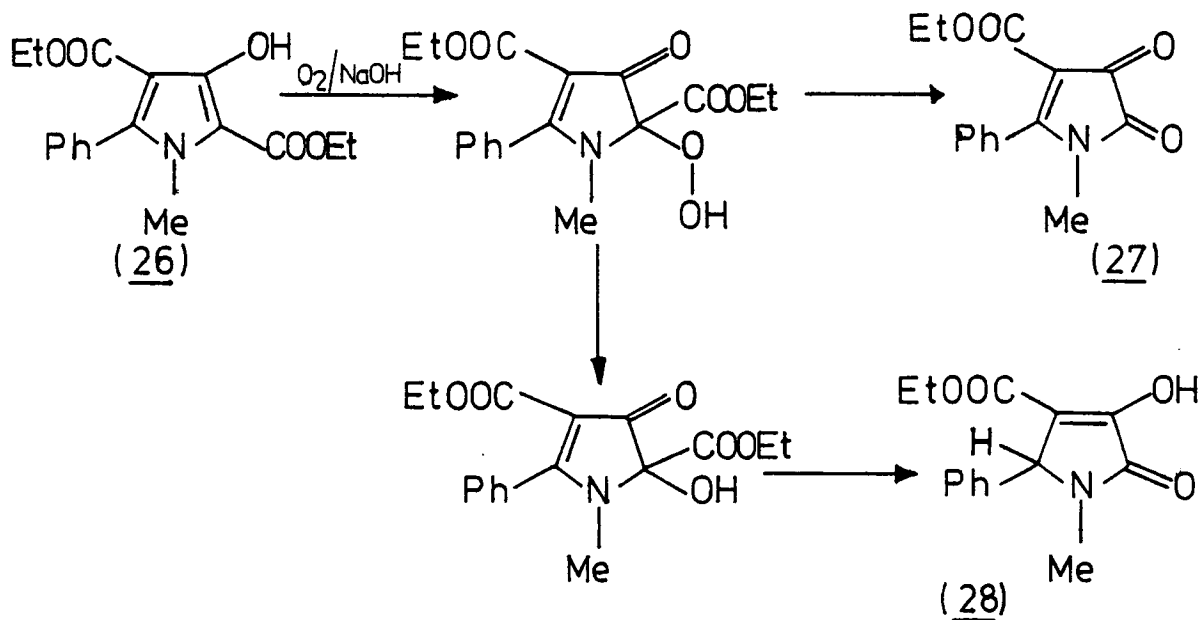
Eicher also isolated an additional product (24) for which he proposed the open-chain structure corresponding to Davoll's product (Scheme 20). The cyclic form can be obtained by heating the acyclic tautomer in 5N sodium hydroxide for four hours. The proton spectra of (24) and (25) are recorded in dimethylsulfoxide and chloroform respectively, which contrasts with results discussed later which indicate the cyclic form is favoured in polar solutions with tautomerism occurring rapidly



Scheme 22

simply on changing solvents. The deactivation of the carbonyl group by the phenyl substituent may account for the less facile equilibrium. It is apparent from Takahashi's results²⁷ (Scheme 21) that the dimer can revert to the oxidised monomer under alkaline conditions and this may be explained by the stabilised captodative nature of the intermediate radical⁵³ (see Discussion Section).

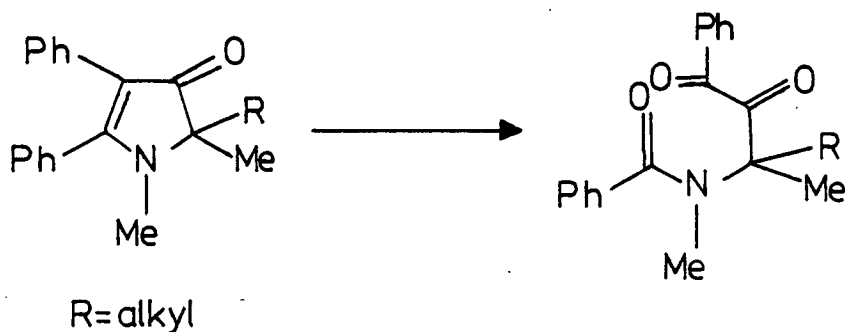
Campaigne⁵⁵ has found the 2,3-dihydro-3-oxo-1H-pyrrole-dicarboxylic ester (26) forms two oxidation products (27 and 28) under alkaline conditions in addition to the sodium salt of the starting material (Scheme 23).



Scheme 23

A peroxy intermediate is proposed as a first step in the oxidation of the 2-monosubstituted compounds by Davoll, Eicher and Campaigne (Schemes 20, 22 and 23) and this type of reaction has analogy in the chemistry of 3-hydroxyfurans.⁵⁶ The dimerisation also has analogy in the chemistry of 3-hydroxyfurans⁵⁶ and indoxyls.⁵⁷

Finally, 2,2-disubstituted-1,2-dihydro-3H-pyrrol-3-ones can be oxidised under ozonolysis conditions to give triketones (Scheme 24).^{23,24}

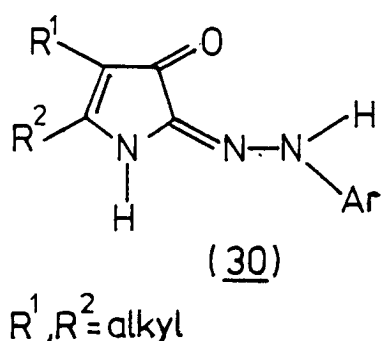
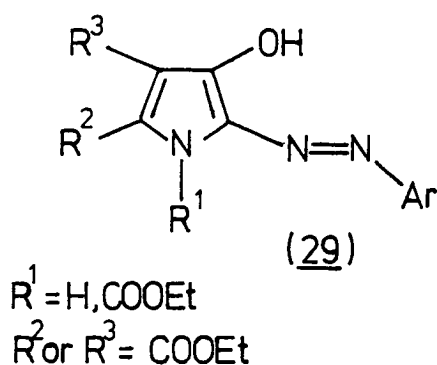


Scheme 24

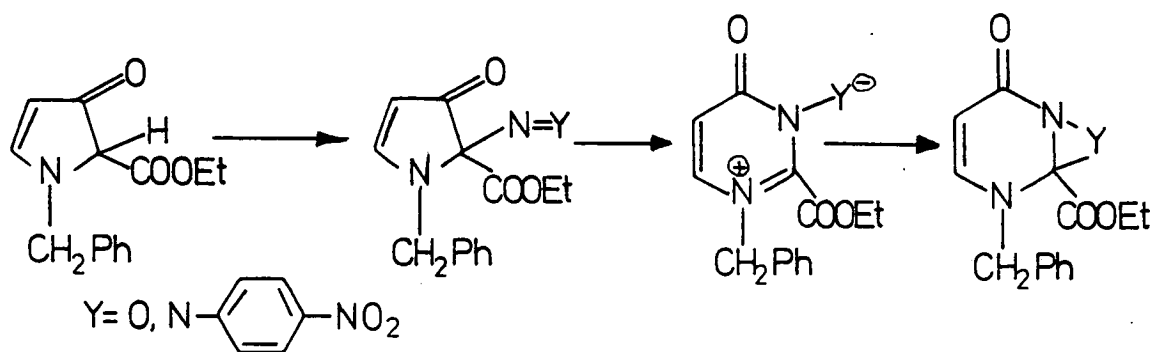
(c) Electrophilic Attack

Electrophilic attack on the 1,2-dihydro-3H-pyrrol-3-one tautomeric form would be predicted to occur in the 2- or 4-positions by consideration of its enaminone character. Most syntheses, however, lead to 4-substitution so, to date, only the reactivity of the 2-position has been studied and in particular the condensation reactions of 2-unsubstituted compounds.

Aryl diazonium salts react at the 2-position in a number of examples with a variety of 4,5-substitution. Benary¹⁷ and Kuhn⁵ reacted compounds with 4- or 5-carboxylate functionality, respectively. Both suggest the azo form (29) for the product, supported in Benary's case by a positive reaction with ferric chloride indicating the hydroxyl group is still present. Bauer⁵⁸, however, finds the hydrazo form (30) for an alkyl-substituted example by comparison of its U.V. spectrum with that of the methoxy analogue¹⁵ which must adopt the azo form. Campaigne⁵⁹ has reacted a 3-alkoxypyrrole with diazonium salt to yield the 2-azo compound. Benary¹⁷ and Bauer¹⁵ have also formed the 2-oximes using nitrous acid.

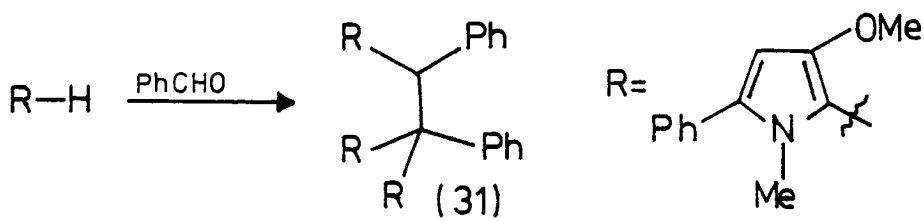


More recently, Momose et al⁶⁰ have reported that 1,2-dihydro-3H-pyrrol-3-ones with ester substitution in the 2-position undergo a ring enlargement on treatment with diazonium salts or nitrous acid (Scheme 25).



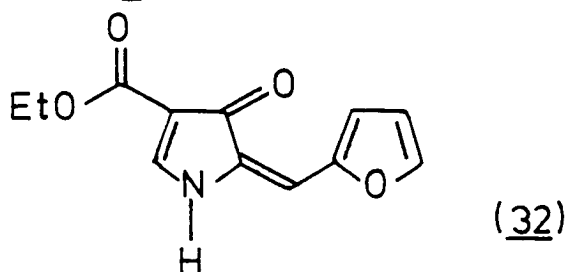
Scheme 25

Condensations which form carbon-carbon bonds at the 2-position have been much investigated because of interest in the synthesis of prodigiosin (1) and analogues. Many 1,2-dihydro-3H-pyrrol-3-ones react with benzaldehydes (including the p-dimethylaminobenzaldehyde of the Ehrlich reaction) to give the 2-arylidene products. Bauer has successfully condensed 4,5-dimethyl-1,2-dihydro-3H-pyrrol-3-one with a range of activated and deactivated benzaldehydes¹⁵ and similarly tetrahydroindoxyl⁴⁸ for which he has studied the effect of N-methylation on the geometry of the double bond in the product. Ester³¹ and aryl³⁸ substituted examples also react, while the locked enol form of a 3-methoxypyrrole undergoes multiple reaction to give good yield of a product proposed to have the structure (31) (Scheme 26).⁶¹ A rather unusual mechanism is proposed and a proton spectrum in which all three heterocyclic rings produce equivalent peaks is the only structural evidence.

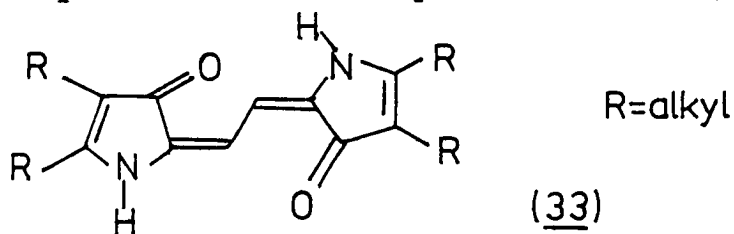


Scheme 26

Heterocyclic aldehydes can also react, for example furan-2-carboxaldehyde condenses with ethyl 2,3-dihydro-3-oxo-1H-pyrrole-4-carboxylate to give (32).⁶²

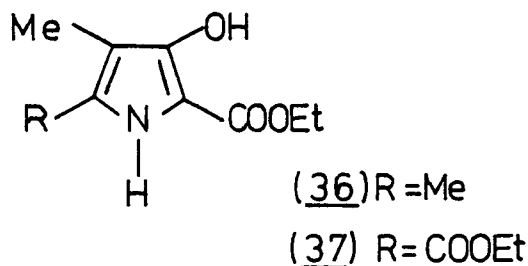
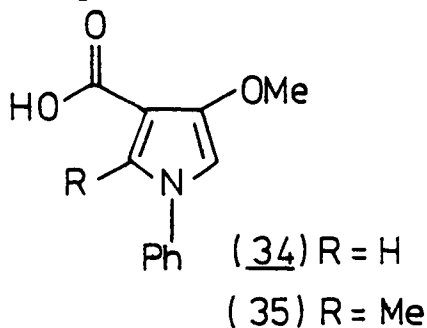


Glyoxal reacts with two moles of 1,2-dihydro-3H-pyrrol-3-one to give the two rings linked by a two carbon bridge (33) and Bauer has again studied the geometry and electronic spectrum of the product.⁴⁸



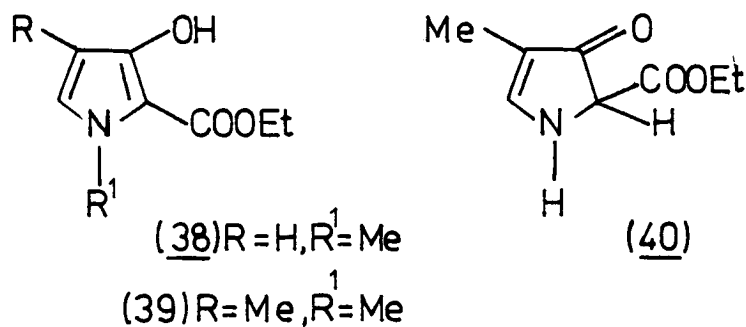
(d) Alkylation and Acylation

The alkylation of 3-hydroxypyrroles has been studied for a number of ester substituted examples. Diazomethane, typically a good O-alkylating agent for phenols, has been found to be unreactive in ether^{19,22}, while, in an isolated example, reaction in ether/methanol mixture produces the methyl ether (34) in poor yield.¹⁹ Dimethyl sulphate in sodium hydroxide has produced the 5-methyl compound (35) in poor yield



but the corresponding N-unsubstituted compound gave no product.¹⁹ Chong and Clezy, however, have reported an improved procedure using dimethyl sulphate and potassium carbonate in acetone for the 2-ester compound (36).²² They found the diester (37) gave the O,N-dimethyl-compound under the same conditions, thought to be due to the increased acidity of the N-H. Campaigne⁵⁵ has shown that isolation of the sodium salt and reaction with benzyl chloride in methanol gives a 2:1 mixture of O- and C-alkylation. This ambident reactivity is also

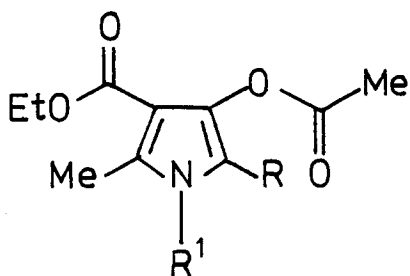
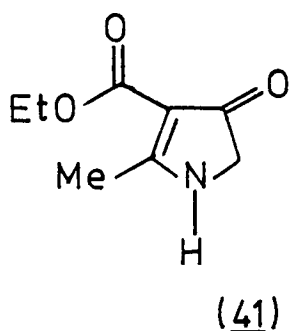
evident in the reaction of ethyl 1-methyl-3-hydroxypyrrole-2-carboxylate (38) with sodium hydride and allyl bromide in benzene.^{10,64}



These conditions lead to a 2:1 mixture favouring C-alkylation and although the O-allyl group can be forced to undergo a Claisen rearrangement this did not occur under the conditions of the reaction and is therefore not the source of C-alkylation. Alkylation with methyl iodide results wholly in C-alkylation of (39)⁶⁵ as would be predicted by hard and soft acid and base theory because of the softer nature of the iodide counter-ion. In the following Discussion Section this theory and other results indicating the enolate reactivity of the system are considered. Alkylation by Michael addition at the 2-position has also been observed^{10,64} using, for example, ethyl acrylate. The acid catalysed reaction with tetrahydropyran shows substrate dependant selectivity²²: ethyl 4-methyl-3-hydroxypyrrole-2-carboxylate (40) gives the tetra-

hydropyranyl ether while additional methyl substitution at the 5-position leads to the C-alkylated product.

Acylation can lead to a number of products dependant on the conditions employed, and problems in structure determination have occurred due to different conformations of the acetate group leading to a doublet absorption in the infra-red spectrum.⁶² Atkinson and Bullock have resolved this problem using n.m.r. spectroscopy⁵⁰ and shown that ethyl 5-methyl-3-hydroxypyrrole-4-carboxylate (41) reacts with sodium acetate



(42) R = R¹ = H

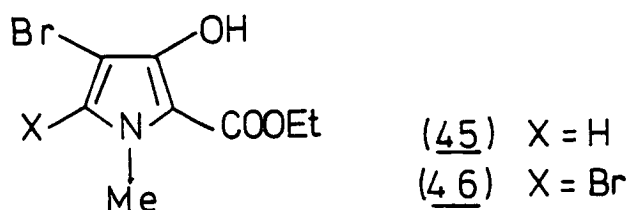
(43) R = H, R¹ = Ac

(44) R = R¹ = Ac

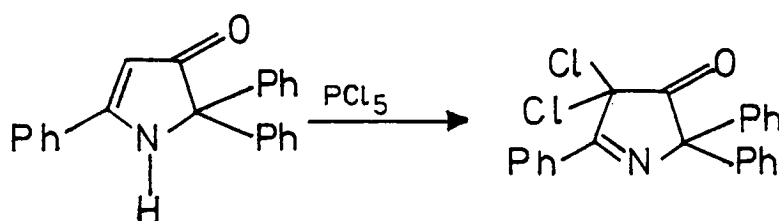
in acetic anhydride to give the O,N-diacetate (43), which can be hydrolysed to the O-acetate (42) or further acetylated with acetic anhydride and a catalytic amount of perchloric acid to the triacetate (44).

(e) Miscellaneous

A single example of bromination has been reported which shows that bromination of ethyl 1-methyl-3-hydroxypyrrole-2-carboxylate (38) with one equivalent of bromine in chloroform gives the 4-bromo compound (45) and 2-equivalents give the dibromo compound (46) with no evidence for reaction at the 2-position.¹¹



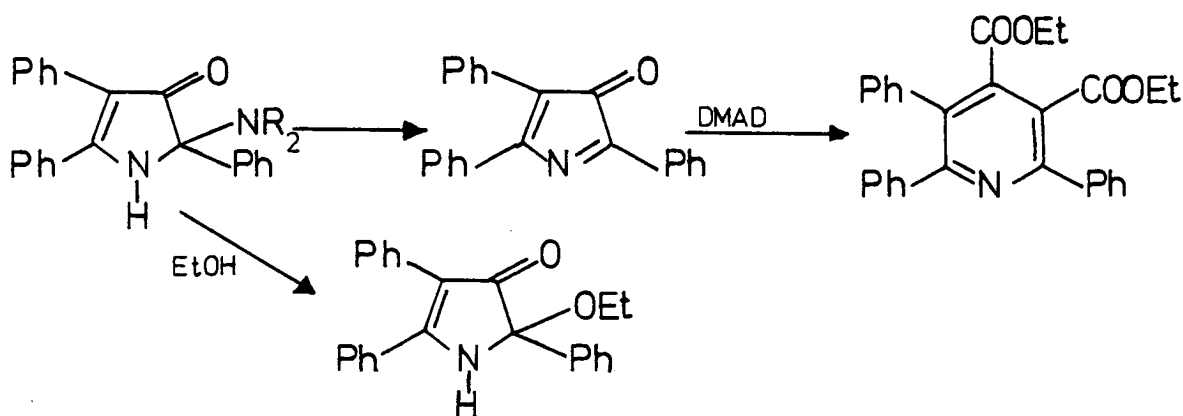
Chlorination of the 2,2,5-triphenyl-1,2-dihydro-3H-pyrrol-3-one using phosphorus pentachloride in benzene at reflux led to the 4,4-dichloro derivative rather than displacement of oxygen as seen in dimedone (Scheme 27).⁶⁶



Scheme 27

The amins formed by the cyclopropenone route²⁶ undergo rapid reaction with nucleophiles to give a variety of 2-substituted-1,2-dihydro-3H-pyrrol-3-ones.

For example, 2-dimethylamino-2,4,5-triphenyl-1,2-dihydro-3H-pyrrol-3-one reacts with alcohols to give 2-alkoxy examples (Scheme 28). Elimination of dimethylamine leads to an azacyclopentadienone which reacts with dimethyl acetylenedicarboxylate in a Diels-Alder reaction. This yields a substituted pyridine after elimination of carbon monoxide (Scheme 28).²⁶

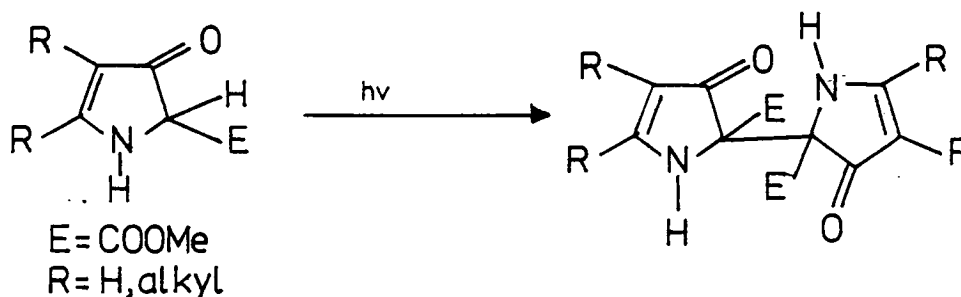


Scheme 28

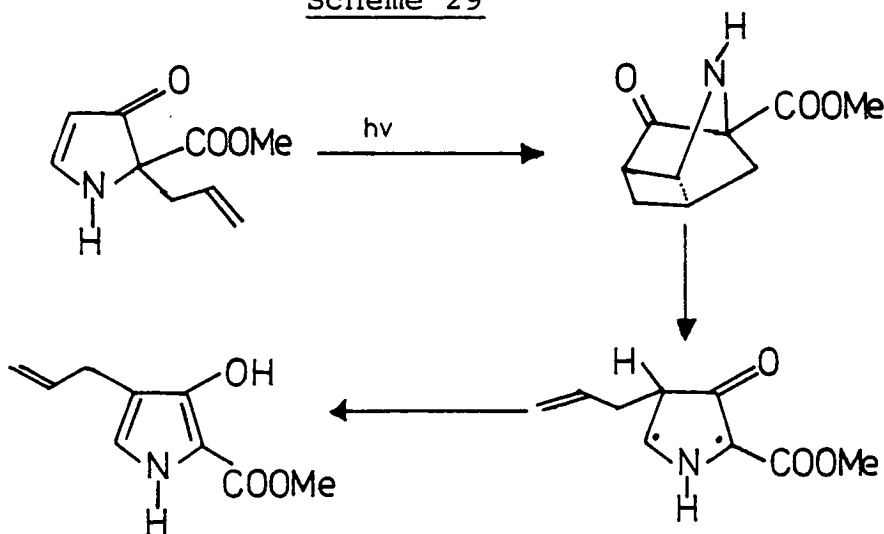
3-Methoxypyrroles with ester and alkyl substitution have been modified by typical procedures to give formyl and hydroxymethyl substitution.^{22,67} These have been used to synthesise unusual porphyrins.⁶⁸

The photolysis of some 1,2-dihydro-3H-pyrrol-3-ones has been studied in order to make comparisons between them and the corresponding furans and thiophenes. It is found that 2-unsubstituted⁶⁹ and 2,2-dialkyl⁷⁰ pyrrolones do not react to give dimers or cyclobutanes as a result of 2+2 cycloaddition, in contrast to the oxygen and sulphur compounds. Instead, only slow

decomposition occurs in acetonitrile. In acetone or other ketonic solvents, however, an aldol condensation occurs⁶⁹ with solvent, to give 2-alkylidene compounds in the same way as aromatic and unsaturated aldehydes react thermally. The reaction is thought to involve initial electron transfer to the excited ketone. 2-Ester substituted compounds undergo dimerisation on irradiation in degassed acetonitrile (Scheme 29)⁶⁵ while the 2-allyl-2,3-dihydro-3-oxo-1H-pyrrole-2-carboxylic esters undergo an allyl migration for which an initial 2+2 cycloaddition is proposed.⁷¹ (Scheme 30).

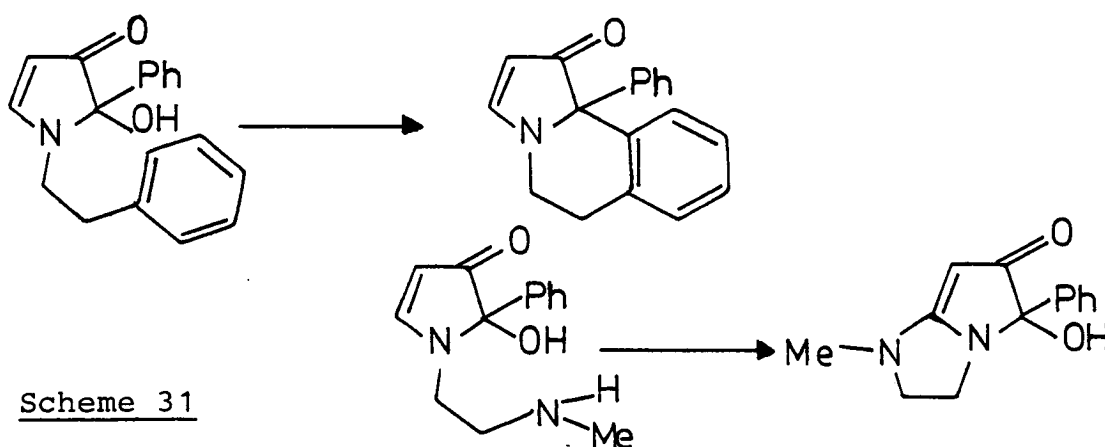


Scheme 29



Scheme 30

2-Hydroxy-1,2-dihydro-3H-pyrrol-3-ones with N-(2-phenyl-ethyl) substituents have been found to undergo Lewis acid catalysed cyclisations to the 2-position while introduction of nitrogen or sulphur to the substituent results in attack at the 5-position (Scheme 31).³²



As already mentioned, a new synthesis of 3-hydroxypyrroles has been developed. It provides an efficient route to simple examples which have been used in an investigation of the properties of the ring system. The synthesis involves flash vacuum pyrolysis of Meldrum's Acid derivatives and the remainder of this section is therefore devoted to a brief review of the technique of flash vacuum pyrolysis and, in particular, the pyrolysis of Meldrum's Acid derivatives.

B. FLASH VACUUM PYROLYSIS

Flash vacuum pyrolysis has been increasingly used to effect high temperature reactions since it eliminates some of the problems associated with conventional solution phase thermolyses: namely undesirable side reactions with solvent or starting material, secondary reactions of initial products and difficulties encountered in the isolation of products. The apparatus used varies considerably in complexity and Brown includes an overview in his comprehensive text on pyrolytic methods.⁷² Essentially, the substrate is sublimed, for example using an air bath or heated tapes, then passes through an externally heated furnace tube and the products are collected in a trap at low temperature, usually that of liquid nitrogen. The system is maintained at the required pressure using suitable vacuum pumps. The method results in short contact times in the hot zone and low concentrations of reactive species, and hence intramolecular, rather than intermolecular, reactions typically occur.

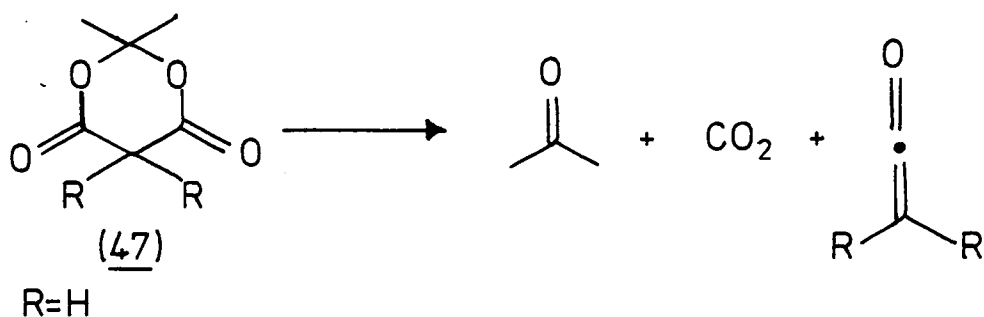
Essentially, there are three types of reaction which occur under flash vacuum pyrolysis conditions and Brown's book⁷² deals with some typical examples and gives leading references to the literature prior to 1980. These types of reaction can be classified as follows:

(i) Homolysis of a weak bond leading to radicals which has been extensively reviewed by Cadogan, Hickson and McNab⁷³,

(ii) Concerted processes such as cis-eliminations and retro Diels-Alder reactions,⁷⁴⁻⁷⁶

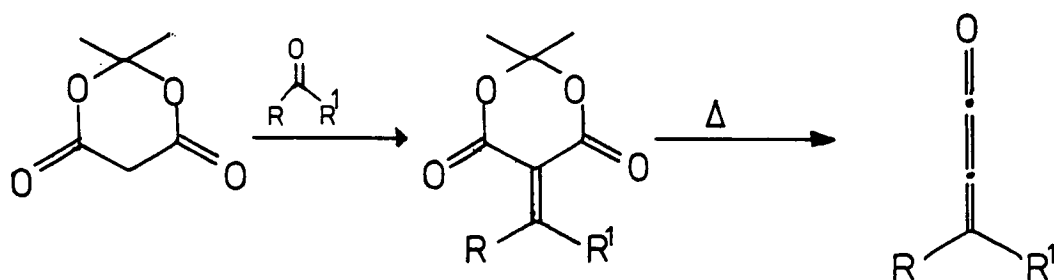
(iii) Cleavage of small molecules which generally leads to reactive species which are subject to further rearrangement or reaction, such as carbenes, nitrenes^{75,77} or arynes resulting from loss of N₂, CO₂, SO₂, etc.

Meldrum's Acid (2,2-dimethyl-1,3-dioxane-4,6-dione)⁷⁸ (47) is an excellent substrate for the reactions of type (iii) and indeed its breakdown to give ketenes is long established⁷⁹ (Scheme 32). More recently, carbon dioxide and acetone have been identified on pyrolysis



Scheme 32

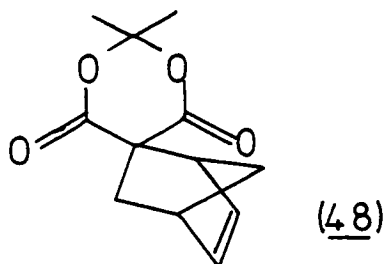
under flash vacuum conditions.⁸⁰ The method has been most often applied to the generation of methyleneketenes⁸¹, the substrates for which are readily available by Knoevenagel condensation of Meldrum's Acid with carbonyl or activated carbonyl compounds (Scheme 33).



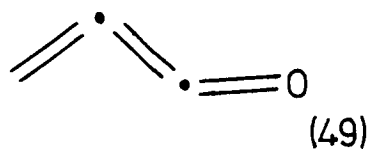
Scheme 33

The loss of acetone and carbon dioxide to give methyleneketenes has recently been shown not to be concerted since intermediate structures of carboxyketenes have been observed.⁸²

There has been considerable interest in the preparation of the parent methyleneketene but condensation of formaldehyde with Meldrum's Acid does not lead to the 5-methylene compound. Other methods of generation, from an epoxide for example,⁸³ lead to an uncharacterised polymeric material which exists as the monomer only in solution. Generation of the parent methyleneketene therefore requires protection of the methylene group and this was achieved by a Diels-Alder reaction with cyclopentadiene. Flash vacuum pyrolysis of the 5,5-spiro adduct (48) proceeded via a retro-Diels-Alder reaction and



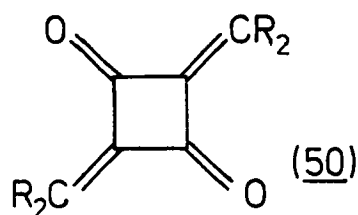
the usual ring cleavage to give the parent methylene-ketene which has been identified by its mass spectrum and infra-red spectrum determined at -196°C .⁸³ The parent compound has also been generated by pyrolysis of acrylic anhydride and this method has been used to produce carbon-13 and deuterium labelled species. These labelled compounds have been studied by microwave spectroscopy^{84,85} and calculated moments of inertia suggest a non-linear equilibrium geometry (49).



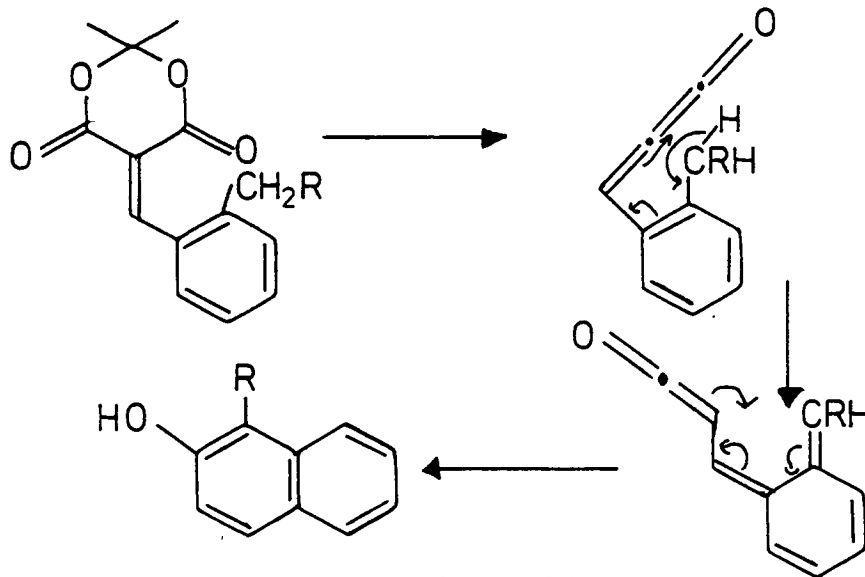
Theoretical calculations of the geometry of methyleneketene have predicted linear equilibrium structure,⁸⁶ but subsequent refinements⁸⁷ have produced the non-linear structure.

Flash vacuum pyrolysis has been used to generate numerous substituted methyleneketenes which exhibit a variety of subsequent reaction pathways. Thus, alkyl and aryl examples have been generated and observed by condensation of the pyrolysate onto KBr discs.⁸⁰ Brown and his co-workers have shown these methyleneketenes can be trapped by aniline or methanol or can

dimerise on warming to yield 2,4-dimethylenecyclobutan-1,3-diones (50). The methoxymethyleneketene can also be detected by infra-red spectroscopy and



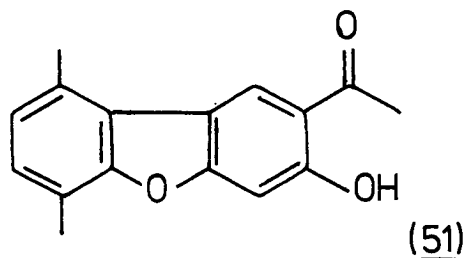
trapping experiments but the dione is not obtained.⁸⁸ Aryl compounds with an ortho alkyl substituent do not simply dimerise. Instead, a hydrogen shift occurs and subsequent cyclisation leads to β -naphthols⁸⁹ (Scheme 34). Similar reaction is observed for a



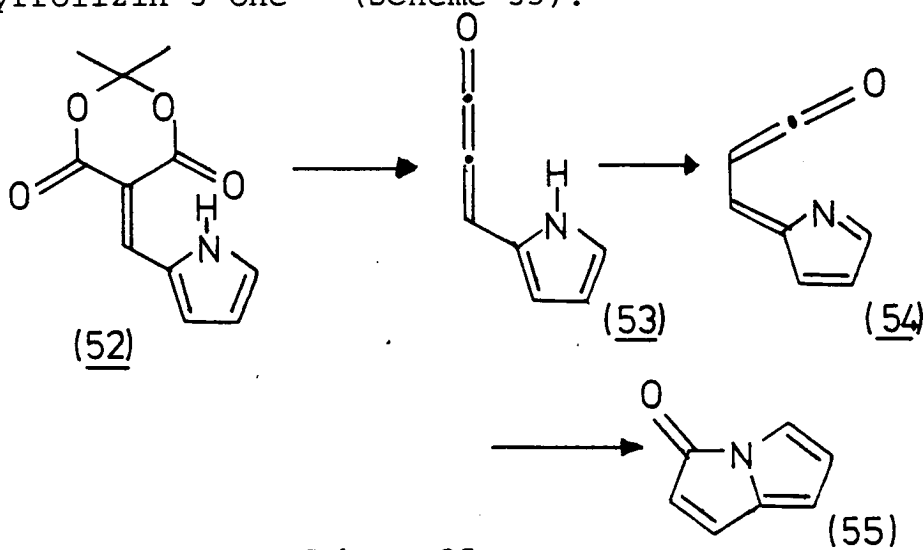
Scheme 34

variety of heteroaromatic substituents^{90,91} which lead, for example, to hydroxybenzofurans. Derivatives arising from ketones allow functionalisation of the aromatic

ring formed by the reaction.⁹² This approach has been used in the synthesis of Rusco-dibenzofuran (51) by pyrolytic formation of the deacylated compound.⁹³



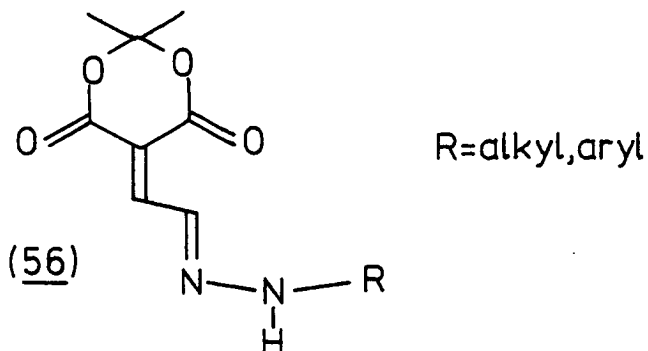
The reactivity of the methyleneketene has also been used to generate an unsaturated lactam function. Thus, the product derived from Meldrum's Acid and pyrrole-2-carboxaldehyde was pyrolysed to give pyrrolizin-3-one⁹⁴ (Scheme 35).



Scheme 35

This strategy has also been extended to give aza-analogues of the pyrrolizin-3-one system from imidazole- and pyrazole-carboxaldehydes,⁹⁵ and a benzo-analogue from indole-2-carboxaldehyde.⁹¹ A similar lactam

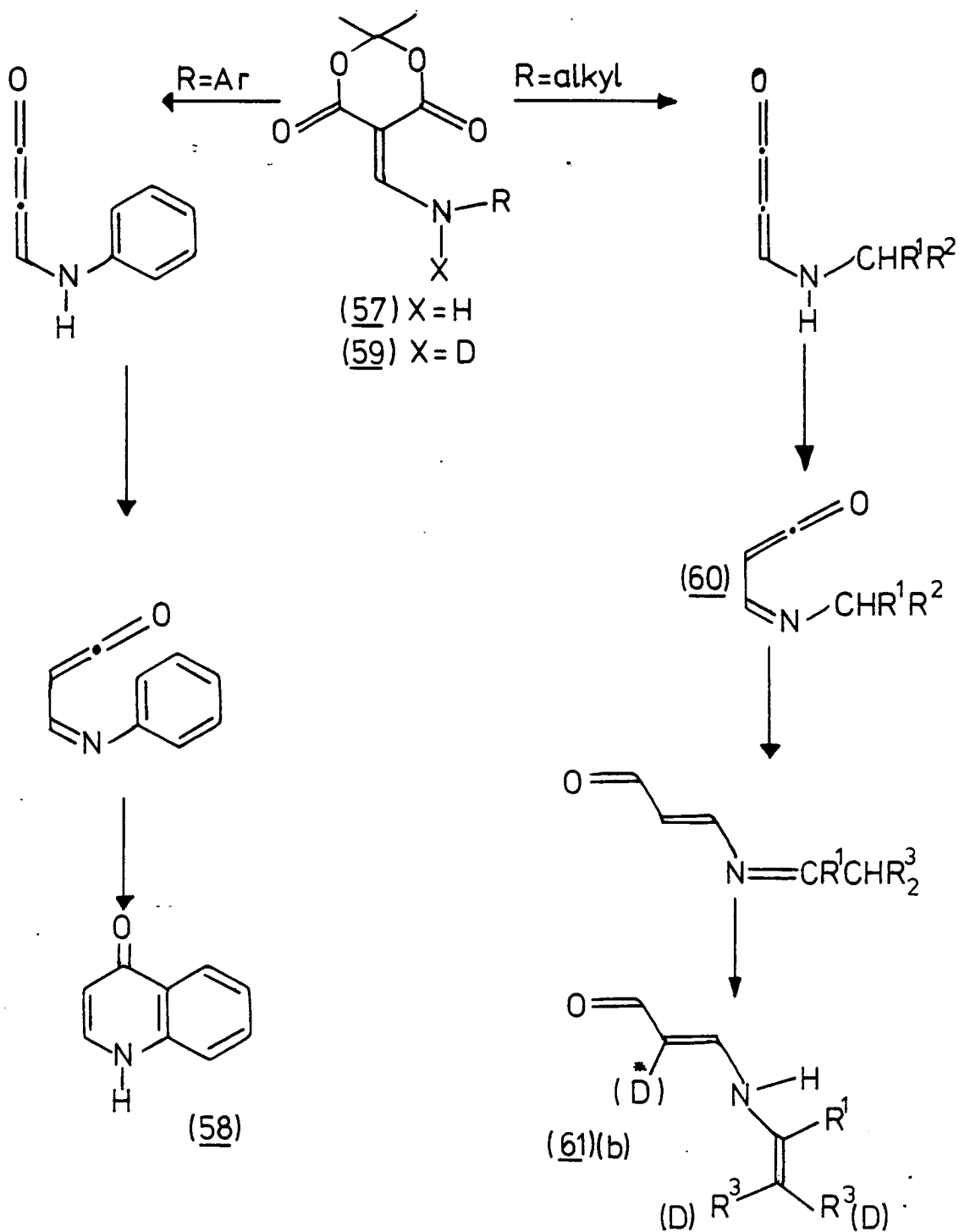
formation also occurs on pyrolysis of the condensation products of Meldrum's Acid and azaenaminones (56) resulting in a preparation of pyridazin-3-ones.⁹⁶



Secondary aminomethylene derivatives do not form azetin-2-ones. Instead the methyleneketene tautomerises to an iminoketene and N-alkyl derivatives give enamino-enaminals while aryl examples form quinolines (Scheme 36).^{4,97,98} These reactions are known to occur at temperatures greater than 200°C in solution⁹⁹⁻¹⁰² although in generally poorer yields.

Wentrup has used infra-red spectroscopy to study the various intermediates involved in the transformation of aminomethyleneketene to product by studying the pyrolysate as it warms from -196°C to room temperature.⁹⁸ This has shown the aminomethyleneketene rearranges on warming to -90°C but the imidoylketene (60) can only be observed at low pyrolysis temperatures as the following H-shift occurs rapidly. The final transformation to the enaminoenamine (61) occurs between -90 and 25°C.

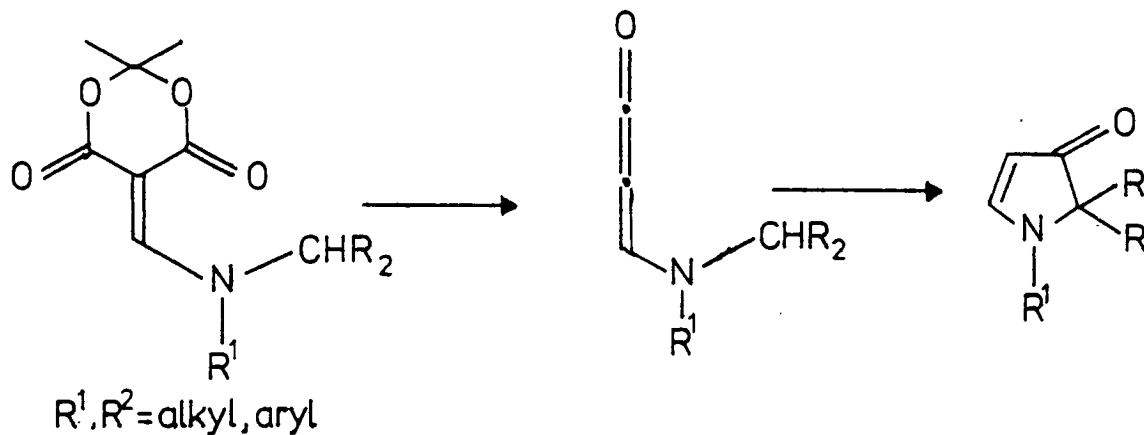




Scheme 36

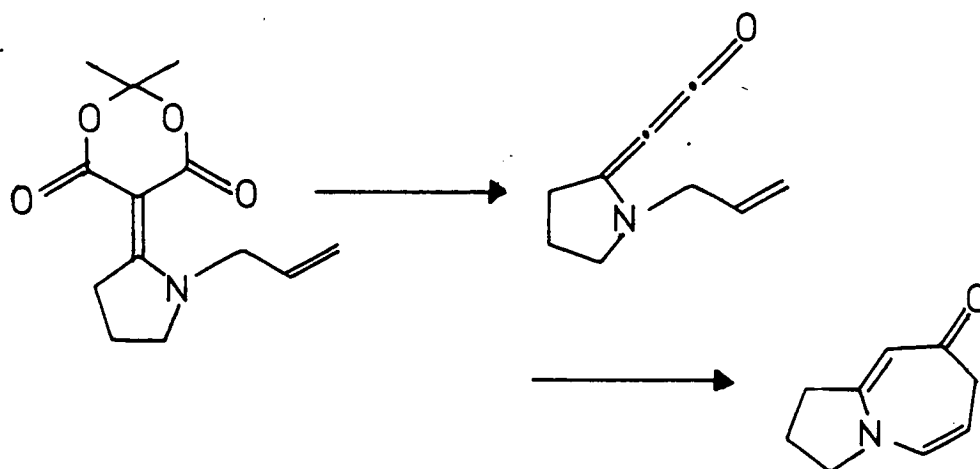
Pyrolysis of the N-deuteriated species (59, X=D) gives the specifically deuteriated compound indicated in Scheme 36 under Wentrup's conditions. McNab has pyrolysed precursors labelled on nitrogen and in α - and β -positions.⁹⁷ The results of these pyrolyses and pyrolysis of an N-deuteriated enaminal indicate that the longer contact times involved in his apparatus result in scrambling of the labels by a series of 1,5-shifts to give the enaminoenaminal labelled in the three positions β to nitrogen, as indicated in (61b).

Tertiary aminomethylene Meldrum's Acid derivatives undergo an unusual hydrogen transfer and cyclisation to give 1,2-dihydro-3H-pyrrol-3-ones (Scheme 37).^{4,103-106} The study of this reaction forms a major part of this



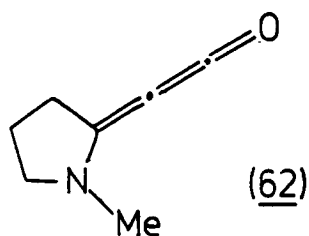
Scheme 37

thesis and is discussed in a later chapter but it should be noted that other workers have observed the reaction for N-allyl compounds where a competing cyclisation leads to seven-membered rings¹⁰³ (Scheme 38).

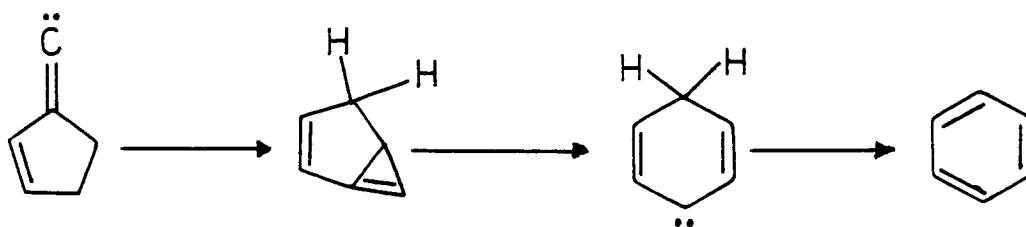


Scheme 38

A methyleneketene of this type has been shown by infra-red and carbon-13 nuclear magnetic resonance spectroscopy to be remarkably stable. Thus, the ketene (62) is found to be reasonably stable in solution at room temperature.¹⁰⁴

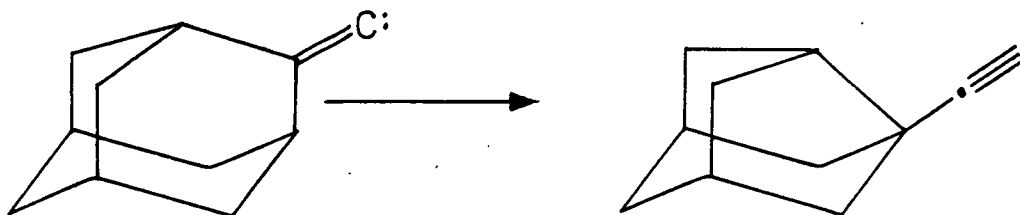


Methyleneketenes from Meldrum's Acid derivatives can also decarbonylate at higher pyrolysis temperatures to give carbenes. The carbenes can then undergo isomerism to acetylenes when there is aryl substitution^{89,107} or ring expansion as in the unsaturated cyclopentyl derivative¹⁰⁸ (Scheme 39).



Scheme 39

Wiersum has shown the adamantylidene Meldrum's Acid derivative rearranges to 3-noradamantylacetylene (Scheme 40) rather than undergoing ring expansion, presumably because it would lead to an anti-Bredt olefin.¹⁰⁹

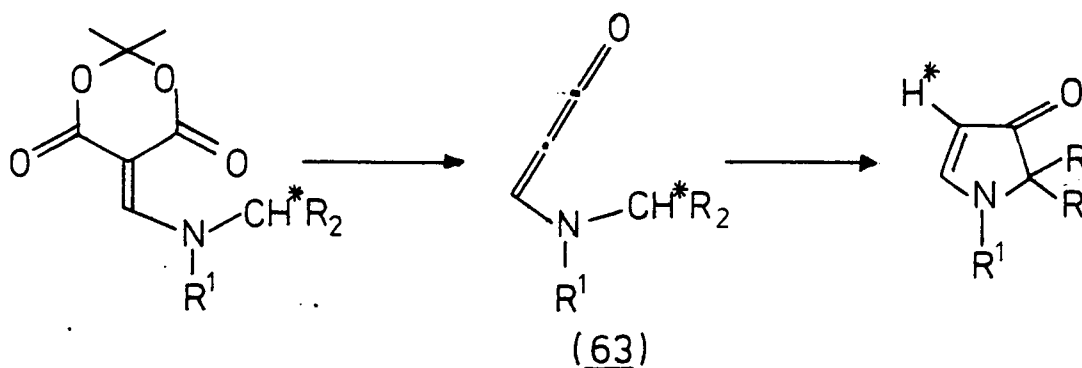


Scheme 40

DISCUSSION

A. INVESTIGATION OF THE MECHANISM AND SCOPE OF
1,2-DIHYDRO-3H-PYRROL-3-ONE FORMATION FROM
5-AMINOMETHYLIDENE-2,2-DIMETHYL-1,3-DIOXANE-
4,6-DIONES

The formation of pyrrolones which occurs on flash vacuum pyrolysis of aminomethylidene derivatives of Meldrum's Acid^{†4,103-105} (Scheme 41) was introduced previously and evidence for intermediates leading to the methyleneketene (63) mentioned.¹⁰⁴



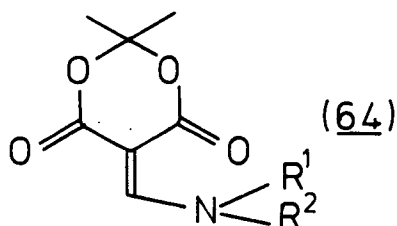
Scheme 41

The hydrogen atom indicated in the scheme has been labelled with [²H] and shown to be transferred exclusively to the C-4 position of the pyrrolone, by an intramolecular process.¹⁰⁵ Prior to the present work, this reaction had been shown to occur for examples where the nitrogen atom was substituted with cyclohexyl groups or formed

[†] Throughout this section 2,2-dimethyl-1,3-dioxane-4,6-dione will be referred to as Meldrum's Acid.

part of a piperidine ring.⁴ The remainder of this chapter deals with evidence for the involvement of a further intermediate in the formation of pyrrolones from the methyleneketene and establishes the scope of the reaction.

PREPARATION OF 5-AMINOMETHYLIDENE-2,2-DIMETHYL-
1,3-DIOXANE-4,6-DIONES



The title compounds (64) were prepared by reaction of the appropriate amine with a 5-alkoxymethylidene derivative. Initially, a literature method¹¹⁰ in which 5-ethoxymethylidene Meldrum's Acid was prepared and reacted in situ was used. Meldrum's Acid and an excess of triethylorthoformate were heated to reflux and then the amine was added and heating continued. However, this required a two times excess of amine and did not proceed satisfactorily with bulky amines, since reasonable yields could only be obtained if the derivatives crystallised from the triethylorthoformate solution. An adapted method was therefore sought, and it was found that isolation of the 5-methoxymethylidene derivative and its reaction with a 5-10% excess of amine in cyclohexane at reflux led to the required products. The methoxy

rather than ethoxy derivative was used because its higher melting point (137°C cf. 87°C) meant isolation of a good yield of a crystalline product was possible. Generally, good yields were obtained by this second method although the insolubility of the methoxy compound created some difficulties, particularly with solid amines. It was later found that the method of choice involved reaction of the methoxy compound with the appropriate amine in acetonitrile at room temperature. Reaction proceeded exothermically in 10-15 minutes to give the aminomethylidene derivatives as precipitates or as solids after the evaporation of the solvent. A number of these derivatives were prepared and they are listed in Tables 1 and 2.

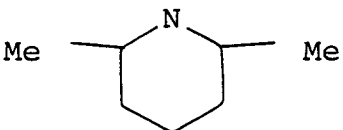
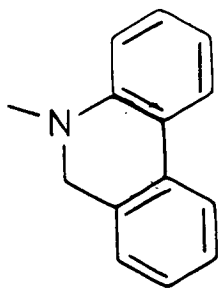
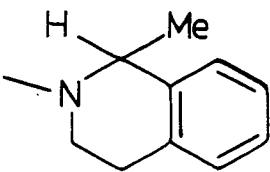
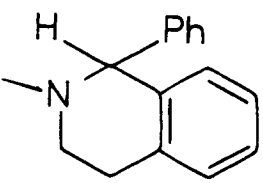
[$^2\text{H}_3$] and [^{13}C] labelled N-methyl derivatives were prepared by alkylation of secondary aminomethylidene derivatives with labelled methyl iodide but this did not prove a generally applicable method, as discussed in the Experimental Section.

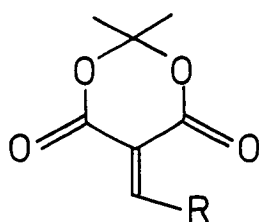
Chiral derivatives of (78), (89) and (90) were prepared from optically active amines. Both R and S forms of (78) were obtained and the optical purity of the derivatives prepared was determined by use of a chiral lanthanide shift reagent (see Experimental Section). This showed no evidence for the second enantiomer after the signals for the ring methyl groups and the

Table 1 5-Aminomethylidene-2,2-dimethyl-1,3-dioxane-4,6-diones

(64)	R ¹	R ²	C5-CH	C2-Me ¹ s
(65)	Pr ⁱ	Pr ⁱ	8.21	1.69
(66)	Et	Et	8.02	1.61
(67)	cycloheptyl	cycloheptyl	8.01	1.58
(68)	CH ₂ Ph	CH ₂ Ph	8.38	1.47
(69)	CHMePh	CHMePH	8.36	1.69
(70)	Et	cyclohexyl	8.09	1.62
(71)	Pr ⁱ	cyclohexyl	8.02	1.55
(72)	Pr ⁱ	Ph	8.35	1.58
			(8.12)	(1.72)
(73)	Et	Ph	8.22	1.71
			(8.27)	(1.59)
(74)	CH ₂ Ph	Ph	8.35	1.27
(75)	CH ₂ Ph	Me	8.32	1.69
			(8.16)	(1.50)
(76)	CH ₂ Ph	Pr ⁱ	8.26	1.39
(77)	CHMeEt	cyclohexyl	8.26	1.69
(78)	CHMePh	Pr ⁱ	8.30	1.74
(79)	Bu ^t	H	8.05	1.26
(80)	Bu ^t	Me	8.43	1.71
(81)	p-Bu ^t -Ph	H	8.58	1.31
(82)	p-Bu ^t -Ph	Me	8.33	1.75
(83)	Ph	Me	8.26	1.66
(84)	cyclohexyl	Me	8.25	1.72
(85)	Me	Me	8.08	1.67

Table 2 2,2-Dimethyl-5-methylidene-1,3-dioxane-
4,6-diones

(<u>86</u>)	R	C5-CH	Me ¹ s
(<u>87</u>)		7.99	1.55
(<u>88</u>)		8.40	1.78
(<u>89</u>)		8.35	1.68
(<u>90</u>)		8.56	1.69



methyl groups of the nitrogen substituents were shifted by ≈ 0.3 p.p.m. which was sufficient to give separate signals for each enantiomer in the racemic case. The optical purity of the commercially obtained precursor methylbenzylamines was stated to be $>98\%$. The tetrahydroquinoline precursors for (89) and (90) were resolved by recrystallisation of their tartrates until a constant melting point was obtained and α_D values were consistent with those recorded in the literature (see Experimental Section). It seems unlikely that the optical purity of the site α to nitrogen would be lost in the nucleophilic attack of the amine on the methoxymethylidene Meldrum's Acid.

The n.m.r. spectra of the Meldrum's Acid derivatives give rise to two sets of signals representing the nitrogen substituents due to restricted rotation around the C-N bond. Where the nitrogen substitution is unsymmetrical, different proportions of the two rotamers are observed as a result of steric effects. The delocalisation (Figure 4A) which gives partial double bond character to the C-N bond also allows rotation about the formal C-C double bond, and this can be observed in the ^{13}C n.m.r. spectra where the carbonyl groups generally give rise to a broad signal at room temperature, as they are close to coalescence. The derivatives with only monosubstitution on the

nitrogen atom (79 and 81) give rise to two well resolved signals as a result of H-bonding (Figure 4B) which increases the barrier to rotation. The bulky phenyl substituted examples (74 and 88) also give well resolved signals which may be explained by the lower availability of the lone pair to become involved in the

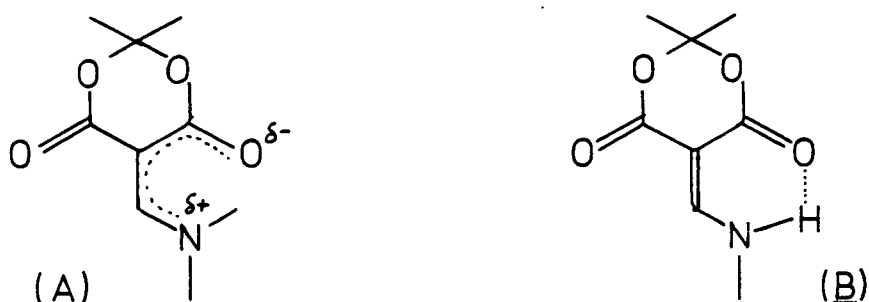
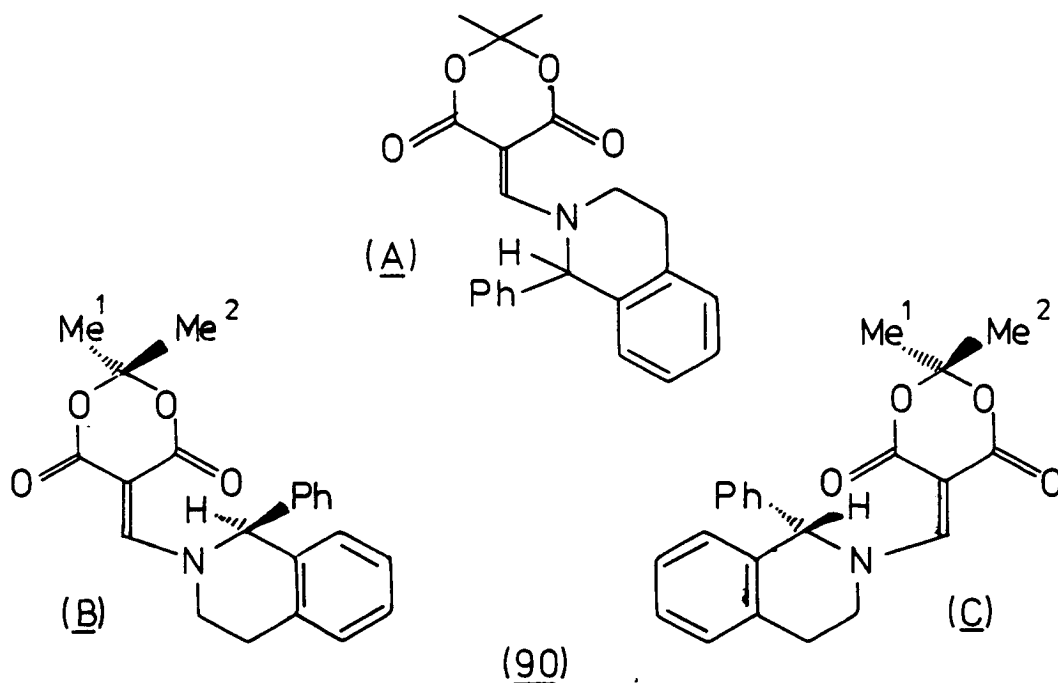


Figure 4

delocalisation. Approximate rate constants for the restricted rotations can be obtained by variable temperature n.m.r. studies¹¹¹ (Table 3), and some related malonic acid derivatives have been studied by K"olle, Kolbe and Mannschreck.¹¹² The dimethylamino-methylidene Meldrum's Acid derivative (85) was initially studied since the C-N rotation could be readily monitored by examining the resonance corresponding to the N-methyl groups in the ¹H n.m.r. spectrum. The C-C rotation could not be measured by proton spectroscopy as in the examples studied previously¹¹² (e.g. the

dimethyl malonate derivative) but the carbonyl resonances in the ^{13}C n.m.r. spectra gave the required information. The cyclic derivative (90) proved particularly interesting for a study of both restricted rotations. The unsymmetrical substitution of this example results in two unequal singlets corresponding to the olefinic proton in the rotamers (A) and (B) and their coalescence therefore gives a measure of the rate of C-N rotation.



The two rotamers also give rise to different signals corresponding to the C2-methyl groups. The two methyl groups have been shown to be equivalent even at -80°C in Meldrum's Acid itself, indicating the very rapid interconversion of the two boat conformers of the ring but the minor rotamer (B) shows non-equivalence corresponding to the two rotamers arising from C-C

rotation [(B) and (C)]. The effect of the phenyl ring on the chemical shift of the methyl group on the same side of the Meldrum's Acid ring is sufficient, in this case, to allow the observation of a coalescence temperature for these signals and hence an approximate rate constant for the C-C rotation.

Table 3 Variable temperature study of 5-amino-methylidene Meldrum's Acid derivatives

Derivative	Solvent ^a	C-N rotation		Solvent ^a	C-C rotation	
		T _c /K	ΔG/kJ mol ⁻¹		T _c /K	ΔG/kJ mol ⁻¹
(85)	(C[² H ₃]) ₂ SO	435±1	90.5±0.2	C[² H]Cl ₃	280±1	54.0±0.3
(90)	(C[² H ₃]) ₂ SO	420±2	86.5±0.5	C[² H]Cl ₃	301±2	62.6±0.4

^a Changes in coalescence temperature due to changes in solvent have been found to be minimal.¹¹¹

The values found for the C-N rotation are very similar to those found for a range of cyclic and acyclic malonic acid derivatives which fall in the range 83-98 kJ mol⁻¹.¹¹² In the other examples which have been studied, changing the amino-substitution has had little effect; for example, changing an N-methyl group to a benzyl group in the cyclic amide (Figure 5) gives an increase of less than 2 kJ mol⁻¹. The change observed here is somewhat greater, although it is still less than 5%, but the decrease

observed, despite increasing bulk, is of interest. The decrease in the free energy of C-N rotation on changing the amino substituent is accompanied by an increase in C-C rotation. This would appear to be consistent with an electronic effect; decreased delocalisation of the nitrogen atom's lone pair, would promote the formal single bond character of the C-N, and double bond character of the C-C linkages. The percentage change in the free energy of rotation about the C-C bond is considerably greater than in the C-N bond, but the effect of changing the solvent cannot be completely ignored. The C-C bond rotation of the amides, illustrated in Figure 5 (R=Me),

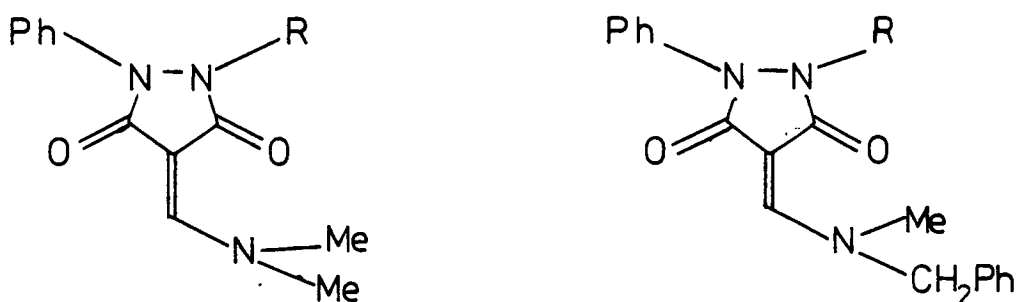
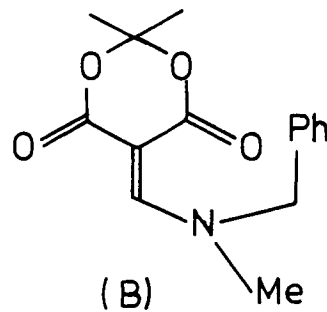
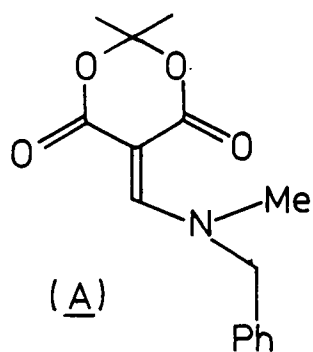


Figure 5

has also been studied and shown to increase with benzyl substitution, but by only around 4 kJ mol⁻¹. Interestingly, it was the rotamer shown in Figure 5 which was studied and this would seem to minimise steric effects in the

result, whereas in the example studied here the steric effect is likely to be greatest in the stereoisomer where coalescence has been observed.

Disubstituted derivatives give characteristic signals in the proton n.m.r. spectra arising from the methyldene proton which gives a sharp singlet (or two singlets for unsymmetrical cases) at between δ_H 8.0 and 8.55 (see Tables 1 and 2) while monosubstituted examples exhibit coupling of around 15 Hz to the -N-H. The ring methyl groups also produce a characteristic resonance; the six proton singlet occurs at δ_H 1.55-1.75 with the exception of the benzyl substituted examples which give more shielded values (e.g. (76), δ_H 1.39) which must result from the orientation of the aromatic ring and the associated ring current effects. This appears to be confirmed by the difference in the chemical shift of the signals, due to the two rotamers of (75). The ring methyl groups of (B) would be predicted to give a more shielded signal; rotamer (A) has a value of δ_H 1.69 while (B) occurs at δ_H 1.50.



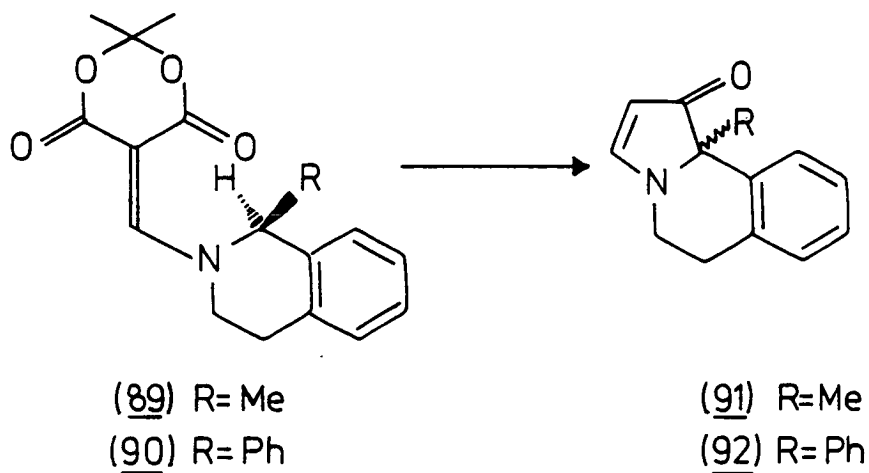
(75)

The methyl signals in the ^{13}C n.m.r. spectra of N-benzyl compounds are also slightly more shielded than the typical δ_{C} 26.25-26.65 range (e.g. (76), δ_{C} 25.85). In monosubstituted examples (79) and (81) these methyl signals are also shielded. The C-5 carbon atom gives rise to a characteristic signal at δ_{C} 102 in the ^{13}C n.m.r. spectra for the disubstituted derivatives while the monosubstituted examples have a value of δ_{C} 104. The C-2, C5-CH and carbonyl signals come consistently in δ 82.7-87.1, δ 155-159.5 and δ 159-165 ranges, respectively, with no obvious trends within the spread of chemical shifts.

The mass spectra of Meldrum's Acid derivatives typically show loss of m/z 58 (cleavage of acetone), followed by loss of m/z 44 (cleavage of carbon dioxide), and this pattern is followed by the majority of the present examples. In some cases an alkyl fragment is lost prior to cleavage of carbon dioxide (e.g. 65 gives peaks at M^+ , 154.0506, (M- $\text{C}_3\text{H}_6\text{O}_2$ - C_3H_7) requires 154.0504 and M^+ , 153.1153, (M- $\text{C}_3\text{H}_6\text{O}_2$ - CO_2) requires 153.1154. The only significant deviation from the expected breakdown arises when saturated cyclic substituents are present; in these cases (67, 70, 71 and 84) cleavage of acetone is followed by loss of m/z 18 to give a very stable fragment. Accurate mass measurement has shown this to be a result of loss of H_2O in the related dicyclohexyl example (64, $\text{R}^1=\text{R}^2=\text{cyclohexyl}$)¹⁰⁶ but the structure of the ion formed is unclear.

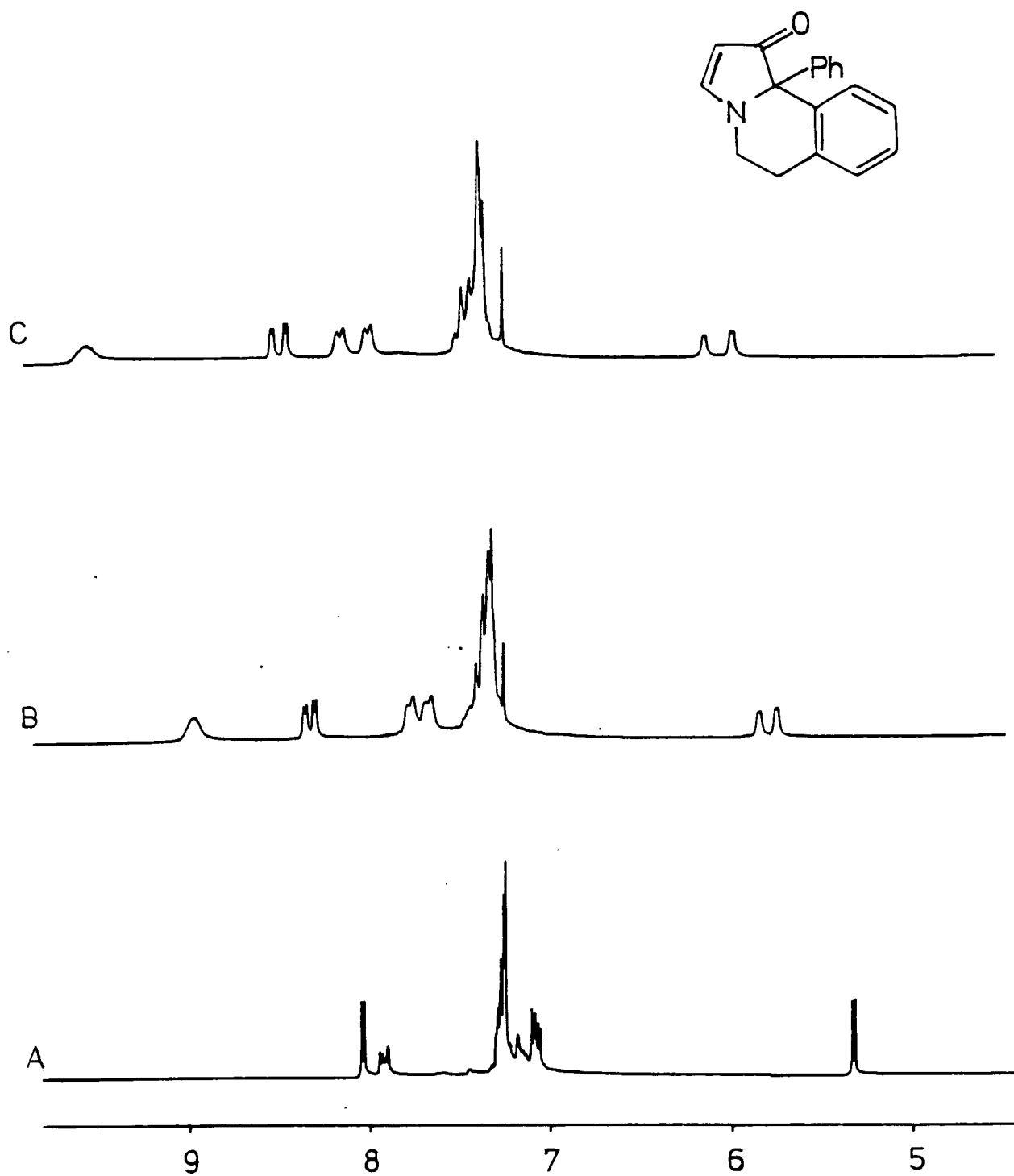
MECHANISM OF PYROLYSIS OF 5-AMINOMETHYLIDENE-
2,2-DIMETHYL-1,3-DIOXANE-4,6-DIONES

The H-transfer and ring closure involved in the formation of 1,2-dihydro-3H-pyrrol-3-ones from methyleneketenes (63), shown in Scheme 41, was thought unlikely to be a fully concerted process as this would involve a very strained transition state. Pyrolysis of substrates such as (89) and (90) in which the site of hydrogen transfer is an enantiomerically pure chiral centre could be expected to provide information on these latter stages of the pyrrolone formation. If the H-transfer and ring closure was one concerted process, the optical activity of the chiral centre should remain intact, although the configuration need not necessarily remain the same. If the H-transfer led to a further intermediate, however, some loss of optical activity would be predicted; the degree of this loss of chirality would be dependent on the relative rates of ring closure and equilibration of configuration at the chiral centre. Under flash vacuum pyrolysis conditions, chiral forms of (89) and (90) were shown to give racemic mixtures of the pyrrolones (91) and (92) (Scheme 42).



Scheme 42

The analysis of the crude pyrolysates was carried out by ^1H n.m.r. spectroscopy using the effect of a chiral lanthanide shift reagent (see Experimental Section) on the signal corresponding to the olefinic proton next to the carbonyl group. This occurs as a doublet at about δ_{H} 5.3, well removed from other signals. The spectra of the pyrrolone (92) obtained from pyrolysis of chiral (90) without shift reagent, and with increments of the complex added, are shown in Figure 6. Pyrolysis of one enantiomeric form of (78) however, leads to a 75:25 mixture of the enantiomers of the pyrrolone formed while the alternative configuration gives the reverse ratio (Scheme 43 and Figure 7).

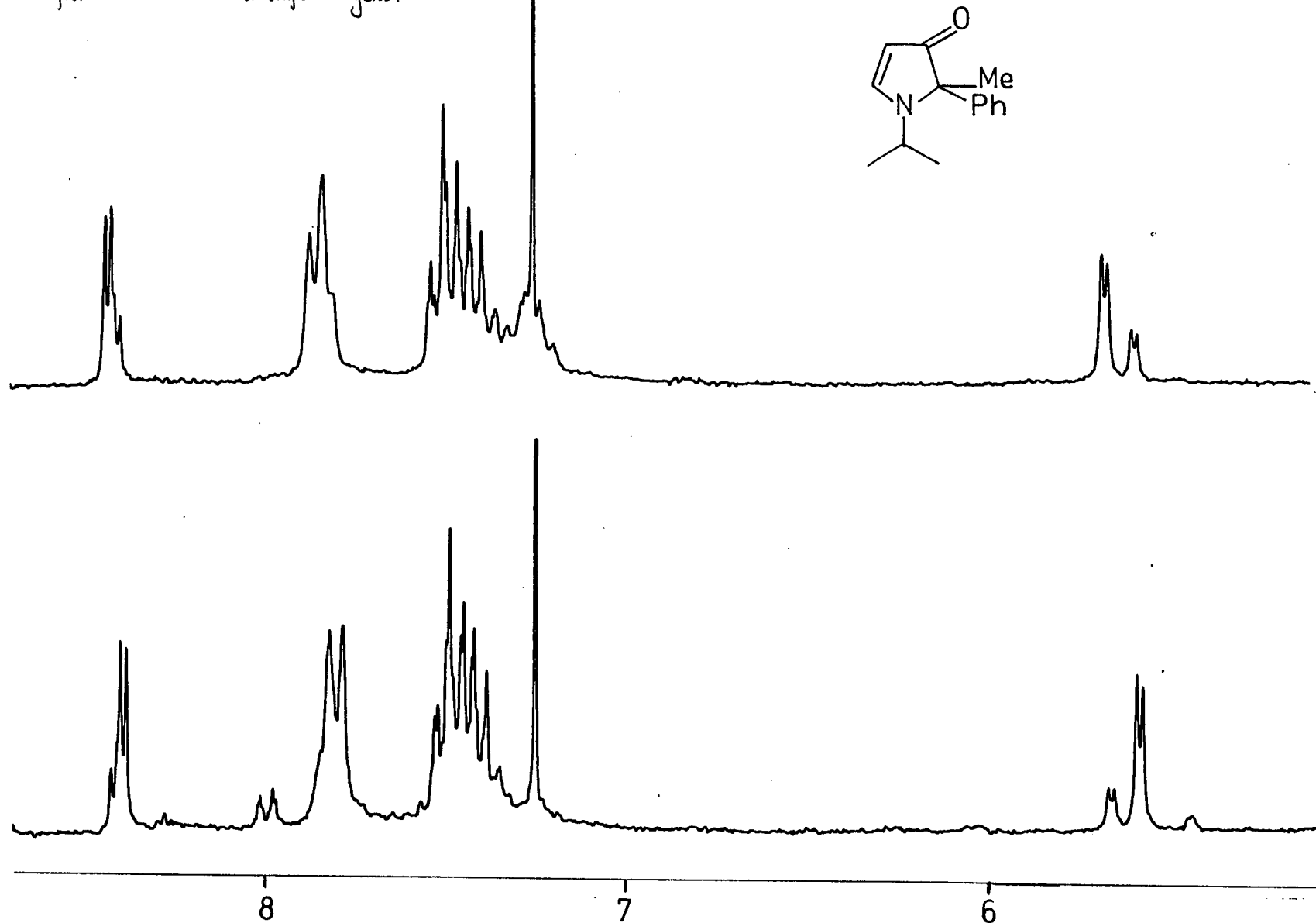


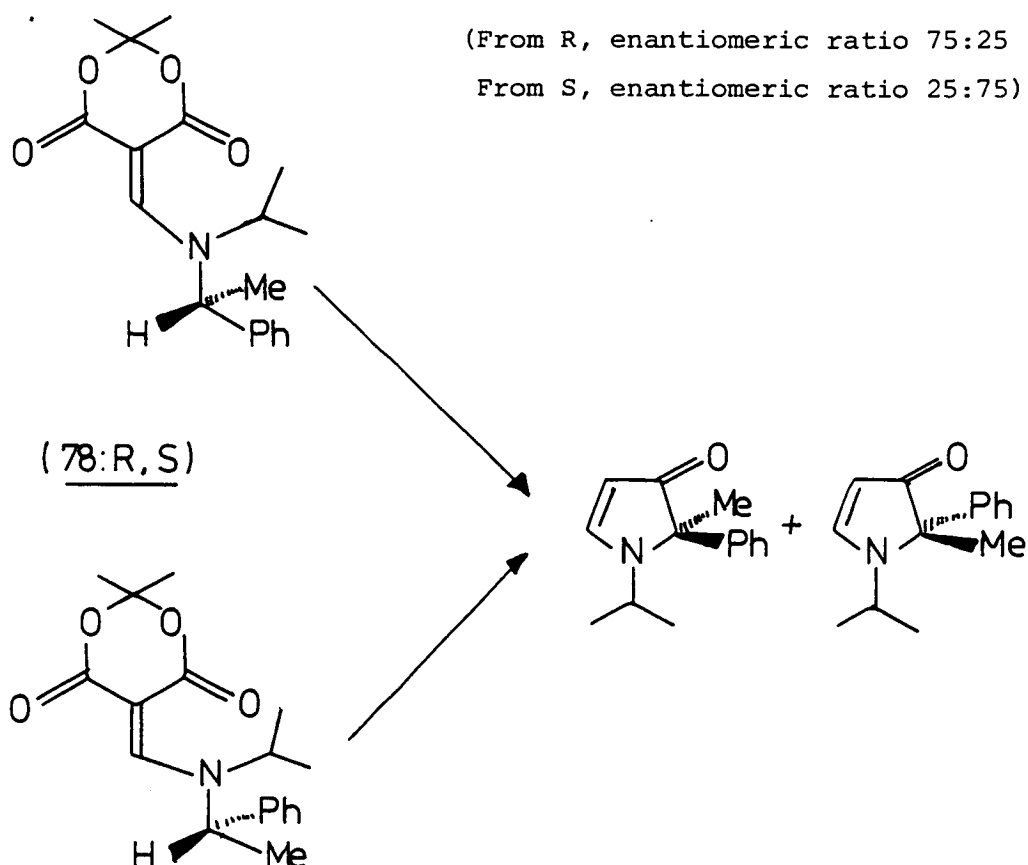
A. ¹H n.m.r. spectrum of pyrrolone (92)

B, C. Spectra after incremental addition of shift reagent

Figure 6

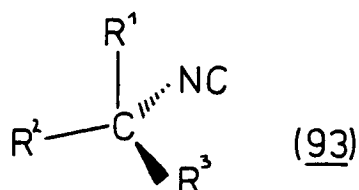
Figure 7 ¹H.n.m.r. spectra of pyrolysates
from 78 R+S + chiral shift reagent.





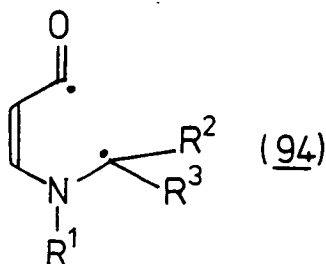
Scheme 43

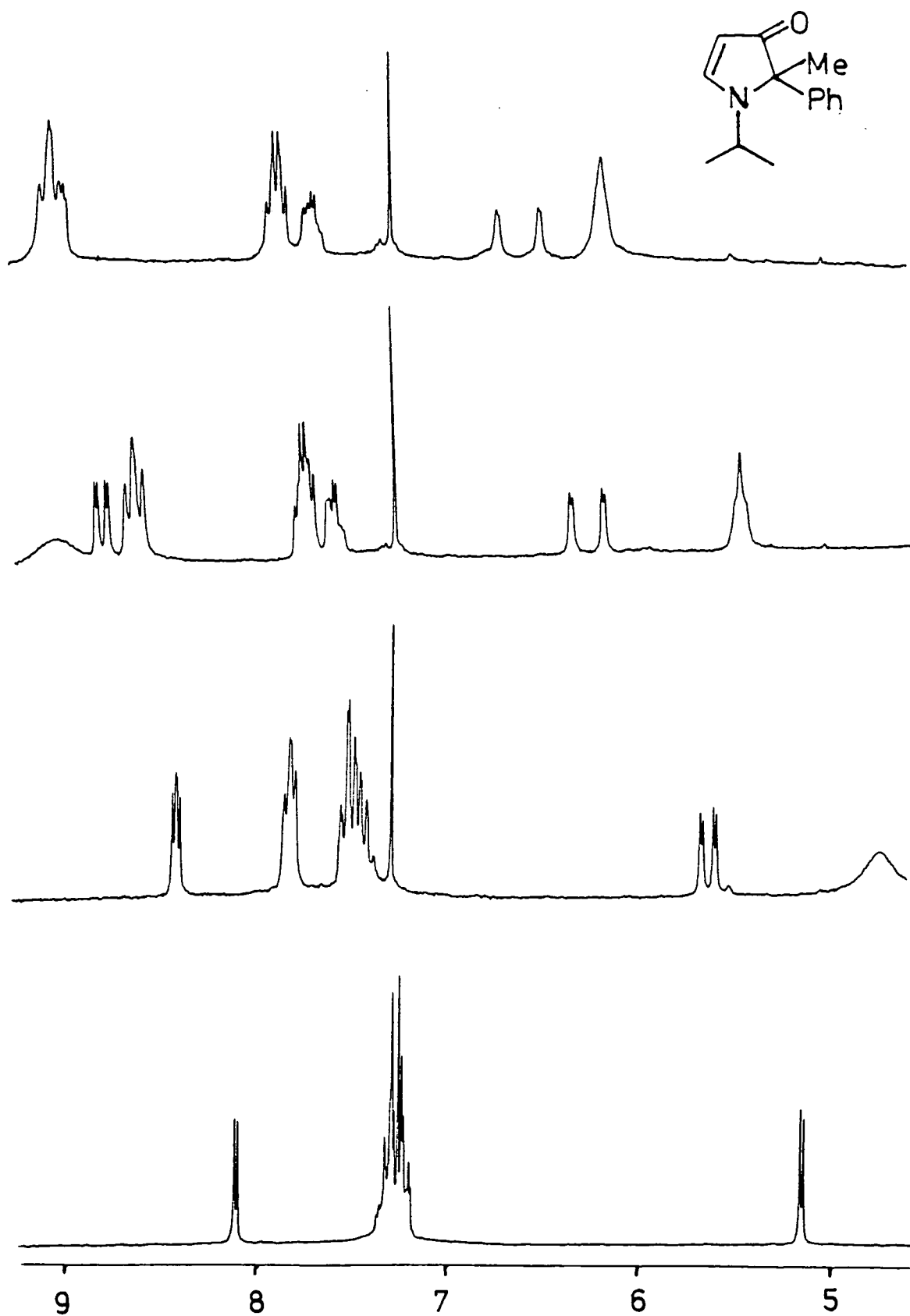
The exclusive hydrogen transfer from the benzylic site will be discussed later. The validity of these results rests on the absence of racemisation purely as a result of the conditions of the reaction: pyrolysis of a chiral form of (78) at 400°C gives recovered starting material with its optical activity retained and repyrolysis of the 75:25 mixture of enantiomeric pyrrolones does not lead to racemisation. This is in line with the results of Meier and Rüchardt¹¹⁴ who observe complete retention of stereochemistry in the pyrolysis of isonitriles (93) at 500-550°C and 10^{-2} Torr.



The separation of the corresponding signals for enantiomeric protons as a function of added shift reagent provides an indication of the site of complexation. A series of spectra of the pyrrolone (97) with known quantities of shift reagent, added in increments, were recorded (Figure 8) and a graph of the results obtained is shown in Figure 9. The doublet corresponding to the C4-proton is by far the most affected followed by the singlet arising from the C2-methyl group, implying the complex is formed with the carbonyl group, as might be expected.

Having established the presence of an intermediate with sufficient lifetime to allow some rotation around the C-N bond, the nature of this intermediate was investigated. An obvious possibility is the diradical structure (94) as suggested for a related pyrrole formation.¹¹⁵ However, a series of experiments in which





Effect of chiral shift reagent on pyrrolone (98)

Figure 8

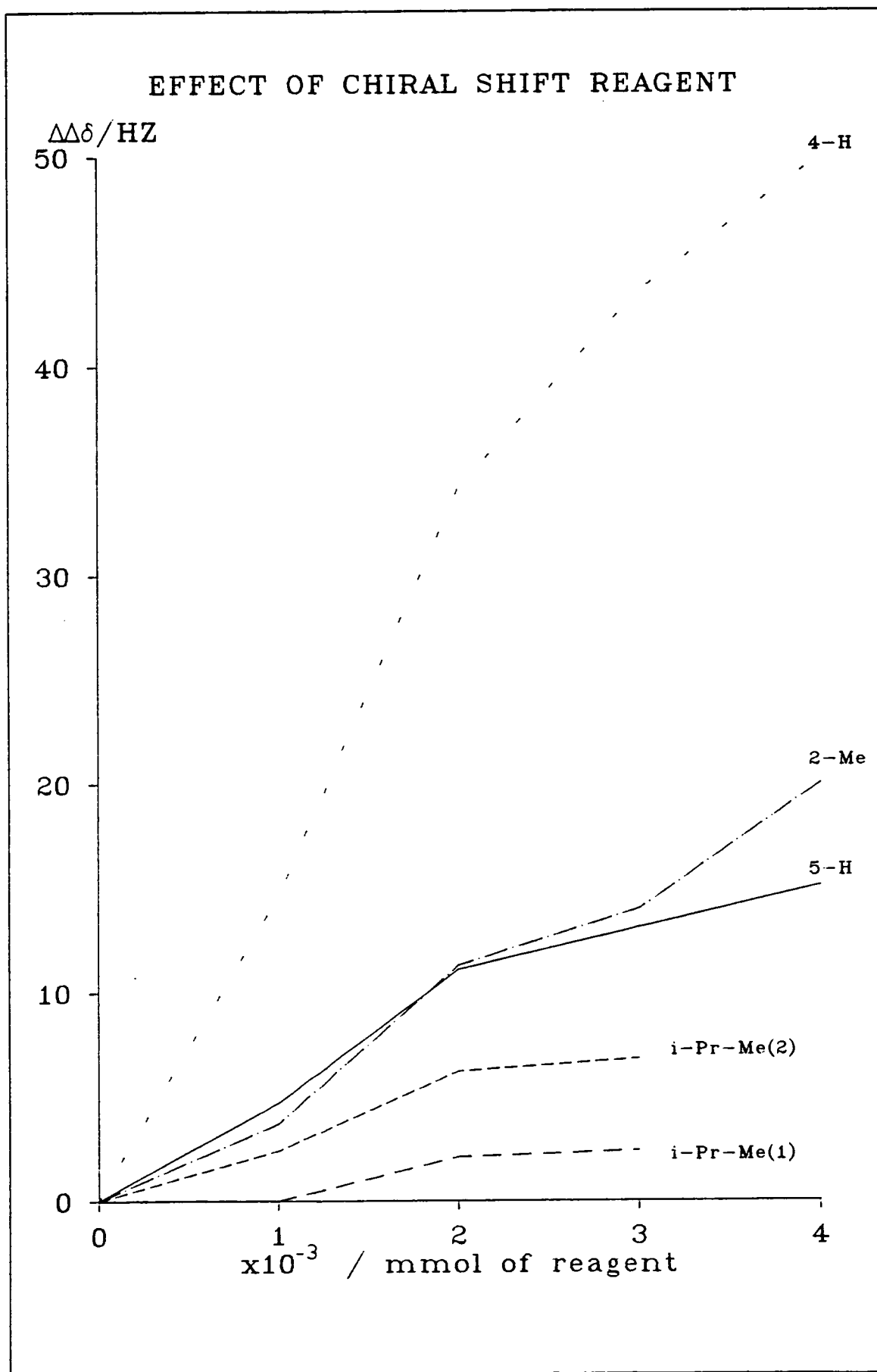
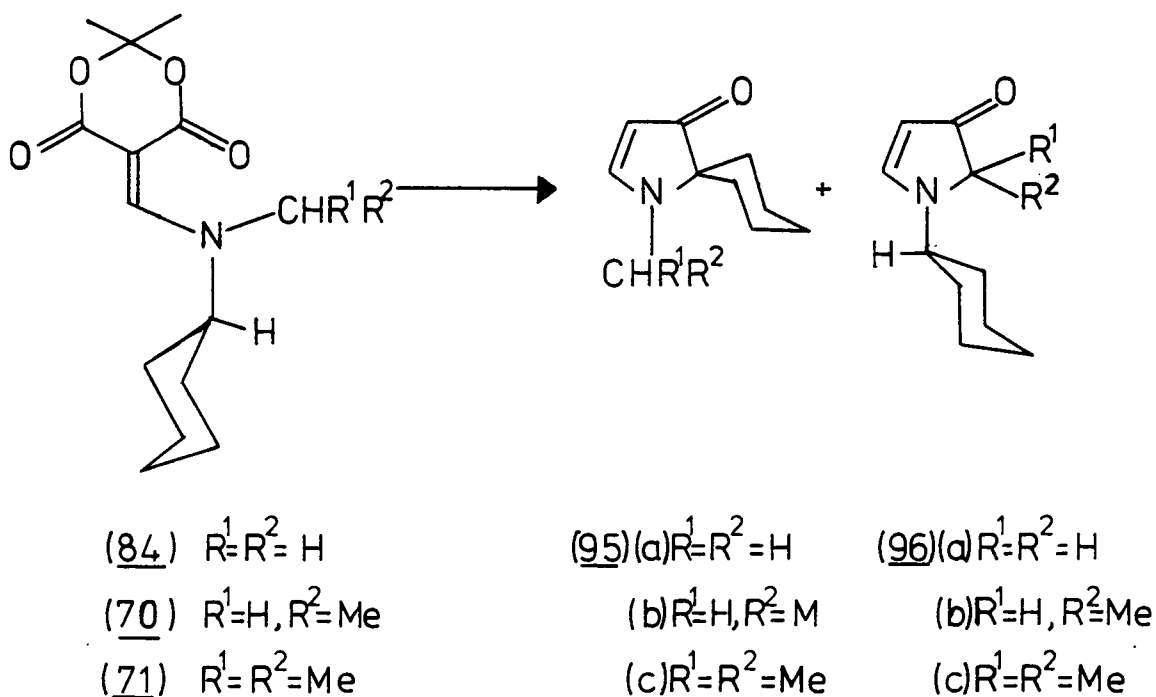


Figure 9

the nitrogen substituents were varied to give internal competition between primary and tertiary, secondary and tertiary, and tertiary and tertiary sites does not support this postulate. Radicals normally show selectivity for tertiary, over secondary, over primary, hydrogen abstraction because of the stability of the radical formed, but the ratio of (95):(96) (Scheme 44) does not show this trend.



Scheme 44

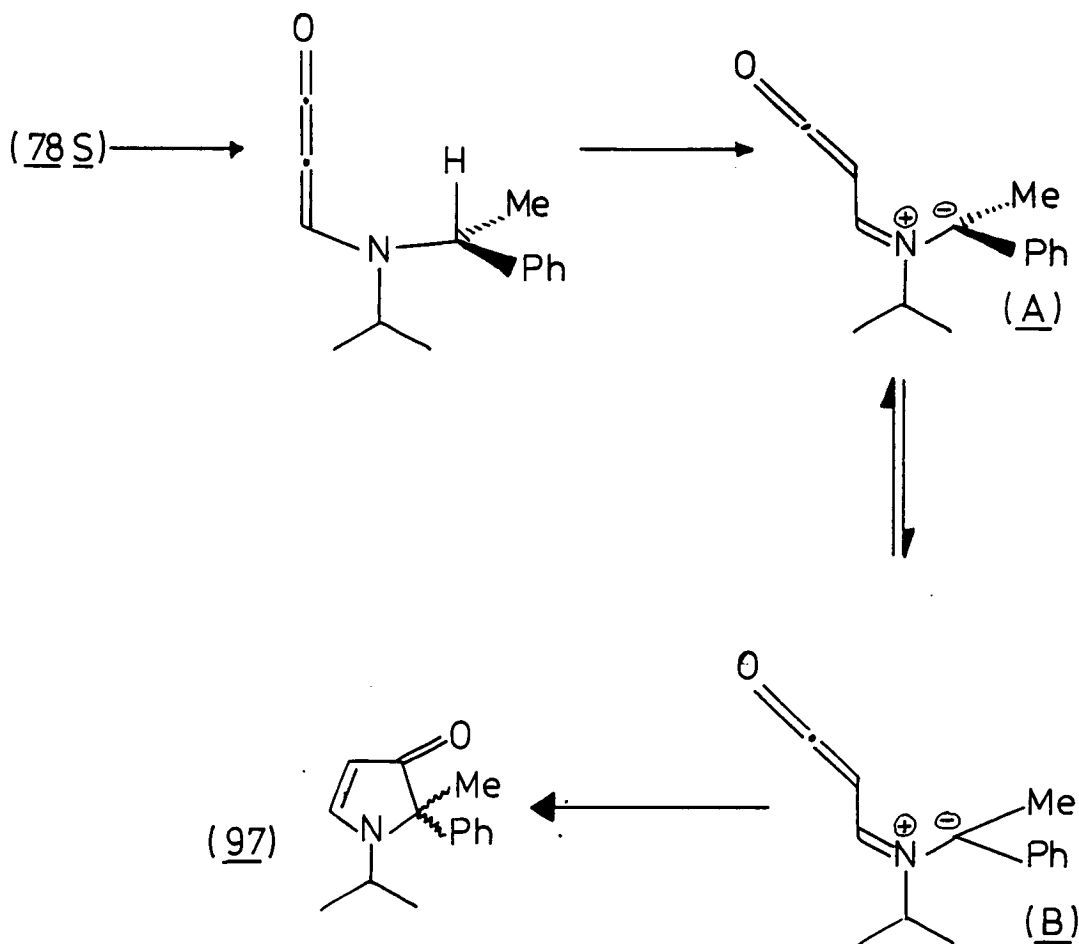
Pyrolyses of N-methyl, N-ethyl and N-isopropyl derivatives (84, 70 and 71) provide a measure of the selectivity of abstraction from these groups against an internal standard (the cyclohexyl group). The ratio of products can be determined from the proton n.m.r. spectra of the pyrolysates by measurement of the integral values of the doublets corresponding to the C5-proton which are clearly discernable. The isolation of (95) and (96) (c) allowed the assignment of the relevant signals and evidence of long-range coupling to the C2-proton in (96) (a) and (b) established the assignments in the pyrolysates from (84) and (70). The statistically corrected results, including consideration of an enol form where appropriate (see following chapter), are listed in Table 4.

Substrate	(<u>95</u>) : (<u>96</u>)	Selectivity
(<u>84</u>)	1 : 6.5	1 : 2.2 3 ^Y : 1 ^Y
(<u>70</u>)	1 : 1.35	1 : 0.7 3 ^Y : 2 ^Y
(<u>71</u>)	5 : 4	1 : 0.8 3 ^Y : 3 ^Y

Table 4

It seems reasonable to assume typical radical selectivity would be observed under the reaction conditions, given the evidence for carbene selectivity (1^Y : 2^Y : 3^Y; 1 : 4 : 9) shown by Crow and McNab for similar conditions.¹¹⁶

Hydrogen transfer via a 6π -electron transition state could lead to a dipolar intermediate and the results of pyrolysis of the chiral precursors support this structure. The initially formed dipole (A) (Scheme 45) has a spiral geometry and thus the ketene portion of the intermediate will undergo ring closure to the same face of the dipole (and therefore give retention of configuration) regardless of the direction of rotation about the newly formed single bond.



Scheme 45

However, the dipole will be most stable as its planar form (B) and rotation about the new single bond to give ring closure will now give both enantiomers, depending on the direction of the rotation. The observed, partial, retention of configuration suggests that rotation to give ring closure, in this acyclic case, occurs faster than the dipole can achieve planarity. In the cyclic examples (Scheme 42), the initially formed dipole has a much less pronounced spiral due to the geometric constraints of the ring, which favour a more planar structure. The completely planar dipole [analogous to (B)] is therefore more readily formed and this can occur before ring closure, to give complete racemisation.

These observations are reinforced by the results of pyrolyses of single diastereomers of the derivatives (69) and (87); these were shown to be single diastereomers by inspection of their ^1H and ^{13}C n.m.r. spectra which showed no evidence for a second product. The relative orientation of the two methyl groups in the piperidine example (87) was established as cis by preparation of the hydrochloride salt of the starting amine and comparison of its melting point with literature values. Pyrolysis of this cyclic precursor gave a 50:50 mixture of diastereomeric products which were isolated and the relative configurations of the two chiral centres were determined by n.O.e. experiments (Figure 10).

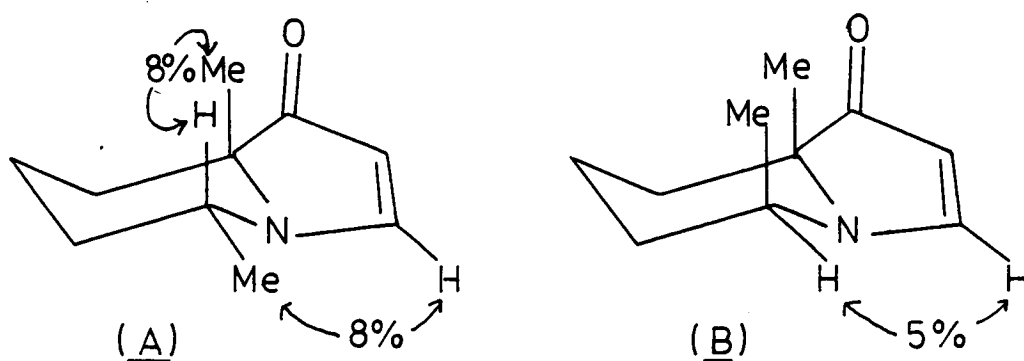


Figure 10

The second diastereomer eluted after chromatographic separation, was shown to be (A). Irradiation of the singlet methyl signal (corresponding to the bridgehead substituent) gives an n.O.e. effect of 8% on the aliphatic proton next to the nitrogen atom, while irradiation of the doublet methyl signal affects the olefinic proton next to the nitrogen atom by the same amount. In the other isomer (B) irradiation of both methyl signals (because they are too close to irradiate separately) produces no enhancement of the alpha protons and irradiation of the aliphatic H-resonance affects the olefinic signal by 5%. The small n.O.e. may be due to a low concentration of the diaxial configuration. These results indicate that (A) has been produced by inversion at the bridgehead centre to give the trans orientation of methyl groups while the cis configuration of the starting piperidine is maintained in (B). Pyrolysis of the acyclic precursor (69) did not result in a 50:50 mixture of products:

one stereochemistry is favoured in the mixture of products as observed for the chiral example (78). These results are therefore very similar to those from chiral precursors; it seems that the presence of a ring forces the intermediate to more readily adopt a form in which the stereochemistry at the site of hydrogen transfer will be lost.

Further indirect evidence for a dipolar intermediate will be discussed in a later chapter in connection with the related seven-membered ring formation.

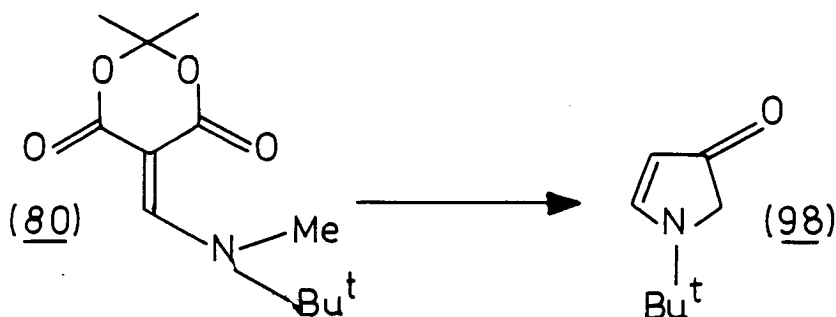
SCOPE OF 1,2-DIHYDRO-3H-PYRROL-3-ONE FORMATION

The experiments described in the preceeding section on the mechanism of pyrrolone formation have indicated that the hydrogen transfer can occur from methyl, methylene or methine sites and this has been shown to be quite general, leading to pyrrolones which are unsubstituted, monosubstituted or disubstituted in the 2-position. Unsymmetrical substrates can give rise to a mixture of products while single diastereomers (69 and 87) give two diastereomeric products, due to incomplete retention of stereochemistry at the site of hydrogen transfer as already discussed in connection with the mechanistic results. The 2,2-disubstituted pyrrolones produced as mixtures can be readily separated

by column chromatography. Pyrolysis of substrates which have a benzylic and alkyl hydrogen atom in competition for abstraction (75, 76, 78, 89 and 90), however, gives a single product resulting from preferential transfer of the benzylic hydrogen atom which implies that the intermediate formed is considerably stabilised by the aryl substituent, although this does not allow any distinction between diradical and dipolar structures. Unsymmetrical substrates in which one alpha position is blocked (phenyl or tert-butyl substitution) cleanly give one product and this has been found to give the best route to 2-unsubstituted pyrrolones; the N-phenyl and N-tert-butyl pyrrolones can be more easily handled than the N-methyl compound produced by pyrolysis of the symmetrical substrate (85).

Examples without substitution on nitrogen cannot be prepared directly since secondary aminomethylidene Meldrum's Acid derivatives undergo an alternative series of hydrogen shifts (see Introduction). Tert-butyl substitution appeared to provide a possible route to the unsubstituted compounds via elimination of an alkene as has been observed for N-tert-butyl-pyridazin-3-ones⁹⁶, but although pyrolysis of (80) to give (98) (Scheme 46) proceeds with the production of a considerable amount of black, insoluble material, there is no evidence for the presence of the parent pyrrolone, and increasing

the furnace temperature from 600°C to 700°C, which would be expected to increase the amount of alkene elimination, appears to have little effect on the yield.



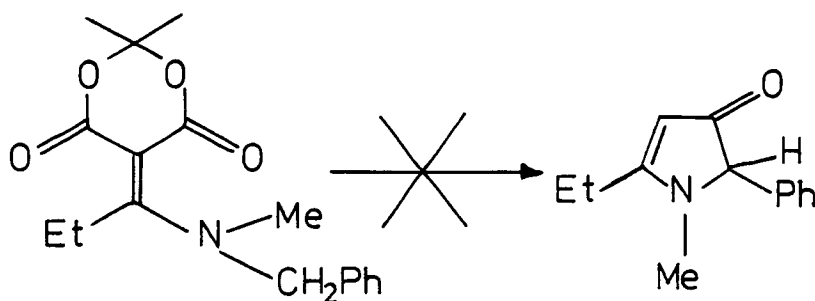
Scheme 46

Another possible route to the N-H compounds is by hydrogenation of N-benzyl examples but the selectivity of hydrogen abstraction from benzylic sites, which has already been mentioned, precludes the preparation of these compounds. This area has not been pursued but the vast amount of information on nitrogen protection which is available from, for example, peptide work, seems likely to provide a suitable entry to these compounds.

Of the derivatives shown in Tables 1 and 2, only the one derived from dihydrophenanthridine (88) did not lead to the expected pyrrolone. Instead, phenanthridine was isolated from the pyrolysate and it is thought that this is the result of radical cleavage of the C-N bond,

possibly due to the involatility of the substrate. A number of bi- and tri-cyclic pyrrolones have been formed, however, by pyrolysis of substrates derived from cyclic amines.¹¹⁷

Finally, the pyrolysis of the ethyl substituted derivative (99) does not lead to a 5-ethyl pyrrolone (Scheme 47). Instead, at least four products are



Scheme 47

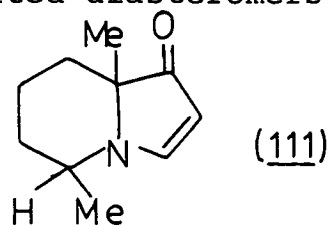
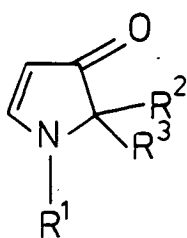
obtained which have not been isolated, but the lack of signals corresponding to ethyl groups in the ¹H n.m.r. spectrum of the crude pyrolysate suggests the reaction is diverted via a hydrogen transfer from the alkyl substituent. Surprisingly, a related example in which the alkyl substituent forms a ring with the amino substituent has been found to undergo H-transfer from the exocyclic N-substituent.^{103,104}

Table 5 shows the 1,2-dihydro-3H-pyrrol-3-ones which have been prepared and their isolated yields, which are not generally optimised.

Table 5

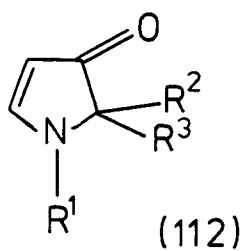
Substrate	Pyrrolone	R ¹	R ²	R ³	Yield
(89)	(91)		see Scheme	42	82%
(90)	(92)		see Scheme	42	86%
(71)	(95c)	Pr ⁱ	-(CH ₂) ₅ -		22%
(71)	(96c)	cyclohexyl	Me	Me	21.5%
(78)	(97)	Pr ⁱ	Me	Ph	55%
(80)	(98)	Bu ^t	H	H	62%
(65)	(100)	Pr ⁱ	Me	Me	64%
(66)	(101)	Et	H	Me	77%
(67)	(102)	cycloheptyl	-(CH ₂) ₆ -		64%
(68)	(103)	CH ₂ Ph	H	Ph	51%
(69)	(104)	CHMePh	Me	Ph	12.5% ^a
(72)	(105)	Ph	Me	Me	64%
(73)	(106)	Ph	H	Me	73%
(74)	(107)	Ph	H	Ph	56%
(75)	(108)	Me	H	Ph	80%
(82)	(109)	p-Bu ^t -Ph	H	H	35%
(83)	(110)	Ph	H	H	63%
(87)	(111)		see diagram		31% ^a

^a Combined yield of two isolated diastereomers



These results show that the formation of pyrrolones by pyrolysis of Meldrum's Acid derivatives provides a very general and efficient route to examples of these heterocycles without electron-withdrawing substituents, and without substituents blocking the potentially reactive 4- and 5-positions. A variety of 1-mono-, 1,2-di- and 1,2,2-tri-substituted compounds can be prepared which have been essentially unobtainable prior to this work; for example, the only previously synthesised, 1-monosubstituted examples were prepared by Momose et al¹¹ via a five step route (Scheme 4 and subsequent removal of the ester groups) and yields for the final step are not recorded. This new route provides a synthesis of 1,2-dihydro-3H-pyrrol-3-ones (3-hydroxypyrroles) in two simple, generally high-yielding, steps from amines and thus allows entry into the study of the chemistry of simple examples of these series. The monosubstituted examples (98) and (110) and the trisubstituted compound (100) were chosen as representative compounds and used to examine the properties of the system.

B. THE STRUCTURE, PHYSICAL AND SPECTROSCOPIC
PROPERTIES OF 1-SUBSTITUTED-1,2-DIHYDRO-3H
PYRROL-3-ONES



The pyrrolones which have been prepared can be divided into three categories on the basis of their substitution at the 2-position. Disubstituted examples (112; R^2, R^3 = alkyl, aryl) are stable crystalline compounds which can be readily distilled and recrystallised. The unsubstituted examples (112; $R^2 = R^3 = H$) can also be distilled (although prolonged heating leads to the formation of the corresponding N-methylamine) and can be stored indefinitely at -20°C . However, elemental analysis and mass spectroscopy show evidence for some facile oxidation of these compounds. The 2-mono-substituted examples (112; $R^2 = H, R^3$ = alkyl, aryl) are generally sticky oils which can only be distilled with care and which are very susceptible to oxidation (see later chapter on the reactivity of these systems), forming the 2-hydroxy compounds.

The mass spectra of the pyrrolones generally give the molecular ion as the base peak and a further intense peak due to cleavage of the nitrogen substituent, although the intensities are occasionally reversed.

The examples with at least one hydrogen atom at the 2-position can adopt either a keto or enol tautomeric form (Figure 1) and it was therefore of interest to investigate the nature of these compounds in the solid state and in solution.

STRUCTURE IN THE SOLID STATE

The infra-red spectrum of 1-phenyl-1,2-dihydro-3H-pyrrol-3-one (110) showed three absorptions at 1530, 1595 and 1640 cm^{-1} which is typical of enaminones¹¹⁸ and the keto tautomer for this example was confirmed by X-ray structural determination (Figure 11). The crystallographic numbering system is shown in Figure 11, and the structural parameters are listed in Tables 6 - 8. The pyrrolone (110) shows little deviation of structure from the 1-cyclohexyl-2,2-pentamethylene example¹⁰⁶ (113) which is fixed in the keto form, although the C(2)-C(3) bond length ($1.520\text{ \AA}$) is slightly shorter than in the substituted case (1.557). The bond angles around nitrogen and the carbonyl carbon C(3) indicate planarity in the pyrrole ring which allows delocalisation of the π -electrons of the enaminone system. The shortening

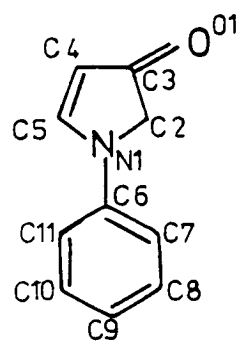
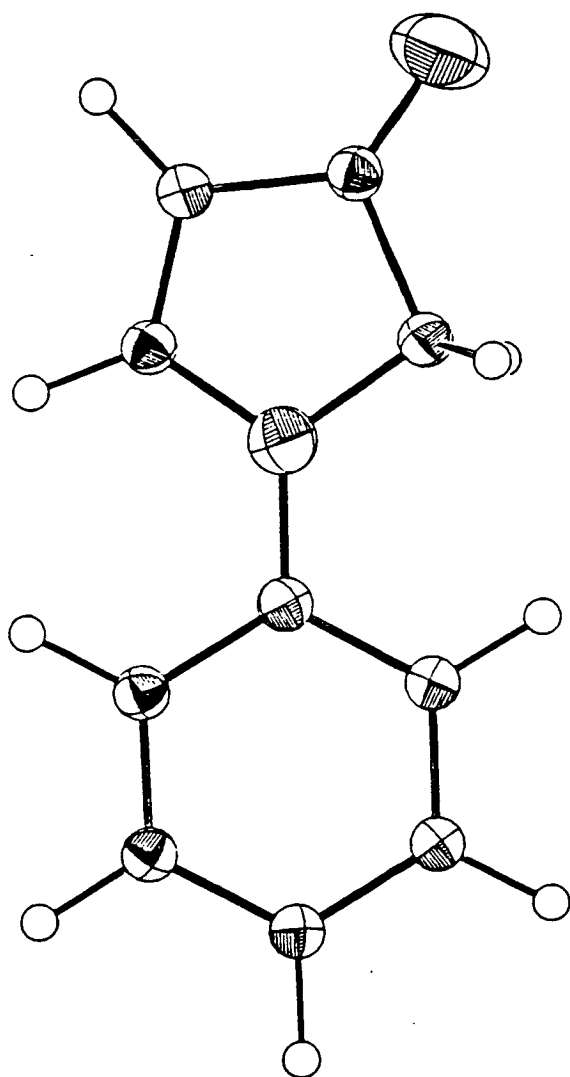


Figure 11

Table 6 Bond Lengths(A) with standard deviations

N(1) - C(2)	1.4582(20)	C(6) - C(7)	1.3967(22)
N(1) - C(5)	1.3605(21)	C(6) - C(11)	1.3941(22)
N(1) - C(6)	1.4009(20)	C(7) - C(8)	1.3822(24)
C(2) - C(3)	1.5202(23)	C(8) - C(9)	1.383(3)
C(3) - O(1)	1.2354(22)	C(9) - C(10)	1.378(3)
C(3) - C(4)	1.4233(24)	C(10) - C(11)	1.383(3)
C(4) - C(5)	1.3562(24)		

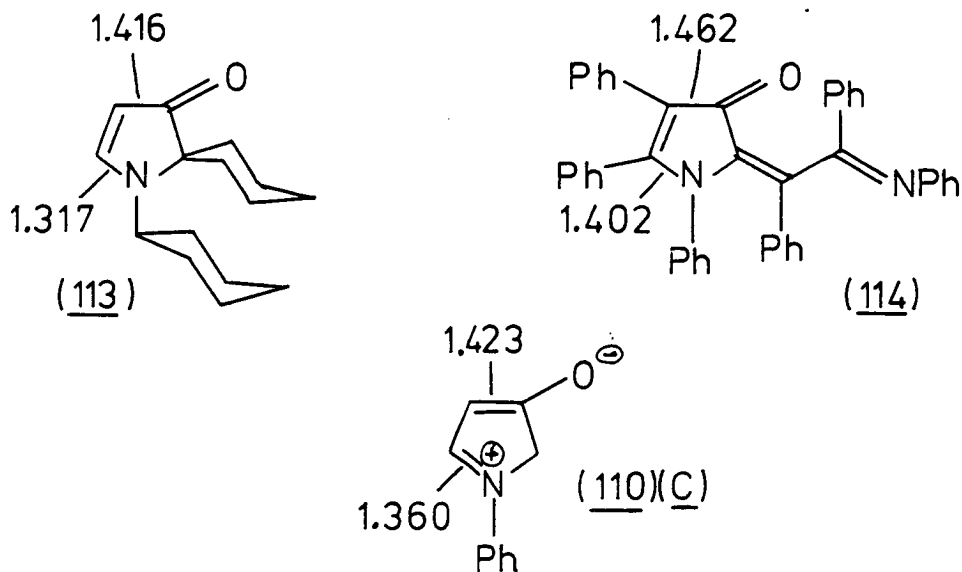
Table 7 Angles(degrees) with standard deviations

C(2) - N(1) - C(5)	108.70(13)	N(1) - C(6) - C(7)	121.57(13)
C(2) - N(1) - C(6)	124.39(13)	N(1) - C(6) - C(11)	119.60(14)
C(5) - N(1) - C(6)	126.77(13)	C(7) - C(6) - C(11)	118.83(14)
N(1) - C(2) - C(3)	103.42(13)	C(6) - C(7) - C(8)	119.76(15)
C(2) - C(3) - O(1)	123.17(15)	C(7) - C(8) - C(9)	121.32(16)
C(2) - C(3) - C(4)	106.50(14)	C(8) - C(9) - C(10)	118.85(17)
O(1) - C(3) - C(4)	130.33(17)	C(9) - C(10) - C(11)	120.88(17)
C(3) - C(4) - C(5)	108.46(15)	C(6) - C(11) - C(10)	120.36(16)
N(1) - C(5) - C(4)	112.89(15)		

Table 8 Torsion angles(degrees) with standard deviations

C(5) - N(1) - C(2) - C(3)	1.70(16)	O(1) - C(3) - C(4) - C(5)	-179.39(18)
C(6) - N(1) - C(2) - C(3)	-174.20(13)	C(3) - C(4) - C(5) - N(1)	0.12(20)
C(2) - N(1) - C(5) - C(4)	-1.25(19)	N(1) - C(6) - C(7) - C(8)	129.19(15)
C(6) - N(1) - C(5) - C(4)	174.52(15)	C(11) - C(6) - C(7) - C(8)	-0.24(24)
C(2) - N(1) - C(6) - C(7)	167.67(14)	N(1) - C(6) - C(11) - C(10)	-179.09(15)
C(2) - N(1) - C(6) - C(11)	-12.90(22)	C(7) - C(6) - C(11) - C(10)	0.35(24)
C(5) - N(1) - C(6) - C(7)	-7.48(24)	C(6) - C(7) - C(8) - C(9)	0.0(3)
C(5) - N(1) - C(6) - C(11)	171.95(15)	C(7) - C(8) - C(9) - C(10)	0.2(3)
N(1) - C(2) - C(3) - O(1)	178.71(16)	C(8) - C(9) - C(10) - C(11)	0.0(3)
N(1) - C(2) - C(3) - C(4)	-1.58(17)	C(9) - C(10) - C(11) - C(6)	-0.2(3)
C(2) - C(3) - C(4) - C(5)	0.93(19)		

of the formal single bonds N(1)-C(5) and C(3)-C(4) relative to those in the example (114)¹¹⁹ in which exocyclic delocalisation can take place, supports a significant contribution to the structure from the dipolar canonical form (110) (c).



The phenyl ring lies almost coplanar with the heterocyclic system which allows delocalisation of the nitrogen lone pair into the phenyl group and this is clearly seen in the considerable shortening of bond between the nitrogen atom and the substituent [1.401 in (110) compared with 1.458 in (113)]. There is also a slight lengthening of the N(1)-C(5) bond in the N-phenyl example where the contribution from the nitrogen lone pair to the bonding in the pyrrole portion of the system has been decreased.

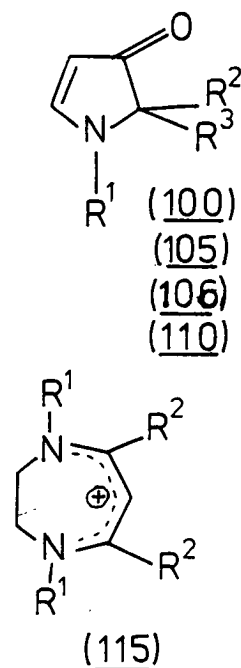
TAUTOMERISM IN SOLUTION

U.V. spectroscopy has been used in the past to determine the tautomeric form¹⁹ in solution but additional substitution complicates analysis.

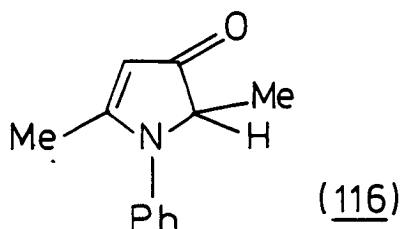
Enaminones fixed in the cis-s-trans geometry of the pyrrolones typically absorb in the 300-320 nm range⁴⁹ and 2,2-dimethyl-1-isopropyl-1,2-dihydro-3H-pyrrol-3-one (100) shows an absorption maximum at 325 nm in chloroform solution. Phenyl substitution on the nitrogen appears to have little effect on the conjugated system in the 2,2-dimethyl-1-phenyl substituted example (105) ($\lambda_{\max}$, 330 nm) but removal of substituents at the 2-position gives a shift of 20 nm to longer wavelength ($\lambda_{\max}$ of (106) is 350 nm and of (110) is 353 nm). A similar effect has been observed in dihydrodiazepine chemistry where replacement of N-alkyl by N-phenyl substitution has little effect when adjacent methyl groups are present, but results in a shift of around 20 nm in their absence (Table 9). This can be explained by the steric effect of the methyl groups forcing the phenyl ring out of the plane of the delocalised system and therefore limiting its participation in conjugation. One methyl group at the 2-position appears to be insufficient to promote this effect [cf. (106)] although Davoll¹⁹ found the 2,5-dimethyl pyrrole (116) has $\lambda_{\max}$ 324 nm; however the sp^2

Table 9 λ_{max} for some 1,2-dihydro-3H-pyrrol-3-ones and dihydrodiazepines

	R ¹	R ²	R ³	λ_{max}
(100)	Pr ⁱ	Me	Me	325
(105)	Ph	Me	Me	330
(106)	Ph	Me	H	350
(110)	Ph	H	H	353
(115a) ¹²⁰	Me	Me	-	335
(115b) ¹²⁰	Ph	Me	-	347
(115c) ¹²⁰	Me	H	-	340
(115d) ¹²⁰	Ph	H	-	380



hybridised 5-position will have a considerable steric effect (see following n.m.r. data). Other pyrrolones with carboxylic acid or ester substitution¹⁹ give absorption maxima at 290-310 nm but it is unclear whether these slightly lower values are a result of the additional substitution or a contribution from the hydroxy form which absorbs at around 240 nm. These spectra were recorded in methanol solution which is known to promote the hydroxy tautomer.¹¹



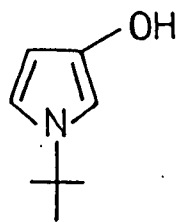
U.V. spectroscopy thus does not give a straightforward picture of the tautomerism, but ^1H n.m.r. spectroscopy provides an easily interpreted method of analysis for the tautomerism in solution as both forms give rise to identifiable signals when either ^1H or ^{13}C nuclei are observed. The nature of the resonances corresponding to each form may be readily predicted and may be confirmed by analogy with examples fixed in these forms. Thus, 2,2-disubstituted pyrrolones give rise to widely separated doublets corresponding to the 4- and 5-protons and these are observed in the keto form of examples capable of tautomerism. In 3-alkoxypyrroles the 4- and 5-protons have resonances with much closer chemical shifts and smaller coupling constants, as anticipated for an aromatic structure, and these characteristics are observed in enol tautomer.

The effect of solvent on keto-enol equilibria has been observed previously (e.g. in β -diketone systems)¹²¹ and arises from either preferential H -bonding between the solvent and one tautomer, or changes in the dielectric constant which leads to

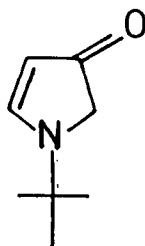
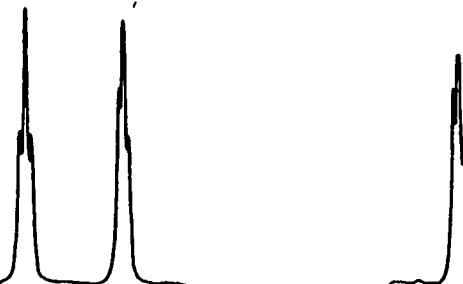
greater amounts of the more polar tautomer of a system in more polar solvents.

The equilibrium illustrated in Figure 12 has been found to be remarkably solvent dependent. This is best illustrated by the ^1H n.m.r. spectrum of 1-tert-butyl-1,2-dihydro-3H-pyrrol-3-one in $[\text{}^2\text{H}]$ chloroform and $[\text{}^2\text{H}_6]$ dimethylsulphoxide solution (Figure 12) which shows almost complete reversal of the equilibrium to give the enol form in the more polar solvent. Theoretical studies⁴⁴ have predicted a much greater dipole moment for the keto tautomer in this equilibrium and consideration of experimentally found dipole moments for enamines⁴⁹ ($>6\text{D}$) and pyrrole^{2a} (1.8) suggests that the keto form is indeed more polar. The results depicted above therefore suggest that hydrogen bonding is important in this system (a factor not apparently considered in a theoretical study of the -NH compounds which predicts that the keto form will be more stable in polar solvents).⁴⁴ However, the absence of nitrogen substitution may be important. This contrast with other keto-enol equilibria which follow the predictions based on dipole moments, is probably a result of the inability of the pyrrolone system to undergo internal H-bonding. The ratio of the tautomers in solution, which is easily determined from the ^1H n.m.r. spectra, can be used to calculate

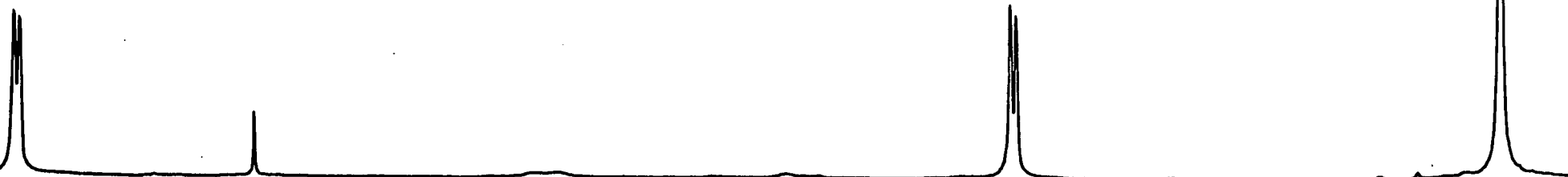
Figure 12



DMSO



CDCl₃



the difference in free energy between them.¹²² The results for the system illustrated in Figure 12 in a variety of solvents are shown in Table 10. A number of other systems with different substitution patterns were studied in chloroform and dimethylsulphoxide solutions and these results are also shown in the table.

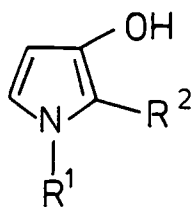
The importance of H-bonding on the tautomerism is confirmed by the results found for the N-tert-butyl compound (98) in tetrahydrofuran, dimethylformamide and methanol. The former two solvents can only participate in H-bonding with the enol form and it is therefore considerably stabilised; in contrast, methanol can form H-bonds to either form and polarity becomes important.

The most striking influence of substituents is the presence of phenyl groups in the 2-position. These greatly increase the proportion of the enol form in both solvents studied and this is doubtless a result of the extended conjugation between the phenyl group and the pyrrole ring, which the enol form can afford. In the diphenyl substituted example (107), the somewhat lower percentage of enol than might be predicted can be explained by steric interactions destabilising the completely planar structure, and the conjugation to the N-substituent remaining intact at the expense of the hetero-aromatic tautomer. The considerable amount of the keto tautomer of (106) in both solvents supports the

Table 10 The relative free energy of 3-hydroxypyrroles
and 1,2-dihydro-3H-pyrrol-3-ones

Compound	R ¹	R ²	solvent (deuteriated)	keto:enol	$\Delta G^{\circ}/\text{kJ mol}^{-1}$
<u>98</u>	Bu ^t	H	CHCl ₃	90 : 10	-18.36
			MeOH	74 : 26	- 8.7
			THF	17 : 83	+13.2
			DMF	16 : 84	+13.8
			DMSO	5 : 95	+24.5
<u>110</u>	Ph	H	CHCl ₃	>99 : 1	-38.2
			DMSO	5 : 95	+24.5
<u>103</u>	CH ₂ Ph	Ph	CHCl ₃	45 : 55	+ 1.7
			DMSO	<1 : 99	+38.2
<u>106</u>	Ph	Me	CHCl ₃	>99 : 1	-38.2
			DMSO	30 : 70	+ 7.0
<u>107</u>	Ph	Ph	CHCl ₃	80 : 20	-11.5
			DMSO	<1 : 99	+38.2
<u>108</u>	Me	Ph	CHCl ₃	30 : 70	+ 7.0
			DMSO	<1 : 99	+38.2

$$\Delta G = 8.314 \ln \frac{[\text{keto}]}{[\text{enol}]}$$



conclusions on steric effects made from the U.V. spectroscopic data of these systems. In the keto tautomer of (106) the sp^3 hybridisation of the 2-position allows the N-phenyl group to lie in the plane of the pyrrole ring and thus give further conjugation which is observed in the U.V. spectrum. This greatly enhances the stability of the keto with respect to the enol form, where the planarity of the methyl group which results from sp^2 hybridisation forces the N-phenyl group into a different orientation. The twisted nature of the N-phenyl group in this form is confirmed by the chemical shift of the p-carbon atom in the phenyl ring which is deshielded (by 1.7 p.p.m.) with respect to that of the 2-unsubstituted example, indicating less influence from the nitrogen atom's lone pair of electrons.

ASSIGNMENT OF THE PROTON AND CARBON-13 RESONANCES OF 1,2-DIHYDRO-3H-PYRROL-3-ONES AND 3-HYDROXYPYRROLES

The widely spaced doublets characteristic of the pyrrol-3-one proton spectra have already been mentioned and thus the 4H- and 5H-resonances are readily assigned for this tautomer. The aliphatic proton(s) of the 2-position can also be easily identified simply by inspection. The 2-unsubstituted-3-hydroxypyrroles give rise to three doublet of doublet signals due to coupling from each ring proton to the other two. In some cases

these are not fully resolved and appear as triplets because the values of the couplings are very close. Observation of the ^1H n.m.r. spectrum of the 1-tert-butyl-3-hydroxypyrrole in $[\text{}^2\text{H}_4]\text{methanol}$ solution (where it exists predominantly as the keto form) shows that rapid exchange of the 2-H signal occurs and thus the 2-deuteriated compound could be prepared simply by removal of the solvent. Solution of this material in $[\text{}^2\text{H}]\text{chloroform}$ or $[\text{}^2\text{H}_6]\text{dimethylsulphoxide}$ allowed assignment of the 2-resonances in the ^1H and ^{13}C n.m.r. spectra for the pyrrol-3-one and 3-hydroxypyrrole forms, respectively. Thus, the expected aliphatic signal was significantly decreased in the ^{13}C n.m.r. spectrum in $[\text{}^2\text{H}]\text{chloroform}$, while the central olefinic resonances in both the ^1H and ^{13}C n.m.r. spectra in $[\text{}^2\text{H}_6]\text{dimethylsulphoxide}$ were assigned to the 2-position of the 3-hydroxypyrrole form. On some occasions, exchange of the 4-position also occurred in $[\text{}^2\text{H}_4]\text{methanol}$ (this was apparently dependent on adventitious traces of impurity, possibly acid) and the 2,2,4- $[\text{}^2\text{H}_3]$ -trideuteriated pyrrol-3-one could be isolated in the same manner as previously. This allowed assignment of the more shielded olefinic signal in the ^{13}C n.m.r. spectrum of the pyrrolone to the 4-position and the most shielded signals in both the ^1H and ^{13}C n.m.r. spectrum of the hydroxypyrroles to the same position. The $\underline{\text{C}}3$ -resonance for both forms could be easily assigned by inspection in most examples,

but in the 1-phenyl-3-hydroxypyrroles the quaternary aromatic resonance occurs in the same region as the C3-signal. However, the characteristic triplet observed for the aromatic carbon atom attached to nitrogen in the fully coupled spectrum allowed authoritative assignment in all cases. Proton-proton and carbon-proton couplings were assigned by consideration of the deuteriated and substituted examples.

CHARACTERISTICS OF THE N.M.R. SPECTRA OF 3-HYDROXYPYRROLES

In heteroaromatics the proton chemical shifts are generally related to the electron density at the adjacent carbon atom which is dependent on the mesomeric and inductive effects of the electronegative element.¹²² Thus, N-substituted pyrroles give rise to two resonances, the α -protons more deshielded than those at the β -position. This trend is also observed in the 3-hydroxy series where the chemical shifts of the ring protons are assigned such that δ_H 5-H > 2-H > 4-H. The α -position adjacent to the hydroxy substitution is shielded with respect to the 5-position, as would be expected by consideration of the mesomeric form (B) illustrated in Figure 13. The proton chemical shifts and coupling constants of various

3-hydroxypyrroles are listed in Table 11.[†]

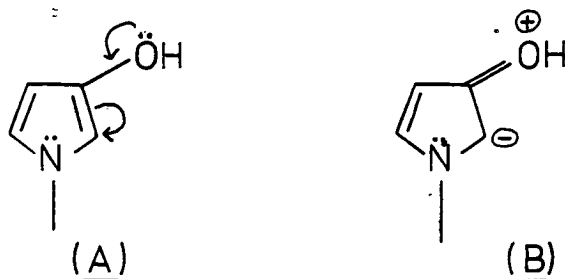
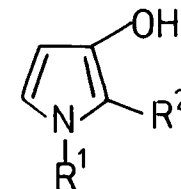


Figure 13

N-Alkyl examples give more shielded signals than N-phenyl compounds with the same substitution of the 2-position which is the same effect as seen in other N-substituted pyrroles (e.g. 1-tert-butylpyrrole gives signals at δ_H 5.98 and 6.65 compared to 1-phenylpyrrole which gives signals at δ_H 6.19 and 6.95). This is because the heterocyclic ring is in competition with the phenyl substituent for the effect of delocalisation of the nitrogen atom's lone pair of electrons. The effect is also observed for the C4-atom in the ^{13}C n.m.r. spectra (see later).

[†] Throughout this section, chemical shifts are quoted in p.p.m. from tetramethylsilane and coupling constants are quoted in Hertz. Proton-proton couplings are designated $J_{A,B}$ where A and B are the carbon atoms to which the protons are attached. Carbon-proton couplings are tabulated for a particular carbon atom with the proton involved again defined by a subscript; thus $J_H(A)$ indicates coupling to the proton attached to carbon atom (A).

Table 11 Proton chemical shifts and coupling constants in
3-hydroxypyrroles



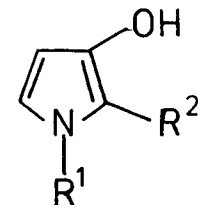
3-hydroxypyrrole	R ¹	R ²	C2-H	C4-H	C5-H	³ J _{4,5} /Hz	⁴ J _{2,4} /Hz	⁴ J _{2,5} /Hz
(<u>110B</u>)	Ph	H	6.74	5.85	7.06	3.1	1.9	2.6
(<u>98B</u>)	Bu ^t	H	6.26	5.50	6.49	2.9	2.2	2.8
(<u>106B</u>)	Ph	Me	-	5.78	6.56	3.0		
(<u>107B</u>)	Ph	Ph	-	5.97	6.78	3.1		
(<u>108B</u>)	Me	Ph	-	5.72	6.51	2.8		
(<u>103B</u>)	CH ₂ Ph	Ph	-	5.94	6.48	3.0		
(<u>101B</u>)	Et	Me	-	5.52	6.30	3.0		

The proton-proton couplings across the C4-C5 bond are in the range 2.8-3.2 Hz which is in the typical range for pyrroles, but the ^4J couplings, 2-H to 4-H and 5-H are, respectively, 1.9-2.1 Hz and 2.6-2.8 Hz which are somewhat larger than the values in pyrroles generally (1.35-1.8 Hz and 1.95-2.3 Hz, respectively)^{2a}.

Little information is available on the ^{13}C n.m.r. spectra of substituted pyrroles, although one study has been carried out in relation to work on prodigiosin antibiotics.¹²³ This shows the effect of alkyl and carboxylate groups on the ring carbon resonances and includes one example with a 3-methoxy group. The additional substitution of this example, however, makes it little use in defining the effect of the oxygen substituent. The ^{13}C n.m.r. chemical shifts and proton-carbon coupling constants for the 3-hydroxypyrroles observed are shown in Tables 12 and 13.

The effect of the hydroxy substitution on N-substituted pyrroles is shown in Table 14 for the 2-unsubstituted compounds and consistent shifts in the same direction as those found in benzene occur, although their magnitude is greater. Thus, the carbon atom directly attached to the substituent is deshielded by 36 p.p.m. relative to its 3-unsubstituted analogue, due to the electronegative oxygen atom which compares

Table 12 ^{13}C Chemical shifts in 3-hydroxypyrroles



3-Hydroxypyrrole	R^1	R^2	C2	C3	C4	C5	R^2
(110B)	Ph	H	101.5	146.1	102.2	116.0	-
(98B)	Bu^t	H	101.2	143.5	97.6	114.2	-
(106B)	Ph	Me	110.5	141.5	100.5	116.4	9.25
(107B)	Ph	Ph	115.0	144.0	101.2	121.5	
(108B)	Me	Ph	116.5	141.6	98.1	120.3	
(101B)	Et	Me	109.9	139.4	97.7	114.2	7.53

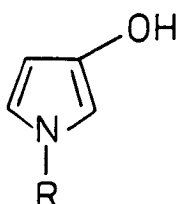
Table 13 Carbon-proton coupling constants in 3-hydroxypyrroles

3-Hydroxy- pyrrole	R ¹	R ²	C2		C3			C4		C5		
			¹ J _{H(2)}	³ J _{H(4)} = ³ J _{H(5)}	² J _{H(2)}	³ J _{H(5)}	³ J _{H(Me)}	¹ J _{H(4)}	² J _{H(5)} = ³ J _{H(2)}	¹ J _{H(5)}	² J _{H(4)} = ³ J _{H(2)}	³ J _{H(Me)}
(110b)	Ph	H	185.8	4.1	3.8	9.8	-	170.9	7.0	186.5	6.6	-
(98b)	Bu ^t	H	182.7	4.3	4.3	9.0	-	167.9	6.8	182.5	6.9	-
(106b)	Ph	Me	-	-	-	8.0	4.0	170.8	6.5	186.2	7.3	-
(107b)	Ph	Ph	-	-	-	9.4	-	171.5	7.5	188.0	7.5	-
(108b)	Me	Ph	-	-	-	7.8	-	170.0	7.8	184.3	6.9	3.5
(101b)	Et	Me	-	-	-	9.3	4.0	161.1	7.5	182.7	7.7	4.1

with the shift due to hydroxy substitution in benzene of 26.9 p.p.m. The two 'ortho' positions are shielded by around 15 and 9 p.p.m. for C2 and C4, respectively, while a shift of 12.7 p.p.m. is found in benzene,

Table 14 Hydroxy substituent effect in 3-hydroxy-pyrroles

3-hydroxypyrrole	R	C ₂	C ₃	C ₄	C ₅
(110B)	Ph	-16.8	+36.0	-8.6	-3.0
(98B)	Bu ^t	-15.5	+35.5	-9.5	-2.5



and this weighted effect can be explained by the resonance structures illustrated in Figure 14. In order to create a mesomeric increase of negative charge on

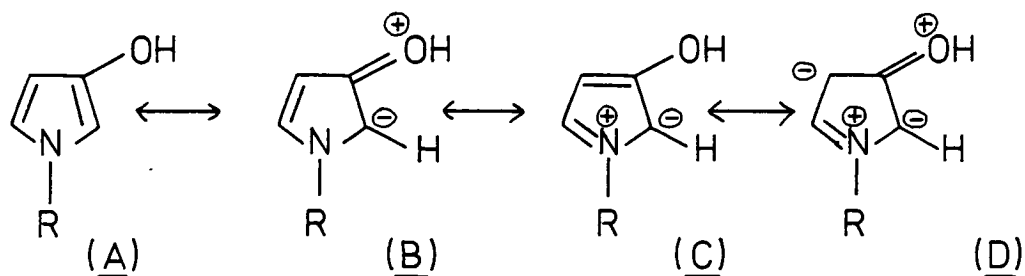


Figure 14

the C4-position (cf. Figure 13), the tetrapolar structure (D) must be invoked and the magnitude of the effect at this position is therefore considerably less than at C2, where the mesomeric effect can occur through (B). The shift of the C5-atom is minimal, as would be predicted for meta positions of any substituted benzenes, although it is surprising that shielding of this position is observed; only the electronegative nature of the substituent is expected to influence the chemical shift since no mesomeric effect is possible at this position, and benzene exhibits a shift of +1.4 p.p.m. compared with around -3 p.p.m. here.

Alkyl or aryl substitution of the 2-position induces an increase in the chemical shift of the 2-carbon atom of 8 to 13 p.p.m. with respect to the corresponding 2-unsubstituted-3-hydroxypyrroles, while the 3-position is shielded by up to 4.6 p.p.m. These shifts are in the same direction as expected for benzene derivatives but are again somewhat larger. The shifts of the 4- and 5-resonances, from the corresponding 2-unsubstituted examples, are minimal (<1 p.p.m. generally). The substituent effect of the hydroxy function on the ring carbon atoms for 2-unsubstituted examples does not agree fully with the values shown in Table 14, but this is almost certainly due to changes in through space

effects which occur as a result of steric interactions in the more crowded molecule; for example, as already discussed in relation to the U.V. spectra of these compounds, 2-methyl substitution tends to change the orientation of the N-phenyl group and will therefore alter the areas influenced by its ring current effects.

Substituent methyl groups give the highly shielded resonances typical of pyrroles (δ_C 9.25 and 7.53 for the 1-phenyl- and 1-ethyl-2-methyl-3-hydroxypyrroles respectively). Pyrrole methyl substituents generally give values of δ_C 13-16 compared with δ 21-28 for pyridines and benzenes, thus it appears that the increased electron density due to the hydroxy substitution, is contributing to the observed chemical shift in these examples.

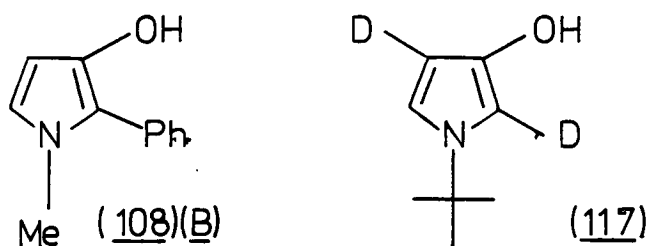
One bond carbon-proton couplings for the C4- and C5-positions are fairly constant at 170 ± 2 Hz and 185 ± 3 Hz, respectively. In fact, there is even less spread if the N-phenyl and N-alkyl examples are considered separately (Table 13). In the 2-unsubstituted cases the additional one bond coupling is of the same magnitude as the coupling observed at the C5-atom. These well defined one bond coupling constants allowed the assignment of the resonances corresponding to the C2- and C4-atoms of 1-phenyl-3-hydroxypyrrole (110B); the coupling constant of the signal at δ_C 101.54 (185.8 Hz)

compared with that of the signal at δ_C 102.18 (170.9 Hz) indicated that in this example the C2-atom was, in contrast to other examples, the more shielded. The one bond coupling constants in the phenyl substituted examples are all around 3 Hz larger than those in the other cases.

Long-range couplings were assigned by substitution of the 1- and 2-positions with phenyl or tert-butyl groups which are incapable of exhibiting long-range couplings to the ring resonances, and by deuteration of the 2- and 4-positions as described earlier.

The 2-unsubstituted compounds give triplets of doublets corresponding to the C2-, C4- and C5-atoms. Thus, each of these carbon atoms couples to the hydrogen atoms attached to the other two with approximately the same coupling constant. Both the ^2J and ^3J couplings to the C4- and C5-positions are thus between 6.5 and 7.0 Hz which are reasonably close to the corresponding ^3J couplings in pyrrole itself (7.43 for C4-2(H) and 6.63 Hz for C5-2(H) but rather less than the related ^2J couplings which are 8.69 and 8.34 Hz. The ^3J couplings observed to the 2-position are 4.1 and 4.4 Hz for the N-phenyl- and N-tert-butyl-3-hydroxy-pyrroles, respectively, which are considerably less than those observed in the parent compound (7.45 Hz to 4-H and 6.63 Hz to 5-H). 2-Substituted-3-hydroxypyrroles give unresolved multiplets for the

signals corresponding to the C2-atom, due to coupling to the substituent, but show well resolved ^2J coupling for the C4- and C5-atoms. The C5-resonances are sometimes further split by coupling to the N-substituent and this is found to be 3.5 Hz in 1-methyl-2-phenyl-3-hydroxypyrrole (108B).



The long-range coupling to the carbon atom attached to the hydroxy function is more complex but has been resolved with the aid of the deuteriated examples. A doublet of doublets pattern is observed for the 2-unsubstituted cases with couplings of around 4 and 9 Hz. The 2,4- $^{2}H_2$ -1-tert-butyl-3-hydroxypyrrole (117) gives rise to a doublet of 9.6 Hz and the larger value is therefore assigned to the three bond coupling to 5-H. As the 2-substituted compounds do not give rise to the smaller coupling it is assumed this is the two bond coupling to 2-H. The long-range coupling pattern of 1-tert-butyl-3-hydroxypyrrole is depicted in Figure 15.

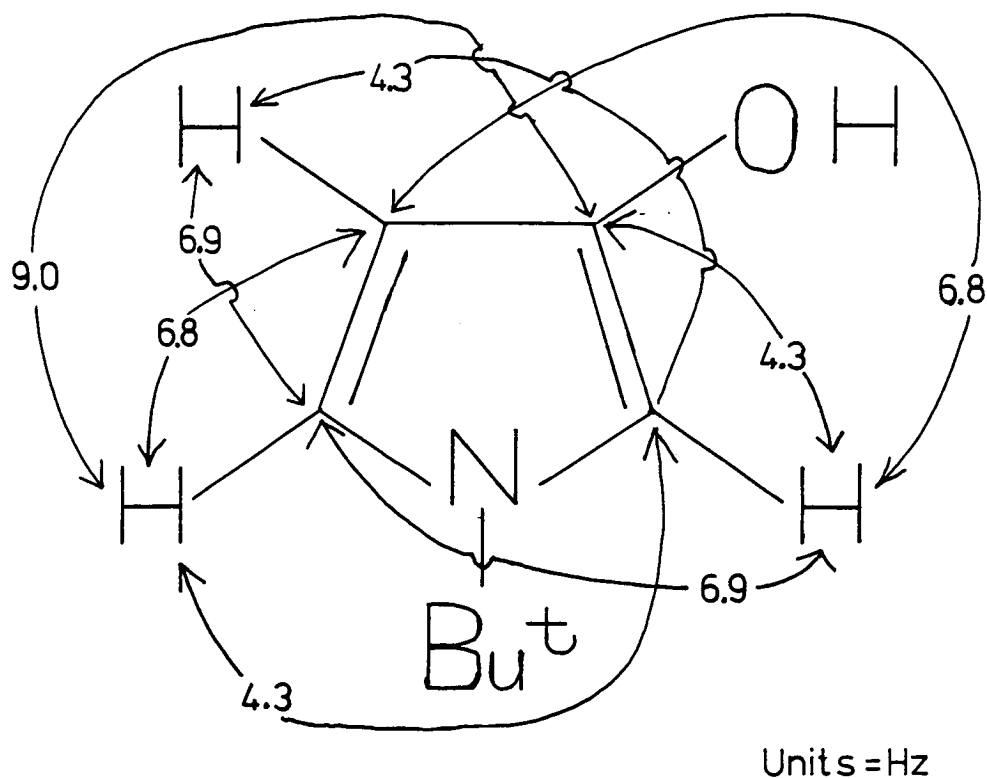


Figure 15

In one example, 1-methyl-2-phenyl-3-hydroxypyrrole (108B) a coupling of less than 2 Hz is also observed which must be due to a ^2J coupling to 4-H which is not resolved in more complex cases; the small value is to be expected across the C3-C4-bond which has less double bond character than a typical aromatic bond. The 2-methyl compounds further split the C3-atom signal into quartets with a coupling of around 4 Hz.

CHARACTERISTICS OF THE N.M.R. SPECTRA OF
1,2-DIHYDRO-3H-PYRROL-3-ONES

The electronic structure of 1,2-dihydro-3H-pyrrol-3-ones is dominated by their enaminone backbone and this is clearly observed in their n.m.r. spectra as has already been mentioned. A number of 2,2-disubstituted examples are considered here, along with the parameters obtained for the keto tautomer of compounds which have a proton at the 2-position and are therefore capable of enolisation.

The spectra of open-chain enaminones are solvent dependent because of the possible existence of different cis and trans configurations,¹²⁴ which are influenced, in N-monosubstituted cases, by the possibility of internal hydrogen bonding (Figure 16). The pyrrol-3-ones are fixed in the Z-s-E configuration, so limited

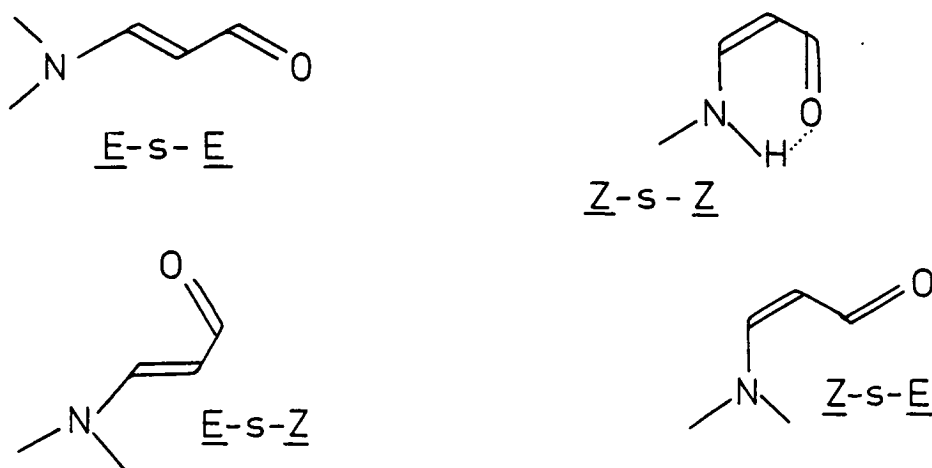
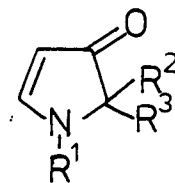


Figure 16

comparisons are possible with available examples which exist in the E-s-E form, unless there is an N-H which favours the all cis (Z-s-Z) form in non-polar solvents. One example where the Z-s-E form is fixed by a six-membered ring is available in the literature.¹²⁵

The proton chemical shifts and coupling constants for the series of pyrrol-3-ones are recorded in Table 15. The chemical shift of the 4-proton is at δ_H 4.9 to 5.15 for N-alkyl examples while the N-phenyl examples give more deshielded values (δ_H 5.34 - 5.45). The corresponding resonance for the Z-s-Z form of tert-butylaminoacrolein is δ_H 4.95 while the E-s-E is δ_H 5.34 which indicates the influence of the ring current of the carbonyl group when it is 'cis' to the 4-proton; this effect would be predicted to be less in the 5-membered ring where geometrical constraint will reduce the overlap. The deshielding for the N-phenyl examples is also shown by the C4-atom in the ^{13}C n.m.r. spectra and the 2-proton(s) and can be explained by a decreased influence of the nitrogen atom's lone pair of electrons which can now be delocalised into the phenyl ring. The spread of values for the 5H-resonance is greater (δ_H 7.6 - 8.6) with the values for N-phenyl examples again more deshielded. This wider spread of chemical shifts might be expected as the 5-H is closer to the site of changed substitution and is, therefore, more likely to be influenced by through space effects from the various nitrogen atom substituents.

Table 15 Proton chemical shifts and coupling constants in 1,2-dihydro-3H-pyrrol-3-ones



Pyrrol-3-one	R ¹	R ²	R ³	2-H	4-H	5-H	³ J _{4,5}
(110)	Ph	H	H	4.10	5.46	8.40	3.6
(98)	Bu ^t	H	H	3.95	5.09	7.93	3.3
	Me	H	H	3.65	5.05	7.68	3.2
(96a)		H	H	3.68	5.06	7.83	3.5
(106)	Ph	Me	H	4.15	5.42	8.30	3.6
(107)	Ph	Ph	H	5.04	5.45	8.62	3.7
(101)	Et	Me	H	3.44	4.92	7.71	3.3
(96b)		Me	H	not identified	5.00	7.82	3.2
(103)	CH ₂ Ph	Ph	H	4.43	5.15	8.18	3.4
(108)	Me	Ph	H	4.34	5.08	7.86	3.2
	Pr ⁱ	Ph	H	4.53	5.12	8.07	3.3
	Ph	Ph	Me	-	5.44	8.57	3.7
(104) *	CHMePh	Ph	Me	-	5.14	8.03	3.4
					5.19	8.32	3.5
	CH ₂ Ph	Ph	Me	-	5.03	7.78	3.3
(97)	Pr ⁱ	Ph	Me	-	5.11	8.08	3.3
	Me	Ph	Me	-	5.07	7.89	3.3
(96c)		Me	Me	-	5.04	7.86	3.4
(100)	Pr ⁱ	Me	Me	-	4.99	7.84	3.4
	Bu ^t	Me	Me	-	5.03	7.99	3.5
(105)	Ph	Me	Me	-	5.37	8.10	3.6
(102)		-(CH ₂) ₆ -	-	-	4.93	7.78	3.3

Table 15 (contd.)

Pyrrol- 3-one	R ¹	R ² R ³	2-H	4-H	5-H	³ J _{4,5}
(<u>95c</u>)	Pr ⁱ	-(CH ₂) ₅ -	-	4.99	7.84	3.4
(<u>95b</u>)	Et	-(CH ₂) ₅ -	-	4.93	7.73	3.4
(<u>95a</u>)	Me	-(CH ₂) ₅ -	-	4.94	7.62	3.2

* Two diastereomers found; major diastereomer quoted first.

The vicinal proton-proton coupling across the C4-C5-bond is generally 3.2 - 3.5 Hz but N-phenyl examples give slightly larger values (3.6 - 3.7 Hz). These are all considerably smaller than those observed for the open-chain enaminones (7 Hz for the Z-s-Z, and 12 Hz for the E-s-E) but the constraint of the 5-membered ring increases the angle between each proton and the double bond and thus creates a major influence.¹²¹ The combination of the ring geometry and the electronegative nitrogen substituent¹²⁶ leads to the low values observed.

The 5H-signal is broadened in examples with 2-proton(s) but the coupling is only normally resolved for the 2-position in the 2-unsubstituted examples and is less than 1 Hz. In the 1-tert-butyl-1,2-dihydro-3H-pyrrol-3-one, however, line narrowing of the ¹H n.m.r. spectrum (LB, -1; GB, 0.6) gave completely resolved signals. Thus, the 5-proton gives rise to a doublet of triplets (³J_{4,5} 3.4 Hz; ⁴J_{2,5} 0.9 Hz) and the 2-protons give rise to a doublet (⁴J_{2,5} 0.9 Hz), with baseline separation.

The chemical shifts for the ring atoms in the ¹³C n.m.r. spectra and carbon-proton coupling constants are presented in Tables 16 and 17.

Table 16 ^{13}C Chemical shifts of 1,2-dihydro-3H-pyrrol-3-ones

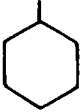
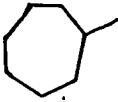
Pyrrol-3-one	R ¹	R ²	R ³	C2	C3	C4	C5
(110)	Ph	H	H	55.65	198.71	103.81	158.31
(98)	Bu ^t	H	H	54.19	199.76	99.13	162.58
(106)	Ph	Me	H	61.13	202.92	101.36	158.73
(107)	Ph	Ph	H	69.39	199.81	101.26	159.60
(101)	Et	Me	H	61.85	203.07	96.46	163.93
(103)	CH ₂ Ph	Ph	H	69.89	201.31	97.30	166.13
(104) ^a	CHMePH	Ph	Me	72.85	204.04	95.53	161.82
				73.31	203.64	94.80	161.33
	CH ₂ Ph	Ph	Me	71.96	203.53	94.80	163.56
(97)	Pr ⁱ	Ph	Me	72.69	203.50	94.34	160.73
	Me	Ph	Me	71.52	203.67	94.48	164.80
	Ph	Ph	Me	not observed	203.50	99.36	159.16
(96c)		Me	Me	67.61	204.61	94.02	159.22
(100)	Pr ⁱ	Me	Me	67.56	204.68	94.28	158.78
	Bu ^t	Me	Me	69.56	204.68	94.35	161.05
(105)	Ph	Me	Me	68.65	205.73	99.11	160.19
(102)		-(CH ₂) ₆ -		71.86	205.89	93.59	156.85
(95c)	Pr ⁱ	-(CH ₂) ₅ -		67.61	204.61	94.02	159.22

^a 2 diastereomers found; major diastereomer quoted first.

The C2-atom gives rise to a range of shifts which follow the expected trends for the substituent pattern (methylene, methine or quaternary carbon with alkyl or aryl substitution). The carbonyl carbon atom resonances occur at around δ_C 200 which is in the range anticipated for $\alpha\beta$ -unsaturated compounds but is rather more deshielded than open-chain enaminones and a related 2,3-dihydropyridin-4-one.¹²⁵ This may be attributed to the effect of the five-membered ring which causes deshielding relative to both four- and six-membered rings. There is also a trend towards greater shielding of the 3-position with less substitution of the 2-position; unsubstituted compounds give $\delta_C < 200$, 2-monosubstituted give δ_C 200-203 and 2,2-disubstituted give $\delta_C > 203.5$. The C4-atom gives a signal at $\delta_C \sim 94$ for N-alkyl examples, while N-phenyl examples are deshielded ($\delta_C \sim 100$) as already discussed. For the C5-position a wider spread of values (δ_C 156 - 166) is found, with N-phenyl substitution generally giving a decrease in chemical shift. Both the C4- and C5-resonances are similar to those found for open-chain enaminones.

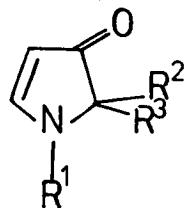
The one bond carbon-proton coupling constant for the C4-position is 176 - 179 Hz, with values for 1,2,2-trialkyl substitution between 176.1 and 176.6 Hz and the presence of 1- or 2-phenyl substitution increasing ^1J values. Similarly, the one bond C5-H

Table 17 Carbon-proton coupling constants of 1,2-dihydro-3H-pyrrol-3-ones

	R ¹	R ²	R ³	C2		C4		C5		
				¹ J _{H(2)}	³ J _{H(4)&H(5)}	¹ J _{H(4)}	² J _{H(5)}	¹ J _{H(5)}	² J _{H(4)}	³ J _{a,b}
(110)	Ph	H	H	143.2	4.4	179.2	6.2	176.7	9.4	3.6 ^a
(98)	Bu ^t	H	H	141.2	5.2	176.5	6.8	173.0	8.5	4.0 ^a
(106)	Ph	Me	H	146.3	c	178.9	6.4	175.8	8.9	3.1 ^a
(101)	Et	Me	H	140.0	c	176.5	6.8	173.2	8.4	4.2 ^b
(103)	CH ₂ Ph	Ph	H	c	c	178.3	7.0	c	c	c
(97)	Pr ⁱ	Ph	Me	-	c	177.5	6.6	171.2	8.9	5.2 ^b
(96c)		Me	Me	-	c	176.6	6.75	170.2	8.6	5.5 ^b
(100)	Pr ⁱ	Me	Me	-	c	176.1	6.6	170.0	8.6	5.9 ^b
(105)	Ph	Me	Me	-	c	178.2	7.0	175.6	8.7	-
(102)		-(CH ₂) ₆ -	-	-	c	176.4	6.45	170.2	8.7	5.9 ^b
(95c)	Pr ⁱ	-(CH ₂) ₅ -	-	-	c	176.35	6.25	171.6	8.5	5.6 ^b

^a Coupling to C₂-protons; ^b Coupling to α-CH on nitrogen atom substituent;

^c Complex pattern - not assigned.



coupling (170 - 177 Hz) and C2-H coupling (140 - 146 Hz) are increased on phenyl substitution and this effect was also found in the 3-hydroxypyrroles. The ^2J couplings across the double bond are fairly large [6 - 7 Hz for C4-C5(H) and 8.4 - 9.4 Hz for C5-C4(H)] which is consistent with observations in other five-membered rings.¹²² These compare with values of 3.2 and 3.4 Hz for the Z-s-Z open-chain enaminone and 2.2 Hz¹²⁴ for the E-s-E configuration. The C5-atom also exhibits a three-bond coupling to 2-proton(s), where they are present, of ~ 4 Hz and to α -hydrogen atoms in N-substituents of ~ 6 Hz. The C2-atom couples to both C4-H and C5-H with approximately the same coupling constant but 2-substituents give further splitting and the C2-signals were only resolved for unsubstituted examples. The long-range couplings to the carbonyl carbon atom have been analysed for the simple 1-tert-butyl-3H-pyrrol-3-one (98) using specific decoupling experiments and the 2,2,4-trideuteriated species. The deuteriated compound gave a clean doublet of 10 Hz so this value corresponds to the three bond coupling to 5-H. Specific decoupling at the 2-proton gave rise to a doublet of doublets for which the larger value has already been assigned and the smaller coupling (~ 3 Hz) must arise from a two bond coupling to 4-H. Decoupling of the 4H- or 5H-resonances did not simplify the

C. THE REACTIVITY OF 1,2-DIHYDRO-3H-PYRROL-3-ONES
(3-HYDROXYPYRROLES)

The potential of the title ring system for varied reactivity has already been mentioned (see Introduction) but it has been little studied because of the scarcity of suitable examples. To date, only reactions of examples containing additional electron-withdrawing substitution, or having potentially reactive sites blocked, have been investigated. The following chapter considers some aspects of the reactivity of simple examples of the ring system, available by the flash vacuum pyrolysis route, in relation to pyrroles, enones and enaminones.

PROTONATION

Simple pyrroles are very sensitive to acids and undergo rapid polymerisation, although it has been suggested that if conditions are such that complete protonation occurs, solutions can be stable.¹²⁹ Crystalline salts can be obtained¹³⁰ by treatment with anhydrous hydrogen halides but these have often dimeric or trimeric structures. Some monomeric, tert-butyl substituted, pyrrole salts have been isolated¹³¹ which have helped confirm that pyrroles protonate on carbon.

Enaminones, however, give stable salts with strong acids⁴⁹ and these have been studied by U.V., i.r.¹³² and n.m.r.¹³³ spectroscopy. The results indicate a predominance of O-protonation.

In contrast to the corresponding pyrroles without electron-donating substitution, simple 3-hydroxypyrroles- (1,2-dihydro-3H-pyrrol-3-ones) are smoothly protonated in trifluoroacetic acid to give solutions which are stable indefinitely at room temperature. The protonated species, which are Wheland intermediates for the electrophilic substitution of this system, can be readily isolated as their picrates. The 1-tert-butyl-, 1-phenyl and 2,2-dimethyl-1-isopropyl-1,2-dihydro-3H-pyrrol-3-ones have all been protonated instantly, by picric acid in ethanol, to give stable crystalline salts (65-95%) which can be stored at room temperature, although the 1-phenyl example decomposed on attempts at recrystallisation. A crystal structure of the 1-tert-butyl-3-hydroxypyrrol-3-one picrate has been obtained and indicates protonation which can be considered as O-protonation of the pyrrol-3-one, as observed in enaminones, or C-protonation of the 3-hydroxypyrrole, analogous to other pyrroles. The bond lengths, bond angles and torsion angles are shown in Tables 18-20 and depicted in Figure 18, along with the crystallographic numbering system. Two molecules, unrelated by symmetry, were in fact observed, and the parameters for both are listed; the atom numbers have additional A and B classifications distinguishing each set of data. The anticipated, alternately shorter and longer bonds relative to the related, unprotonated structure (110) are observed.

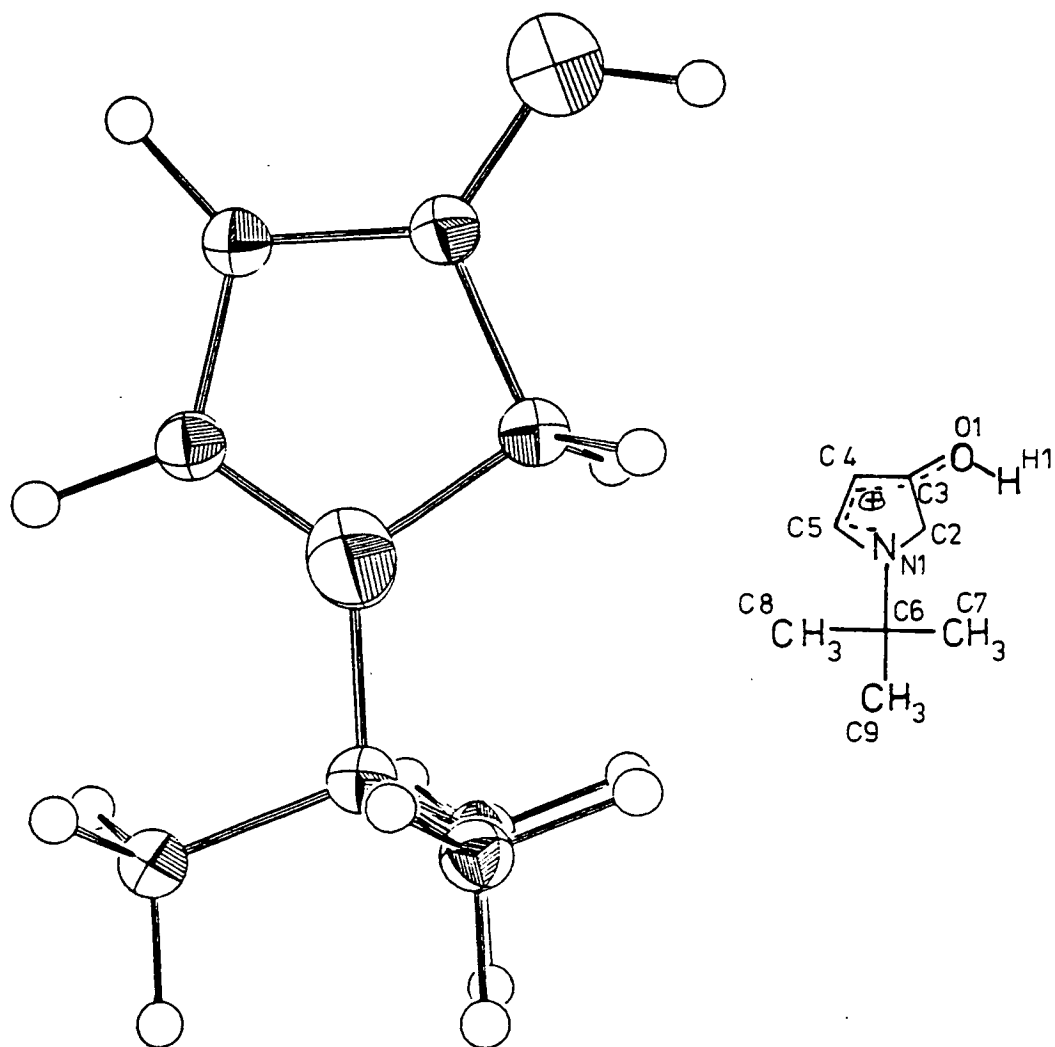


Figure 18

Table 18

Bond Lengths(A) with standard deviations

O(1A) -H(1A)	0.96(3)	O(1B) -H(1B)	0.94(4)
O(1A) -C(3A)	1.311(4)	O(1B) -C(3B)	1.313(5)
C(3A) -C(4A)	1.352(5)	C(2B) -C(4B)	1.330(6)
C(3A) -C(2A)	1.478(5)	C(3B) -C(2B)	1.479(5)
C(4A) -C(5A)	1.406(5)	C(4B) -C(5B)	1.396(6)
C(5A) -N(1A)	1.295(5)	C(5B) -N(1B)	1.290(5)
C(2A) -N(1A)	1.450(5)	C(2B) -N(1B)	1.451(5)
N(1A) -C(6A)	1.491(5)	N(1B) -C(6B)	1.494(5)
C(6A) -C(7A)	1.489(7)	C(6B) -C(7B)	1.506(6)
C(6A) -C(8A)	1.517(7)	C(6B) -C(8B)	1.517(6)
C(8A) -C(9A)	1.481(8)	C(6B) -C(9B)	1.494(6)

Table 19

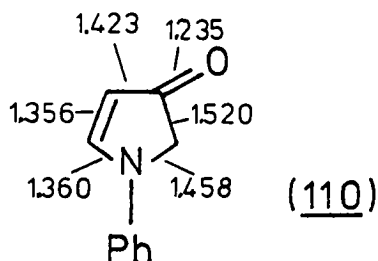
Angles(degrees) with standard deviations

H(1A) -O(1A) -C(3A)	113.4(19)	H(1B) -O(1B) -C(3B)	108.2(22)
O(1A) -C(3A) -C(4A)	126.2(3)	O(1B) -C(3B) -C(4B)	126.9(4)
O(1A) -C(3A) -C(2A)	124.2(3)	O(1B) -C(3B) -C(2B)	124.0(3)
C(4A) -C(3A) -C(2A)	109.6(3)	C(4B) -C(3B) -C(2B)	109.2(4)
C(3A) -C(4A) -C(5A)	105.8(3)	C(3B) -C(4B) -C(5B)	107.0(4)
C(4A) -C(5A) -N(1A)	113.3(3)	C(4B) -C(5B) -N(1B)	112.8(4)
C(3A) -C(2A) -N(1A)	102.7(3)	C(3B) -C(2B) -N(1B)	102.6(3)
C(5A) -N(1A) -C(2A)	108.6(3)	C(5B) -N(1B) -C(2B)	108.4(3)
C(5A) -N(1A) -C(6A)	128.4(3)	C(5B) -N(1B) -C(6B)	128.2(3)
C(2A) -N(1A) -C(6A)	123.0(3)	C(2B) -N(1B) -C(6B)	123.3(3)
N(1A) -C(6A) -C(7A)	109.5(4)	N(1B) -C(6B) -C(7B)	109.0(3)
N(1A) -C(6A) -C(8A)	107.5(4)	N(1B) -C(6B) -C(8B)	107.5(3)
H(1A) -C(6A) -C(9A)	108.8(4)	N(1B) -C(6B) -C(9B)	108.3(3)
C(7A) -C(6A) -C(8A)	109.2(4)	C(7B) -C(6B) -C(8B)	109.1(4)
C(7A) -C(6A) -C(9A)	112.0(4)	C(7B) -C(6B) -C(9B)	112.5(4)
C(8A) -C(6A) -C(9A)	109.7(4)	C(8B) -C(6B) -C(9B)	110.4(4)

Table 20

Torsion angles(degrees) with standard deviations

H(1A) -D(1A) -C(3A) -C(4A)	167.7(21)	H(1B) -D(1B) -C(3B) -C(4B)	171.1(23)
H(1A) -D(1A) -C(3A) -C(2A)	-13.8(21)	H(1B) -D(1B) -C(3B) -C(2B)	-9.6(23)
D(1A) -C(3A) -C(4A) -C(5A)	-178.8(3)	D(1B) -C(3B) -C(4B) -C(5B)	179.8(4)
C(2A) -C(3A) -C(4A) -C(5A)	2.5(4)	C(2B) -C(3B) -C(4B) -C(5B)	0.3(5)
D(1A) -C(3A) -C(2A) -N(1A)	178.6(3)	D(1B) -C(3B) -C(2B) -N(1B)	179.9(3)
C(4A) -C(3A) -C(2A) -N(1A)	-2.6(4)	C(4B) -C(3B) -C(2B) -N(1B)	-0.7(4)
C(3A) -C(4A) -C(5A) -N(1A)	-1.4(4)	C(3B) -C(4B) -C(5B) -N(1B)	0.2(5)
C(4A) -C(5A) -N(1A) -C(2A)	0.3(4)	C(4B) -C(5B) -N(1B) -C(2B)	-0.7(5)
C(4A) -C(5A) -N(1A) -C(6A)	-178.4(3)	C(4B) -C(5B) -N(1B) -C(6B)	174.2(4)
C(3A) -C(2A) -N(1A) -C(5A)	1.7(4)	C(3B) -C(2B) -N(1B) -C(5B)	0.8(4)
C(3A) -C(2A) -N(1A) -C(6A)	180.0(3)	C(3B) -C(2B) -N(1B) -C(6B)	-174.3(3)
C(5A) -N(1A) -C(6A) -C(7A)	4.3(5)	C(5B) -N(1B) -C(6B) -C(7B)	18.9(5)
C(5A) -N(1A) -C(6A) -C(8A)	122.8(4)	C(5B) -N(1B) -C(6B) -C(8B)	136.9(4)
C(5A) -N(1A) -C(6A) -C(9A)	-118.4(4)	C(5B) -N(1B) -C(6B) -C(9B)	-103.8(5)
C(2A) -N(1A) -C(6A) -C(7A)	-173.6(4)	C(2B) -N(1B) -C(6B) -C(7B)	-167.0(3)
C(2A) -N(1A) -C(6A) -C(8A)	-55.0(5)	C(2B) -N(1B) -C(6B) -C(8B)	-49.0(4)
C(2A) -N(1A) -C(6A) -C(9A)	63.7(5)	C(2B) -N(1B) -C(6B) -C(9B)	70.3(4)



units = Å

Thus, the carbon-oxygen bond is 0.086 Å longer in the cation and is approaching a typical single bond value, while the remaining single and double bonds of the enaminone backbone are shortened and lengthened, respectively, indicating the expected delocalisation of charge. The C2-C3-bond is also shorter but there is no change in the N-C2-bond length.

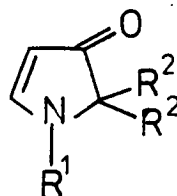
^1H and ^{13}C n.m.r. spectroscopy has been used to study numerous charged systems¹³⁴ and has proved particularly useful in the determination of the site of protonation in pyrroles.^{129,135} The spectra of some representative 1,2-dihydro-3H-pyrrol-3-ones in trifluoroacetic acid were therefore obtained and the ^1H and ^{13}C n.m.r. chemical shifts and coupling constants are listed in Tables 21-23 alongside results previously obtained for the comparable 3-(tert-butylamino)propenal (118).¹³⁴ It can be seen that the same trends are followed by the pyrrol-3-ones as by the open-chain compound. Thus, the proton signals

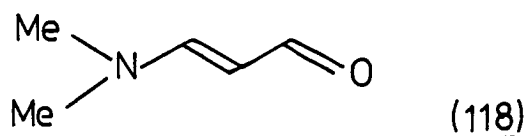
are all shifted to more deshielded positions and, most significantly, the vicinal coupling constant across the formal double bond of the neutral species is markedly decreased (by >30%), indicating the delocalisation present in the cation. The change in the chemical shift of the 2-protons and the increase in the $^4J_{2,5}$ must reflect the overall charge of the molecule as the 2-position is not part of the delocalised system.

Table 21 Proton chemical shifts and coupling constants of protonated 1,2-dihydro-3H-pyrrol-3-ones and enaminones^a

Enaminone	R ¹	R ²	2-H	4-H	5-H	$^3J_{4,5}$	$^4J_{2,5}$
(98)	Bu ^t	H	4.81 (+0.86)	5.99 (+0.9)	8.62 (+0.69)	2.2 (-1.3)	1.9 (+1.1)
(110)	Ph	H	5.26 (+1.16)	6.26 (+1.2)	8.93 (+0.53)	2.3 (-1.1)	1.7 (+1.1)
(100)	Pr ⁱ	Me	-	5.98 (+0.99)	8.61 (+0.75)	2.3 (-1.1)	-
(118)			-	6.12 (+1.01)	8.08 (+0.71)	11.2 (-1.3)	-

^a Protonated species quoted with difference from neutral species given in brackets.





Protonation leads to the most marked changes in the ^{13}C chemical shifts of the 3- and 5-positions. The 3-position is shielded by more than 10 p.p.m. and this may be attributed to the change in the π -system of the carbonyl group on protonation, which leads to a considerable reduction in the anisotropic¹²⁷ effect. The C5-atom is deshielded by 7-11 p.p.m. which is a very similar effect to that found in the open-chain system,¹³⁴ and must be a result of the electron density at that site (a resonance form exists in which the positive charge is located on this site). Minimal change in chemical shift is observed at the C4-atom which is again in agreement with results from the open chain form and the absence of a resonance form with the positive charge at that site (Figure 19).

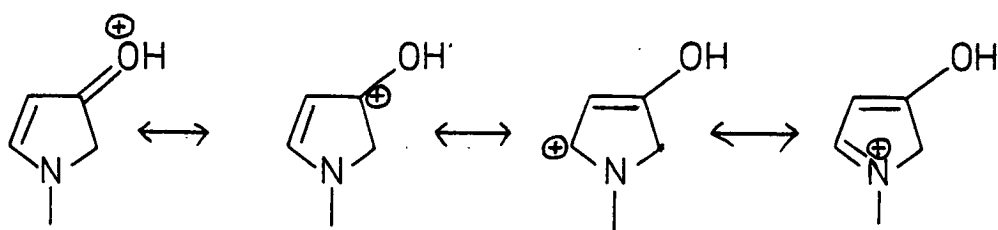


Figure 19

Table 22 ^{13}C chemical shifts for protonated 1,2-dihydro-3H-pyrrol-3-ones and enaminones^a

Enaminone	R ¹	R ²	C2	C3	C4	C5
(98)	Bu ^t	H	56.51 (+3.32)	186.84 (-11.87)	100.86 (+1.73)	170.04 (+7.46)
(110)	Ph	H	59.06 (+3.41)	189.52 (-10.24)	102.35 (-1.46)	168.89 (+10.58)
(100)	Pr ⁱ	Me	74.13 (+6.57)	192.65 (-12.03)	96.32 (+2.04)	166.71 (+7.93)
(118)			-	176.93 (-10.79)	104.68 (+2.63)	167.53 (+10.68)

^a Protonated species quoted with difference from neutral species given in brackets.

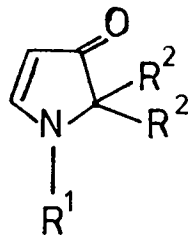
The increase in one-bond coupling constants which is found on protonation of pyridines^{134b} has been attributed to the inductive effect of the cationic centre. The amino-propenal (118)^{134a} has also been shown to exhibit this increase in ^1J values on protonation, despite relatively small changes in chemical shift, and this is again found in the pyrrol-3-one examples where the C4- and C5-atoms show increases in one-bond coupling of 7.0-9.5 Hz and 10.2-13.2 Hz, respectively. The

Table 23 Carbon-proton coupling constants of protonated 1,2-dihydro-3H-pyrrol-3-ones and enaminones^a

Enaminone	R ¹	R ²	C2		C3 ^b			C4		C5		
			¹ J	³ J _{H(4)} = ³ J _{H(5)}	² J _{H(2)}	² J _{H(4)}	³ J _{H(5)}	¹ J	² J _{H(5)}	¹ J	² J _{H(4)}	³ J _{H(3)}
(98)	Bu ^t	H	144.6 (+3.4)	5.6 (+0.4)				185.0 (+8.5)	7.8 (+1.0)	184.6 (+11.6)	6.8 (-1.7)	5.0 (+1.0)
(110)	Ph	H	146.3 (+3.1)	5.6 (+1.2)				186.2 (+7.0)	7.8 (+1.6)	186.9 (+10.2)	7.9 (-1.5)	5.0 (+1.4)
(100)	Pr ⁱ	Me	-	-	-			185.6 (+9.5)	7.6 (+1.6)	183.2 (+13.2)	6.5 (-2.1)	6.5 (+0.6)
(118)			-	-	-			164.9 (+9.6)	-	168.4 (+7.5)	-	-

^a Protonated species quoted with difference from neutral species in brackets.

^b Couplings of ~4.5 Hz observed to at least two protons but not assigned.



C2-resonance also shows an increased ^1J coupling, although of only 3 Hz. The two-bond couplings across the double bond are increased for C4 but decreased for C5 by fairly consistent amounts.

In order to study the exchange processes involved in protonation of the pyrrol-3-ones, the 1-tert-butyl compound (98) was dissolved in [^2H]-trifluoroacetic acid and its ^1H n.m.r. spectrum was monitored at intervals. The most rapid exchange is found at the 4-position with a half-life for the reaction of less than a minute, while exchange occurs at the 2-position with a half-life of approximately six minutes. No exchange was observed at the 5-position after several days. Thus, a dynamic equilibrium exists in solution in which the pyrrol-3-one protonates and deprotonates rapidly at the 2- and 4-positions but not at the 5-position. Simple pyrroles without hydroxy functionality are found to protonate most rapidly at β -positions, while the thermodynamically most stable cation is formed by protonation at C2 and C5¹³⁷, but the absence of exchange at the 5-position in this system, in addition to the reactivity of the 4-position is reminiscent of the properties of the conjugated system of enaminones. When the 2-position is blocked by dialkyl substitution, as in 2,2-dimethyl-1-isopropyl-

1,2-dihydro-3H-pyrrol-3-one (100), exchange occurs exclusively at the 4-position. The obvious mechanism for exchange at the 2-position is via the free base, 3-hydroxypyrrole form, and the absence of exchange in a salt locked in the protonated form (see following section) indicates that exchange at the 4-position also occurs via a free base. The rates of deuterium exchange in 3-alkoxypyrroles have also been monitored,¹⁵⁴ and while exchange at the 2-position was complete after less than 2 hours (similar to the 3-hydroxypyrroles) the 4-position was only fully deuteriated after a number of days. This suggests that in examples which are not locked in the pyrrole form, the major exchange mechanism for the 4-position of the neutral species involves the protonation of the 1,2-dihydro-3H-pyrrol-3-one tautomer [Figure 20(a)] which is considerably more rapid than exchange at the 4-position via the enol tautomer [Figure 20(b)], although this occurs.

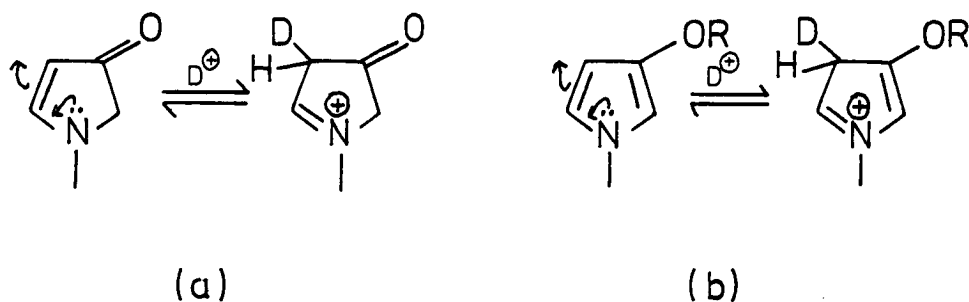


Figure 20

The fact that exchange at the 2-position of the 3-hydroxypyrroles is faster in neutral solvents (e.g. [$^2\text{H}_4$]methanol) than acid, despite the latter apparently occurring via the free base, indicates that the rate of exchange at each site is influenced by the rate of deprotonation at that site, and therefore does not give a true indication of the electrophilic reactivity of each position.

REACTIONS WITH ELECTROPHILES

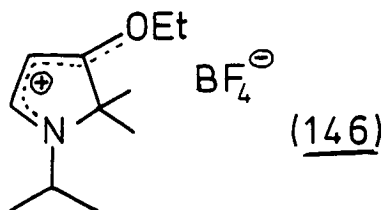
In agreement with the results of protonation studies, electrophilic attack at oxygen is observed on treatment of the 2,2-dimethyl-1-isopropyl-1,2-dihydro-3H-pyrrol-3-one with triethyloxonium tetrafluoroborate. The salt (146) was obtained as a crystalline solid (70%) after evaporation of solvent and storage in ether at -20°C ; the changes observed in its n.m.r. spectra (Table 24) relative to the parent compound were similar to those of the protonated species discussed earlier and therefore consistent with O-alkylation.

Table 24 N.m.r. parameters of pyrrol-3-one (100) and its salts

	4-H	5-H	$^3J_{4,5}$	C2	C3	C4	C5
(<u>100</u>) ^a	4.99	7.84	3.4	67.56	204.68	94.28	158.78
(<u>146</u>) ^b	+1.04	+1.09	-1.0	+3.05	-14.44	+0.86	+9.50
protonated (<u>100</u>) ^b	+0.99	+0.75	-1.1	+6.57	-12.03	+2.04	+7.93

^a Chemical shifts and coupling constants

^b Change in chemical shift and coupling constants from (100)

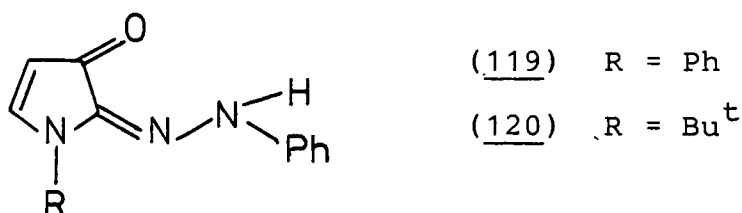


Solution of the salt in [^2H]trifluoroacetic acid does not give deuterium exchange at the 4-position as was observed on solution of the pyrrolone (100) in the same solvent. This shows that the deuterium exchange observed must occur via protonation of the free base which is not available in the salt locked in the cationic form. The salt is also completely unreactive towards electrophilic substitution by either molecular bromine or N-bromosuccinimide. This contrasts sharply with 2,3-dihydro-1,4-diazepines which contain a similar conjugated system, but where the terminal oxygen atom is replaced by a nitrogen atom. The diazepinium salts are reactive to electrophilic substitution,¹²⁰ and thus it appears that the more electronegative oxygen must considerably alter the electron distribution and reactivity in the conjugated system.

Nitrogen Electrophiles and the Reactions of Products

Electrophilic substitution reactions are also in accord with the results of deuterium exchange in acid; reaction occurs at the 2- and 4-positions of representative 1,2-dihydro-3H-pyrrol-3-ones.

Thus, benzene diazonium chloride reacts at the 2-position of the 2-unsubstituted examples to give 2-phenylhydrazono compounds, (119) (60%), and (120) (71%). The phenyl compound precipitated from solution, but the tert-butyl example was obtained by extraction from the aqueous reaction mixture.



The hydrazono rather than the alternative azo structure is assigned to these compounds on the basis of their n.m.r. spectra which show proton-proton couplings of 4.0 and 3.9 Hz for the 4- and 5-protons, which correspond to the keto rather than enol tautomer, where couplings are considerably less. The structure is further supported by ¹J couplings to these positions which do not show the difference of around 15 Hz observed for the α- and β-position in 3-hydroxypyrroles and other pyrrole derivatives. Bauer has reacted other 1,2-dihydro-3H-pyrrol-3-ones⁴⁸ with diazonium salts and obtained analogous products, but in his examples the other ring carbon atoms were substituted, and reaction at other

potentially reactive sites was, therefore, blocked. He also assigned the hydrazono structure to his product while Benary¹⁷ and Kuhn⁵ suggest the azo form for 4-carboxylate substituted examples (see Introduction), but the earlier assignments were based only on a positive reaction with ferric chloride, thought to indicate the presence of a hydroxyl group.

In the ¹³C n.m.r. spectra of these compounds the point of attachment (C2) shows, not surprisingly, a huge deshielding of around 90 p.p.m. from the parent compounds to the range typical of hydrazones. The carbonyl function is considerably shielded (~20 p.p.m.) which must be a result of increased delocalisation since hydrogen-bonding is expected to cause a shift in the opposite direction.¹²¹ In fact, the chemical shift of the 3-position falls midway between that of the keto and enol tautomers, and this may indicate a dynamic equilibrium between the two structures. The 5-position is deshielded by around 10 p.p.m., the explanation for which could be the increased pull on the electrons of the enone system towards the carbonyl group caused by hydrogen bonding, or of competitive, exocyclic delocalisation of the ring nitrogen atom's lone pair of electrons (Figure 21).

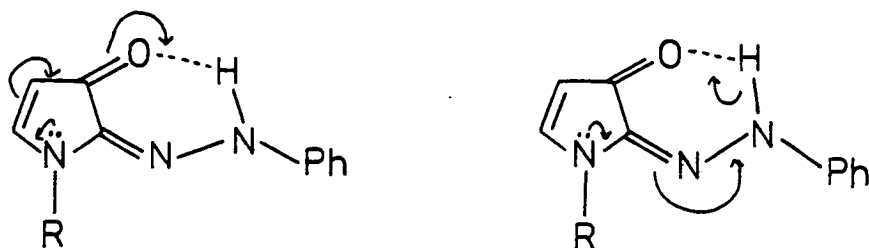
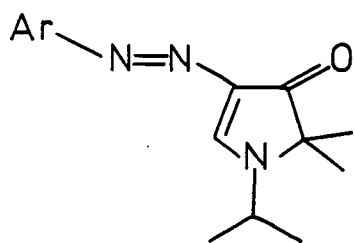


Figure 21

If the 2-position is blocked, as in 2,2-dimethyl-1-isopropyl-1,2-dihydro-3H-pyrrol-3-one (100) reaction with benzene diazonium chloride, generated in situ, gives only recovered starting material (58%), but with isolated aryldiazonium tetrafluoroborates in acetonitrile, occurs at the 4-position to yield the arylazo products (121-123) (62-76%). The phenylazo compound, although spectroscopically pure, could not be obtained as a solid, but p-substituted analogues were readily isolated as their tetrafluoroborate salts, and the crystalline free bases were obtained by neutralisation of an aqueous solution and extraction. This ready formation of salts is somewhat unusual as azo compounds generally are rather weakly basic and few salts have been isolated.¹³⁸ However, these compounds may also be considered as 1,2,5-triazapentadienes which are readily protonated.¹³⁹



(121): Ar = Ph

(122): Ar = pNO₂Ph

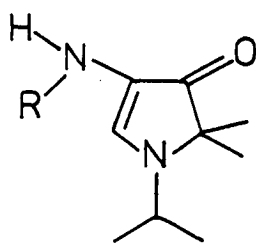
(123): Ar = p-COOHPh

The reaction of this ring system with diazonium salts indicates considerable reactivity, since coupling usually only occurs to activated aromatics, and there does not appear to be any examples of acyclic, or the widely investigated cyclic, trans-s-trans enaminones undergoing this reaction.⁴⁹

Further evidence for the reactivity and sensitivity of the pyrrolones was found in attempts to nitrate the system. A variety of conditions led only to decomposition, the system apparently being too reactive to withstand the typical nitric acid mixtures. Reaction with nitrosonium tetrafluoroborate also resulted in decomposition.

The amino-substituted 1,2-dihydro-3H-pyrrol-3-one system was of particular interest as an indicator of the aromatic or other type of reactivity in the system, since aromatic and aliphatic amines have markedly different properties. However, since the nitro compounds could not be obtained, the amino system was not available by the usual reductive procedures. Another method was

therefore sought, and although the reduction of azo compounds is a little used route to amines¹⁴⁰, the simple isolation of 4-arylaazo compounds, described above, suggested it may provide a viable method of synthesis of the 4-amino compound (124).



(124): R = H

(126): R = Ac

This synthesis of amines requires a p-substituted azo compound for the reduction, as under these conditions, phenylazo compounds themselves undergo the benzidine rearrangement. Preliminary experiments showed that the p-nitrophenylazo compound could be cleaved to give the desired amine and p-nitroaniline but this would require a chromatographic separation of the amines. Since the reduction is carried out in acid and the reaction mixture must, therefore, be basified and the product extracted, the p-carboxyphenylazo compound was prepared; the p-aminobenzoic acid resulting from the reductive cleavage could then be removed in work-up.

The reduction was carried out successfully using the tetrafluoroborate salt of the azo compound and did not require isolation of the free base. The reaction involved stirring the highly coloured solution of the salt and tin chloride in concentrated hydrochloric acid at room temperature until the colour cleared (around 2 h). After work-up, the amine could be isolated by distillation to give a yellow liquid (72%) which appeared to be reasonably stable at room temperature in its pure form. In chloroform solution the amine precipitated as a salt (possibly its carbonate), which gives an indication of its basicity. This facile salt formation allowed the simple isolation of the amine picrate (73% from the azo compound) and the proton and ^{13}C n.m.r. spectra of the salt were recorded. The changes observed in the ^{13}C n.m.r. spectrum (Table 25) of the picrate, relative to the free base, are markedly different from those observed on protonation of the 1,2-dihydro-3H-pyrrol-3-one itself; the carbonyl carbon atom shows a shielding of only 3 p.p.m. compared to 12 p.p.m. in the unsubstituted compound, while the C_4 -atom is shielded by more than 15 p.p.m. compared to a deshielding of 2 p.p.m. Thus protonation appears to occur on the exocyclic nitrogen atom.

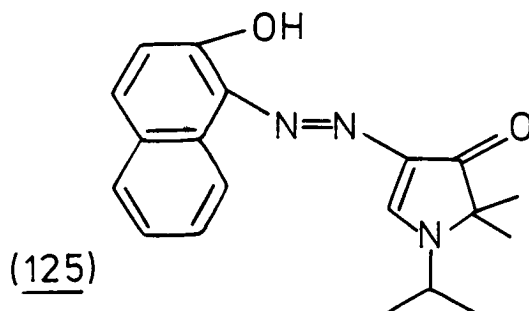
Table 25 ^{13}C n.m.r. chemical shifts of the amine (124) and its picrate

	C2	C3	C4	C5
(<u>124</u>) ^a	66.57	197.97	115.28	149.79
(<u>124</u>) ^b	+1.77	-3.06	-15.55	+5.63
(<u>100</u>) ^b	+6.57	-12.03	+2.04	+7.93

^a Chemical shifts of species.

^b Change in chemical shift on protonation of given species.

The free amine could be diazotised and reacted, in situ, with β -naphthol to give the expected coupled product (125) (33%) as shown by ^1H and ^{13}C n.m.r. spectroscopy. The compound also gave a clear, highest mass peak at m/z 323 in its mass spectrum shown to be consistent with $\text{C}_{19}\text{H}_{21}\text{N}_3\text{O}$. Unfortunately, the solid could not be satisfactorily recrystallised.



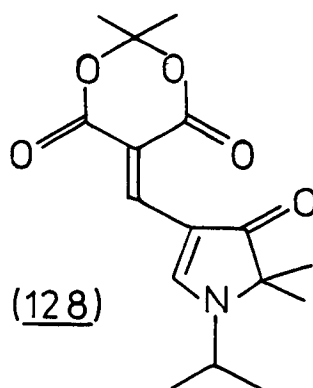
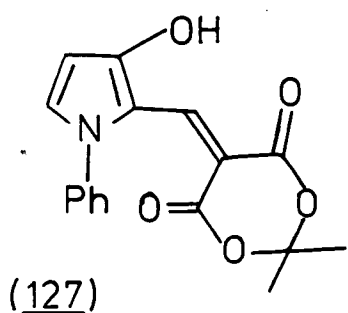
This provides further evidence for the influence of the delocalised electronic structure of the enaminone on its reactivity; only aromatic amines are expected to form stable diazonium salts capable of undergoing coupling reactions.

By altering the conditions of the reduction (using acetic acid instead of concentrated hydrochloric acid, and applying heat) the 4-acetylaminopyrrolone (126) could be obtained directly. This type of reaction has been observed previously in the reduction of azo compounds.¹⁴¹

The spectra of the 4-amino and 4-acetyl amino compounds will be discussed later in relation to other 4-substituted products.

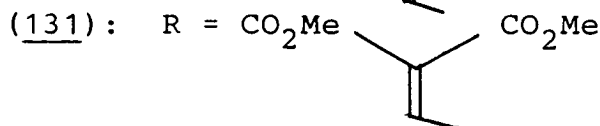
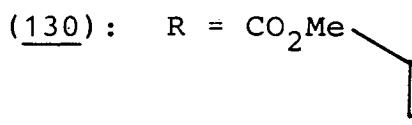
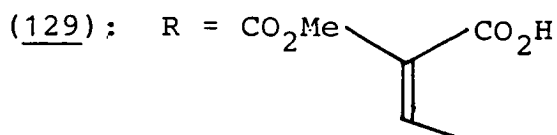
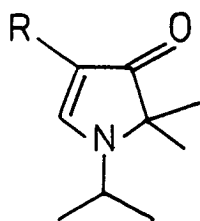
Carbon Electrophiles and the Reactions of Products

Methoxymethylidene Meldrum's Acid has been found to be a useful carbon electrophile capable of reacting with a number of aromatic systems under mild conditions (see following Chapter). Thus, it reacts with both 2-unsubstituted- and 2,2-disubstituted-1,2-dihydro-3H-pyrrol-3-ones (110 and 100) in the same manner as diazonium salts to give the 2- and 4-substituted products (127) (62%) and (128) (73%). Reaction of the 2-unsubstituted compound occurs at room temperature overnight,



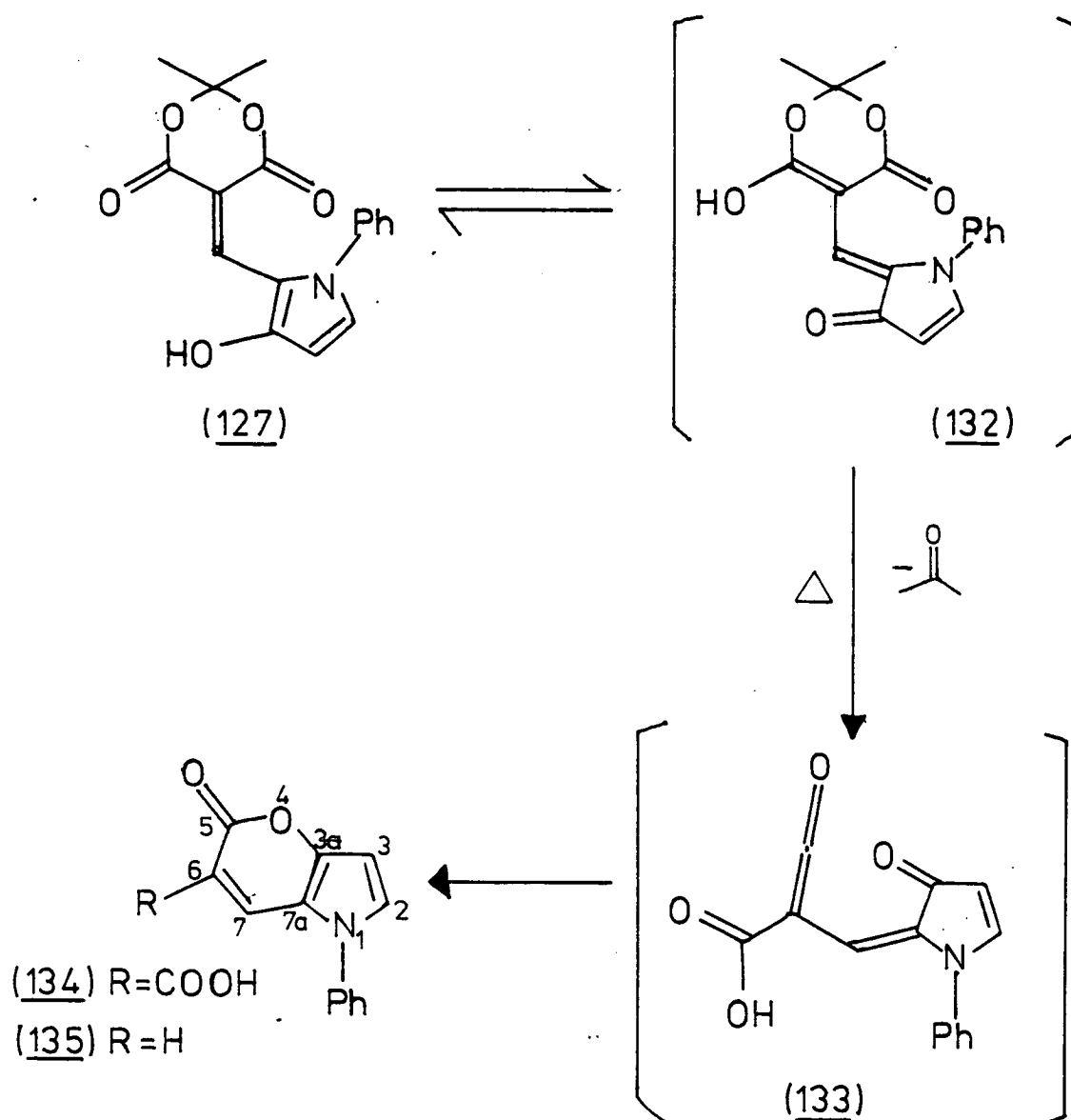
conditions very similar to those required for pyrrole itself, while the fixed enaminone form reacts more rapidly; complete reaction requires less than two hours.

Treatment of Meldrum's Acid derivatives with methoxide is known to result in the cleavage of acetone and the formation of methyl methylenemalonate derivatives.¹⁴² The pyrrolone derivative (128) reacts to give a quantitative yield of the half ester (129), which can be decarboxylated, by vacuum distillation, to give the acrylate (130) (65%). The product is shown to have the trans geometry indicated, by the proton-proton coupling constant across the double bond (15.5 Hz) and there is no evidence for any of the cis-isomer, in contrast to other examples.¹⁴²



Alternatively, the initially formed half-ester anion can be treated with methyl iodide to give the dimethyl methylidenemalonate derivative (131) (50%).

The derivative (127) is assigned the structure illustrated on the basis of its n.m.r. spectra. In particular the relatively close chemical shifts and small coupling constant in the ^1H n.m.r. spectrum are typical of the enol rather than keto form of the five-membered ring. The presence of the ortho-hydroxy function allows its use in a different synthetic route. Under flash vacuum pyrolysis conditions acetone is cleaved from the Meldrum's Acid ring to form the pyranopyrrole (134) which is accompanied by its decarboxylated analogue (135). The products could be readily separated by dissolving the mixture in base and extraction of the non-acidic pyranopyrrole.



Scheme 48

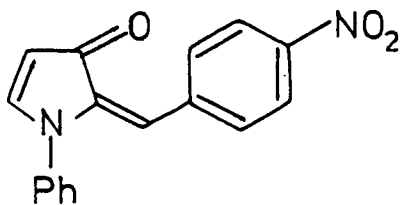
The products (134) and (135) are formed in an approximately 1:1 ratio on pyrolysis at 550°C, while at 600°C greater than 99% of the product mixture is decarboxylated. Wentrup has studied the breakdown pattern of other methyldene

Meldrum's Acid derivatives⁸² capable of tautomerism and found a stepwise fragmentation occurs. An analogous reaction pathway in this system (Scheme 48) gives the acid ketene (133) which undergoes electrocyclisation to the acid product. A simple decarboxylation gives the second product and thus this mechanism appears probable. The reaction is similar to the formation of δ -lactams from the condensation products of Meldrum's Acid and azaenaminones⁹⁶ (see Introduction).

The pyranopyrrole products exhibit slightly larger proton-proton coupling across the 2,3-bond than typical hydroxypyrroles (3.2 Hz) and also give rise to a small five bond coupling between 3-H and 7-H (confirmed by decoupling) of 0.8 Hz.

Reaction of 2-unsubstituted pyrrolones with substituted benzaldehydes has been found in previous work to yield 2-benzylidene products.^{15,31,38,48} A mixture of 1-phenyl-1,2-dihydro-3H-pyrrol-3-one and p-nitro-benzaldehyde in methanol rapidly gives a creamy coloured precipitate, which is very insoluble in most organic solvents and decomposes over a period of one hour in dimethylsulphoxide solution. The mass spectrum shows a peak at m/z 292 which is consistent with the formation of the condensation product (136) but the peak has fairly low intensity and the most significant peaks are

at m/z 159 and m/z 151 which are those expected of the starting materials.



(136)

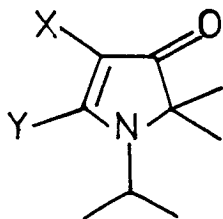
The ^1H n.m.r. spectrum is not consistent with the condensation product, although clear multiplets can be distinguished (see Experimental Section). Further, the elemental analysis appears to be consistent with a considerable amount of extra oxygen ($\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_6$ compared with $\text{C}_{17}\text{H}_{12}\text{N}_2\text{O}_3$ required for the condensation product).

Reaction of 1-tert-butyl-1,2-dihydro-3H-pyrrol-3-one with p-nitrobenzaldehyde resulted only in the formation of the acetal and hemiacetal of the aldehyde, presumably produced due to the presence of trace amounts of acid. No other reaction could be detected after twenty-four hours at 60°C .

It is interesting that all the observed examples of benzaldehyde condensations with 1,2-dihydro-3H-pyrrol-3-ones have involved -NH species and there seem to be some problems with stability. For example, Severin³⁸ could only purify his products by washing with ether.

Halogeno Electrophiles and the Reactions of Products

The 2,2-disubstituted pyrrolone (100) also reacts readily with the chloro-, bromo- and iodo-succinimides to give the 4-substituted products (137-139) in almost quantitative yield. The conditions (room temperature in methanol) are typical of those used in reactions of enamminones¹⁴³ and are thought to promote electrophilic, rather than radical, halogenations. Electrophilic bromination can also be carried out by treatment with



(137): X=Cl, Y=H (140): X=Cl, Y=D

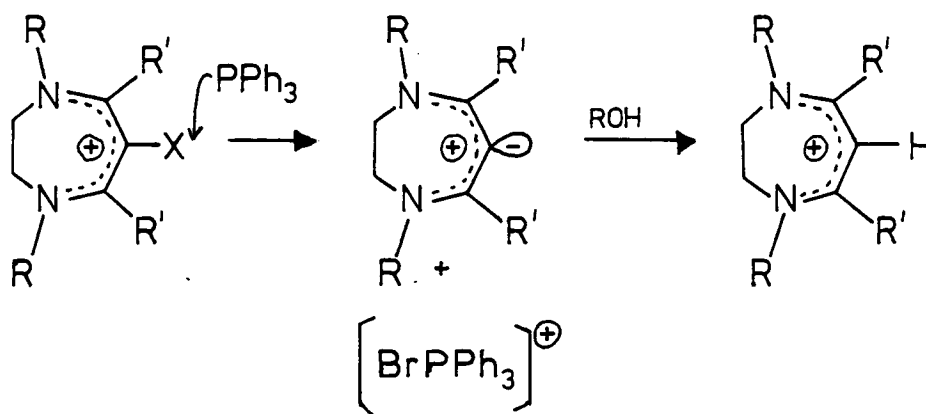
(138): X=Br, Y=H (141): X=Br, Y=D

(139): X=I, Y=H (142): X=I, Y=D

molecular bromine in methanol, but these simple conditions give a 50:50 mixture of product and starting material. However, the addition of sodium hydrogen carbonate to the reaction mixture resulted in total conversion to product, and the incomplete reaction is thought to be due to the formation of an unreactive hydrobromide salt; the

O-alkylated salt of the starting material (146) has been shown to be completely unreactive to both N-bromo-succinimide and molecular bromine under the reaction conditions.

Unlike the related 6-halogeno-2,3-dihydro-1,4-diazepines,¹⁴⁴ brominated enaminoketones have been found to be poorly reactive species,¹⁴³ although an example of the removal of iodine by sodium cyanide in ethanol is reported.¹⁴³ Treatment of the 2,2-dimethyl-4-halogeno-1-isopropyl-1,2-dihydro-3H-pyrrol-3-ones with the soft nucleophile, triphenylphosphine, results in protodehalogenation of the iodo compound in less than 30 minutes at room temperature, while the bromo compound required a number of hours, and the chloro compound showed less than 50% reaction even after 3 weeks. Similar removal of halogens has been observed in the dihydro-diazepine series¹⁴⁵ and the proposed mechanism is shown in Scheme 49.



Scheme 49

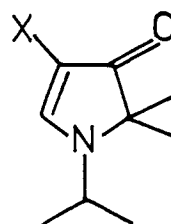
This is supported by the increasing reactivity with decreasing electronegativity, by the isolation of appropriate by-products, and by the incorporation of deuterium when the reaction is carried out in [^2H]-methanol. In the pyrrolone case this mechanism would result in the formation of a vinyl anion, a species known to be inherently more stable than aliphatic anions¹⁴⁶ without stabilising substitution; more rapid reaction at the less electronegative, softer, iodine atom supports initial attack at the halogen atom by triphenylphosphine and the anion is trapped by deuterium when the reaction is carried out in [$^2\text{H}_4$]methanol, lending further support to a similar mechanism. Other examples of dehalogenation with triphenylphosphine have been reported by Cadogan and Burn.¹⁴⁷

The 4-halogenopyrrolones (137-139) react with sodium methoxide at reflux temperature, to yield, in [$^3\text{H}_4$]methanol, 5- [^2H]-2,2-dimethyl-4-halogeno-1-isopropyl-3H-1,2-dihydro-pyrrol-3-ones (140-142). The kinetics of this deuterium exchange was examined by ^1H n.m.r. spectroscopy. A solution of the three halogeno compounds and the corresponding, unsubstituted, pyrrolone in [$^2\text{H}_4$]methanol showed three singlets (δ_{H} 8.60, 8.59 and 8.57) and a doublet (δ_{H} 8.44) due to the protons at the 5-position. These signals could be resolved to give baseline

separation using line narrowing at a spectrometer frequency of 200 MHz. Rate constants could, therefore, be obtained by recording the ^1H n.m.r. spectra (δ_{H} 8-9 range) (Figure 22) at intervals while the sample was maintained at 55°C in the probe of the spectrometer. Measurement of the integral values for each of the signals relative to the 4-unsubstituted compound (which showed no sign of deuterium incorporation after several days) gave the change in concentration and plots of log of concentration against time (Figure 23) gave reasonably straight lines from which the first order rate constants could be calculated (Table 26).

Table 26 Rate constants for deuterium exchange in
1,2-dimethyl-4-halogeno-1-isopropyl-1,2-
dihydro-3H-pyrrol-3-ones

Pyrrolone	X	Rate constant/ 10^2 s^{-1}
(137)	Cl	6.7 ± 0.2
(138)	Br	5.2 ± 0.1
(139)	I	1.5 ± 0.03



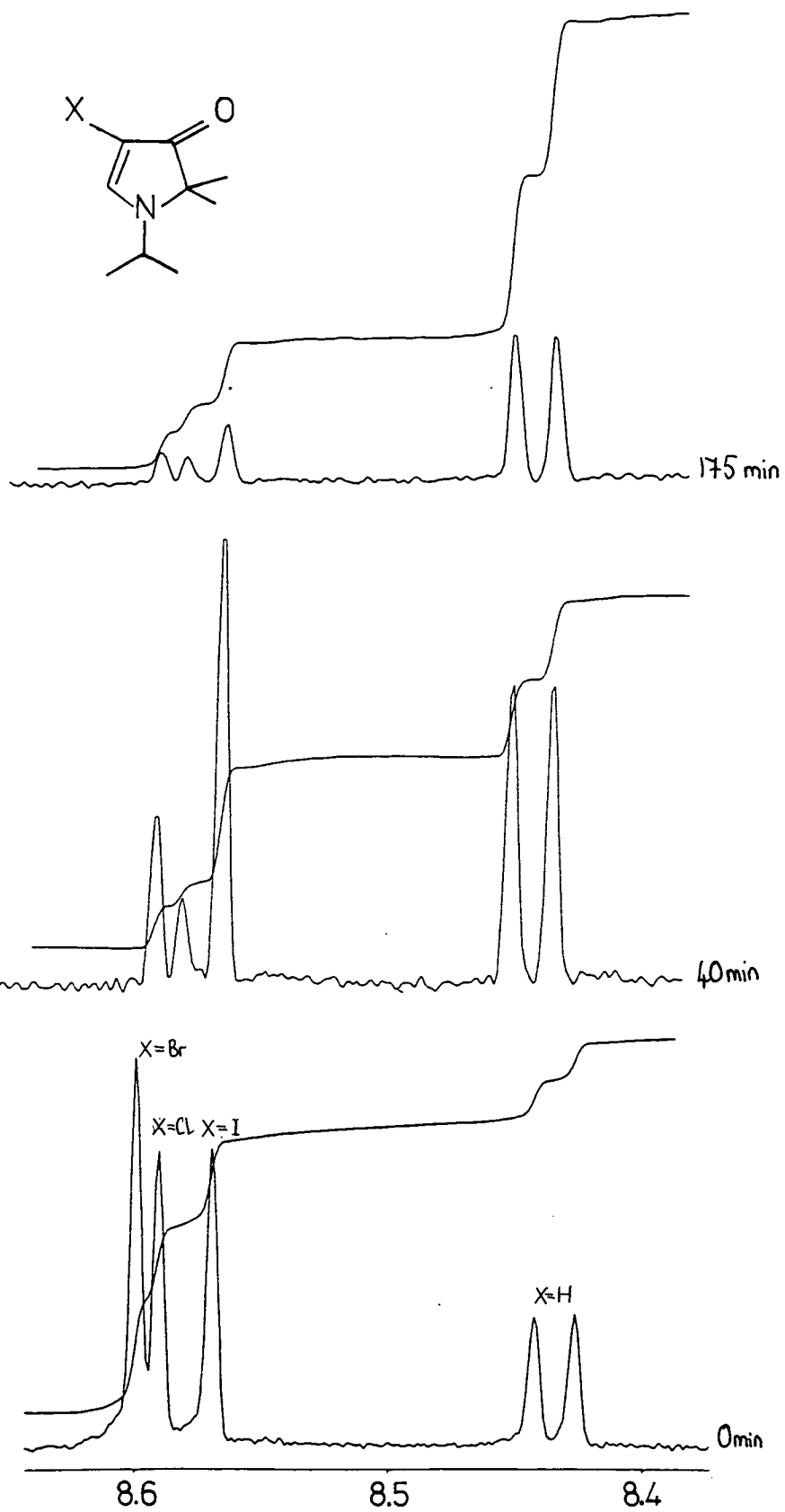


Figure 22

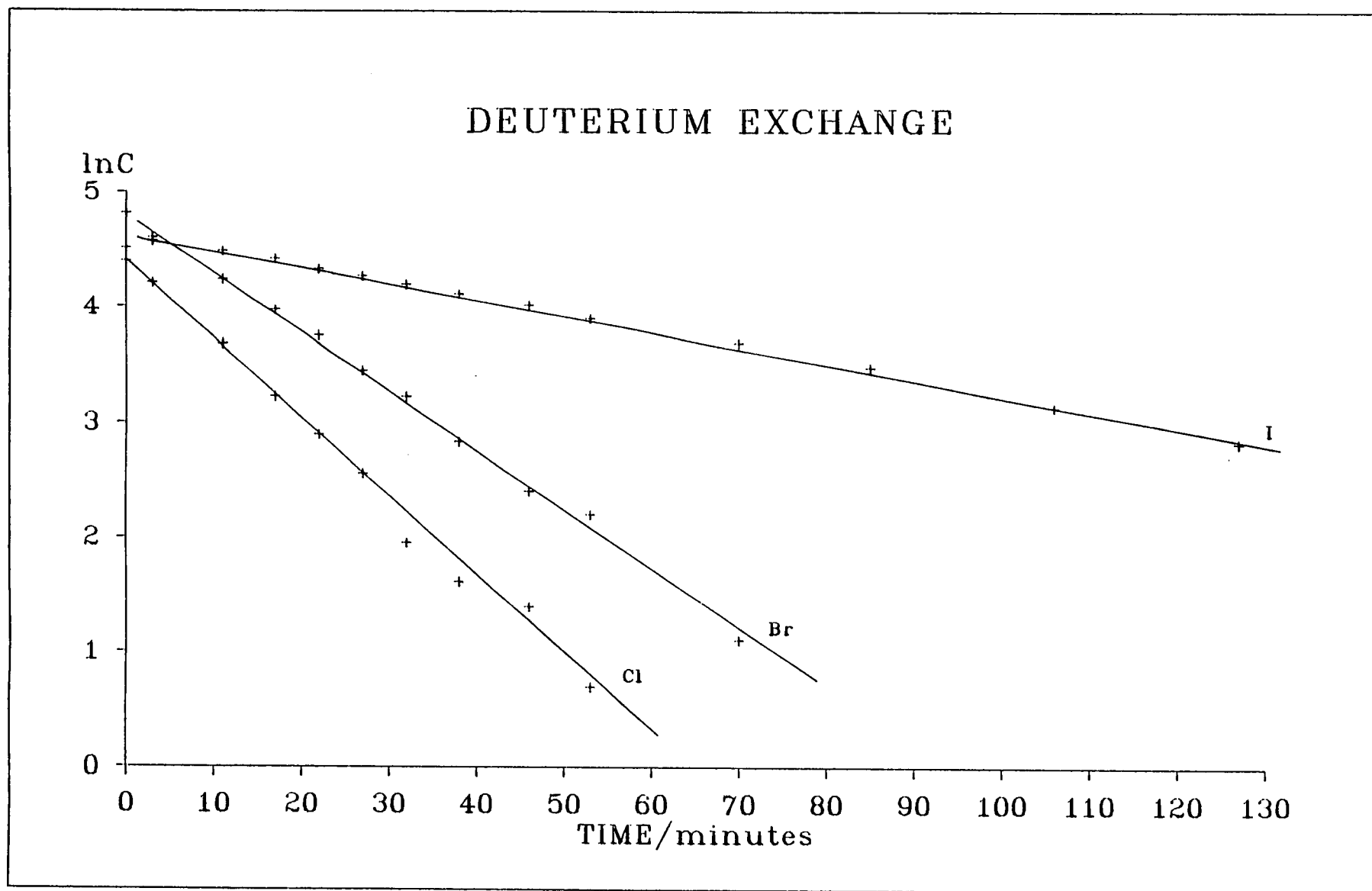


Figure 23

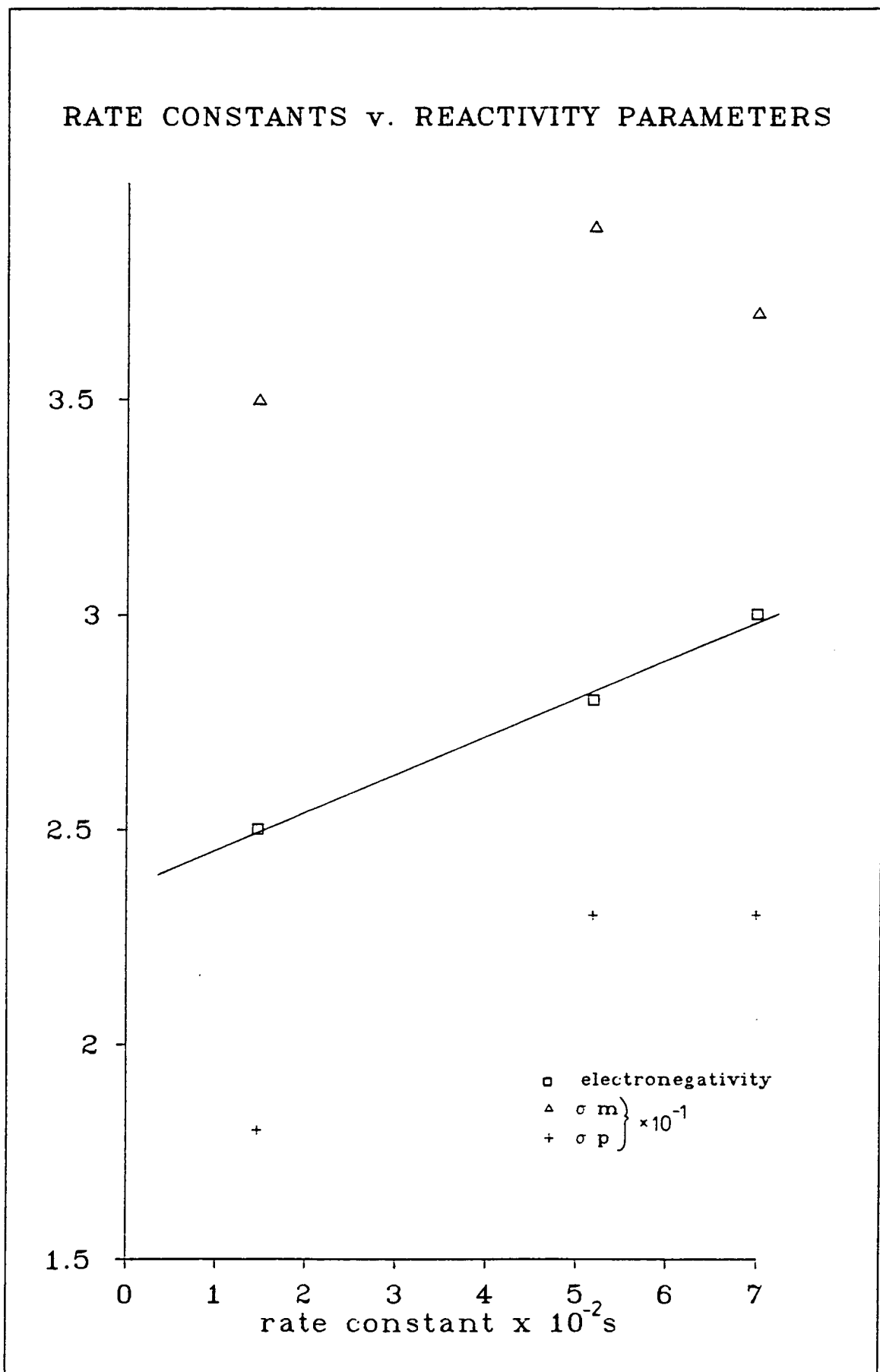
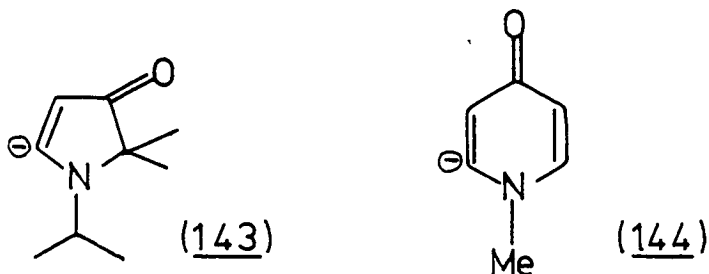


Figure 24

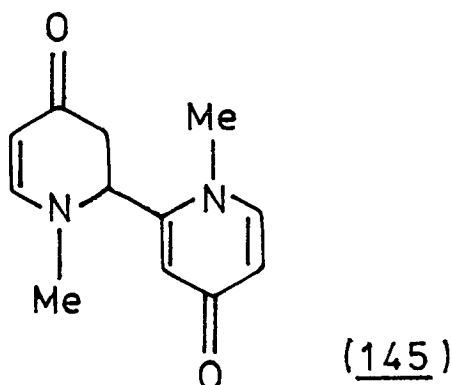
These are found to correlate reasonably with electro-negativity rather than Hammett sigma values (Figure 24) and this supports a mechanism involving formation of a vinyl anion (143). Such anions are proposed in exchange



processes of 4-pyridones (144)¹⁴⁸ but much harsher conditions (butyl lithium in tetrahydrofuran or hot sodium hydroxide) were involved.

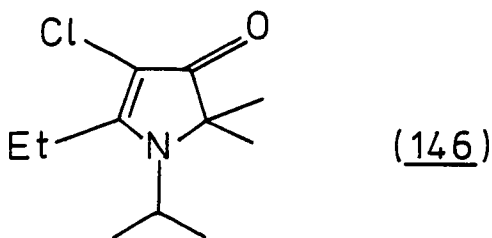
Reactions of the 4-chloropyrrol-3-one (137) with excess lithium di-isopropylamide in tetrahydrofuran also support the formation of a vinyl anion. Thus, treatment with base and quenching with water and [²H₂]water produced starting material and the 5-[²H] compound (140) respectively. However, the recovered yields were only 22 and 27%, respectively, after chromatography and the remaining material appeared to be at least two compounds when examined by g.c. This material was eluted from the column before the deuteriated starting material and showed only aliphatic resonances in its ¹H n.m.r. spectrum.

Two carbonyl resonances were observed in the ^{13}C n.m.r. spectrum and the major component by g.c. had a retention time of around three times that of the starting material. Some sort of dimeric structure seems possible and a dimer (145) has been isolated from reaction of the 4-pyridone (144) with lithium di-isopropylamide.¹⁴⁸ However, the only high mass peak observed in the mass spectrum was at m/z 306 which would require loss of chlorine from and addition of hydrogen to, two molecules of starting material.



When the anion was quenched with excess methyl iodide a creamy coloured solid was obtained after chromatography (130 mg from 185 mg of starting material).

N.m.r. spectroscopy showed this to be mainly 4-chloro-2,2-dimethyl-5-ethyl-1,2-dihydro-3H-pyrrol-3-one (146) and it could be obtained in pure form by repeated recrystallisation.



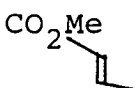
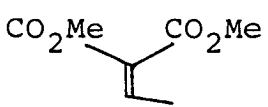
This facile formation of the ethylated product results from reaction of the initial methylation product with excess base, and further alkylation. This has been previously observed in a number of heterocyclic systems,¹⁴⁹ and gives an indication of the reactivity of the substituent alkyl group.

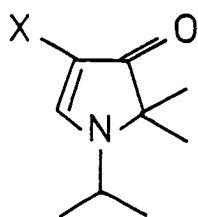
The elimination of chloride anion to give a triple bond has been observed in vinyl anion formation from halogenopyridines¹⁴⁹ and may be the cause of the formation of additional products, but the conditions employed (quenching at -78°C) have usually precluded this side reaction.

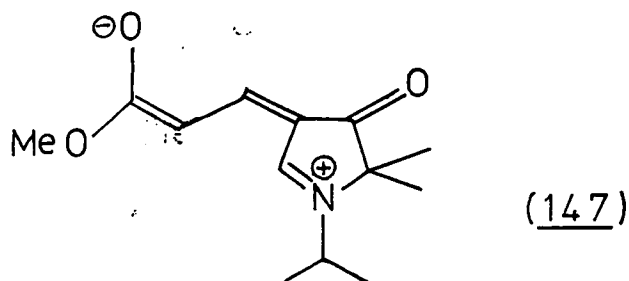
The characteristic resonance in the ^1H n.m.r. spectra of the 4-substituted pyrrol-3-ones discussed in this section is the singlet due to the 5-proton. This occurs at a similar chemical shift to that of the unsubstituted compound for the majority of examples (δ_{H} 7.6-8.0), but for the 4-azo derivatives (121-123 and 125) and the N-acyl compound (126) a considerable deshielding is observed (δ_{H} 8.65-9.3) due to the ring current effects generated by the double bond in the substituents.

The chemical shifts of the ring carbon atoms of the 4-unsubstituted compound (100) and the changes observed on 4-substitution for some of the compounds discussed in this section are shown in Table 27. The value observed for C-4 shows the same direction of shift as the ipso carbon atom in the corresponding benzene derivatives, but the magnitude varies considerably. The shifts are generally larger although they are increased by different degrees (e.g. the shift due to iodo substitution is 43.5 p.p.m. compared to 32.3 p.p.m. in benzene, while for amino substitution the shift is only 0.8 p.p.m. greater than in benzene). The carbonyl signal is shielded in all examples and this can be attributed to a decrease in the polarity of the carbonyl bond. The substituent, X, can promote this effect

Table 27 Changes in ^{13}C chemical shifts on 4-substitution of 1,2-dihydro-3H-pyrrol-3-ones

Compound	X	C2	C3	C4	C5
(100)	H	67.56	204.68	94.28	158.78
(121)	Ph-N=N-	+3.48	-10.69	+31.02	-4.56
(122)	p-NO ₂ Ph-N=N-	+4.28	-11.55	+35.80	-2.76
(123)	p-COOHPh-N=N-	+3.42	-11.54	+35.48	-1.57
(124)	-NH ₂	-0.99	-6.71	+21.0	-8.99
(125)	-NHCOCH ₃	-1.43	-9.85	+16.14	-8.47
(130)		+2.22	-4.90	+10.69	+0.83
(131)		+1.68	-4.76	+10.00	+2.62
(137)	Cl	+1.24	-8.47	+4.15	-2.43
(138)	Br	+0.92	-7.86	-10.67	-0.40
(139)	I	+0.19	-4.57	-43.54	+3.41





either by its electronegativity or by competitive exocyclic delocalisation [e.g. (147)]. The C5-atoms show somewhat smaller shifts which, where significant, are in the same direction as the ortho shifts in the corresponding benzene derivatives, except for chloro substitution. The 4-chloro compound (136) showed some shielding of the 5-position (-2.43 p.p.m.) while in benzene the ortho shift is +0.4 p.p.m., but the C2-atom in chloroethylene is shielded by 5.5 p.p.m. and it seems that in alkenes generally the mesomeric effect from chlorine is more important than the electronegativity for the carbon atom adjacent to the site of substitution.¹²⁷

GENERATION AND ATTEMPTED OBSERVATION OF ANIONS

The 1-tert-butyl-1,2-dihydro-3H-pyrrol-3-one was dissolved in [$^2\text{H}_6$]dimethylsulphoxide and treated with sodium hydride in an attempt to record the n.m.r. spectra of the anion. The solution immediately became a deep red colour, but the proton n.m.r. spectrum showed only a number of broad peaks and some sharper signals which had relatively insignificant integral values. The ^{13}C n.m.r. spectrum showed a large number of peaks. No marked changes were observed in the n.m.r. spectra when a similar experiment was carried out in [$^2\text{H}_8$]tetrahydrofuran and the reaction mixture was cooled to -55°C in the probe of the spectrometer.

The 1-phenyl-1,2-dihydro-3H-pyrrol-3-one was also treated with sodium hydride in dimethylsulphoxide and again the marked colour change was observed. When two portions of the solution were quenched with methyl iodide and [$^2\text{H}_4$]acetic acid, respectively, the colour faded, rapidly. The products observed from these reactions were the expected alkylated species (see following Section) and the 2-[^2H]-3-hydroxypyrrole (the enol tautomer is present almost exclusively in [$^2\text{H}_6$]dimethylsulphoxide).

It therefore appears that the anion, or a similarly reactive species, is formed; the possibility of radicals causing the broad n.m.r. spectra was considered, but no e.s.r. signals were observed from the reaction mixture.

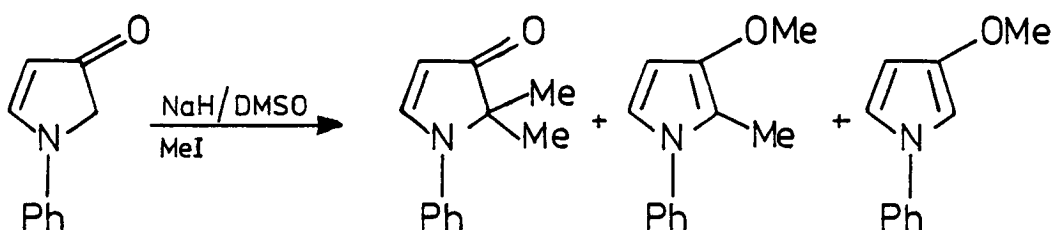
It seems possible that the broad ^1H n.m.r. spectra and the presence of too many peaks for a single species in the ^{13}C n.m.r. spectra of basic solutions of 1,2-dihydro-3H-pyrrol-3-ones may be a result of the presence of a number of species and some rapid exchange processes.

ALKYLATION AND ACYLATION

The ambident reactivity of the 1,2-dihydro-3H-pyrrol-3-one system under basic conditions was mentioned briefly in the Introduction to this thesis; the results of an investigation of the alkylation of simple examples of this system, which illustrate and define this reactivity are now reported.

The pyrrolones (or 3-hydroxypyrroles in the aromatic tautomer) were found to be inert to conditions which quantitatively alkylate phenols (e.g. methyl iodide and potassium carbonate in dimethylformamide or potassium hydroxide in dimethylsulphoxide). However, treatment of dimethylsulphoxide solutions with excess sodium hydride and quenching with methyl iodide at room temperature, did give reaction. Reaction of the 1-phenyl-3-hydroxypyrrole under these conditions led to three products and

t.l.c. and g.c. showed the major product to be the result of C,C-dialkylation. Thus, under these conditions, the carbon atom site of the ambident nucleophile was subject to greater attack, although other products were formed (Scheme 50).



Scheme 50

This contrasts with phenoxide which rarely shows C-alkylation which would destroy aromaticity and thus it appears that the system exhibits enolate reactivity and there is little influence from the aromatic tautomer. Since there are few direct routes to 3-alkoxypyrroles, and alkylation of the previously available 3-hydroxypyrroles has had limited success (see Introduction), it was of interest to investigate the factors influencing O- vs. C-alkylation in attempts to find a synthetically useful route to 3-alkoxypyrroles.

Many of the factors influencing the alkylation of ambident anions can be explained by the "Hard and Soft

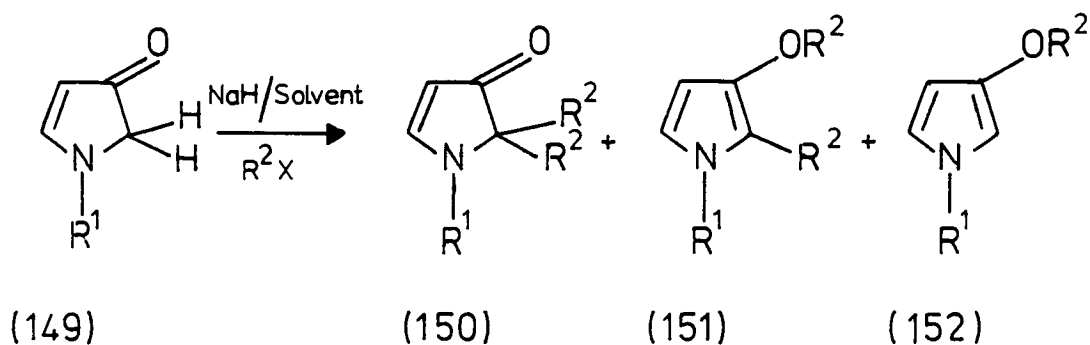
Acid and Base Theory" (HSAB) and a useful review has appeared.¹⁵⁰ Pearson first proposed HSAB in the 1960's¹⁵¹ and its use to explain and predict chemoselectivity is now widespread.¹⁵² It is based on the premise that hard acids will have strong interactions with hard bases and soft acids with soft bases and thus, where reaction may occur at sites of different 'hardness' the selectivity of a reagent can be predicted on the basis of its own 'hardness'. The factors influencing this effect can be summarised as follows:

(a) Bases will show increasing hardness as
(i) polarisability decreases; (ii) electronegativity increases; (iii) oxidation becomes more difficult, and
(iv) empty orbitals increase in energy.

(b) Acids will show increasing hardness as (i) positive charge increases; (ii) size decreases, and (iii) outer electrons become more easily excited.

Thus, in the ambident anion generated on treatment of pyrrol-3-ones with base, C-alkylation corresponds to reaction at the 'soft' site while the oxygen provides the 'hard' site.

The factors considered in this investigation were the leaving group, the structure of the alkylating agent, solvent and the nature of the substrate. A general representation of the reaction is given in Scheme 51,



Scheme 51

for the 2-unsubstituted examples. The products (150) and (151) result from C-alkylation followed by C- or O-alkylation, respectively; none of the C-monoalkylated product is observed under our conditions. The product (152) results from initial O-alkylation which locks the system in the enol form and prevents further alkylation. The comparative experiments now discussed were carried out using an excess of base and alkylating agent, and altering one of the influential parameters at a time. The crude reaction mixture was quenched and extracted with methylene chloride. The solvent was removed in vacuo and the residue dissolved in [²H]chloroform and analysed by ¹H n.m.r. spectroscopy.

Results shown in Table 28 indicate that changing the solvent from dimethylsulphoxide to tetrahydrofuran decreases the amount of O-alkylation when other parameters

Table 28 The effect of solvent on C- v. O-alkylation

Substrate	Solvent	Alkylating Agent	<u>C</u> -alkylation	<u>O</u> -alkylation	<u>C</u> + <u>O</u> -alkylation
1-phenyl-3-hydroxypyrrole	DMSO	MeI	75	13	12
1-phenyl-3-hydroxypyrrole	THF	MeI	100	0	0
1-benzyl-2-phenyl-3-hydroxypyrrole	DMSO	MeI	31	69	-
1-benzyl-2-phenyl-3-hydroxypyrrole	THF	MeI	77	23	

are unchanged. This can be explained in terms of the solvation of the cation; O-alkylation is favoured when the anion is as free as possible¹⁵⁰ and thus, greater solvation of the cation and disruption of potential ion pairs in aprotic, polar solvents results in attack at the more electronegative site.

Increasing the hardness of the leaving group is expected to promote the amount of O-alkylation and the results shown in Table 29 confirm that this occurs. Thus comparison of methyl bromide with methyl iodide or ethyl bromide with ethyl iodide showed a marked increase in attack at oxygen on changing from the very soft iodide anion as leaving group. Comparison of the results for methyl tosylate and methyl iodide is not strictly possible as only one equivalent of tosylate was used and some starting material was present in the crude reaction mixture. Triethyloxonium tetrafluoroborate was expected to be a particularly good O-alkylating agent, since enol ethers have been obtained by its reaction with simple ketones,¹⁵³ but a direct comparison could not be made as attempts to carry out this reaction in dimethylsulphoxide were unsuccessful and changing solvent has been shown to affect the reaction. Reaction in tetrahydrofuran did, however, lead to O-alkylation as the major product (87% for the 1-phenyl-1,2-dihydro-3H-pyrrol-3-one) with the remaining product a result of C-, O-dialkylation.

Table 29 The effect of leaving group on C- v. O-alkylation

Substrate	Solvent	Alkylating Agent	<u>C</u> , <u>C</u> -alkylation	<u>O</u> -allylation	<u>C</u> + <u>O</u> -alkylation
1-phenyl-3-hydroxy-pyrrole	THF	MeI	100	0	0
"	THF	MeTos	2	82	16
"	DMSO	MeI	75	13	12
"	DMSO	MeBr	14	60	26
"	DMSO	EtI	43	43	14
"	DMSO	EtBr	13	63	24

Similarly, the structure of the alkylating group itself should influence the chemoselectivity, and the results for the series, methyl, ethyl, isopropyl are given in Table 30. As the carbon of attachment becomes more substituted the 'hardness' of the cation increases and O-alkylation becomes more favoured. The increasing steric bulk encountered in the series, from methyl to isopropyl, is undoubtedly also important as it must interfere to a greater extent with C-alkylation. This is found to be the case; thus, isopropyl bromide gives none of the C,C-dialkylated product (152; $R^2 = Pr^i$) although some C,O-dialkylation occurs. The effect of increasing hardness is particularly striking when the anion is acetylated using acetyl chloride. The acyl group is considerably harder than alkyl groups, and also chloride is a harder leaving group, so this results in the observation of 100% attack at oxygen. Direct comparison is not possible since acetyl chloride apparently reacted with dimethylsulphoxide so the solvent was also changed.

Changes in the substitution pattern of the substrate also influence the ambident reactivity of the anion (Table 31), but since any stabilisation by resonance must affect both sites through the inherent conjugation of the enolate system, it seems likely that the substituent effects are a result of steric rather than electronic factors.

Table 30 The effect of cation structure on C- v. O-alkylation

Substrate	Solvent	Alkylating Agent	<u>C</u> , <u>C</u> -alkylation	<u>O</u> -alkylation	<u>C</u> & <u>O</u> -alkylation
1-phenyl-3-hydroxy-pyrrole	DMSO	MeI	75	13	12
"	DMSO	EtI	43	43	14
"	DMSO	MeBr	14	60	26
"	DMSO	EtBr	13	63	24
"	DMSO	Pr ⁱ Br	-	90	10
"	THF	AcCl	-	100	-

Table 31 Effect of substrate structure on C- v. O-alkylation

3-hydroxy-pyrrole	Solvent	Alkylating Agent	<u>C</u> -alkylation	<u>O</u> -alkylation	<u>C</u> & <u>O</u> -alkylation
1-phenyl	DMSO	MeI	75	13	12
2-methyl-1-phenyl	DMSO	MeI	77	23	-
1,2-diphenyl	DMSO	MeI	63	37	-
1-methyl-2-phenyl	DMSO	MeI	54	46	-
1-benzyl-2-phenyl	DMSO	MeI	31	69	-
1-tert-butyl	DMSO	MeI	50	33	17

However, the 1-phenyl examples with 2-methyl and 2-phenyl substitution show 77 and 63% C-alkylation respectively, despite methyl groups generally having greater steric demands than planar phenyl rings; the change of selectivity with 2-substitution may be a result of a positive inductive effect from the methyl group increasing the electron density at the 2-position and increasing the rate of the reaction at this site.

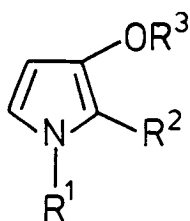
Although the majority of alkylation conditions described in this section produce a mixture of products and are, therefore, of limited use synthetically, the 2,2-disubstituted-1,2-dihydro-3H-pyrrol-3-ones could be readily separated from 3-alkoxypyrroles by chromatography and thus pure 2-substituted 3-alkoxypyrroles (35-55%, using methyl iodide as the electrophile) could be obtained from 2-monosubstituted substrates. However, separation of the O-monoalkylated and C-, O-dialkylated products, which were obtained from 2-unsubstituted substrates, proved difficult and completely pure 3-alkoxypyrroles without 2-substitution were not obtained. The results discussed provided information which suggested a number of combinations of hard leaving group, bulky alkylating agent and polar solvent which appeared possible candidates for the synthetic method of choice for 3-alkoxypyrroles without 2-substitution. Clearly both the use of the tosylate leaving group and an aprotic polar solvent had a considerable effect on the selectivity of

alkylation but they were not successfully combined as the tosylate appeared to react with dimethylsulphoxide which was the more polar solvent used. A study of the literature revealed that hexamethylphosphorous-triamide (HMPT) had proved a useful aprotic solvent in alkylations and that more recently 1,3-dimethyl-2-imidazolidinone (DMEU) had been found to be a favourable alternative on the grounds of the carcinogenic character of HMPT. Subsequent to this work, the method of choice for O-alkylation has been found to involve the use of methyl tosylate in DMEU.¹⁵⁴ Reaction occurs in fifteen minutes at room temperature to give completely O-alkylation. Comparison of the selectivity of methyl iodide in DMEU and dimethylsulphoxide showed that DMEU was, in fact, better at promoting O-alkylation (44% compared with 13%) and the use of methyl tosylate in dimethylsulphoxide, had it been successful, may not have been sufficient to give complete O-alkylation.

The ^1H and ^{13}C n.m.r. spectra of the 3-alkoxy- and 3-acetyloxy-pyrroles have been examined, but care must be taken in drawing direct comparisons between the data obtained for these fixed aromatic systems and the corresponding hydroxy compounds (the enol tautomer of the equilibrium discussed in detail earlier), since the information was obtained for the fixed systems using [^2H]chloroform as solvent whereas [$^2\text{H}_6$]dimethylsulphoxide was used for the 3-hydroxypyrroles.

Table 32 Proton chemical shifts and coupling constants
of 3-alkoxy- and 3-acetyloxypyrroles

3-Oxy- pyrrole	R ¹	R ²	R ³	2-H	4-H	5-H	³ J _{4,5}	⁴ J _{2,4}	⁴ J _{2,5}
<u>153</u>	Ph	H	Me	6.73	6.135	6.95	3.1	2.0	2.5
<u>154</u>	Bu ^t	H	Me	6.37	5.80	6.56	2.8	2.0	2.5
<u>155</u>	Ph	H	Et	6.69	6.09	6.90	2.9	2.0	2.5
<u>156</u>	Bu ^t	H	Et	6.36	5.78	6.54	3.0	2.0	2.6
<u>157</u>	Ph	H	Pr ⁱ	6.67	6.05	6.88	3.1	2.0	2.5
<u>158</u>	Ph	H	Ac	7.16	6.19	6.90	3.2	1.8	2.6
<u>159</u>	Bu ^t	H	Ac	6.86	5.88	6.63	3.1	1.9	2.6
(<u>160</u>)	Ph	Me	Me	-	6.18	6.68	3.2	-	-
(<u>161</u>)	Ph	Ph	Me	-	6.19	6.73	3.2	-	-
(<u>162</u>)	Me	Ph	Me	-	5.97	6.47	3.0	-	-
(<u>163</u>)	CH ₂ Ph	Ph	Me	-	6.38	6.78	3.1	-	-



The 4H- and 5H- signals show little variation from those of the corresponding 3-hydroxypyrroles (Table 32) and the shifts which are observed can probably be accounted for by the change in solvent. The 2H- signals, however, appear to show genuine shielding of 0.2-0.3 p.p.m. on alkyl substitution and deshielding of the same extent on acetyl substitution. This can be explained by through space effects from the alkyl or acetyl group (e.g. the ring current of the carbonyl function), and by the mesomeric donation of the lone pair on oxygen which is expected to be decreased on acetyl substitution, therefore decreasing the electron density at the 2-position (Figure 25).

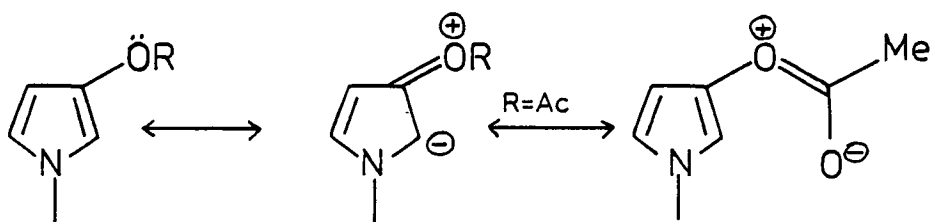


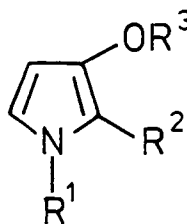
Figure 25

The ^{13}C n.m.r. spectra of the 2-unsubstituted examples, in accord with the results found for the 3-hydroxypyrroles, show consistent shifts in the same direction as those observed for similar substitution in benzene (Table 33).

Table 33 ^{13}C chemical shifts of 3-alkoxy- and
3-acetyloxy-pyrroles ^a

Pyrrole	R ¹	R ²	R ³	C2	C3	C4	C5
(153)	Ph	H	Me	100.9 (-18.1)	150.8 (+40.7)	100.3 (-9.8)	117.0 (-2.0)
(154)	Bu ^t	H	Me	99.75 (-16.95)	148.35 (+41.35)	96.8 (-11.2)	115.05 (-1.65)
(155)	Ph	H	Et	101.5 (-17.5)	149.6 (+39.5)	100.8 (-9.3)	116.8 (-2.2)
(156)	Bu ^t	H	Et	100.5 (-16.2)	147.3 (+40.3)	96.5 (-10.5)	114.8 (-1.9)
(157)	Ph	H	Pr ⁱ	103.0 (-16.0)	147.8 (+37.7)	101.6 (-8.5)	116.4 (-2.4)
(158)	Ph	H	Ac	108.6 (-10.4)	139.1 (+29.0)	103.3 (-6.8)	116.3 (-2.5)
(159)	Bu ^t	H	Ac	106.8 (-9.9)	136.8 (+29.8)	99.7 (-7.3)	114.4 (-2.3)

^a Chemical shifts given with change from corresponding
2,3-unsubstituted pyrrole in brackets.



Again the shifts are somewhat larger than the corresponding ones in benzene (for example the C3-resonance is shifted by 41 and 29 p.p.m. on methoxy and acyloxy substitution respectively, while in benzene values of 31.4 and 23 p.p.m. are found). Also analogous with the hydroxy case, there are differential effects on the C2- and C4-signals, and the C5-atom shows shielding, which contrasts with the observed effects on the signals of the meta positions in benzene.

2-Substitution influences the signals for the C2- and C3-atoms as expected for alkyl or aryl substitution on alpha- and ortho-atoms, with slightly greater magnitude than in benzene. Steric effects begin to play a part in determining the chemical shifts which results in deviations from the predicted substituent effect of the 3-substituent. The 2-substituted-3-methoxypyrroles have the chemical shifts shown in Table 34.

Table 34 ^{13}C chemical shifts of 2-substituted-3-methoxypyrroles

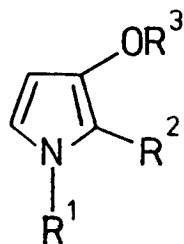
3-methoxy-pyrrole	R ¹	R ²	R ³	C2	C3	C4	C5
(160)	Ph	Me	Me	112.93	145.42	97.21	116.75
(161)	Ph	Ph	Me	116.81	146.93	99.29	120.43
(162)	Me	Ph	Me	118.44	145.48	95.52	119.53
(163)	CH ₂ Ph	Ph	Me	118.03	145.22	96.05	118.84

Table 55 Carbon-proton coupling constants for 3-alkoxy- and 3-acyloxy-pyrroles

3-Oxy- pyrrole	R ¹	R ²	R ³	C2		C3		C4		C5	
				¹ J	³ J _{H(4)} = ³ J _{H(5)}	² J _{H(2)}	³ J _{H(5)}	¹ J	² J _{H(5)} = ³ J _{H(2)}	¹ J	² J _{H(4)} = ³ J _{H(2)}
(153)	Ph	H	Me	185.7	3.9	a	a	172.5	7.0	186.0	6.6
(154)	Bu ^t	H	Me	182.3	4.6	a	a	170.9	6.85	183.3	6.7
(155)	Ph	H	Et	185.8	4.2	a	a	172.0	7.0	186.2	6.4
(156)	Bu ^t	H	Et	182.8	4.3	a	a	170.3	7.0	183.0	6.8
(157)	Ph	H	Pr ⁱ	185.7	4.2	a	a	172.5	7.1	185.7	6.3
(158)	Ph	H	Ac	191.5	4.2	3.4	9.9	175.2	7.1	b	6.3
(159)	Bu ^t	H	Ac	188.0	4.5	2.8	10.8	173.8	6.9	184.5	6.8
(160)	Ph	Me	Me	-	a	a	a	170.8	7.7	185.7	6.8
(161)	Ph	Ph	Me	-	a	a	a	171.9	7.6	187.4	6.7
(162)	Me	Ph	Me	-	a	a	a	170.4	7.9	186.8	a

^a Complicated by further coupling

^b Overlapping peaks

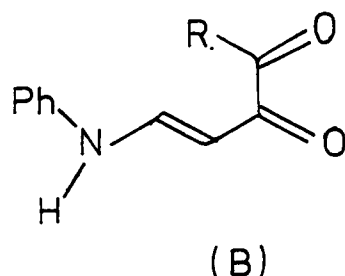
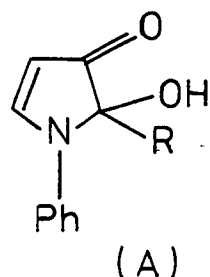


The one bond carbon-proton coupling constants of the 3-alkoxypyrroles are very similar to those of the corresponding 3-hydroxypyrroles. Thus, for the 1-phenyl series values of 185.7, 172.2 and 186.0 ± 2.0 Hz were found for the C2-, C4- and C5-signals, respectively, compared with 185.8, 170.9 and 186.5 Hz for the 1-phenyl-3-hydroxypyrrole. The acetylated examples, however, show an increase in coupling constants of 6 Hz for C2-H, 3 Hz for C4-H and 1.5 Hz for C5-H of both the 1-phenyl and 1-tert-butyl examples. The long range couplings to C2, C4 and C5 seem to be completely unaffected by changes in O-substitution but the C3-signal shows a decrease in the two bond coupling (about 0.4 Hz) and an increase in the three bond coupling (about 0.5 Hz) for both the 1-phenyl- and 1-tert-butyl-3-acetyloxypyrroles. The carbon-proton couplings are detailed in Table 35.

REACTIONS WITH RADICALS

The varied reactivity of 1,2-dihydro-3H-pyrrol-3-ones to oxidation has been discussed in the Introduction to this thesis. During the present work, the 2-mono-substituted compounds have been found to undergo facile oxidation as shown by an M +16 peak in their mass spectra and the presence of additional oxygen when they are subjected to elemental analysis. Evidence for the

formation of the corresponding 2-hydroxy compound from 2-substituted-pyrrol-3-ones, (106 and 107), is also present in the ^1H n.m.r. spectra if chloroform solutions are allowed to stand at room temperature.



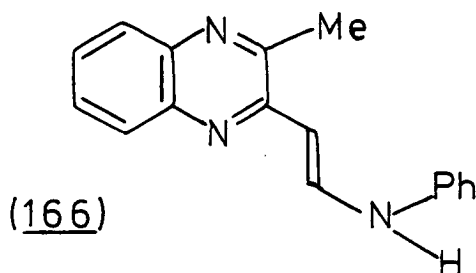
(164) R = Ph

(165) R = Me

Thus, (107) shows additional doublets [δ_{H} (CDCl_3) 8.8 and 5.6], due to the 4- and 5-protons of the oxidised material (164) and signals which may arise from the open-chain form of this hemi-aminal (164B). The 2-methyl compound (106) undergoes particularly rapid oxidation and the oxidised product (165B) could be isolated after aerial oxidation in chloroform solution, removal of solvent, and purification by bulb-to-bulb distillation (25%). Alternatively, one electron oxidation with potassium ferricyanide gave the product (165B) in better yield (40%). In agreement with Davoll's results which indicated that a similar pyrrol-3-one (Scheme 20) reacted as both its cyclic and open-chain tautomers¹⁹;

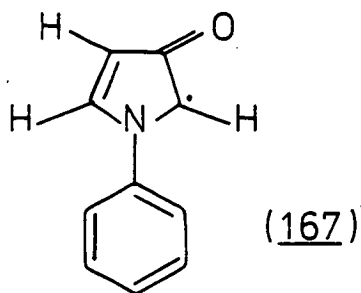
the tautomers, (165A and 165B) were found to interconvert simply on changing solvent. Thus, the ring form (165A) is observed in [$^2\text{H}_6$]dimethylsulphoxide solution, while the open-chain form exists in [^2H]chloroform.

Reaction of (165) with 1,2-diaminobenzene, in ethanol at reflux, followed by addition of water, led to an orange precipitate. The ^1H n.m.r. spectrum of this material indicated that the expected quinoxaline (166) may be present, but that there was more than one product, and the spectrum was possibly complicated by tautomerism. The product could not be obtained completely reproducibly which is in agreement with Davoll's results.¹⁹ It is thought that the mixture consists of the expected quinoxaline (166) with other contaminants such as the product resulting from exchange of the 1,2-diaminobenzene and the anilino substituent.



The proposal of a peroxy intermediate as the first step in the oxidation of a number of pyrrol-3-ones was discussed earlier and it seems likely that radical intermediates are involved. However, attempts to observe a radical formed on abstraction of a hydrogen atom from

the 2-monosubstituted compounds, by electron-spin resonance spectroscopy led to only weak, poorly resolved signals. In contrast, the 1-phenyl-1,2-dihydro-3H-pyrrol-3-one, on irradiation in the presence of ditert-butyl-peroxide, gave rise to a strong signal (Figure 26) which persisted for several minutes after the removal of the light source. This persistent radical was only observed after irradiation for several minutes at around room temperature. Analysis of the e.s.r. spectrum by inspection showed it to consist of a large triplet (~ 4.8 G), a medium quintet (~ 1.35 G), a small triplet (~ 0.8 G), and a very small doublet (~ 0.5 G). This, obviously, was far too complex to be a result of coupling within the 5-membered ring if the radical (167) was formed by abstraction at the 2-position, and suggested coupling to the phenyl ring.



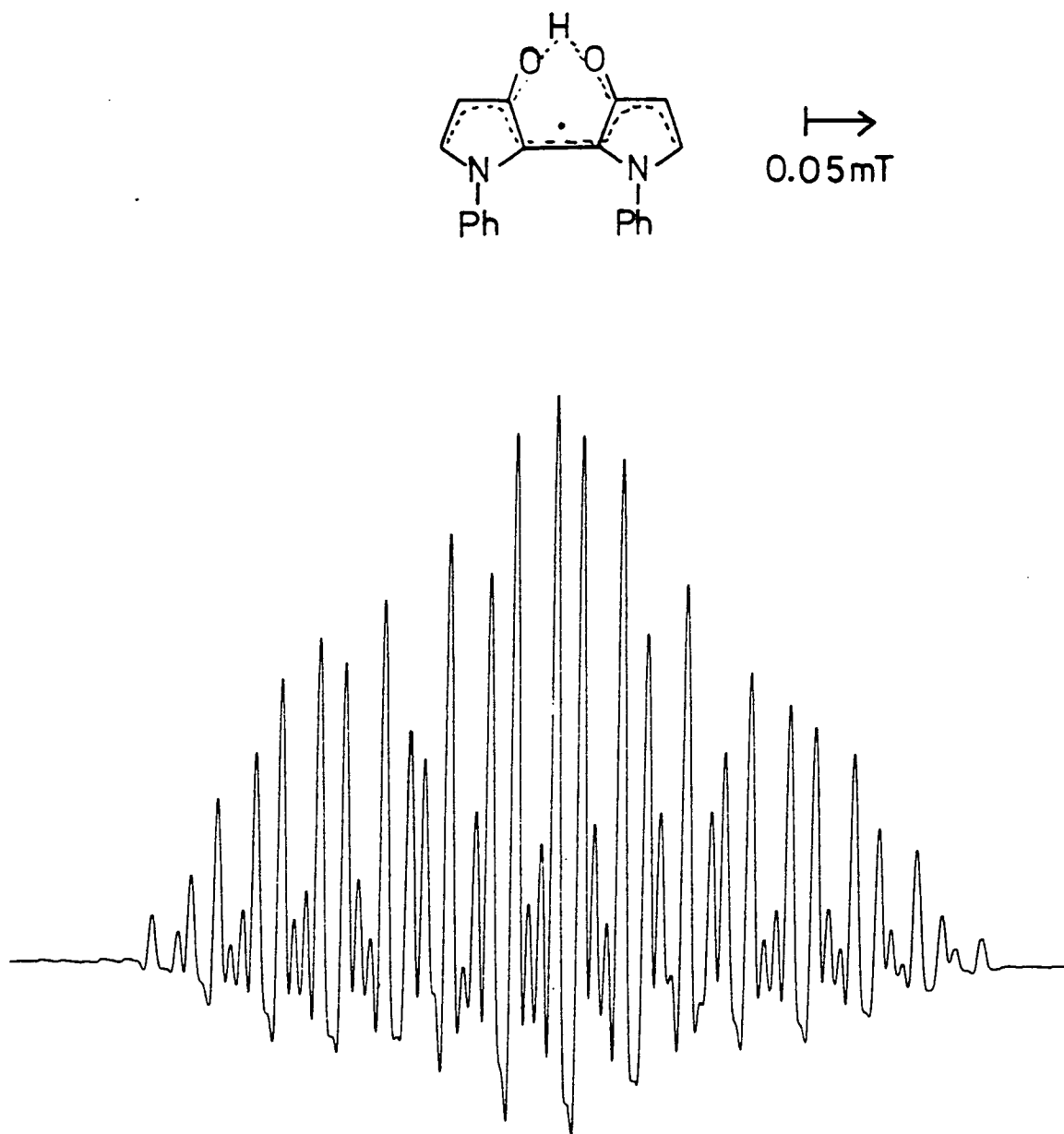
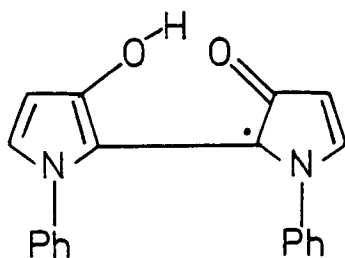


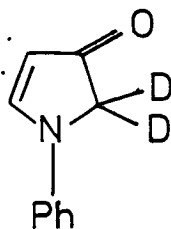
Figure 26

However, the *p*-tert-butylphenyl analogue was synthesised and gave rise to an identical e.s.r. spectrum, thus eliminating the possibility of coupling to the *p*-position and making other couplings to the phenyl ring seem unlikely. The dimeric structure (168) has all the required features of the observed spectrum; the hydrogen atom can

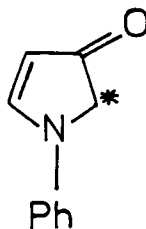


(168)

be attached to either oxygen atom and the radical delocalised throughout both rings thus giving two equivalent nitrogen atoms (the quintet), two pairs of equivalent protons (the triplets) and one unique proton (the doublet). 1-Phenyl-1,2-dihydro-3H-pyrrol-3-ones labelled at the 2-position with deuterium (169) or carbon-13 (170) were synthesised and the e.s.r. spectra



(169)



* = ^{13}C

(170)

obtained. Simulation of the initial spectrum with the small doublet removed in the deuterium case, and additional coupling to two carbon atoms superimposed in the carbon-13 case, gave spectra which were in close agreement to those obtained experimentally (e.g. Figure 27). The optimum splittings, obtained by simulation, for the three species are shown in Table 36. It is thought that the deuteriated analogue was contaminated with some of the 4-[²H] species which would explain the rather poorer fit.

Table 36 Optimum hyperfine splittings in e.s.r. spectra of the dimeric radical (168)

Pyrrolone	2 x N	2 x H	2 x H	1 x H	2 x C
(<u>110</u>)	1.35	4.85	0.85	0.55	-
(<u>169</u>)	1.17	4.68	0.77	-	-
(<u>170</u>)	1.35	4.82	0.8	0.6	0.8

Viehe has proposed a capto-dative effect⁵³ to explain the unusual stability and persistence of certain radicals without large substituents. The stabilisation of radicals by either electron withdrawing or electron donating substituents is well known and Viehe proposes that radicals

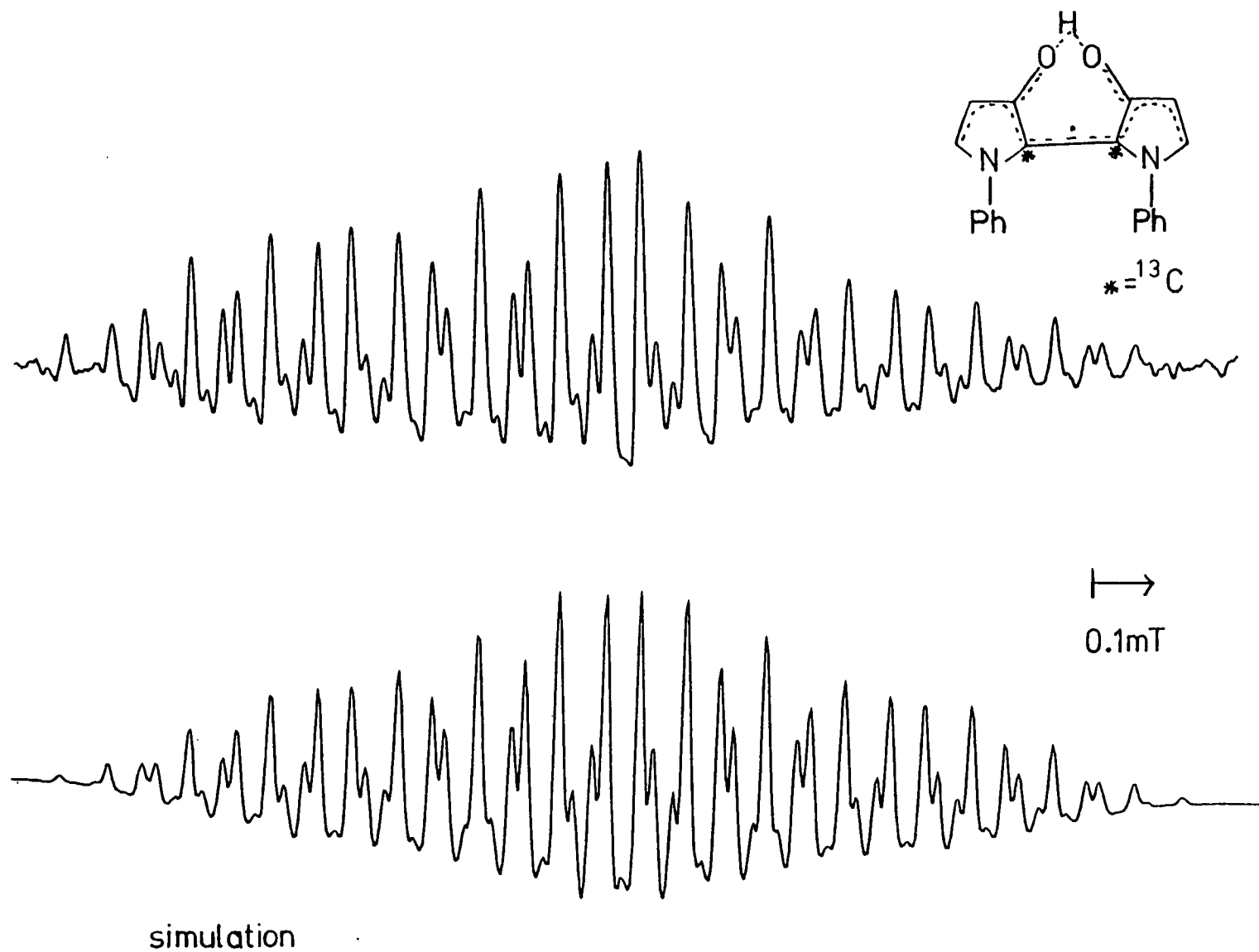
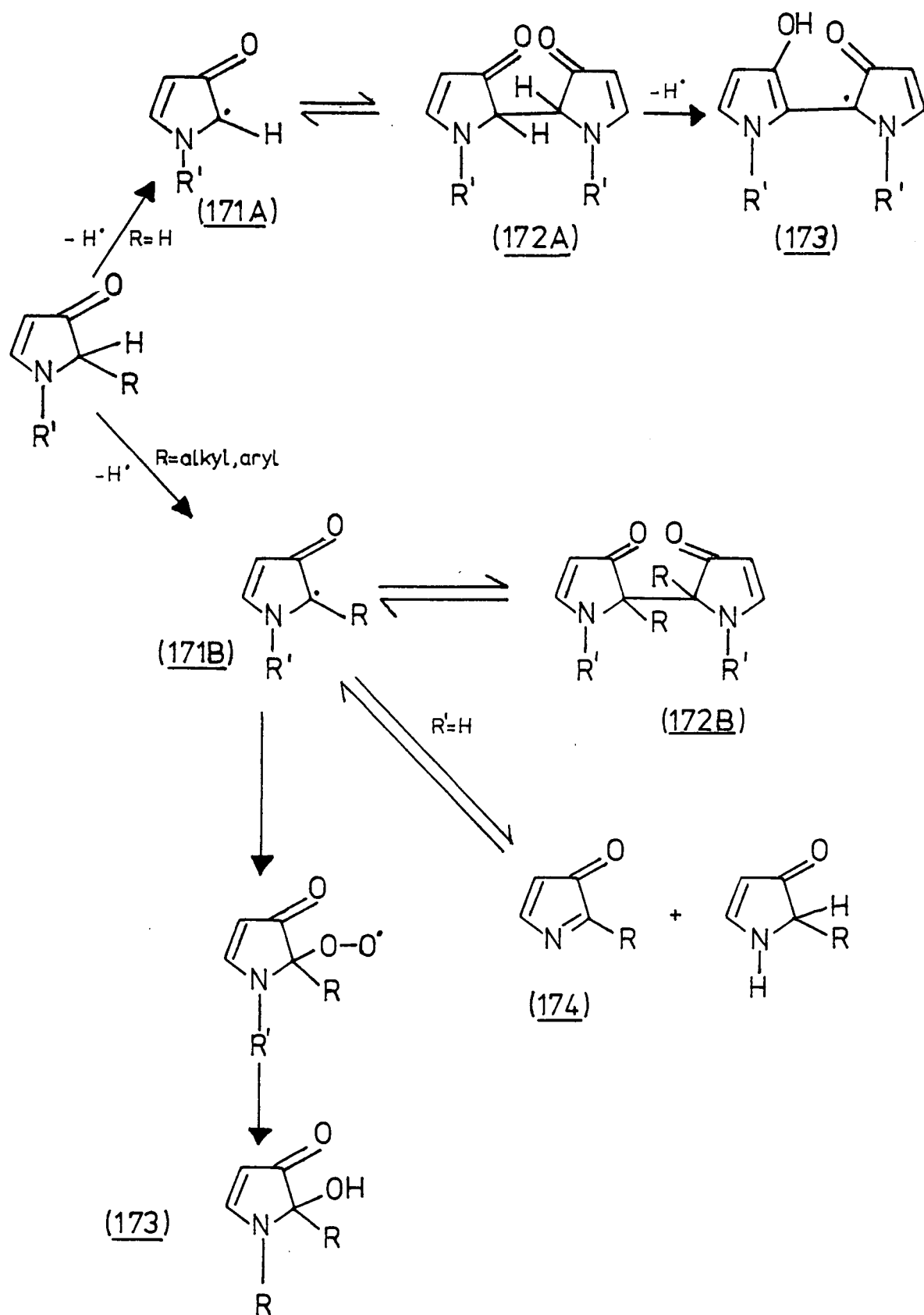


Figure 27

which have both types of stabilisation simultaneously, exhibit a tandem effect which is greater than the sum of the individual effects. The radical produced by hydrogen abstraction at the 2-position of pyrrol-3-ones (e.g. 167) is potentially stabilised by the electron-donating nitrogen atom and the electron-withdrawing carbonyl group and might, therefore, be expected to exhibit the properties of capto-dative radicals, namely to undergo dimerisation, rather than addition or abstraction reactions. This can be used to suggest a reaction scheme which is consistent with the formation of the dimeric radical observed by e.s.r. spectroscopy, and the various oxidation products discussed in the Introduction, and which is illustrated in Scheme 52.

Thus, in the 2-unsubstituted cases, the dimer (172A) is formed, via the capto-dative radical (171A), and it can undergo further hydrogen abstraction to give the observed radical (173). This radical is presumably an intermediate in the formation of the indigo type products observed by Benary¹⁷, Bauer^{15,48} and Atkinson and Bullock⁵⁰. The corresponding dimer (172B), formed from 2-mono-substituted compounds, cannot undergo further hydrogen abstraction, thus dedimerisation, typical of capto-dative systems, gives (171B) which is subject to other reactions. Examples with an N-H group can undergo



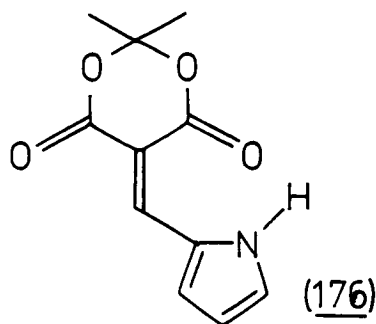
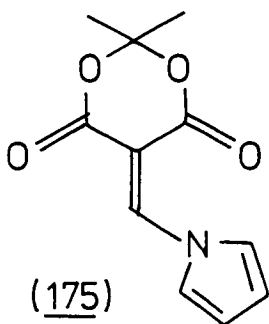
Scheme 52

disproportionation to give the starting compound and the azacyclopentadienone (174) as observed by Freeman and Haddadin,³⁶ while the N-substituted compounds are attacked by oxygen to give peroxy intermediates, which undergo typical radical reactions leading to the 2-hydroxy compounds (173) observed during this work, and by others.^{19,31}

The reaction scheme illustrated (Scheme 52), thus accounts for the varied oxidative reactivity observed in the 1,2-dihydro-3H-pyrrol-3-one system during this and previous work and rationalises it on the basis of the capto-dative stabilisation of radicals which has been proposed by Viehe.

D. ELECTROPHILIC REACTIONS OF 5-METHOXYMETHYLIDENE-
2,2-DIMETHYL-1,3-DIOXANE-4,6-DIONES

The reaction of the title compound with amines to yield aminomethylidene Meldrum's Acid derivatives has already been described as the method of choice for the preparation of these compounds. In relation to this synthesis, it was of interest to discover whether the nitrogen atom in pyrrole was sufficiently nucleophilic to displace the methoxy group and yield the unsaturated derivative (175), but, as is generally the case with pyrrole, the α -carbon atom proved more susceptible to electrophilic attack and the 5-(pyrrolyl-2-methylidene) derivative (176) was obtained. Substitution reactions of 2-alkoxymethylidene-1,3-dicyanopropanes are known¹⁵⁵ and have been used in

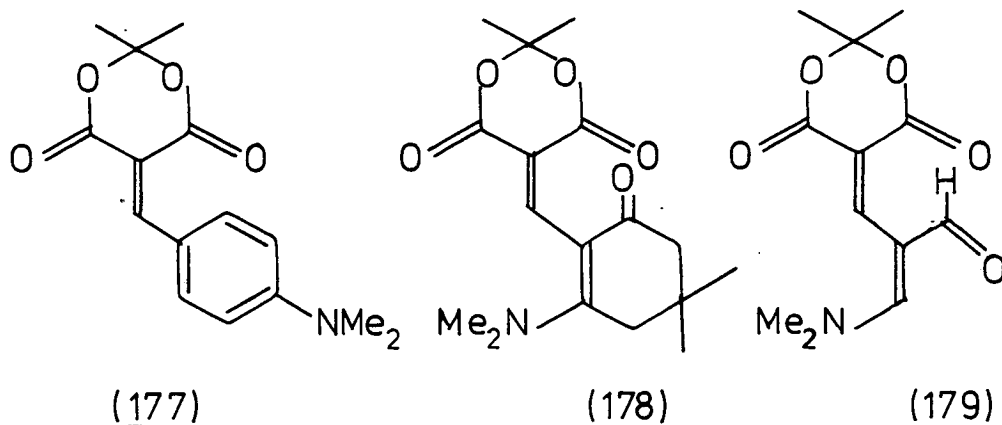


heterocyclic syntheses. Similarly, the electrophilic reactivity of methoxymethylidene Meldrum's Acid seemed to offer potential for the preparation of derivatives suitable for further manipulation. The range of reactivity was therefore investigated and the properties of some of the products were studied.

The reagent may be readily prepared by a literature method,¹¹⁰ and used after simply washing it with ether. However, it is subject to ready decomposition to the hydroxy analogue, even on storage at -20°C, and in reactions with less active substrates it is best to use freshly prepared material.

PREPARATION OF SUBSTITUTED 5-METHYLIDENE-2,2-DIMETHYL-1,3-DIOXANE-4,6-DIONES

The methoxymethylidene Meldrum's Acid was found to react with N,N-dimethylaniline to give the para-substituted derivative (177) after heating to reflux for two hours in acetonitrile, but trimethoxybenzene was found to be inert, even after seventy-eight hours at reflux. Reaction with active heteroaromatics also occurs; pyrrole, as already mentioned, gives the α -substituted product, while indole reacts at the 3-position, as anticipated. The reaction with a 3-hydroxypyrrole has already been described (Section C) but other attempts at substitution of heteroaromatics such as furan and thiophene were unsuccessful.



Reaction with the enaminone backbone of 2,2-dimethyl-1-isopropyl-1,2-dihydro-3H-pyrrol-3-one has also been described previously (Section C) and it has been found that other enaminones react similarly to give the derivatives (178) and (179). The structure of derivative (179) provided an interesting question regarding its configuration, and so a series of n.O.e. experiments were performed. The compound gives rise to three singlets corresponding to the aldehyde and two olefinic protons. These occur at δ_H 9.16, 8.57 and 8.19 and proton-carbon correlation showed that the carbon atom signals occurred in the same relative order. The most deshielded signal was therefore assigned to the aldehyde proton. The four possible conformations (179A-D) have the additional feature of potential rotation of the aldehyde substituent and the structures illustrated are simply those best able to explain the n.O.e. results. Irradiation of the N-methyl signals

CC1(C)OC(=O)C(=C(C(=O)O)C(=O)N)C(=O)O1 (A)CN(C)C(=O)C=C(C)C(=O)OC(C)(C)OC(=O)c1ccccc1

(B)

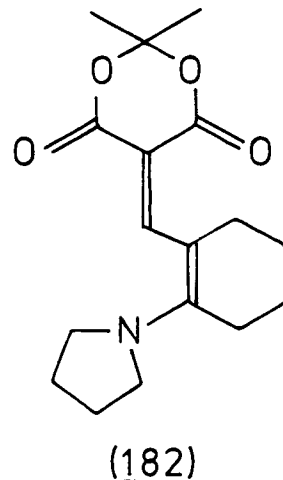
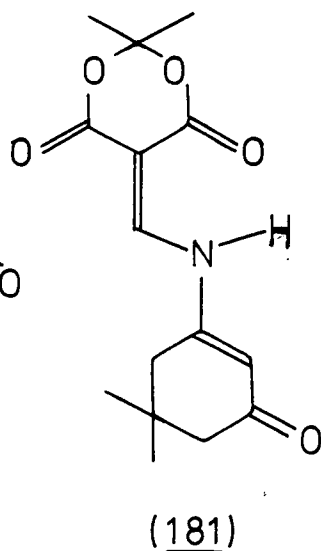
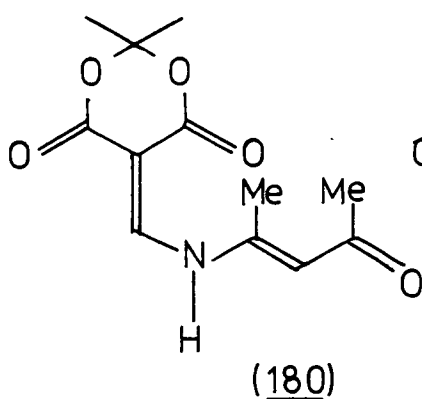
(179)

Chemical structure of 2,2,6,6-tetramethyl-3,4-dihydro-2H-pyran-3-one. The structure shows a six-membered ring with a carbonyl group at position 3 and a double bond between positions 2 and 3. The ring is substituted with four methyl groups at positions 2 and 6. Protons are labeled: H¹ at position 4, H² at position 5, and H³ at position 6. Coupling constants are indicated: 25% between H¹ and H², 15.5% between H² and H³, and 4.5% between H³ and the methyl groups on the nitrogen atom.

CN(C)C(=O)C(=C(C)C(=O)OC(C)(C)C)C(=O)O (D)

affected only one of the olefinic protons and thus structure (A) was eliminated. Further, (B) would not allow the aldehyde signal to affect either of the olefinic protons and an effect is observed at δ_H 8.19 (25%). The remaining structures are both consistent

with the data; thus irradiation of the aldehyde signal affects δ_H 8.19 and vice versa, irradiation at δ_H 8.57 affects one methyl group and nothing else, while irradiation of either methyl group affects δ_H 8.57. Differentiation between the structures (C) and (D) was not possible with the available data. The cyclic analogue (178) of this derivative (179) also seems to adopt the conformation where the substituent carbonyl group is at a distance from the Meldrum's Acid carbonyl function; the olefinic proton in (178) has a particularly deshielded chemical shift thought to be due to the influence of the substituent carbonyl group (δ_H 8.84).



In contrast to these N,N-disubstituted enaminones, N-unsubstituted enaminones react at the nitrogen atom rather than at the unsaturated nucleophilic site, to give novel aminomethylidene derivatives (180) and (181).

The reagent was also found to react with enamines, but its ready reaction with amines requires rigorous removal of any traces of the starting amine from the substrate or only the aminomethylidene product is obtained. Reaction with the pyrrolidino enamine of cyclohexanone gives a product for which the mass spectrum and elemental analysis are in reasonable agreement with those expected for the derivative (182) but its ^1H and ^{13}C n.m.r. spectra are not fully consistent with this structure. The compound is subject to decomposition. Numerous derivatives containing the enamine function have been prepared by a different route (see following Chapter) and are quite stable, as expected, since they can now be considered as extended enaminones. The identity of the product is thus in doubt but the potential use of the expected product in the pyrolysis reaction discussed in the following chapters encourages further work in this area.

Attempts to extend the application of methoxy-methylidene Meldrum's Acid as a carbon electrophile by the use of highly basic substrates such as phenoxide

anion was completely unsuccessful; it was found that under basic conditions (even the presence of imidazole or of a dihydrodiazepine appear to be sufficient) the decomposition to the hydroxy compound is more rapid than the potential reaction with nucleophiles. Attempts to improve the leaving group ability by the in situ formation of tosylate were also unsuccessful.

The derivatives which were successfully prepared show n.m.r. spectroscopic properties of typical Meldrum's Acid derivatives, and exhibit the expected loss of acetone and carbon dioxide fragments under mass spectrometry conditions.

In summary, methoxymethylidene Meldrum's Acid has been found to react, under extremely mild conditions, with a number of nucleophilic substrates and the use of this reactivity in a variety of synthetic routes is discussed in the remainder of this chapter.

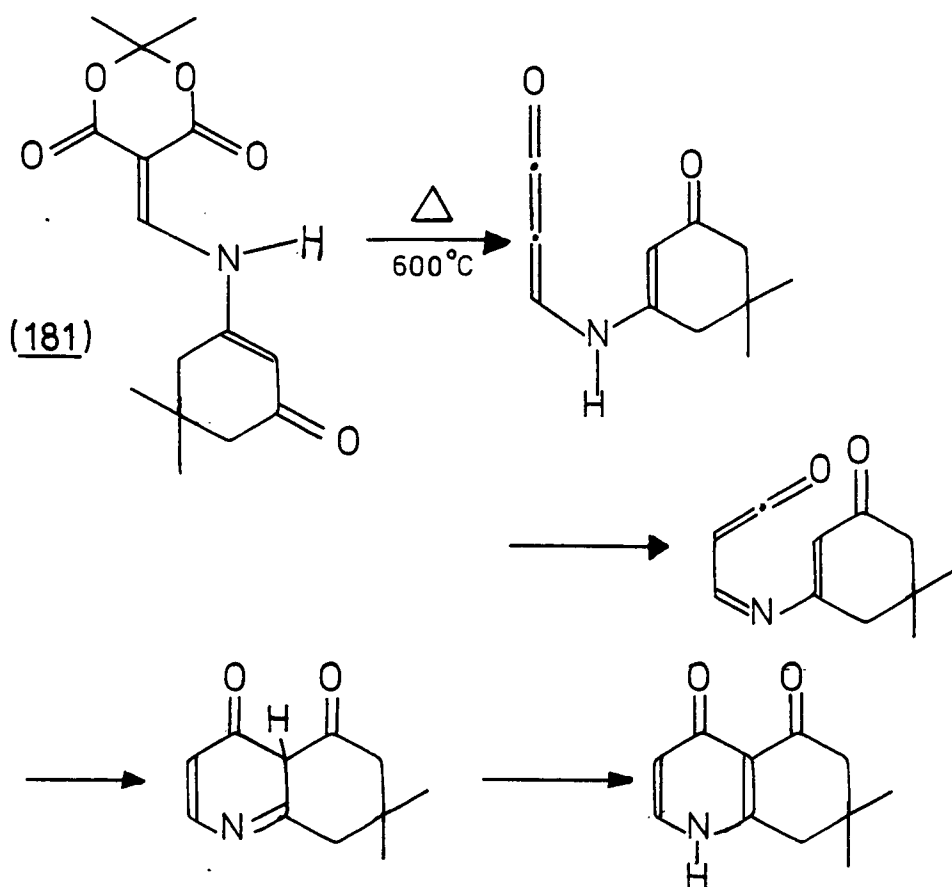
REACTIONS OF PRODUCTS

Meldrum's Acid derivatives have been previously hydrolysed under basic conditions which allows their use as aldehyde synthons [for example, the N,N-dimethylanilino derivative (177) has been reported to be hydrolysed to 4-formyl-N,N-dimethylaminoaniline¹⁵⁶]. Alternatively, these derivatives can be used as three-

carbon, acrylate equivalents, as has already been described for the 1,2-dihydro-3H-pyrrol-3-one derivative (Section C).

Under flash vacuum pyrolysis conditions, the generation of the reactive methyleneketene function from Meldrum's Acid derivatives provides the potential for other synthetically useful reactions of these compounds, examples of which have already been discussed; some interesting pyrolytic reactions of the derivatives described in this section are now reported.

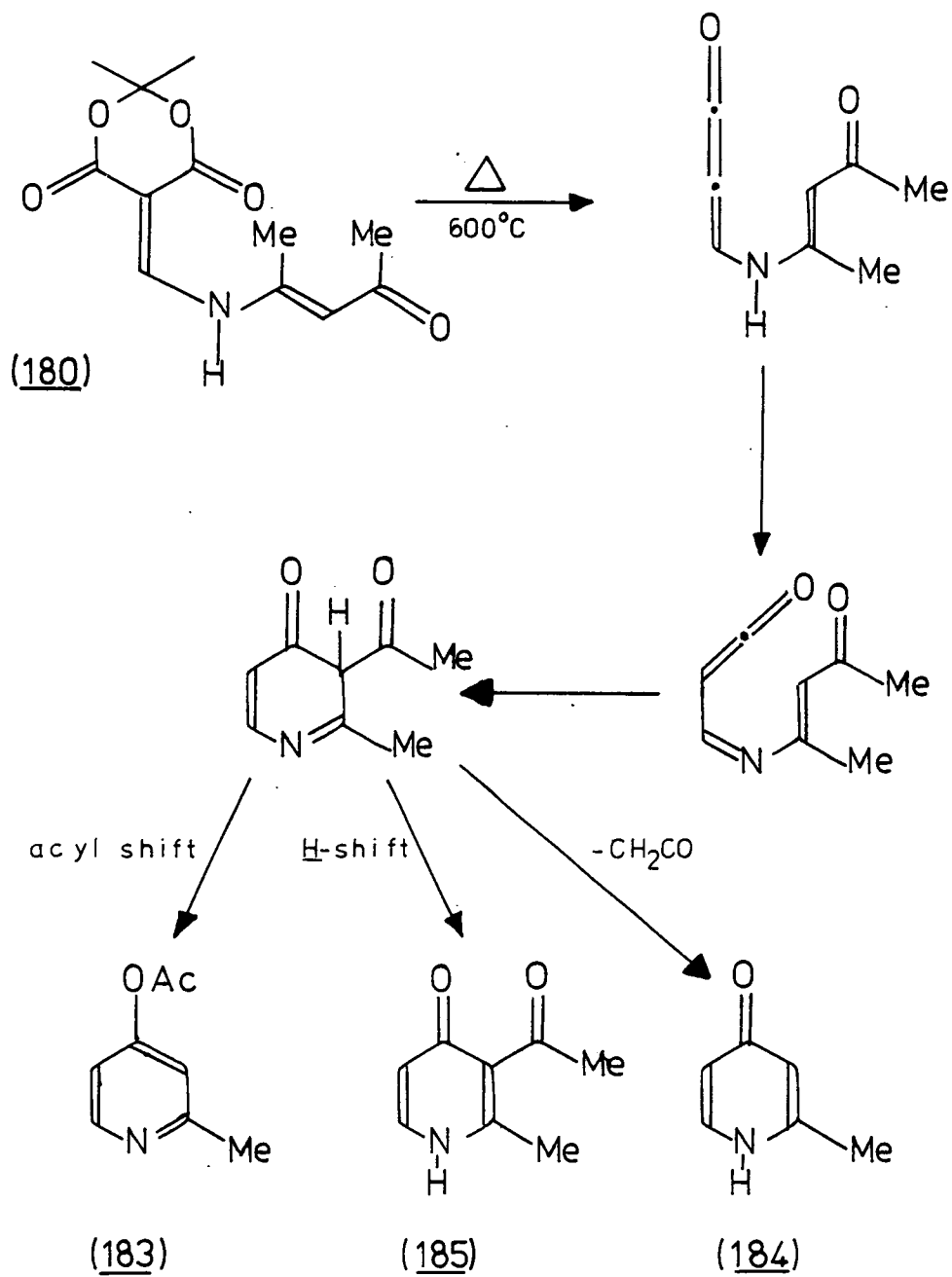
Pyrolysis of the derivative (181) yields a hexahydroquinolinedione (Scheme 53). The proposed methylene ketene intermediate is thought to undergo tautomerism to an iminoketone, electrocyclic ring closure and further tautomerism in an analogous manner to that described for the well studied^{97,98} formation of quinolones from arylaminomethylidene Meldrum's Acid derivatives (see Introduction). The pyrolysis proceeds to give the dione, in good yield, as the sole product. In contrast, pyrolysis of the derivative (180) obtained from an acyclic enammonone, results in three products. The most volatile product was washed from the trap in reasonably pure form and gave a molecular ion peak at m/z 151. The ^{13}C n.m.r. spectrum showed two methyl groups, a signal of



Scheme 53

suitable shift for an acyl carbonyl (δ_C 167.67) and signals at δ_C 160.27, 157.64, 150.16, 115.87 and 113.79. Pyridine has ^{13}C n.m.r. signals at δ_C 149.5, 125.6 and 138.7 for the 2-, 3- and 4-positions respectively, and thus addition of an acetyloxy increment of +23 p.p.m. at C4 and a methyl group effect of +9 p.p.m. at C2 (values typical for benzene)¹²⁷ would give rise to the spectrum of the product. It was therefore assigned the structure (183) (20%). The remaining products condensed at the entrance to the trap and proved extremely polar, rendering chromatographic separation unviable. Recrystallisation yielded one of the compounds

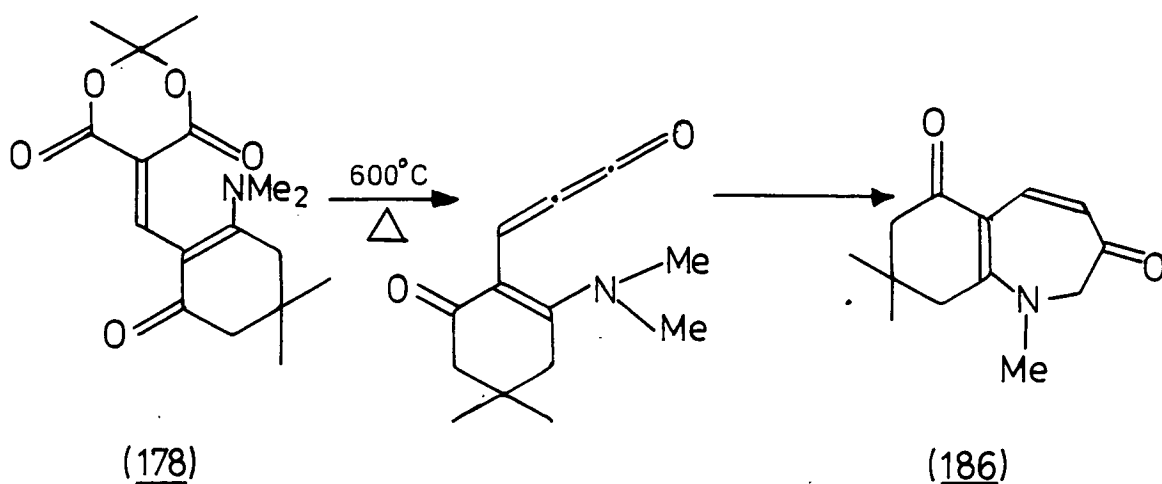
in pure form and the ^1H n.m.r. indicated a similar ring substitution pattern as the acetyloxy compound [δ_{H} 7.52 (d, 7.1 Hz), 6.29 (dd 7.1 and 2.4 Hz) and 6.22 (bs)]. Only one methyl group signal was apparent and comparison of the ^{13}C n.m.r. with that of 1H-pyridine 4-one showed changes of less than 1 p.p.m. for all signals apart from the additional quaternary (C2) which was deshielded by 9 p.p.m. and is consistent with methyl substitution. This compound was therefore assigned the structure (184) (25%). The second product in the mixture could be obtained by extraction of a neutral aqueous solution with methylene chloride. The compound thus obtained gave a peak in its mass spectrum at m/z 151 (60%) and the ^1H n.m.r. spectrum showed only two doublets (J 9.5 Hz) in the olefinic region. Two methyl groups were also apparent and the ^{13}C n.m.r. spectrum showed a deshielded quaternary signal (δ_{C} 195.39) in the range of $\alpha\beta$ -unsaturated carbonyls, and signals similar to those of the 2-, 5- and 6-positions of 2-methyl-1H-pyridin-4-one (184); δ_{C} 152.62, 142.15 and 115.79 compared with 148.95, 138.88, and 115.12. The compound is thus proposed to be 3-acyl-2-methyl-1H-pyridin-4-one (185) (10%). The formation of the three compounds can be readily explained by the mechanism shown in Scheme 54. Initial ring closure analogous to that observed in the cyclic case (Scheme 53) gives an azacyclohexadiene



Scheme 54

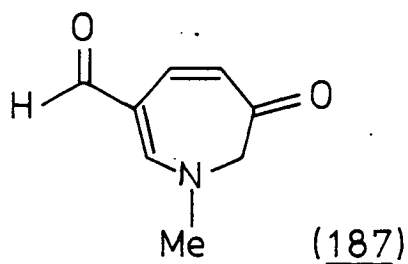
which can undergo either acyl transfer to yield the aromatic pyridine system (183) or hydrogen transfer to give the pyridinone (185). The alternative 1,3-shifts to give -acetyl — 2-methyl-1H-pyridin-4-one and 3-acetyl-2-methyl-pyridin-4-ol may occur but the structures shown are most consistent with the spectroscopic data, although they may result from further migration via 1,5-shifts. The deacetylated compound (184) is thought most likely to result from elimination of ketene from the azacyclohexadiene.

The unusual hydrogen transfer which is observed on pyrolysis of N,N-disubstituted aminomethylidene Meldrum's Acid derivatives, and subsequent collapse of the intermediate formed to 1,2-dihydro-3H-pyrrol-3-ones has been discussed in detail. The derivative resulting from reaction of methoxymethylidene Meldrum's Acid and 5,5-dimethyl-3-N,N-dimethylamino-2-cyclohexen-1-one (178) is a vinylogue of these pyrolysis precursors and, rather surprisingly, the unusual hydrogen transfer also occurs in this system and the seven-membered ring of the 1,2-dihydro-3H-azepin-3-one (186) is produced (Scheme 55). The azepinone was obtained as a highly coloured, crystalline solid after chromatography, and this reaction will be discussed in detail in the following chapter.



Scheme 55

Pyrolysis of the compound derived from N,N-dimethylaminopropenal (179) also appeared to give an azepin-3-one product (187), but only in low yield.



Only preliminary experiments were carried out on this system and the product was not isolated.

E. INVESTIGATION OF THE MECHANISM OF PYROLYSIS
OF VINYLOGOUS 5-AMINOMETHYLIDENE-2,2-DIMETHYL-
1,3-DIOXANE-4,6-DIONES

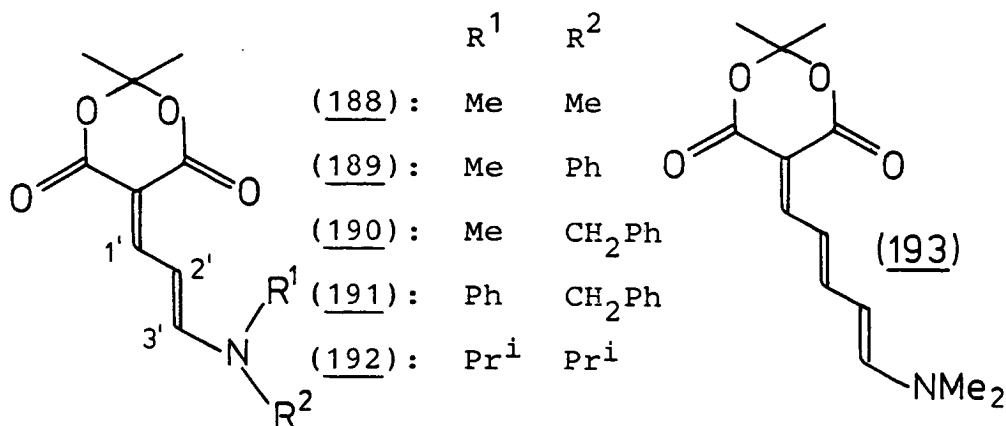
The pyrolysis of 5-aminomethylidene Meldrum's Acid derivatives to give 1,2-dihydro-3H-pyrrol-3-ones has been discussed in detail, and the extension of the reaction to two substituted, vinylogous 5-aminoalkylidene derivatives was mentioned in the last chapter. This chapter is concerned with the pyrolyses of simple examples of extended 5-aminoalkylidene Meldrum's Acid derivatives.

PREPARATION OF VINYLOGOUS 5-AMINOMETHYLIDENE-2,2-
DIMETHYL-1,3-DIOXANE-4,6-DIONES

Preparation of the title compounds was found to be best achieved by condensation of the appropriately substituted aldehyde with Meldrum's Acid, rather than electrophilic attack by methoxymethylidene Meldrum's Acid on enamines as described in the previous chapter.

N,N-Disubstituted-aminopropenals were prepared by oxidation of propargyl alcohol to the corresponding aldehyde and in situ reaction with the appropriate amine,¹⁵⁷ and the vinylogous N,N-dimethylaminopentadienal was also prepared by a literature method.¹⁵⁷ Aldehydes can be

readily condensed with Meldrum's Acid by stirring an equimolar mixture of the two reactants in benzene with catalytic amounts of piperidine and acetic acid,⁹⁶ but the required aldehydes (which may be considered as extended amides) proved to be inert to these conditions. However, the use of conditions normally applied to ketones, namely reaction at room temperature, overnight, using pyridine as solvent,⁹⁶ gave reasonable to good yields (55-95%) of the condensation products. The derivatives prepared are shown (188 - 193).



The proton n.m.r. spectra of these compounds show the typical six proton singlet for the ring methyl groups of Meldrum's Acid and, as in the aminomethylidene derivatives, this occurs at δ_H 1.6-1.7 with the exception of the benzyl substituted example (190). The benzyl example gives rise to a considerably more shielded value (δ_H 1.23), due to ring current effects. The unsaturated portion of the compounds (188) to (192)

gives three signals, two doublets and a doublet of doublets, with the latter (corresponding to the 2' position) the most shielded. The ^3J couplings (1'-H, 2'-H and 2'-H, 3'-H) are large (around 12.2 and 13.0 Hz), indicating a trans-s-trans configuration of the conjugated system in solution. In the extended derivative (193) a number of the signals due to the triene unit are superimposed and unresolved, but the couplings which can be detected are again large (11.8 and 12.7 Hz) so it appears that this, too, exists in an all trans form.

As in the aminomethylidene derivatives, there is evidence for restricted rotation around the C-N bond; two signals are present for the nitrogen substituents in (188) and (192), while the methyl groups of the extended derivative (193) give rise to a broad peak, indicating that coalescence of these signals for the two rotamers occurs close to room temperature. The ^{13}C n.m.r. spectra show sharp singlets for the Meldrum's Acid carbonyl atoms indicating that the barrier to rotation about the C-C double bond is greater than in the aminomethylidene derivatives. Variable temperature n.m.r. studies of the C-N and C-C rotations gave the results shown in Table 37. Additional complications of rotation around the C-C double bonds of the alkylidene substituent are possible for these vinylogous derivatives but there is no evidence for this in the chemical shifts

Table 37 Variable temperature n.m.r. spectroscopy of vinylogous
5-aminomethylidene-2,2-dimethyl-1,3-dioxane-4,6-diones

Compound	C-N			C-C		
	Solvent	T _c /K	ΔG/kJ mol ⁻¹	Solvent	T _c /K	ΔG/kJ mol ⁻¹
(<u>85</u>)	(C[² H ₃]) ₂ SO	435±1	90.5±0.2	C[² H]Cl ₃	280±1	54.0±0.3
(<u>188</u>)	(C[² H ₃]) ₂ SO	413±1	86.7±0.2	(C[² H ₃]) ₂ SO	403±2	81.8±0.4
(<u>193</u>)	(C[² H ₃]) ₂ CO	323±1	67.3±0.2	(C[² H ₃]) ₂ SO	351±5	70.3±1.0

of the olefinic signals at higher temperatures. It is therefore thought that study of the N-methyl groups and carbonyl atoms gives a true indication of the free energy of the processes discussed. The derivative with three double bonds in the substituent (193) proved particularly awkward to monitor when the C-C rotation was studied, because the carbonyl signals were very close to methine signals which made the coalescence temperature more difficult to judge. The rotation about the C-N bond becomes less hindered as the conjugated system increases in length which suggests a decrease in the effect of delocalisation. The barrier to C-C rotation is considerably greater for both the extended cases, which is consistent with a decrease in the influence of delocalisation, but surprisingly, the example with two double bonds inserted in the conjugation shows a lower barrier to C-C rotation than the first vinylogue (70 compared to 82 kJ mol⁻¹). This latter result is particularly surprising in view of the significant decrease in the barrier to C-N rotation on addition of the second double bond (20 kJ mol⁻¹). However, it is not realistic to draw any conclusion from this observation without further examples with which to make comparisons.

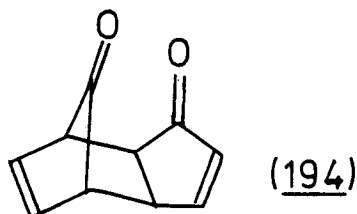
In contrast to the aminomethylidene derivatives, the extended compounds show fairly intense molecular ion peaks in their mass spectra (e.g. the N,N-dimethyl compound has a molecular ion peak of 83% intensity while the methylidene compounds often give a molecular ion peak with less than 1% intensity). The mass spectra do not show the loss of acetone and carbon dioxide, typical of Meldrum's Acid derivatives. They do all exhibit loss of m/z 57 but there are no metastable peaks corresponding to this cleavage, and metastable peaks are present for the usual cleavage of acetone (m/z 58) although this appears to be a minor pathway.

MECHANISM OF PYROLYSIS OF 5-AMINOPROPENYLIDENE-2,2-DIMETHYL-1,3-DIOXANE-4,6-DIONES

Pyrolysis of 5-(N,N-dimethylaminopropenylidene) Meldrum's Acid at 600°C gave a bright yellow liquid and a solid material, both of which condensed at the liquid nitrogen level in the trap. A ¹H n.m.r. spectrum of the crude pyrolysate showed signals at δ_H 6.88, 6.73, 6.19 and 5.18. The coupling observed between these protons indicates they form a conjugated unit (the proton at δ_H 6.88 couples to those at δ_H 5.18 and 6.19, while the signal at δ_H 5.18 couples to both the deshielded signals) and the size of the coupling constants (11.0, 9.1 and 7.2 Hz) indicates the presence of a seven-membered ring.¹²¹

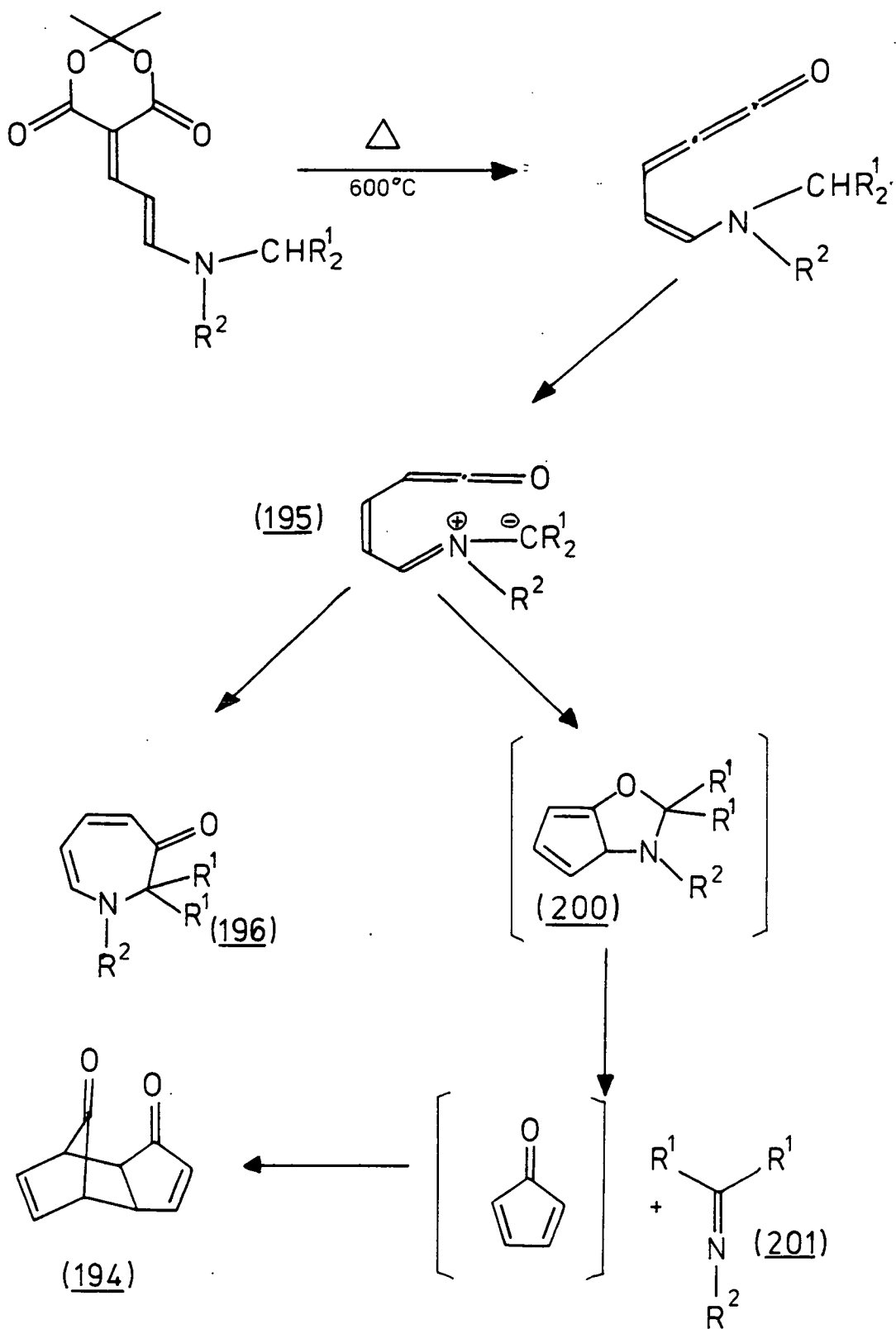
Thus, the presence of a 1,2-dihydro-3H-azepin-3-one was suggested and the full characterisation of this new heterocycle is discussed in the following chapter. However, a second product was also present. Chromatography on alumina yielded the pure azepinone (60%) as an intense, yellow liquid and the other product as a colourless, crystalline solid (24%). The ^1H n.m.r. spectrum of the solid showed four groups of signals in the aliphatic region (δ_{H} 2.8-3.6) each equivalent to one proton, three groups of signals in the olefinic region (δ_{H} 6.15-6.40) and a multiplet, equivalent to one proton, at a more deshielded frequency (δ_{H} 7.39). The ^{13}C n.m.r. spectrum indicated the presence of four aliphatic, methine carbon atoms, four olefinic methine carbon atoms and two quaternary carbon atoms in the carbonyl region. The deshielded multiplet in the ^1H n.m.r. spectrum is typical of the β -olefinic proton of an enone system and the presence of such a unit is further indicated by the lower value of one carbonyl absorption in the i.r. spectrum (ν_{max} 1780 and 1710 cm^{-1}). The mass spectrum of the product showed a highest mass, significant peak at m/z 132. From this data the solid was identified as the cyclopentadienone dimer (194) which contains all the features implied by the spectroscopic data. The absence of a molecular ion peak in the mass spectrum was explained by the facile loss

of carbon monoxide and this has been observed in previous syntheses of the dimer.¹⁵⁸ An authentic sample



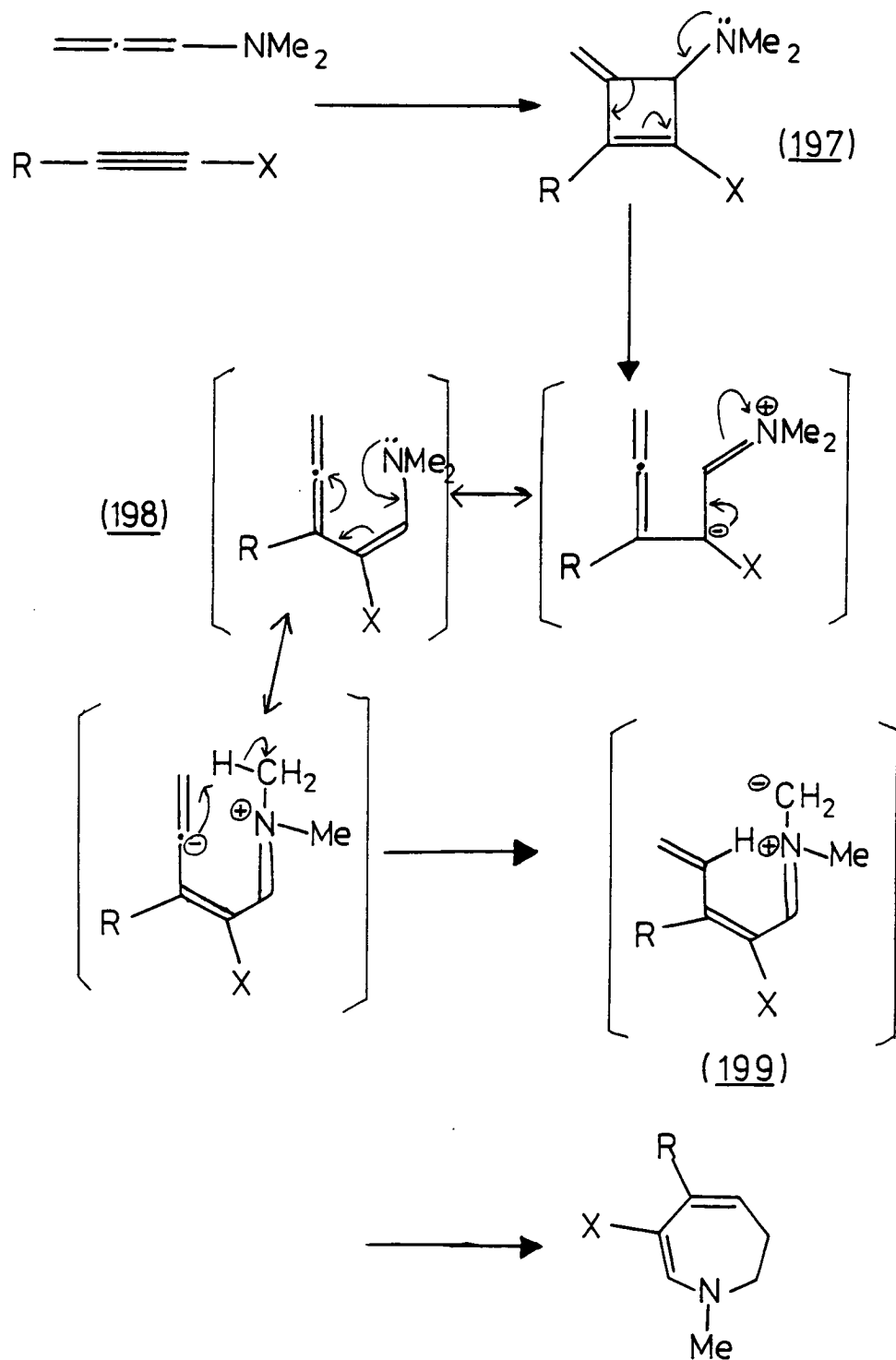
was prepared by elimination of hydrogen bromide from bromocyclopentenone¹⁵⁸ and it allowed confirmation of the assigned structure by g.c. retention time and mixed melting point. The proposal of a dipolar intermediate (97) in the formation of pyrrolones has been discussed and the presence of the cyclopentadienone dimer seems to give further, indirect, evidence for the involvement of such a structure in these unusual hydrogen transfer reactions. Thus, in the amino-propenylidene cases, hydrogen transfer could lead to the dipolar intermediate (195) which then has two alternative reaction pathways (Scheme 56). Electrocyclisation, analogous to that found for the amino-methylidene case, leads to 1,2-dihydro-3H-azepin-3-ones (196).

Interestingly, a closely related species has been proposed as the final intermediate in an unusual formation of 2,3-dihydro-1H-azepines.¹⁵⁹ Klop and Brandsma observed the formation of azepines from methylidenecyclobutenes, which were prepared from amino-allenes and acetylenic esters, and proposed the



Scheme 56

the mechanism of Scheme 57. The methylenecyclobutene (197) was isolated in certain cases and would thus



Scheme 57

appear certain to be the initial product. A thermal ring-opening would then give the allenic enamine (198) directly. This structure (198) is analogous to the methyleneketene intermediate formed on pyrolysis of the aminopropenylidene Meldrum's Acid derivatives and a hydrogen transfer, similar to that proposed for pyrrolone and azepinone formation, would result in the dipolar structure (199) corresponding to the intermediate (195, Scheme 56).

The second pathway open to the dipolar intermediate in the ketene case (195) involves an intramolecular cycloaddition to the carbonyl group, and such selectivity has previously been found in the addition of azomethine ylides to ketenes.¹⁶⁰ This would result in the bicyclic structure (200) (Scheme 56) which can fragment to yield an imine (201), and cyclopentadienone, which rapidly dimerises. Benzyldiene aniline (201: $R^1 = H, Ph$; $R^2 = Ph$) was identified in the pyrolysate from the N-benzyl-N-phenyl- derivative (191); the imino singlet and other recognisable aromatic peaks in the ^1H n.m.r. spectrum were gradually increased as increments of the authentic imine were added to a [^2H] chloroform solution of the crude pyrolysate. The imine was not isolated as it was unstable to chromatographic conditions, but the identification of the imine supports the proposed mechanism for formation of the dimer.

The pyrolysis of aminopropenylidene Meldrum's Acid derivatives was found to be markedly temperature dependent, and this was demonstrated by pyrolysis of the N,N-dimethyl derivative (188) at furnace temperatures of 500, 600 and 700°C. The crude pyrolysates were analysed by ¹H n.m.r. spectroscopy and the pyrolyses were all carried out on a similar scale to allow some assessment of absolute yields, in addition to the determination of relative amounts of the major products. The relative amounts of 1,2-dihydro-3H-azepin-3-one (196: R¹ = H; R² = Me) and cyclopentadienone dimer (194) formed are shown in Table 38.

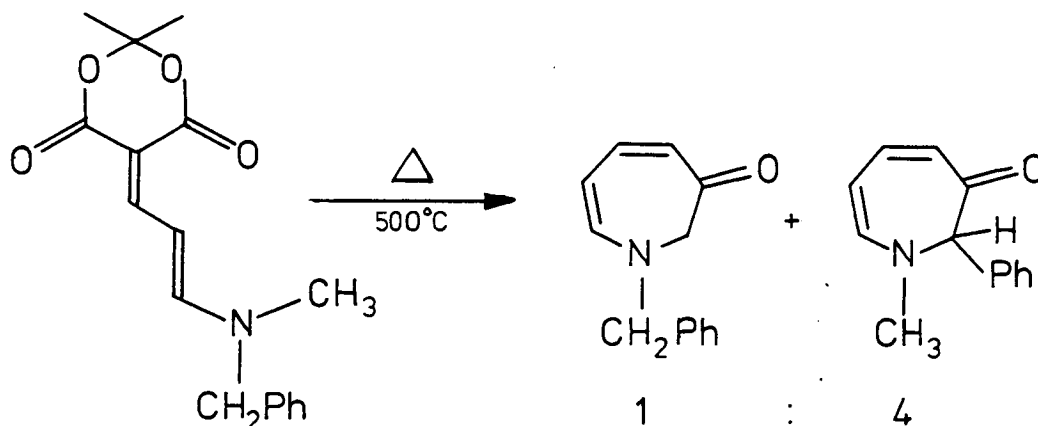
Table 38 Temperature dependance of pyrolysis of a
5-aminopropenylidene Meldrum's Acid

Furnace Temperature	1-Methyl-1,2-dihydro-3H-azepin-3-one	Dimer (<u>194</u>)
500°C	3	1
600°C	2	1
700°C	<1	3

The amount of the dimer (194) relative to the azepinone increases considerably on increasing the furnace temperature and this was partly a result of a decrease in the absolute yield of the azepinone, but there appears

to be a concurrent increase in the absolute yield of the dimer. A similar trend is observed in other cases; for example, at 500°C the N-benzyl-N-phenyl derivative gives six times more azepinone than dimer, while at 600°C there is three times as much dimer (and imine) as azepinone.

The N-benzyl-N-methyl derivative (190) gave two, different, potential sites for hydrogen abstraction. The complete regioselectivity observed in the formation of the analogous five membered ring system did not occur, but the benzylic site was found to be favoured to a notable extent (Scheme 58). However, other work in



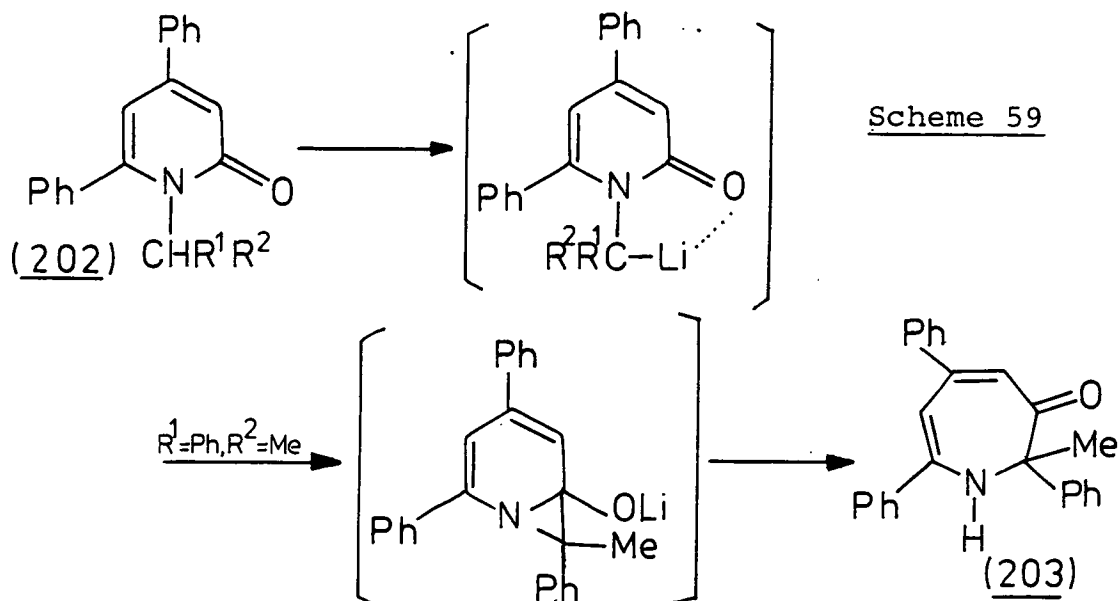
Scheme 58

this laboratory has shown¹⁶¹ that a similar selectivity of primary v. secondary v. tertiary sites exists (2.5 : 1.0 : 1.0 for the seven-membered ring compared to 3.1 : 1.0 : 1.1 for the five-membered system). It may be that stabilisation of the intermediate by resonance, through the phenyl ring, becomes less important when

further delocalisation through the extended conjugated system is possible, as in the case of azepinone formation. Alternatively, a simple steric effect arising from the greater flexibility of the methylene ketene intermediate may be the cause.

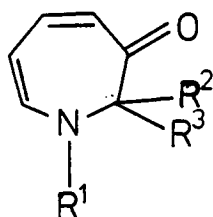
SCOPE OF THE 1,2-DIHYDRO-3H-AZEPIN-3-ONE FORMATION

Only one example of a 1,2-dihydro-3H-azepin-3-one has appeared in the literature prior to the current work. In a study of carbanions¹⁶² generated from pyridones (202), an isolated example (202: $R^1 = \text{Rh}$, $R^2 = \text{Me}$) was found to undergo rearrangement to the azepinone (203) (16%) (Scheme 59). The rearrangement of the originally



formed anion to the bicyclic isomer is thought to occur in this case because of steric effects, and it would, therefore, appear that the synthesis cannot be generally applied.

The pyrolytic synthesis described, thus provides the first viable route to a number of simple azepin-3-ones. A limited number of examples have been isolated during this work (186, 204-207), and the isomeric compounds (208) and (209) were prepared as a mixture. The synthesis has also been used to prepare (210-213).¹⁶¹ The pyrolyses yielding 1-phenyl- and 1-methyl-1,2-dihydro-3H-azepin-3-ones have been carried out on numerous occasions and yields of around 70 and 60%, respectively, have been obtained. The other preparations have not been optimised.



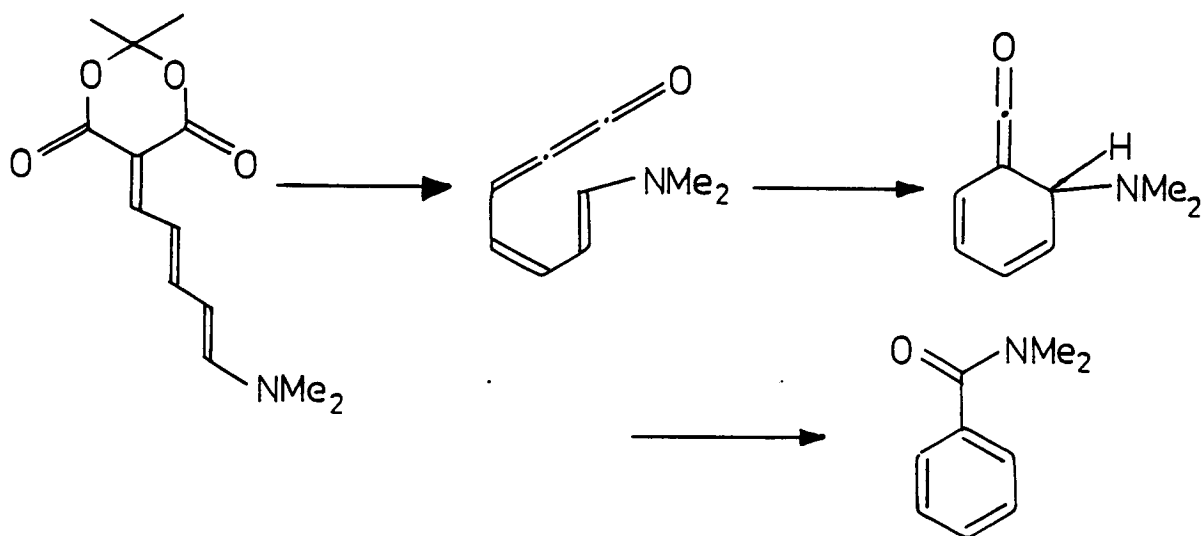
	R ¹	R ²	R ³
(<u>204</u>):	Me	H	H
(<u>205</u>):	Ph	H	H
(<u>206</u>):	Ph	Ph	H
(<u>207</u>):	Pr ⁱ	Me	Me
(<u>208</u>):	Me	Ph	H
(<u>209</u>):	CH ₂ Ph	H	H
(<u>210</u>):	Bu ^t	H	H
(<u>211</u>):	Et	Me	H
(<u>212</u>):	Me	Me	Me
(<u>213</u>):	Pr ⁱ	H	H

This brief survey shows that abstraction of a hydrogen atom can occur from methyl, methylene, methine or benzyl groups, and the successful separation of the two isomers (212 and 213), produced by pyrolysis of the N-isopropyl-N-

methyl example,¹⁶¹ indicates that the substitution pattern in the product is not necessarily restricted to that arising from symmetrical or partially blocked derivatives. Thus, the reaction might be anticipated to be as general as the pyrrol-3-one formation already discussed, although the presence of alternative reaction pathways and the resulting by-products produces complications.

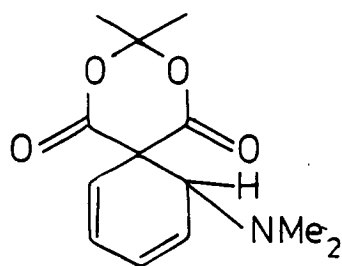
PYROLYSIS OF 5-(N,N-DIMETHYLAMINOPENTADIENYLIDENE) -
2,2-DIMETHYL-1,3-DIOXANE-4,6-DIONE

Pyrolysis of the title compound (193), in which an additional double bond has been introduced to the unsaturated system, does not lead to an analogous nine-membered ring. Instead an electrocyclic process occurs to yield N,N-dimethylbenzamide (72%), thus providing a novel synthesis of an aromatic ring from an acyclic precursor.¹⁶³ This can be envisaged as occurring via a 6π -electron ring closure of the usual methylene-ketene intermediate, and subsequent migration of the dimethylamino group to yield the aromatic product (Scheme 60). However, even at a furnace temperature of 350°C there is evidence for the formation of the benzamide and the cleavage of the Meldrum's Acid ring is not expected to occur in our apparatus at this temperature. It is thought, therefore, that the mechanism



Scheme 60

involves electrocyclisation prior to ring cleavage, and the initial intermediate may be a bicyclic structure (214), or a related structure resulting from electro-



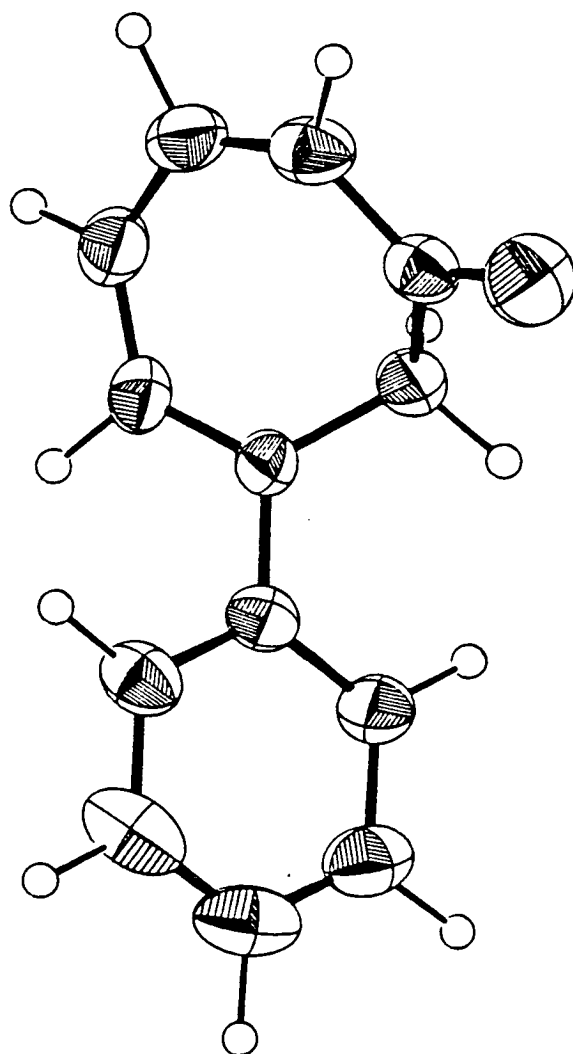
(214)

cyclisation of one of the intermediates formed during the stepwise fragmentation of the ring.⁸²

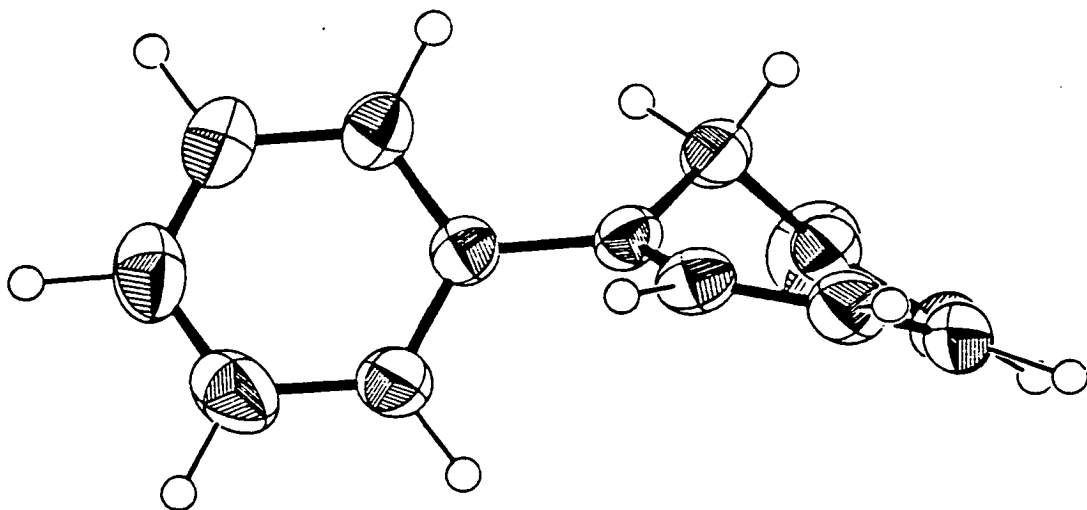
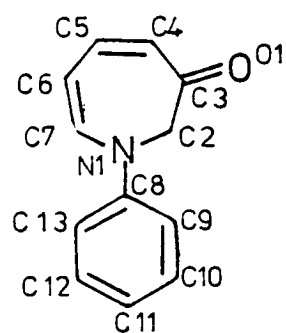
F. THE STRUCTURE, PHYSICAL AND SPECTROSCOPIC
PROPERTIES OF 1-SUBSTITUTED-1,2-DIHYDRO-3H-
AZEPIN-3-ONES

STRUCTURE

The azepin-3-ones which have been prepared are stable compounds and the presence of proton(s) at the 2-position does not lead to the ready oxidation exhibited by the five-membered ring analogues. In contrast to the 1,2-dihydro-3H-pyrrol-3-one system, where the enol form gives rise to a 6π -electron aromatic structure, keto-enol tautomerism of the seven-membered ring would give an 8π -electron anti-aromatic system and, indeed, there is no evidence for the enol form in solution (the n.m.r. spectra will be discussed in detail later). Although the keto form almost certainly existed in the solid state also, there were a number of points of interest with regard to the structure of the ring system; for example, what conformation did the seven-membered ring adopt and how did the additional double bond affect bond lengths in the conjugated system compared with those in the analogous five-membered system? Therefore, the crystal structure of 1-phenyl-1,2-dihydro-3H-azepin-3-one was determined by X-ray diffraction and the parameters obtained are listed in Tables 39-41, and illustrated in Figure 28. Comparison of the bond lengths of the conjugated system (from the nitrogen atom



View 1



View 2

Figure 28

Table 39

Bond Lengths(A) with standard deviations

N(1) - C(2)	1.451(4)	C(6) - C(7)	1.356(4)
N(1) - C(7)	1.356(4)	C(8) - C(9)	1.393(4)
N(1) - C(8)	1.428(3)	C(8) -C(13)	1.382(4)
C(2) - C(3)	1.521(4)	C(9) -C(10)	1.389(5)
C(3) - O(3)	1.228(4)	C(10) -C(11)	1.373(5)
C(3) - C(4)	1.439(4)	C(11) -C(12)	1.380(5)
C(4) - C(5)	1.350(4)	C(12) -C(13)	1.403(5)
C(5) - C(6)	1.428(4)		

Table 40

Angles(degrees) with standard deviations

C(2) - N(1) - C(7)	118.99(23)	N(1) - C(7) - C(6)	125.8(3)
C(2) - N(1) - C(8)	120.92(21)	N(1) - C(8) - C(9)	120.51(24)
C(7) - N(1) - C(8)	118.82(22)	N(1) - C(8) -C(13)	119.15(24)
N(1) - C(2) - C(3)	112.61(23)	C(9) - C(8) -C(13)	120.3(3)
C(2) - C(3) - O(3)	118.5(3)	C(8) - C(9) -C(10)	119.9(3)
C(2) - C(3) - C(4)	117.61(25)	C(9) -C(10) -C(11)	120.0(3)
O(3) - C(3) - C(4)	123.8(3)	C(10) -C(11) -C(12)	120.6(3)
C(3) - C(4) - C(5)	126.5(3)	C(11) -C(12) -C(13)	120.2(3)
C(4) - C(5) - C(6)	130.1(3)	C(8) -C(13) -C(12)	119.1(3)
C(5) - C(6) - C(7)	126.7(3)		

Table 41

Torsion angles(degrees) with standard deviations

C(7) - N(1) - C(2) - C(3)	77.4(3)	C(3) - C(4) - C(5) - C(6)	14.6(6)
C(8) - N(1) - C(2) - C(3)	-115.6(3)	C(4) - C(5) - C(6) - C(7)	10.7(6)
C(2) - N(1) - C(7) - C(6)	-28.5(4)	C(5) - C(6) - C(7) - N(1)	-19.1(5)
C(8) - N(1) - C(7) - C(6)	164.2(3)	N(1) - C(8) - C(9) -C(10)	-177.7(3)
C(2) - N(1) - C(8) - C(9)	-38.1(4)	C(13) - C(8) - C(9) -C(10)	-0.9(4)
C(2) - N(1) - C(8) -C(13)	145.1(3)	N(1) - C(8) -C(13) -C(12)	177.6(3)
C(7) - N(1) - C(8) - C(9)	128.9(3)	C(9) - C(8) -C(13) -C(12)	0.7(4)
C(7) - N(1) - C(8) -C(13)	-47.9(4)	C(8) - C(9) -C(10) -C(11)	0.2(5)
H(1) - C(2) - C(3) - C(3)	122.1(3)	C(9) -C(10) -C(11) -C(12)	0.7(5)
H(1) - C(2) - C(3) - C(4)	-61.9(3)	C(10) -C(11) -C(12) -C(13)	-0.8(6)
C(2) - C(3) - C(4) - C(5)	9.1(5)	C(11) -C(12) -C(13) - C(8)	0.1(5)
O(3) - C(3) - C(4) - C(5)	-175.1(3)		

to the oxygen atom) with those of the corresponding 1-phenyl-1,2-dihydro-3H-pyrrol-3-one shows no significant changes and the C4-C5 double bond of the azepinone is the same length (within the level of accuracy obtained) as the C6-C7 bond. The extra single bond in the extended system is similar in length to the C3-C4 bond and the saturated portion, N-C2-C3, appears identical to that of the five-membered system. The bond lengths in the conjugated system are also very similar to those found for the unsubstituted 1H-pyridin-2-one (Figure 29)¹⁶⁴

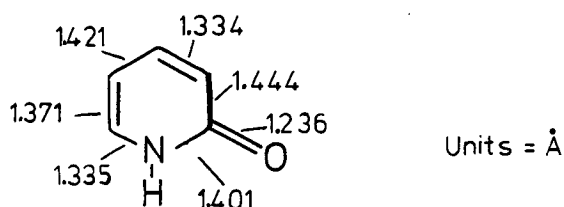


Figure 29

but the additional influence of cyclic delocalisation is evident in the considerable shortening of the N-C2 bond (1.401 Å compared with 1.451 Å in the azepinone and 1.458 Å in the pyrrolone). The influence of the stabilising effect of delocalisation is clearly seen in the conformation adopted by the seven-membered ring; the conjugated unit is almost planar, with the methylene bridge forced considerably out of the plane (Figure 28, View 2), a conformation not expected for seven-membered rings where bond angles favour a puckered system. The structure also shows that, unlike the five-membered system, the phenyl ring is in a markedly different

orientation to that of the conjugated system. Thus, the dihedral angle between the phenyl ring and the N-C7 bond in the azepinone is more than 45° while in the pyrrolone case there is only about 13° between the planes of the aromatic ring and the enaminone system. The effect of this difference in orientation is observed in the length of the bond between the nitrogen atom and the phenyl substituent; in the 1,2-dihydro-3H-pyrrol-3-one, where the nitrogen atom's lone pair of electrons is capable of delocalisation into the phenyl ring, the bond length is 1.401 Å compared with 1.428 Å in the vinylogous case, where phenyl ring is far from planarity with the dienaminone system, and delocalisation is considerably decreased.

The conformation of the seven-membered ring results in chirality in the solid state but in solution the inversion of the methylene bridge is too rapid to allow the observation of the chiral form. A solution of 1-phenyl-1,2-dihydro-3H-azepin-3-one (205) in [$^2\text{H}_6$]acetone was cooled and the ^1H n.m.r. spectrum was observed, but even at -100°C the coalescence temperature of the methylene protons due to ring inversion had not been reached. Similarly the 2,2-dimethyl-1-isopropyl example (207) showed broadening of the singlet due to the 2-methyl groups, but resolution to separate signals was not observed at -100°C and the analysis in this case

was hampered by the additional non-equivalence of the doublet corresponding to the isopropyl methyl groups, observed at low temperatures.

N.M.R. SPECTRA

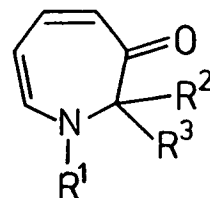
The proton n.m.r. spectroscopic parameters of the 1,2-dihydro-3H-azepin-3-ones which have been prepared are shown in Table 42. The signals for the olefinic protons show the same trend as the pyrrolones discussed earlier, and enones generally, towards widely spaced signals for the two vicinal protons of the double bonds; the difference is not, however, as marked in these examples (only around 1.5 p.p.m. across the C6-C7 bond and as little as 0.2 p.p.m. across the C4-C5 bond, compared with an average 2.9 p.p.m. for the 5-membered ring system). The shielded signals (due to 4-H and 6-H) and the deshielded signals (due to 5-H and 7-H) can be readily distinguished by their splitting patterns; the resonances due to the central protons are doublets of doublets (or apparent triplets), while the outer protons (4-H and 7-H) are simple doublets. Thus, the most shielded signal (δ_H 5.0 - 5.5) is identified as corresponding to 6-H, the next most shielded (δ_H 6.05 - 6.45) as 4-H, while the remaining two are fairly close (δ_H 6.6-7.0) and do not always follow the same pattern. Only the 7-H signal appears to be affected by nitrogen substitution; the phenyl examples have signals around

Table 42 Proton n.m.r. parameters of 1,2-dihydro-3H-azepin-3-ones

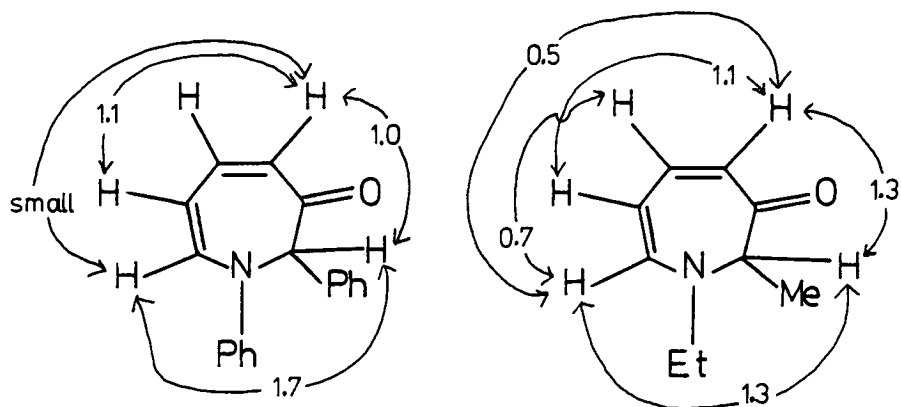
Azepinone	R ¹	R ²	R ³	2-H	4-H	5-H	6-H	7-H	³ J _{4,5}	³ J _{5,6}	³ J _{6,7}	⁴ J _{4,6}
(204)	Me	H	H	3.52	6.17	6.84	5.17	6.72	11.0	9.1	7.2	0.9
(205)	Ph	H	H	4.14	6.34	6.89	5.48	6.99	11.3	8.6	8.0	0.8
(206)	Ph	Ph	H	5.95	6.44	6.64	5.32	6.90	11.5	8.5	8.5	1.1
(207)	Pr ⁱ	Me	Me	-	6.08	6.61	5.31	6.63	11.4	8.3	8.3	1.1
(208)	Me	Ph	H	5.03	6.25	6.57	5.03	6.74	11.3	9.0	7.8	a
(209)	CH ₂ Ph	H	H	3.58	6.38	6.8-7.0	5.25	6.8-7.0	b	a	a	a

a not observed

b not recorded



0.2 p.p.m. more deshielded, probably due to ring current effects. The $^3J_{4,5}$ coupling is particularly large (11.0-11.5 Hz); the crystal structure indicates a wider angle at C5 of the ring (130° compared with 126°) which means the angle between 5-H and the double bond is less, an effect known to increase coupling constants (for example, the effect of ring size).¹²¹ The remaining three-bond couplings are around 8 Hz and it is rather surprising that the couplings due to the remaining double bond and the connecting single bond are of such similar magnitudes, and that the larger coupling, where they are distinguishable, arises from $^3J_{5,6}$ (e.g. (204) $^3J_{5,6}$ 9.1 Hz - $^3J_{6,7}$ 7.2 Hz). A four bond coupling of around 1 Hz from 4-H to 6-H is also observed. A number of other long-range couplings are evident from line-narrowed spectra of these compounds. In the 2-unsubstituted cases these could not be resolved but, with the aid of selective decoupling experiments, long-range couplings $^4J_{2,7}$, $^4J_{2,4}$ and $^5J_{2,7}$ were detected for the 1,2-diphenyl example (206). These are in reasonable agreement with values for the 1-ethyl-2-methyl compound (211), prepared during other work in this laboratory,¹⁶² which shows particularly good resolution (Figure 30).



Units=Hz

Figure 30

The ^{13}C n.m.r. chemical shifts are shown in Table 43; assignments were confirmed for (204) and (205) by proton-carbon correlations (e.g. for (204), specific irradiation at δ_{H} 6.84 resulted in a sharp singlet at δ_{C} 142.01 which could therefore be assigned to the C_6 -atom.

The quaternary signal corresponding to the carbonyl group is considerably shielded with respect to that in the corresponding five-membered ring system (e.g. the 1-phenyl monosubstituted examples show shifts of δ_{C} 183 and δ_{C} 199, respectively). This is consistent with the expectation of shielding on increased delocalisation¹⁶⁵ but the corresponding open-chain systems, dimethylamino-pentadienal and -propenal show shifts of δ_{C} 191 and 187, respectively. It therefore appears that in this case the effect observed is due to the change in

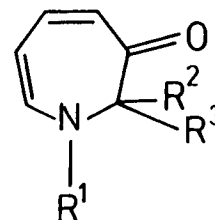
Table 43 ^{13}C n.m.r. of 1,2-dihydro-3H-azepin-3-ones

Azepinone	R ¹	R ²	R ³	C-2	C-3	C-4	C-5	C-6	C-7
(204)	Me	H	H	62.65	180.21	123.33	142.01	99.41	147.19
(205)	Ph	H	H	59.38	182.87	126.71	140.17	103.86	141.54
(206)	Ph	Ph	H	73.92	184.74	127.64 ^b	139.88 ^a	104.64	139.13 ^a
(207)	Pr ⁱ	Me	H	63.76	184.11	121.67	138.11	102.68	137.50
(208)	Me	Ph	H	75.26	c	121.75 ^b	140.72 ^a	100.16	144.76 ^a

^a Assignment may be reversed

^b Tentatively assigned - p-aromatic carbon atoms have similar chemical shifts

^c Not available - only D.E.P.T. spectrum obtained.



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.¹²⁷ The signals corresponding to the 2-position are somewhat deshielded (by 3-8 p.p.m.) with respect to the smaller ring system with similar substitution. The olefinic signals of both double bonds in the diene unit exhibit similar trends to those observed in enaminones; thus, the C₄- and C₆-signals are shielded by mesomeric donation of the nitrogen atom's lone pair of electrons, while the C₅- and C₇-positions have shifts which are influenced by the electron withdrawing nature of the carbonyl group and the dipolar resonance structures which it allows. The mesomeric donation from the nitrogen atom has considerably less effect on the C₄-shift ($\delta_C \sim 124$ compared with δ_C 102 for C6) but it is undoubtedly present as substitution of the nitrogen atom with a phenyl group still has an effect (an increase of 3-4 p.p.m. is observed for both the C₄- and C₆-positions). The C₅- and C₇-atoms have similar chemical shifts and, in fact, the assignment is not completely assured in some cases. This suggests an equal influence of the two dipolar canonical forms (B and C), shown in Figure 31, which is surprising in view of the interruption to conjugation present in (C).

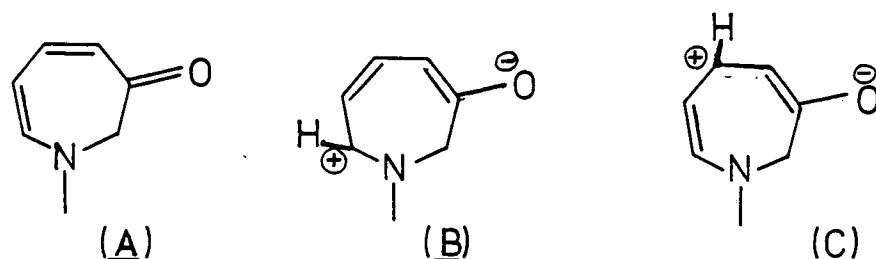


Figure 31

The carbon-proton coupling constants of some 1,2-dihydro-3H-azepin-3-ones were also determined (Table 44) and assigned by selective decoupling experiments [e.g. low power irradiation at δ_H 5.17 (6-H in (204)) removed the long-range coupling to the C4-atom allowing its assignment as $^3J_{H(6)}$]. The one-bond coupling constants are smaller than the corresponding values in 1,2-dihydro-3H-pyrrol-3-ones; thus the C4-H and C6-H couplings are all close to 160 Hz, compared with 176 - 179 Hz for C4-H in the five-membered ring, and values of approximately 152 and 170 Hz are found for the C5-H and C7-H couplings, respectively, while C5-H in the pyrrolone has an average value of 174 Hz. These values contrast with the corresponding chemical shifts, where the 5- and 7-positions are similar to each other and the 4- and 6-positions are markedly different from each other. It appears that the coupling constants are affected by different factors than the chemical shifts (for example the electronegativity of the nitrogen is now thought to

Table 44 Carbon-proton coupling constants for 1,2-dihydro-3H-azepin-3-ones

(a) ^1J Couplings

Azepinone	R ¹	R ²	C2	C4	C5	C6	C7
(204)	Me	H	141.4	159.6	151.7	161.7	169.8
(205)	Ph	H	141.4	160.1	152.6	161.5	173.1
(207)	Pr ⁱ	Me	-	158.4	152.5	161.4	166.5

(b) Long-range Couplings

Azepinone	R ¹	R ²	C2		C3		C5	C6		C7 ^a	
			$^3J_{H(4)}$	$^3J_{H(7)}$	$^2J_{H(2)}$	$^4J_{H(7)}$	$^3J_{H(7)}$	$^2J_{H(7)}$	$^3J_{H(4)}$	$^3J_{H(2)}$	$^3J_{H(5)}$
(204)	Me	H	b	b	3.7	11.6	8.2	4.4	10.5	4.1	4.1
(205)	Ph	H	4.3	4.3	3.8	11.2	8.2	4.6	10.6	4.3	4.3
(207)	Pr ⁱ	Me	c	c	-	c	8.7	2.8	10.8	-	4.7

^a Further unresolved coupling observed in (204) and (205). Further coupling of same magnitude to 3 other protons in (207).

^b Not resolved due to additional coupling to N-methyl group.

^c Not resolved due to additional coupling to 2-methyl groups.

be significant and its effect may not be transmitted to the C5-atom, whereas the mesomeric donation of its lone pair, which is important in determining chemical shift, affects the 5- and 7-positions equally). The relative magnitudes of the C4-H and C5-H coupling constants are now reversed with C5-H about 8 Hz smaller. Long range couplings for the 1-phenyl-1,2-dihydro-3H-azepin-3-one are recorded in Figure 32. The large two-bond coupling constant (~ 8.8 Hz) present for C5-4(H) in the 1,2-dihydro-3H-pyrrol-3-ones is absent in the azepinone system and only one ^2J is observed. The $^2J_{C6,H(7)}$ is 4.5 Hz for the 2-unsubstituted examples (204) and (205) but only 2.8 Hz for the 2,2-dimethyl case (207), which compares with values of around 7 Hz for the corresponding coupling in the five-membered ring. A coupling of ~ 4 Hz is observed from C7 to the methylene protons at the 2-position and this is very similar to $^3J_{C5,H(2)}$ in the pyrrolone series. The carbonyl carbon atom exhibits a large coupling to H-7 (11.5 Hz) and a smaller coupling to the methylene protons (3.8 Hz) which are comparable with $^4J_{C3,H(5)}$ and $^2J_{C3,H(2)}$ in the smaller ring. The C2-atom shows three bond couplings to H4 and H7 of the same magnitude (4.3 Hz) while the corresponding pyrrol-3-ones couple to H4 and H5 with coupling constants of 4.4-5.2 Hz.

magnitude (4.7 Hz) to four protons and it is therefore assumed to couple to the three olefinic protons and the CH of the N-isopropyl group. This is supported by selective decoupling of the N-methyl signal in 1-methyl-1,2-dihydro-3H-azepin-3-one (204), which shows a sharpening of the extremely complex C7-signal. The characteristic splitting patterns found for the C5- and C7-atoms which were assigned, in the 2-unsubstituted cases, by carbon-proton correlations, allowed the unequivocal assignment of these two signals in the 2,2-dimethyl example (207); in this case the simple doublet of doublets due to C5 was more deshielded (δ_C 138.11) than the more complex doublet (δ_C 137.50), and although the pattern was reversed for the two-unsubstituted cases, the assignment could be made with confidence.

U.V. SPECTRA

The U.V. spectrum of the 1-methyl-1,2-dihydro-3H-azepin-3-one exhibits a maximum at 414 nm and the change observed when the nitrogen substitution is changed to an aromatic group (Table 45), is considerably less than for the 1,2-dihydro-3H-pyrrol-3-ones (10-15 nm compared with 25-28 nm). This might be expected as the crystal structure shows that the phenyl ring lies at a

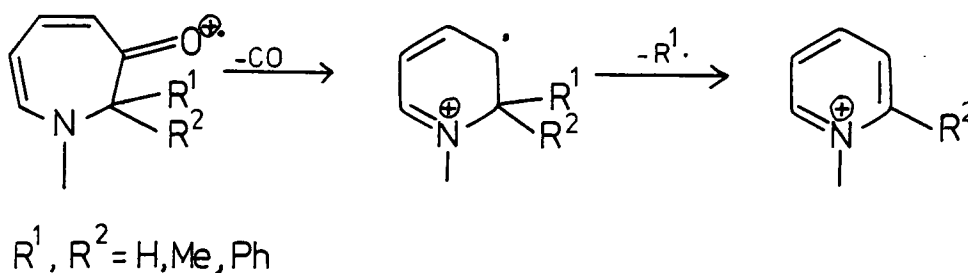
Table 45 U.V. Maxima of 1,2-dihydro-3H-azepin-3-ones

Azepinone	$\lambda_{\max}/\text{nm}$
(<u>204</u>)	414
(<u>205</u>)	428
(<u>206</u>)	425

considerable angle to the plane of seven-membered ring and much less conjugation will be possible.

MASS SPECTRA

In the mass spectra of the 1,2-dihydro-3H-azepin-3-ones the molecular ion peak is reasonably intense, (50-60%), except in the 1,2-diphenyl case (206), (9%). The most significant breakdown in examples containing hydrogen atom(s) on C2 is loss of m/z 29, and this leads to the base peak in the 1-methyl and 1-phenyl cases (204) and (205). This is thought to arise from extrusion of carbon monoxide followed by loss of a hydrogen atom to give aromatisation (Scheme 61; $R^1 = \text{H}$).



Scheme 61

In the 1,2-diphenyl case the most intense peak (apart from those due to phenyl and benzyl groups) occurs at $\underline{M}^+ - 105$ which would result from cleavage of a phenyl group after loss of carbon monoxide (Scheme 61: $R^1 = Ph$) to give the aromatised product. A reasonably intense peak (36%) is also present at $\underline{M}^+ - 43$ (loss of carbon monoxide and a methyl radical) in the 2,2-dimethyl example (207).

G. THE REACTIVITY OF 1,2-DIHYDRO-3H-AZEPIN-3-ONES

INTRODUCTION

The pyrolytic synthesis of the title compounds (208) described in Chapter E provides the first viable route to this ring system, and thus the first opportunity to study its reactivity. A number of potentially reactive features are immediately obvious; the ring contains enone, extended enaminone and diene units, as well as an apparently activated methylene group. Some of these features are comparable with those of the 1,2-dihydro-3H-pyrrol-3-one system (209) which has been discussed in detail and of which the 1,2-dihydro-3H-azepin-3-one may be considered a vinylogue. Further, the introduction of an additional double bond produces the conjugated system of 1H-pyridin-2-ones (210) and the azepin-3-ones may be considered as homologues of these rings, with the methylene bridge removing cyclic conjugation; the isomeric azepin-2-one (211) may also be considered in this manner. Thus, study of the properties of the new ring system considered as a vinylogue and homologue of the five- and six-membered rings, as well as comparison with its seven-membered ring isomer, which has been previously prepared,¹⁶⁶ was of interest (Figure 33).

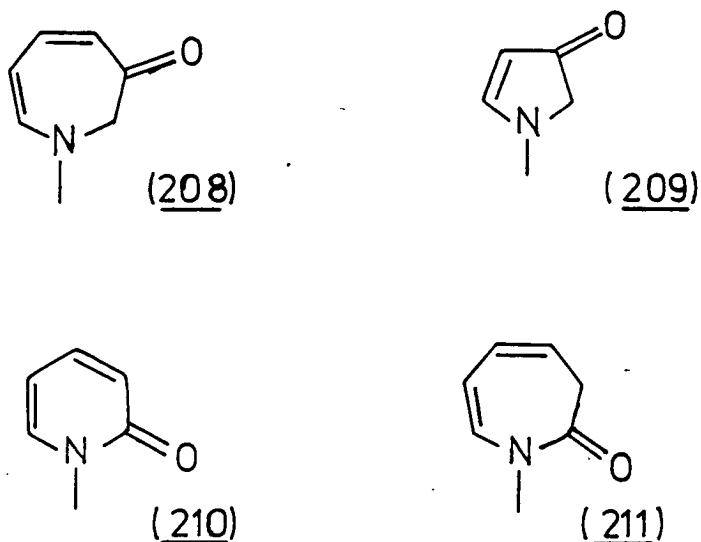


Figure 33

Some features of the reactivity of the systems (210) and (211), relevant to the chemistry of 1,2-dihydro-3H-azepin-3-ones are now discussed.

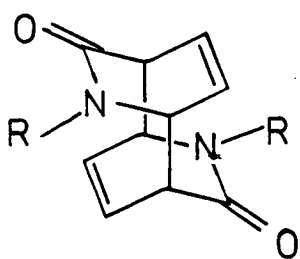
1H-Pyridin-2-ones

1H-Pyridin-2-ones have been widely studied and their chemistry has been reviewed^{167,168}. Of particular interest, in relation to 1,2-dihydro-3H-azepin-3-ones, are the N-substituted examples which are fixed in the pyridone tautomer and cannot exist in the cyclically conjugated pyridinol form.

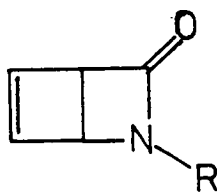
Deuterium exchange in acid conditions gives a simple method for examining the reactivity of compounds to

electrophilic substitution¹⁶⁹ and has shown that 1H-pyridin-2-ones undergo exchange at the 3- and 5-positions when heated ($\sim 100^\circ\text{C}$) in [$^2\text{H}_2$]sulphuric acid.¹⁷⁰ Study of the 3- and 5-monosubstituted examples and comparison of rates has suggested that exchange at the 3-position is faster.¹⁶⁹ Other electrophilic substitutions occur, as predicted, at these positions; thus nitration¹⁷¹, sulphonation,¹⁶⁸ diazo coupling¹⁷² and halogenation, have been observed. Early suggestions that halogenation was non-selective and that only 3,5-disubstituted compounds could be obtained¹⁶⁸ have been shown to be incorrect by the isolation of the 5-monochloro example,¹⁷³ formed by reaction with N-chlorosuccinimide in methylene chloride at reflux for twenty-four hours (electrophilic rather than radical attack was shown through examination of the reaction mixture by e.s.r. spectroscopy).

The diene unit of 1H-pyridin-2-ones has been found to be susceptible to photolytic conditions. In aqueous solution, irradiation leads to dimerisation¹⁷⁴ which yields compounds such as (212). Reaction in ether at -20°C , however, results in intramolecular reaction to give bicyclic species (213).¹⁷⁵



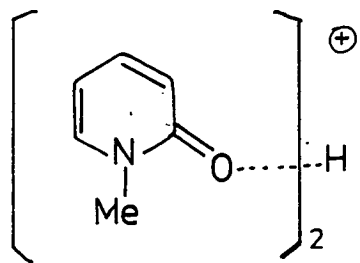
(212)



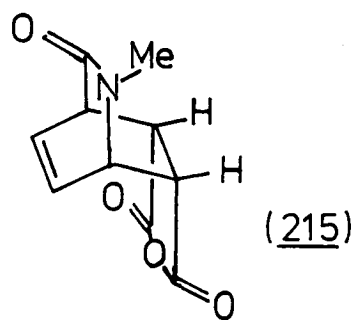
(213)

The azabicyclohexene (213; R = Me) was subject to a facile ring opening and was obtained in pure form by distillation from a molecular still at room temperature.

Early attempts to react 1H-pyridin-2-ones with maleic anhydride resulted in unstable 2:1 adducts¹⁷⁶ and with tetracyanoethylene the product is the pentacyanopropene salt (214).¹⁷⁷ However, Diels-Alder adducts have been prepared; for example, reaction with maleic anhydride in toluene at reflux for seventy-two hours gave the adduct (215),¹⁷⁸ while a 10% yield at the benzyne adduct¹⁷⁹ was obtained by reaction with diazotised anthranilic acid.



(214)

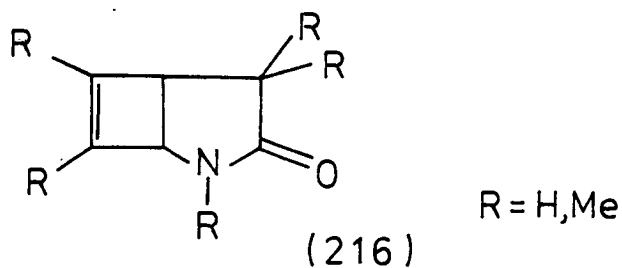


(215)

2,3-Dihydro-1H-azepin-2-ones

The properties of the diene unit of the azepin-2-ones reflect those described for the six-membered ring. Thus, chlorination with N-chlorosuccinimide yields the 6-chlorinated product under similar conditions¹⁷³ to those employed for pyridin-2-ones.

Photolysis gives intramolecular reaction resulting in the bicyclo products (216)¹⁸⁰ which could be isolated by chromatography and purified by sublimation or recrystallisation. The photoproducts were considerably more stable than those of the corresponding pyridin-2-ones, requiring pyrolysis at 430°C^{180b} to revert to the monocyclic compounds.



Diels-Alder reaction with dimethyl acetylene-dicarboxylate has been observed (20%) when the reactants were heated to 130°C for three hours without solvent. No reaction was found, however, with maleic anhydride or N-phenylmaleimide after extended reaction times at high

temperatures. In contrast, reaction with tetracyanoethylene at room temperature results instantly in a colour change in solution. (indicating formation of a π -complex) which fades over thirty minutes as the Diels-Alder adduct is formed in quantitative yield.

PROTONATION

1-Methyl-1,2-dihydro-3H-azepin-3-one protonates smoothly in trifluoroacetic acid to give a solution which is stable for several weeks. Marked changes are observed in the ^1H and ^{13}C n.m.r. spectra as a result of protonation and these are recorded in Tables 46 and 47.

Table 46 ^{13}C N.m.r. parameters for protonated azepinone (217)

	C2	C3	C4	C5	C6	C7
δ_{C}	56.47	153.70	109.07	151.21	115.67	159.63
$\Delta\delta_{\text{C}}^{\text{a}}$	-6.18	-26.51	-14.26	+9.20	-16.26	+12.44
^1J	147.8	-	164.1	161.8	170.8	175.2
$\Delta^1\text{J}^{\text{a}}$	+6.4	-	+4.5	+10.1	+9.1	+5.4

^a Difference from unprotonated species.

The proton n.m.r. spectrum showed two pairs of olefinic signals, as in the unprotonated species, and these could be readily assigned; the deshielded pair corresponded to 5-H and 7-H and could be identified by their different coupling patterns (doublet of doublets and doublet, respectively) and similarly for the more shielded pair (4-H and 6-H). Carbon-proton correlations then allowed the assignment of the carbon atom signals (Table 46).

O-Protonation would lead to the canonical forms illustrated in Figure 34 and would be expected on the basis of the observed protonation of open-chain enaminones¹³⁴ and vinylogous enaminones¹⁸² as well as the analogous five-membered system, (1,2-dihydro-3H-pyrrol-3-ones), which has been discussed earlier. The ¹³C n.m.r. chemical shifts observed are consistent with

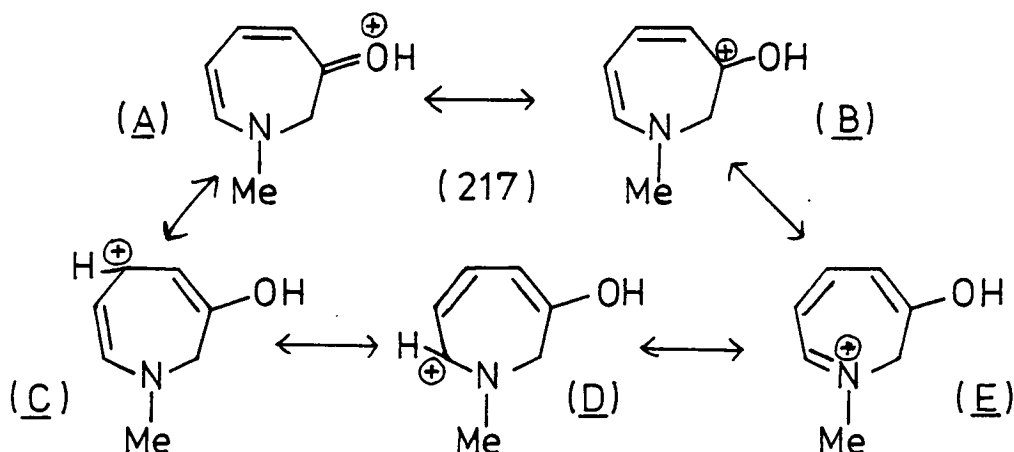


Figure 34

the formation of this species (217), although some differences from the shorter conjugated systems are evident. The sites which accommodate the positive charge in any one of the canonical forms of the protonated species, would be expected to show deshielding relative to the neutral compound as has been observed for the 5-position of the five-membered ring system ($\sim +9$ p.p.m.). A similar effect is also observed for both the 5- and 7-positions of the 1,2-dihydro-3H-azepin-3-one (11 and 12 p.p.m., respectively). However, the carbon atom bearing the oxygen substituent, which can also carry the positive charge, is shielded by approximately 11 p.p.m. in open-chain and cyclic enaminones, an observation best explained by the change in the π -system of the carbonyl group on protonation and the resulting reduction in the anisotropic effect¹²⁷; shielding is also observed for the extended enaminone system of the azepin-3-one (217), but of a much greater magnitude (26 p.p.m.). Predictions based on the observed effects in open-chain enaminones¹³⁴ suggest that sites incapable of formally bearing charge will show only a small deshielding (~ 2 p.p.m.) and the 1,2-dihydro-3H-pyrrol-3-ones do exhibit only minor changes in the chemical shift of the 4-position; shielding (1.5 p.p.m.) is observed in one case. In contrast, protonation of the seven-membered ring gives rise to considerable shielding

of the 4-position (14 p.p.m.) and deshielding of the 6-position (12 p.p.m.).

The apparently anomalous shifts observed for the 4- and 6-positions, as well as the extremely large shift of the 3-position in the extended system can be explained by varying contributions from the different canonical forms. The huge shielding of the 3-position implies that the form (217B) has little importance and the major influence at this site is the loss of carbonyl character. This would also explain the greater shielding of 4-position than expected since an adjacent, charged site is less favoured. The C6-atom, however, is flanked by two sites capable of bearing charge (217C and 217D) and these would seem to be more favoured, resulting in a relatively low electron density and marked deshielding at the central position. The larger deshielding of the C7-atom than the C5-atom may reflect a greater contribution from (217D) than (217C) or may arise from the additional inductive effect on C7 from the positively charged nitrogen atom in (217E).

The ^1J carbon-proton couplings increase as expected, but the change in ^1J for the 4- and 7-positions is somewhat lower than might be expected. However, this may be a result of the complex geometry and numerous potential conformations of this system.

The ^1H n.m.r. spectrum shows the anticipated increase in the chemical shift of all protons (Table 47) but the change in 6-H is particularly marked, reinforcing the suggestion of this position being subject to a particularly strong influence of positive charge at both adjacent sites.

Table 47 Proton n.m.r. parameters for protonated azepinone (217)

	2H	4H	5H	6H	7H	$^3J_{4,5}$	$^3J_{5,6}$	$^3J_{6,7}$
$\delta_{\text{H}}, J_{\text{HH}}$	4.12	6.50	7.67	6.63	8.04	7.7	11.5	5.0
Δ^a	+0.55	+0.33	+0.83	+1.46	+1.32	-3.3	+2.5	-2.2

^a Difference from unprotonated species.

Of particular interest are the ^3J values since they support the arguments for varying contributions of canonical forms; thus, the largest coupling is now observed for the coupling across the C5-C6 bond which exists as a double bond in the canonical forms proposed to be most important (217D and 217E), while the $^3J_{6,7}$ is now the smallest and it is a single bond in these forms. The largest change is observed for $^3J_{4,5}$ and this may be explained by the small contribution from the form (217B) leaving only (217A)

where the C4-C5 bond retains the double bond character it has in the unprotonated species.

Solution of the 1-methyl-1,2-dihydro-3H-azepin-3-one in [^2H]trifluoroacetic acid gave some indication of the relative reactivity of the electrophilic sites of the system by the observation of the rate of deuterium incorporation. ^1H n.m.r. spectroscopy showed immediate changes in the signal of the 5-position and less rapid change of the signal corresponding to the 7-position, thus clearly indicating loss of coupling to the 4- and 6-positions. Since the signals for the 4- and 6-positions were superimposed it was difficult to monitor accurately the rate of deuterium incorporation at each site, but the change in the coupling pattern of the 5- and 7-signals over an hour showed clearly that exchange was considerably more rapid at the 4-position. By assuming exchange at this position was complete after 20 minutes, an approximate half-life for reaction at the 6-position was found and used as a correction factor in the calculation of the half-life for reaction at the 4-position. Exchange at the 2-position could be readily monitored and was found to be considerably slower than at either position in the conjugated system. The trend shown by the half-lives [4 (2.5 min) < 6 (15 min) < 2 (250 min)] is similar to that found in open-chain dienaminones¹⁸² and pyridin-2-ones.¹⁶⁹

ELECTROPHILIC ALKYLATION

Treatment of 1-methyl-1,2-dihydro-3H-azepin-3-one with triethyloxonium tetrafluoroborate, in methylene chloride at room temperature, gave the alkylated salt (218) as a colourless oil. The ^1H and ^{13}C n.m.r. spectra of the product are very similar (Figure 35) to those of

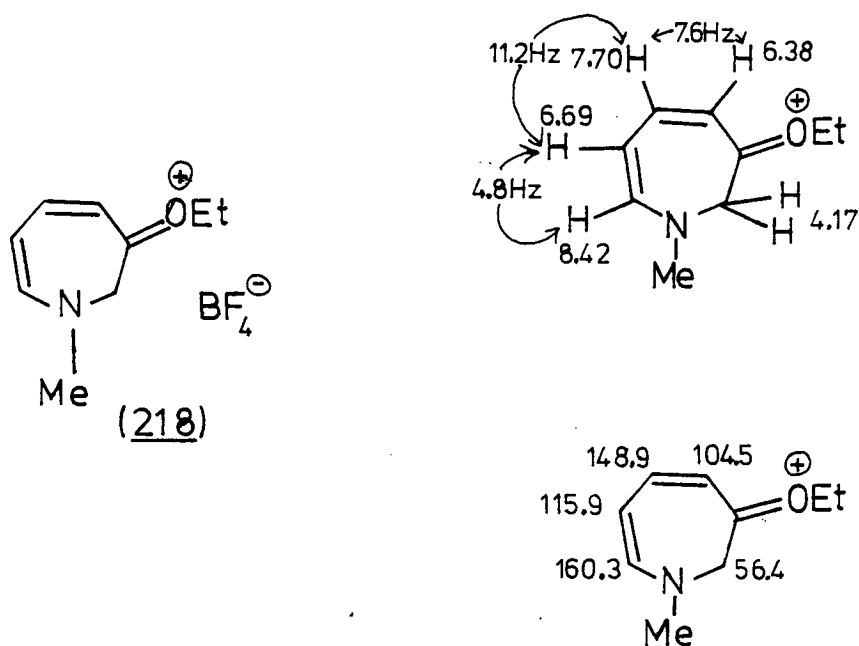
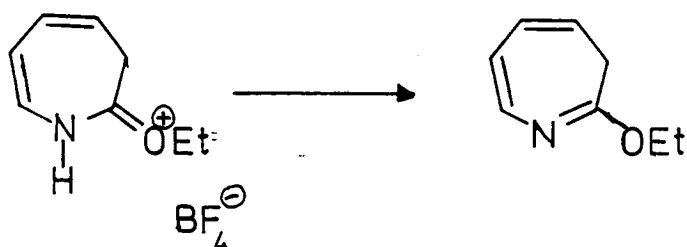


Figure 35

the protonated species (217), and the presence of additional, slightly shifted signals for all bar the ethyl group atoms, indicated the presence of a small amount of the simple protonated form (217), presumably formed by elimination.

This could be removed by the addition of solid potassium carbonate to the solution during reaction, which allowed the isolation of the pure salt (218) (79%). The chemical shifts of the signal for the methylene portion of the ethyl group (δ_{H} 4.19 and δ_{C} 66.81) confirmed the site of alkylation (and by comparison of spectra, protonation) as the oxygen atom. As for the 1,2-dihydro-3H-pyrrol-3-one salt discussed previously, there is no evidence for deuterium incorporation into the 4- and 6-positions of ring system after solution in [^2H]trifluoroacetic acid, even after a number of weeks. However, in the five-membered system, exchange of the 2-position does occur for the 3-alkoxypyrrole in acid solution, presumably via the free base, and exchange by a similar mechanism is possible in the O-alkylated 1,2-dihydroazepinium salt; this exchange is not observed after several weeks. Notably, such an exchange would require the formation of a fully conjugated 3-alkoxyazepine and thus involve an 8π electron, antiaromatic system. This is doubtless the reason for the absence of exchange in the alkylated salt, and the gradual exchange observed for the simple protonated azepinone (217) must occur by some other mechanism involving O-protonation.

Treatment of the alkylated salts of N-unsubstituted 2,3-dihydro-1H-azepin-2-ones with potassium carbonate resulted in abstraction of a proton to give the corresponding azepines (Scheme 62).



Scheme 62

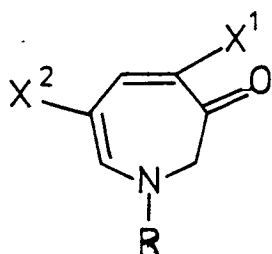
Clearly, in the azepin-3-ones such mild base is insufficient to promote abstraction from the 2-position as would be required to give the fully conjugated system. However, treatment of a solution of the salt (218) in [$^2\text{H}_4$]methanol with deuteriated sodium methoxide resulted in an immediate colour change from yellow to orange-red and the resulting solution appeared to be quite stable at room temperature. The ^1H n.m.r. spectrum of the reaction mixture showed marked changes but these proved difficult to rationalise. The ethyl group is still present, as are two singlets with appropriate integral values for the N-methylene and methyl protons, but these have been dramatically shielded (δ_{H} 3.25 and 3.13 from δ_{H} 4.22 and 3.85 in neutral solution). In addition, multiplets, each corresponding to one proton are present at δ_{H} 6.20 (t, 4.3 Hz) and 6.00 (m). A further triplet corresponding to slightly less than one proton is also present [δ_{H} 4.58 (8.4 Hz)]. The potential for deuterium exchange and possible masking of signals by the

O-H peak (δ_H 5.5) suggest some sources of complications in the interpretation of this spectrum and attempts to isolate product from this preliminary experiment were unsuccessful. Obviously there is considerable potential for further work in this area.

ELECTROPHILIC SUBSTITUTION

Electrophilic substitution of 1,2-dihydro-3H-azepin-3-ones with N-halogenosuccinimides proceeded rapidly to give mixtures of products. The azepinone was dissolved in methanol and cooled to 0°C before addition of the appropriate N-halogenosuccinimide as a solid. T.l.c. on silica plates using ethyl acetate:methylene chloride mixtures as eluant, indicated some reaction occurred instantaneously and additional spots appeared before the complete removal of starting material (regardless of the quantity of succinimide added). Numerous attempts to isolate the products of halogenation failed because of the sensitivity of these compounds; thus it was found that heating to above ~40°C in order to remove solvent resulted in decomposition, as did distillation, and if the compounds were left on silica columns for any length of time material appeared to react with the stationary phase. However, treatment of 1-methyl- and 1-phenyl-1,2-dihydro-3H-azepin-3-ones with one equivalent of N-chlorosuccinimide at 0°C, for forty-five minutes, led to the 4-chloro compounds (219 and 220) in 51 and 41%

yields, respectively, after washing with sodium hydrogen carbonate and dry flash column chromatography. The compounds could be purified by recrystallisation from methanol at -20°C. Using two equivalents of N-chlorosuccinimide, the 4,6-dichloro compound (221) was isolated (44% yield). G.c. analysis of the crude reaction mixtures showed the presence of one other significant component when one equivalent of chlorinating agent was used, but the ^1H n.m.r. spectrum was uninterpretable and attempts to purify the product resulted in decomposition. When two equivalents of N-chlorosuccinimide were employed a mixture of three compounds was obtained in addition to the dichlorinated species. G.c./m.s. implied that these may have included other dichlorinated species, and it is possible that the by-products of these reactions result from chlorination at the 2-position of the ring. This has not been further pursued, but reaction of the 2,2-dimethyl-1-isopropyl-1,2-dihydro-3H-azepin-3-one (207) under the same conditions should provide interesting results.



R	X ¹	X ²
(<u>219</u>)Me	Cl	H
(<u>220</u>)Ph	Cl	H
(<u>221</u>)Ph	Cl	Cl
(<u>222</u>)Me	Br	Br
(<u>223</u>)Me	Br	H
(<u>224</u>)Me	H	Br

Treatment of 1-methyl-1,2-dihydro-3H-azepin-3-one with either one or two equivalents of N-bromosuccinimide, resulted in the isolation of only the dibrominated species (222) in 8% and 60% yield, respectively. These reactions were carried out by addition of the succinimide to a solution of the azepinone at 0°C and stirring the mixture for five minutes, before the usual work-up. Two equivalents of the succinimide yielded the product as a crystalline compound without chromatography on one occasion, but this purity could not be attained reproducibly and generally, chromatography and recrystallisation from a methanol solution at -20°C was necessary. The compound decomposed in solution over a period of hours to give a black, insoluble precipitate, and it was therefore impossible to obtain a ^{13}C n.m.r. spectrum. In addition to the 8% yield of dibromo product obtained from reaction with one equivalent of N-bromosuccinimide a further fraction was obtained after chromatography (11 mg from 60 mg of starting material). The ^1H n.m.r. spectrum of this material showed signals at δ_{H} 7.46 (1H, d, ^3J 10.0 Hz), 6.87 (1H, d, ^3J 6.9 Hz), 5.19 (1H, dd, ^3J 6.9 and 10.0 Hz), 3.71 (2H, s) and 3.22 (3H, s) which are consistent with the formation of 4-bromo-1-methyl-1,2-dihydro-3H-azepin-3-one (223) (see following section on the spectra of the chloro compounds) but additional signals are also present. These have

integral values which are equivalent to those described above and it is not clear whether this fraction contains a one to one mixture of products, or some dimeric species. The fraction decomposed on heating and, in view of the small portion of reaction which it represented, it was not further investigated.

Clearly the electrophilic substitution of the 1,2-dihydro-3H-azepin-3-one system is complex and invites investigation. The reaction of examples in which some of the potentially reactive sites are blocked, or the use of an electrophile which reacts under mild conditions but would be anticipated to give less sensitive products, would appear to offer the best routes for further progress in this study. However, reactions with methoxymethylidene Meldrum's Acid and diazonium salts, both of which gave rise to clean products in the analogous five-membered ring series, resulted only in apparent decomposition.

The n.m.r. spectroscopic characteristics of the halogenated compounds which have been isolated are listed in Tables 48 and 49.

The most significant aspect of the proton spectra is the changes in the coupling constants across the C5-C6 and C6-C7 bonds in the 4-monosubstituted examples. The more expected pattern of a large coupling across the double bond (~ 10 Hz) and a smaller coupling across the

Table 48 Proton n.m.r. parameters for halogeno-1,2-dihydro-3H-azepin-3-ones

Azepin-3-one	R	2-H	5-H	6-H	7-H	R	$^3J_{5,6}$	$^3J_{6,7}$
(<u>222</u>)	Me	3.71	7.12	-	7.72	3.19	-	-
(<u>221</u>)	Ph	4.29	7.46 ^a	-	7.29 ^a	7.1-7.4	-	-
(<u>220</u>)	Ph	4.27	7.10	5.51	b	7.1-7.4	7.5	9.8
(<u>219</u>)	Me	3.63	6.83	5.20	7.20	3.20	6.9	10.0

^a Identified from aromatic signals by presence of long-range coupling $^4J_{5,7}$ and $^4J_{2,7}$

^b Superimposed on aromatic signals

single bond (~ 7 Hz) is observed, in contrast to 7.2 Hz and 9.1 Hz, respectively, in 1-methyl-1,2-dihydro-3H-azepin-3-one. This is almost certainly due to a change in the geometry of the system and may reflect the bulk of the substituent forcing the cis-proton (5H) away. This would in turn alter the angles between the remaining protons and the double bonds, which is known to alter coupling constants.¹²¹ In the unsubstituted compound (205) the angle at the C5-atom is larger than anticipated and may be giving rise to the surprising magnitudes of the coupling constants.

The C5 and C7-resonances in the ^{13}C n.m.r. spectra have very similar chemical shifts, as is found in the azepinones without halogeno substitution. However, these signals of the 1-phenyl and 1-methyl examples were distinguished with the aid of fully coupled spectra; thus it was noted earlier that the C7-resonance gave rise to a doublet of complex signals due to long-range coupling while the C5-resonance was a simple doublet of doublets, and the same pattern was found in the chloro-substituted derivatives. In addition, the one bond coupling for the signal next to nitrogen is expected to be larger and, on the basis of the assignment above, $^1J_{\text{C}7(\text{H})}$ is 180 Hz while $^1J_{\text{C}5(\text{H})}$ is 163 Hz. The marked shielding of the carbonyl carbon atom on substitution of the adjacent atom (6.8 p.p.m.) is similar to that observed in 1,2-dihydro-3H-pyrrol-3-ones and it seems probable that this is due to an electronic effect, as is observed across single bonds in a number of α -chloroketones.¹⁸⁴ This is postulated as being a result of the electronegativity of the chlorine atom countering the effect of the carbonyl oxygen atom. The substituent effects in the remainder of the conjugated system might have been anticipated to be comparable with those observed in benzene and the conjugated systems of heteroaromatics, but no such trends are observed, probably because of the effect of substitution on the geometry of the conjugated system in the azepinones.

Table 49 ^{13}C chemical shifts for chloro-1,2-dihydro-3H-azepin-3-ones

Azepin-3-one	C2	C3	C4	C5	C6	C7
(221)	58.55 (-0.13) ^a	175.44 (-0.6)	130.08 (+0.28)	139.54 ^b (+0.66)	109.49 (+6.42)	139.08 ^b (-2.82)
(220)	58.68 (-0.7)	176.06 (-6.81)	129.80 (+3.09)	138.88 (-1.39)	103.07 (-0.79)	141.90 ^b (+0.46)
(219)	61.31 (-1.34)	173.42 (-6.79)	125.84 (+2.51)	140.62 ^c (-1.39)	98.81 (-0.69)	147.22 ^c (+0.63)

^a Figures in brackets refer to shifts observed from unsubstituted azepinones for (219) and (220) and to shifts from monochloro compound in (221).

^b Assigned by consideration of the fully coupled spectra.

^c Tentatively assigned by comparison with N-phenyl example (220).

Thus, the carbon atom adjacent to the site of substitution is shielded [by 1.4 p.p.m. for both monochlorinated examples and 2.8 p.p.m. when the additional chlorine is added in (221)] which is a similar effect to that observed in the analogous five-membered ring system. In contrast, benzene shows an ortho substituent effect of +0.4 p.p.m., and the shifts of C6- and C7-atoms in the monosubstituted cases are also in the opposite direction to corresponding changes in benzene; it appears that the relative importance

of the mesomeric and inductive effects of the chloro-substituent are altered, possibly as a result of the non-planar geometry of the ring. The presence of a bulkier substituent (chlorine atom for hydrogen atom) may, in itself, alter the chemical shifts simply by forcing the conjugated system further away from planarity than is observed in the 1-phenyl-1,2-dihydro-3H-azepin-3-one.

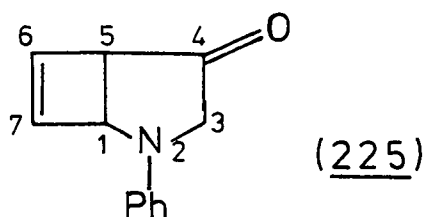
PERICYCLIC REACTIONS

Photolysis

Intramolecular (2+2)-cycloaddition reactions of heterocyclic dienes have been observed for a number of five, six- and seven-membered systems.^{185,186} In addition to the reaction of 1H-pyridin-2-ones and 2,3-dihydro-1H-azepin-2-ones, which have already been mentioned, azepines,¹⁸⁷ oxepines,¹⁸⁸ pyrones,¹⁷⁵ benzo[b]thiepins¹⁸⁹, and a variety of other heterocycles, form bicyclic compounds on irradiation. The photoproducts vary in stability, from species such as a pyrazole product detected only at -50°C¹⁹⁰ to the azepinone products (216) which are stable up to 400°C.¹⁸⁰

Irradiation of 1-phenyl-1,2-dihydro-3H-azepin-3-one in [²H₆]acetone, at room temperature, using a 125 Watt Hg lamp allowed the photolysis reaction to be followed by ¹H n.m.r. spectroscopy. The disappearance of the signals corresponding to the conjugated diene unit could,

therefore, be monitored and once the reaction was complete (the reaction time varied with the concentration of the photolysed solution) the photoproduct could be isolated, as a solid, by dry flash chromatography (64%). The product gave ^1H and ^{13}C n.m.r. spectra which were consistent with the bicyclic isomer (225) of the azepinone; thus, the proton spectrum showed a pair of doublets at δ_{H} 6.60 and 6.33, each corresponding to an olefinic proton, a further pair of doublets at δ_{H} 4.99 and 3.80, each corresponding to an aliphatic proton, and a multiplet at δ_{H} 4.04 corresponding to the two methylene protons. The ^{13}C n.m.r. showed a quaternary absorption in the carbonyl region (δ_{C} 207.92) and the required olefinic (δ_{C} 141.06 and 137.13) and aliphatic (δ_{C} 60.23, 55.14 and 54.55) signals.



A series of n.O.e. experiments were carried out in order to assign the ^1H n.m.r. spectrum. The ortho aromatic signals were irradiated and, in addition to an effect on the meta signals, a significant increase in intensity of

of the signal at δ_H 4.99 (15%) and the two methylene protons (5% each) was observed, thus allowing the assignment of the deshielded signal to 1-H. Further, irradiation of one of the olefinic protons (δ_H 6.33) affects the signal at δ_H 3.80 (4-H) and the reciprocal enhancement is also observed and therefore that signal is due to the 6-proton. The assignments and n.O.e. effects are illustrated in Figure 36.

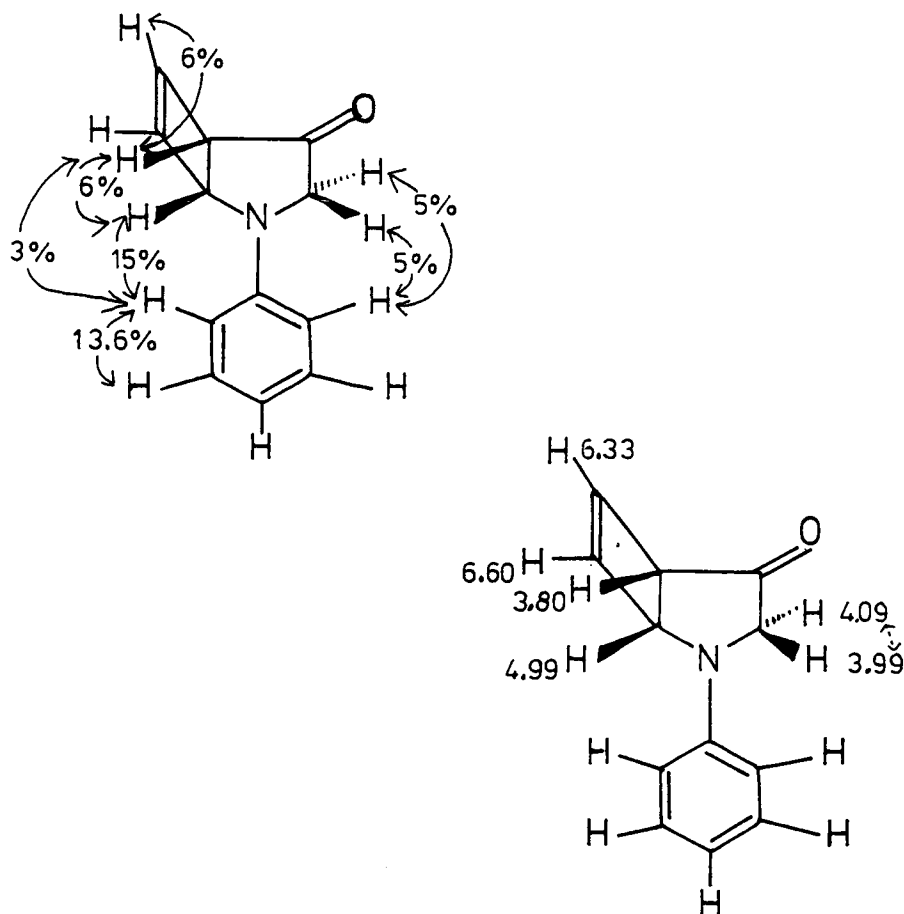


Figure 36

In addition to anticipated three-bond couplings a number of long-range couplings are observed. For example, each of the ring junction protons couples to one of the methylene protons; the methylene protons are in different environments because of the geometry of the fused system and give rise to an AB system (geminal coupling ~ 18 Hz) in which each limb is further split (~ 1 Hz) by one other proton. Interestingly, only one of the olefinic signals (δ_{H} 6.60, 7-H) exhibits coupling to the ring junction protons. It couples to both 1-H (1.1 Hz) and 5-H (1.2 Hz) while the other olefinic shows only $^3J_{7(\text{H})}$ of 2.7 Hz.

The thermal ring opening of the bicyclic system was followed by ^1H n.m.r. spectroscopy in [$^2\text{H}_8$]toluene. The chemical shift range δ_{H} 4.0-5.2 showed a clear signal due to one of the ring junction protons (δ_{H} 4.29) at the start of the reaction and a further triplet at δ_{H} 4.96 due to the 6-proton of the 1,2-dihydro-3H-azepin-3-one appeared as the reaction progressed. The change in concentration of the bicyclic compound was monitored at two temperatures (78°C and 84.5°C) and plots of log of concentration against time are shown in Figure 37 and appear to show 1st order kinetics. These allowed the calculation of rate constants (8.9 ± 0.23 and $14.0 \pm 0.25 \times 10^{-3} \text{ min}^{-1}$, respectively) from which an approximate value for the activation energy of the

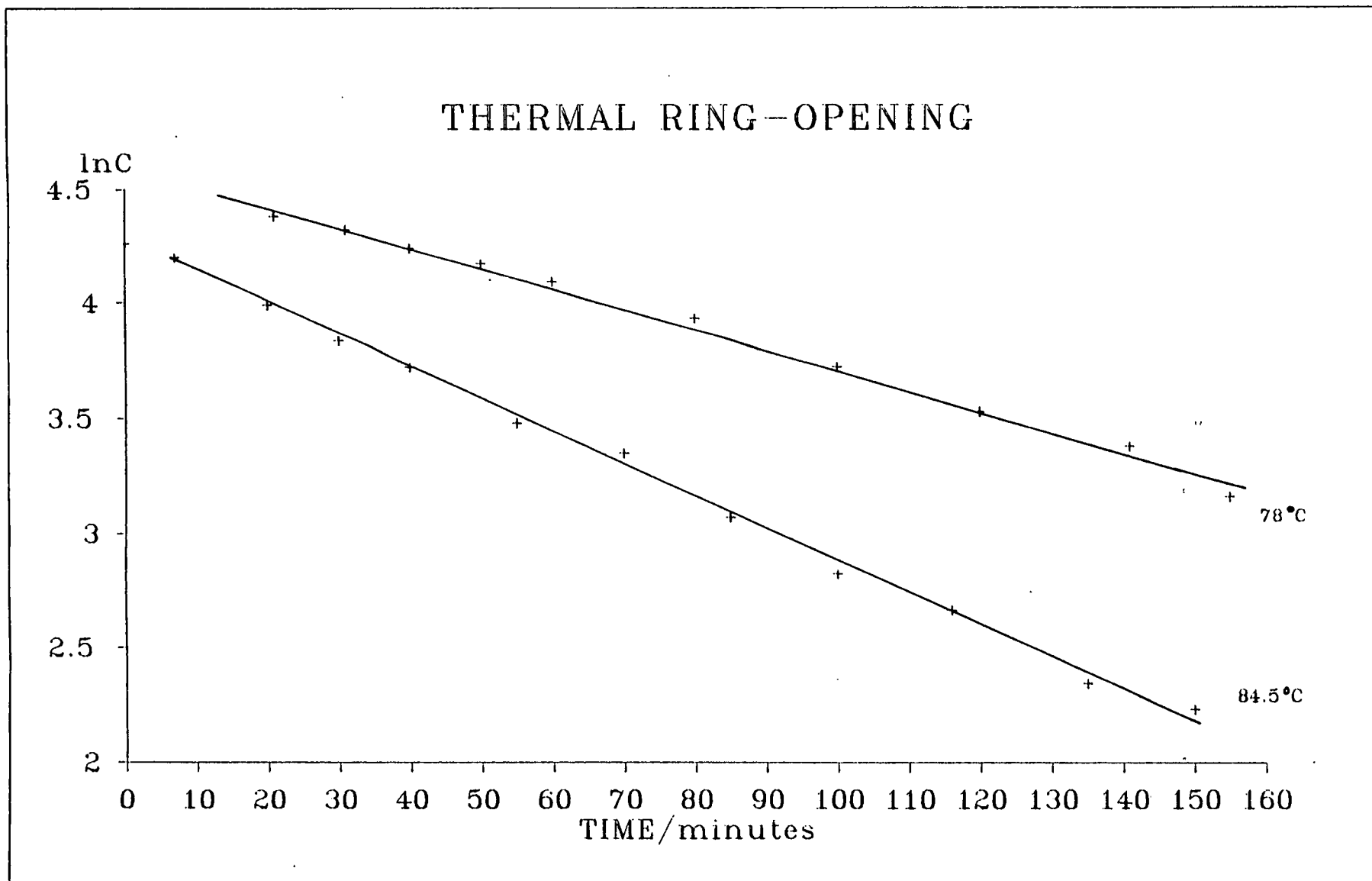


Figure 37

reaction could be obtained (72.4 kJ mol^{-1}). The thermal reversion is considerably more facile than in the isomeric compounds (216) produced by photolysis of azepin-2-ones. This may be due to the delocalisation present in the extended enaminone structure of the azepin-3-ones which gives partial single bond character to the C6-C7 bond and thus allows rotation from the strained trans geometry resulting from a thermally allowed ring opening, which may promote the reversion process (Figure 38).

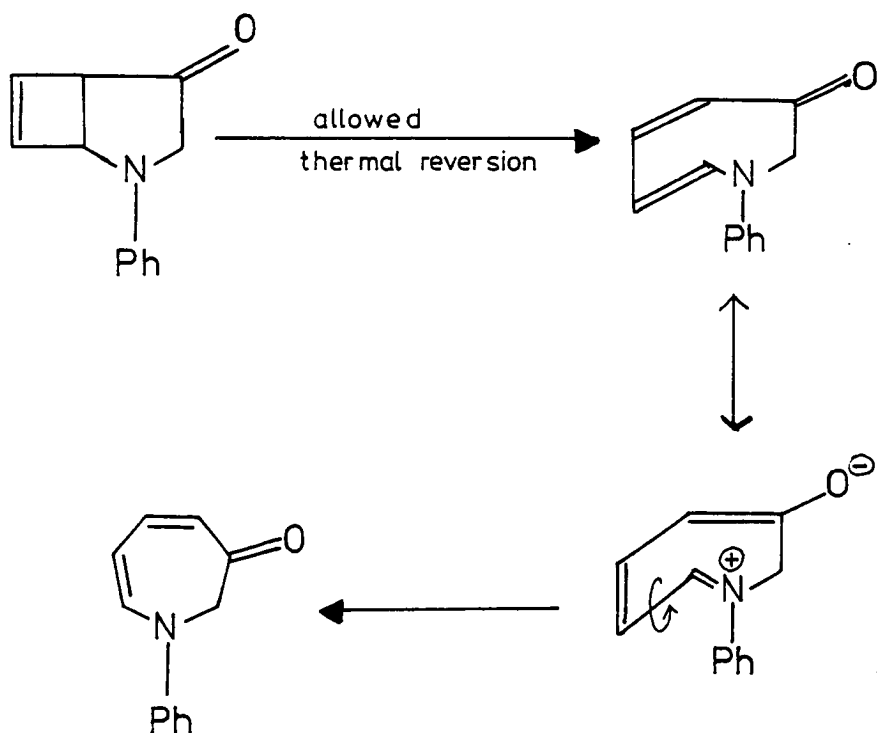
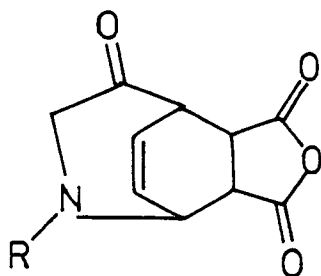


Figure 38

Cycloadditions

The diene unit of 1,2-dihydro-3H-azepin-3-ones is also reactive towards dienophiles. For example, the 1-phenyl substituted compound was found to react with maleic anhydride over a period of forty-eight hours, at room temperature, in benzene to give the cyclo adduct (226) as a solid, which could be recrystallised from methanol (64%).



(226) R = Ph

(227) R = Me

These mild conditions contrast dramatically with those employed in the reaction of 1-methyl-1H-pyridin-2-one (110°C, 72 h.)¹⁷⁸ and the absence of reaction with the isomeric azepin-2-one. Reaction of the 1-methyl-1,2-dihydro-3H-azepin-3-one occurs even more rapidly; the product, (227) (81%), was produced in less than two hours at room temperature, but it was unstable to heat and in solution, decomposing to an unidentified, very insoluble material. The increase in reaction rate observed when the nitrogen atom substitution is changed, indicates that the diene unit is participating in the reaction as a typical, electron-rich system reacting

with the electron-poor dienophile. The carbonyl substituent is apparently less influential in this case than the electron donating power of the nitrogen atom and the N-methyl substituent is better in this capacity than the N-phenyl group; in the analogous pyridone and azepin-2-one systems the nitrogen atom has amide character, drastically reducing its ability as a donor.

The stereochemistry and conformation of the phenyl adduct (226) were determined by n.O.e. experiments. The ^1H n.m.r. spectrum shows two triplets (δ_{H} 7.31 and 6.89) and a doublet (δ_{H} 7.02) corresponding to the meta, para and ortho protons of the aromatic ring. The two olefinic protons give rise to a complicated multiplet at δ_{H} 6.63, while the remaining protons each give rise to a well-defined signal. The most deshielded of these (δ_{H} 5.12) was assigned to the bridgehead proton next to the nitrogen atom. Decoupling of this signal collapsed a small coupling to the signal at δ_{H} 4.09 which was thus assigned to the adjacent, aliphatic proton. The remaining signals could then be readily assigned by their coupling patterns (Figure 39). Irradiation of the ortho protons or one of the methylene protons (δ_{H} 4.02) gave n.O.e. enhancement of the ring-junction protons (3.5% and 2%, respectively) which showed the stereochemistry to be endo. Ring and nitrogen inversion, however, could give rise to four different conformations (Figure 40) and further examination of n.O.e. effects allowed the prediction of the favoured conformation.

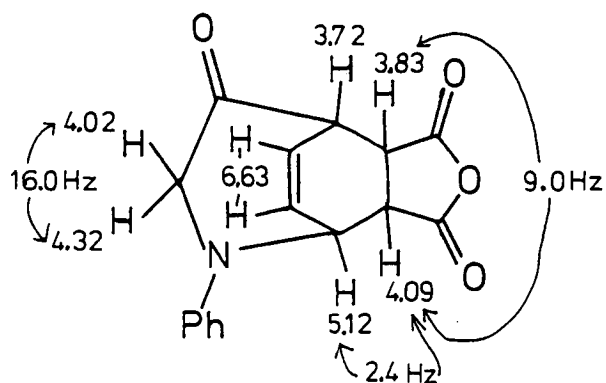


Figure 39

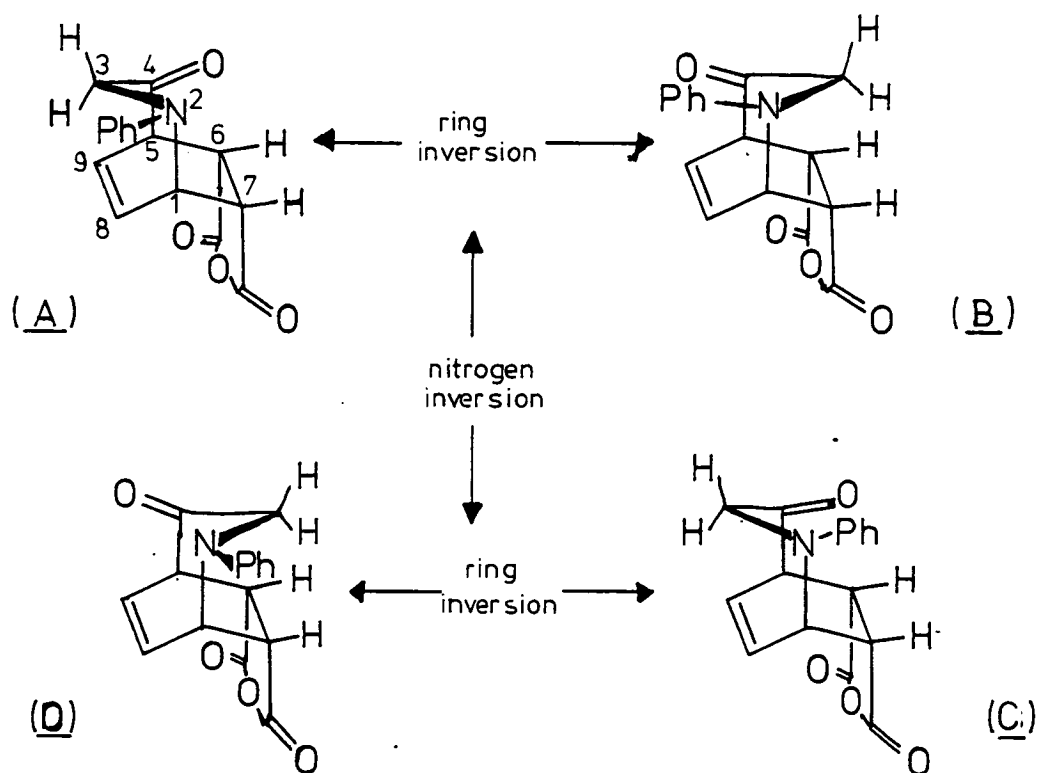


Figure 40

Conformations A and B are ruled out as irradiation of the ortho protons affects the proton at the 7-position (3.5%) which would not be expected. Further, irradiation of the ortho-protons produces n.O.e. enhancement of both the methylene protons (5.2 and 1.5%) which would seem highly unlikely in B or C and thus D is thought to be the dominant conformation (Figure 41).

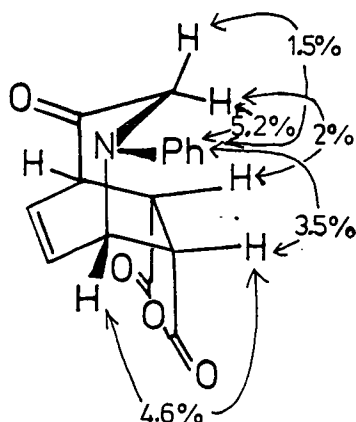


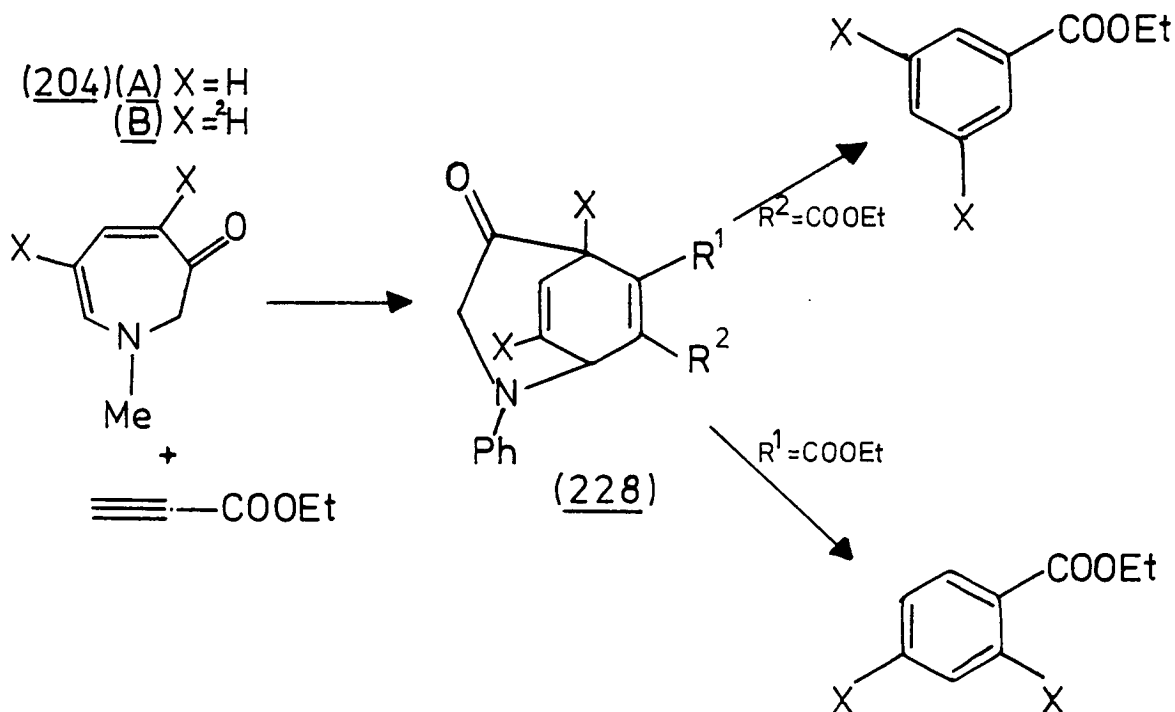
Figure 41

Pyrolysis of the 1-phenyl adduct (226) at 600°C gave 1-phenyl-1,2-dihydro-3H-azepin-3-one and maleic anhydride with no evidence (by ^1H n.m.r. spectroscopy or g.c. analysis) of other fragmentation patterns.

When solutions of 1-phenyl-1,2-dihydro-3H-azepin-3-one and tetracyanoethylene were mixed, a yellow solid precipitated immediately. The solid was extremely insoluble, and when attempts were made to recrystallise it, bright red solutions resulted from which no product could be obtained. A ^1H n.m.r. spectrum of the solid, obtained immediately on solution in $[\text{}^2\text{H}_4]\text{methanol}$, showed only signals corresponding to the starting azepinone. An i.r. spectrum of the solid showed a carbonyl absorption at 1615 cm^{-1} which is consistent with an extended amide such as the starting material, in contrast to the typical saturated ketone value (1770 cm^{-1}) of the maleic anhydride adducts. It is thus proposed that a charge transfer complex is formed between the diene and dienophile.

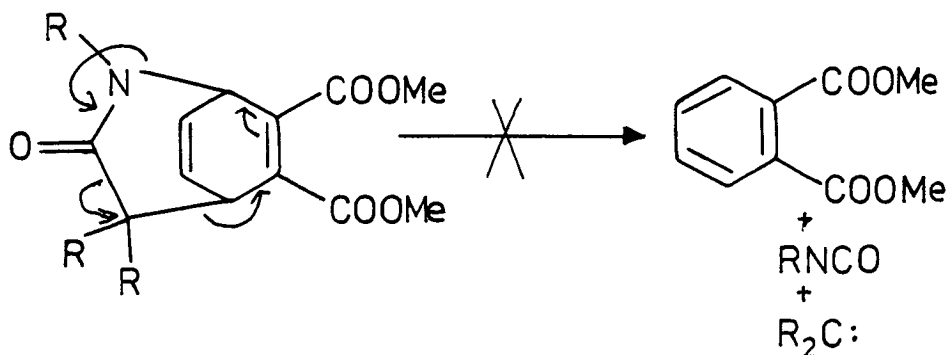
1-Methyl-1,2-dihydro-3H-azepin-3-one was found also to react with acetylenic dienophiles. Ethyl propiolate was added to a solution of the azepinone in $[\text{}^2\text{H}_3]\text{-acetonitrile}$ and the ^1H n.m.r. spectrum of the reaction mixture was recorded at intervals. After several hours at room temperature, traces of new aliphatic signals were observed which may have been due to formation of the cycloadduct but a considerable amount of starting material was still present. However, after a few hours of heating to reflux the major product in the reaction mixture appeared to be benzenoid in character. Reaction appeared to be complete after sixteen hours at reflux and the

product was shown to be ethyl benzoate (80%) (by comparison of g.c. retention time and ^{13}C n.m.r., D.E.P.T. spectrum with those of an authentic sample). The reaction is thought to proceed via the expected cycloadduct (228), which can then undergo elimination of the three atom bridge to yield the aromatic product (Scheme 63).



Scheme 63

The aromatisation can occur with extrusion of carbon monoxide and an imine, thus giving rise to three, stable products (in this case the imine may trimerise). This contrasts with the requirements of the isomeric azepin-2-ones, which form stable adducts with dimethyl acetylenedicarboxylate,¹⁸¹ since these would need to eliminate much less stable, isocyanate and carbene fragments (Scheme 64).



Scheme 64

Dimethyl acetylenedicarboxylate was found to react in the same manner with 1-methyl-1,2-dihydro-3H-azepin-3-one, to yield dimethyl phthalate in good yield (73%). Even under the milder conditions required for this reaction (six days at room temperature) no significant build up of the cycloadduct was observed.

In order to study the regioselectivity of the Diels-Alder reactions of the 1,2-dihydro-3H-azepin-3-ones, the 4,6-[²H₂]-1-methyl example (204B) was prepared by exchange in acid solution. Reaction of this deuteriated

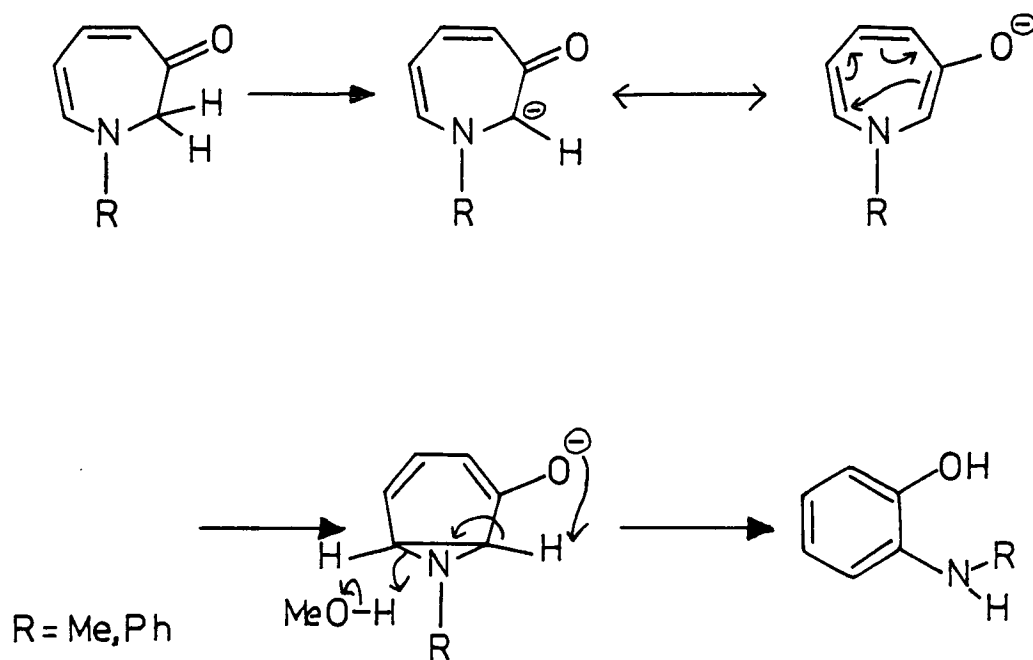
compound with ethyl propiolate could yield either, or both, the cyclo-adducts (228; $R^1 = H$, $R^2 = CO_2Et$) and (228; $R^1 = CO_2Et$, $R^2 = H$) each of which would give rise to a different, specifically labelled benzoate. The former, which would arise from a cycloaddition in which the substituted site of the alkyne interacted with amino-substituted terminal of the diene, would result in ethyl 3,5-[$^2H_2$]benzoate while the latter, corresponding to the opposite regiochemistry, would give ethyl 2,4-[$^2H_2$]benzoate. The ortho protons of ethyl benzoate were clearly resolved as a deshielded doublet (δ_H 8.04) which had collapsed to a singlet in the product isolated from reaction with the deuteriated azepinone. Thus the 3-positions were shown to be the major sites of deuterium incorporation, but in order to show that there was no evidence for the alternative mode of cyclo-addition, the ^2H n.m.r. spectrum was also obtained and it indicated only one site of deuterium incorporation. This regio-selectivity is as expected for electron-rich dienes with electron-poor dienophiles¹⁹¹ and thus supports the earlier conclusions based on the relative rates of reaction of the N-methyl and N-phenyl-1,2-dihydro-3H-azepin-3-ones. This novel synthesis of benzene derivatives from acyclic precursors may provide a suitable route to some specifically, isotopically labelled benzenes.

REACTIONS WITH BASE

The very different properties of the methylene group of 1,2-dihydro-3H-azepin-3-ones with those of the analogous five-membered ring system (1,2-dihydro-3H-pyrrol-3-ones) has already become apparent because of the absence of any of the enol tautomer in solution. The difference undoubtedly arises from the 8- π electron anti-aromatic system which would result and, not surprisingly, treatment with base does not appear to result in the formation of a stable, 8- π electron, enolate system. Thus, treatment of 1-methyl-1,2-dihydroazepin-3-one with aprotic base (sodium hydride in [$^2\text{H}_6$]dimethylsulphoxide) give no change in the ^1H n.m.r. spectrum, while treatment with lithium di-isopropylamide in tetrahydrofuran and simply quenching with water or [$^2\text{H}_2$]water led to a number of products by t.l.c. or g.c. but attempts to isolate these led only to small amounts of recovered starting material with no trace of deuterium incorporation.

Treatment with deuteriated sodium methoxide in [$^2\text{H}_4$]methanol also shows no indication of exchange of the methylene protons. However, an alternative, novel reaction does occur on treatment with methoxide. When 1-methyl-1,2-dihydro-3H-azepin-3-one and two equivalents of sodium methoxide were heated to reflux in [$^2\text{H}_4$]methanol for twenty-four hours, the resulting product was

shown, by ^1H n.m.r. spectroscopy, to be benzenoid in nature. A ^{13}C n.m.r. D.E.P.T. spectrum of the reaction mixture showed four methine signals in the aromatic region in addition to a signal corresponding to the N-methyl group. Comparison with the spectrum of an authentic sample, run under the same conditions, showed the product to be 2-(N-methylanino)phenol. The mechanism of phenol formation has not been investigated, but is assumed to proceed via a route similar to that illustrated in Scheme 65.



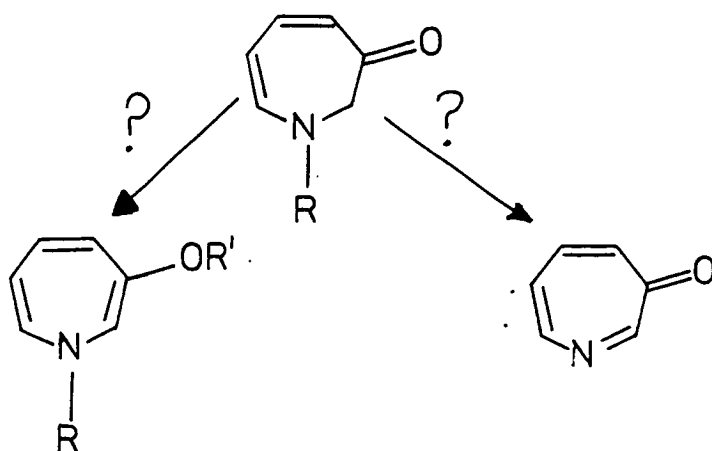
Scheme 65

The absence of any 3-(N-methylamino)phenol requires that the proton attached to the site next to the oxygen atom is transferred in preference to the other proton on the postulated aziridine ring. It therefore seems possible that the oxygen atom promotes the ring-opening of the aziridine in one direction. 1-Phenyl-1,2-dihydro-3H-azepin-3-one also undergoes this rearrangement under basic conditions but the reaction is much more facile (sixteen hours at room temperature) and this is consistent with the requirement of formation of a species with considerable negative charge on nitrogen as the rate determining step, since the phenyl group could delocalise this charge to some extent. The rate determining step, however, may be the initial anion formation which the phenyl substitution would also favour.

Ortho-aminophenols are unstable compounds and so the N-phenyl example was isolated as its methyl ether by removal of methanol from the reaction mixture and treatment, of a solution of the basic residue in dimethylformamide, with methyl iodide. There are numerous examples of ring contractions¹⁹² of seven-membered rings to aromatic compounds under acid conditions (e.g. 1-carboxy-1H-azepines contract to N-phenylurethanes¹⁹³) but no apparently analogous reactions under basic conditions.

CONCLUSIONS

In the previous sections of this chapter, the varied reactivity of a new ring system, the 1,2-dihydro-3H-azepin-3-ones, has been briefly explored and this has laid the framework for a number of interesting and challenging projects. In particular, its potential as a precursor of fully-conjugated, 8π heterocyclic compounds invites further investigation (Scheme 66). For example, the O-alkylation and subsequent treatment with base may provide a route to alkoxyazepines. Alternatively, the diene unit could be masked by formation of an organometallic complex allowing manipulation of the 2-position as an active methylene group before deprotection. Finally, suitable nitrogen substituents might be removed to yield azatropone derivatives.



Scheme 66

EXPERIMENTAL

ABBREVIATIONS

n.m.r.	nuclear magnetic resonance
e.s.r.	electron spin resonance
i.r.	infra-red
u.v.	ultra-violet
g.c.	gas chromatography
g.c./m.s.	gas chromatography/mass spectrometry
t.l.c.	thin layer chromatography
δ	chemical shift
J	coupling constant
s	singlet
d	doublet
t	triplet
q	quartet (^1H spectra)
m	multiplet
q	quaternary (^{13}C spectra)
λ	wavelength
$\underline{\text{M}}^+$	mass of molecular ion
$\underline{\text{m/z}}$	mass to charge ratio
h	hours
min	minutes
mol	moles
mmol	millimoles
m.p.	melting point
b.p.	boiling point

A. INSTRUMENTATION AND GENERAL TECHNIQUES

NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

(a) ^1H n.m.r. spectra were recorded on Bruker WP80 (80 MHz), WP200 (200 MHz) or WH360 (360 MHz) instruments.

(b) ^2H n.m.r. spectra were recorded on the Bruker WP200 (30 MHz) or WH360 (55 MHz) instruments.

(c) ^{13}C n.m.r. spectra were recorded on Varian CFT20 (20 MHz), Bruker WP200 (50 MHz) or WH360 (90 MHz) instruments.

The WP80 was operated by Dr. H. McNab and Mr. L.H. Bell; the WP200 by Dr. H. McNab and Mr. J.R.A. Millar; the WH360 by Dr. D. Reed and the CFT20 by Dr. H. McNab, Mr. J.R.A. Millar and Miss E. Stevenson.

Spectra were recorded in [^2H]chloroform, unless otherwise indicated, and chemical shifts (δ_x) are quoted in parts per million, relative to tetramethylsilane.

MASS SPECTROMETRY

Mass spectra were recorded by Mr. D. Thomas, Miss E. Stevenson and Mr. A. Thomson on an A.E.I. MS902 spectrometer and latterly by Mr. A. Thomson on a Kratos MS50TC instrument.

INFRA-RED SPECTROSCOPY

I.r. spectra were obtained as liquid films or nujol mulls on a Perkin Elmer 781 spectrometer.

ULTRA-VIOLET SPECTROSCOPY

U.V. spectra were recorded on a Unicam SP800A spectrometer; the solvent used is indicated.

ELEMENTAL ANALYSES

Microanalyses were obtained by Mr. J. Grunbaum operating a Perkin Elmer 240 instrument, the St. Andrews University analytical service and Mrs E. McDougall on a Carlo-Erba Elemental Analyser, Model 1106.

STRUCTURE DETERMINATION

X-ray crystallographic data was obtained by Dr. A. Blake on a Nonius CAD-4 diffractometer, with graphite monochromator.

ELECTRON SPIN RESONANCE SPECTROSCOPY

E.s.r. spectra were recorded by Dr. J. Walton on a Bruker ER200D, X-Band instrument. Photolysis was carried out in the cavity of the spectrometer by irradiation with a 500 W super-pressure mercury arc.

CHROMATOGRAPHY

Qualitative gas-liquid chromatography was carried out on a Carlo Erba Strumentazione Fractovap 2450 instrument with flame ionisation detector on a 4.5 mm x 1.5 m column of 5% SE30 on Gas-Chrom (80-100 mesh).

Gravity column chromatography was carried out using Laporte Industries, Type H alumina deactivated by 6% water.

Dry-flash column chromatography was carried out on silica gel (Merck, grade 60, 230-400 mesh) using the method of Harwood¹⁹⁴.

Thin-layer chromatography was carried out using glass plates coated with aluminium oxide (0.3 mm, Merck, 60G, type E) with Woelm fluorescent green indicator or pre-coated plastic sheets (0.25 mm silica gel or 0.2 mm aluminium oxide) both with U.V. indicator from Machery-Nagel.

SOLVENTS

Commercially available solvents were used without purification except for light petroleum which was distilled and the fraction boiling at 40-60°C was used unless otherwise stated. Ether was dried by distillation from lithium aluminium hydride. Tetrahydrofuran was dried by distillation from calcium hydride.

B. PYROLYSIS APPARATUS AND METHODS

The apparatus used for flash vacuum pyrolysis experiments is illustrated in Figure 37, and is based on the design of W.D. Crow, Australian National University. The system is evacuated to 10^{-2} - 10^{-3} Torr by an Edwards Model ED100 high capacity oil pump and the pressure is monitored between the trap and the pump. Experiments involve heating the substrate, contained in the inlet until it is volatilised. A glass Buchi Kuglerohr oven is generally used for heating as it allows the sublimation to be monitored easily, but for temperatures greater than 200°C a metal oven is used. The substrate then passes through a silica tube (30 x 2.5 cm). The temperature of the tube is monitored by a platinum/platinum 13% rhodium thermocouple at its centre and is maintained at the required level by a Stanton Redcroft laboratory tube furnace. The estimated contact time in the hot zone is 1-10 milliseconds. The products are collected at the exit to the furnace in a trap surrounded by liquid nitrogen. The U-shaped trap illustrated in Figure 37 was used for pyrolyses involving up to 2 g of substrate, but on a larger scale the by-products of Meldrum's Acid pyrolyses - acetone and carbon dioxide - can block the trap and the trap illustrated in Figure 38 was used.

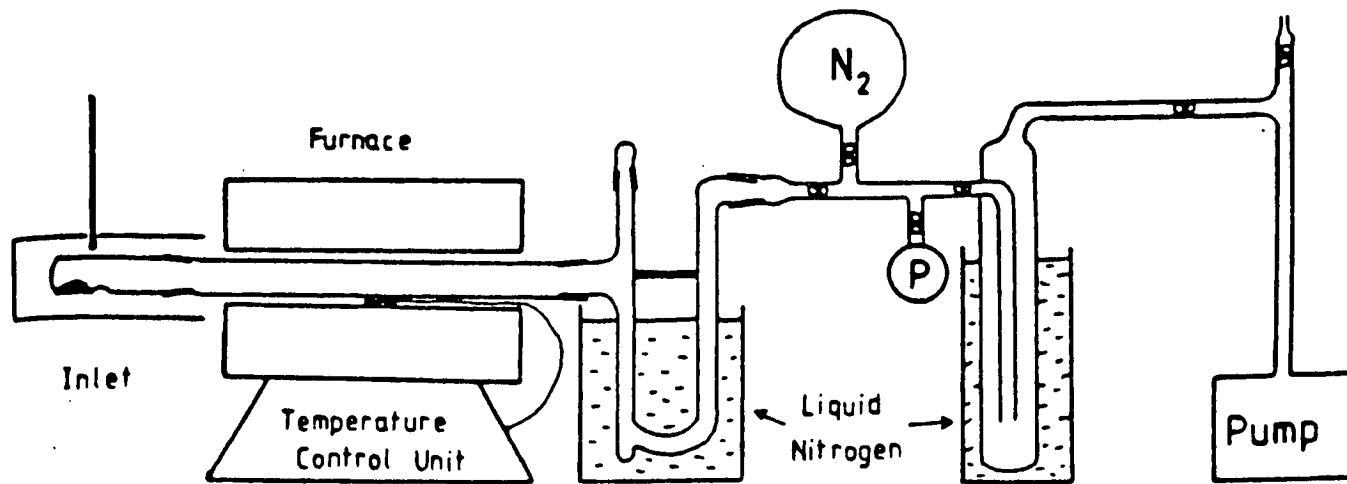


Figure 37

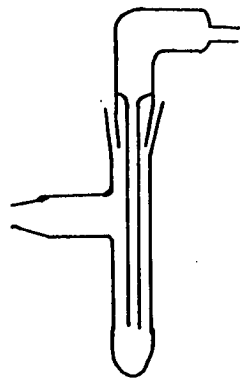


Figure 38

Large scale pyrolyses refer to scales of 2-5 mmol unless otherwise indicated: the entire pyrolysate was generally removed by washing with acetone and experimental details of subsequent manipulations are given for particular examples in the following chapters.

Small scale pyrolyses refer to 20-60 mg of substrate and the entire pyrolysate was removed in deuteriated solvent (chloroform, unless otherwise stated) and examined by ^1H n.m.r. spectroscopy without isolation of products. Determination of yields by integral standard refers to the introduction of a known amount of cyclohexane to the sample.

Pyrolysis parameters are quoted in the following order throughout this section: furnace temperature, inlet temperature, pyrolysis time, residue, if significant.

C. INVESTIGATION OF THE MECHANISM AND SCOPE OF
1,2-DIHYDRO-3H-PYRROL-3-ONE FORMATION

PREPARATION OF SECONDARY AMINES

The required amines were obtained commercially or prepared by literature procedures. Two routes were used: Method A involved alkylation of primary amines¹⁹⁵ while Method B require imine formation using (i) a Dean and Stark trap¹⁹⁶ or (ii) molecular sieve¹⁹⁷ to remove the water formed, followed by reduction.¹⁹⁶ The following amines were prepared: di(-(α-methyl)benzylamine (Method A, 52%) b.p. 125°C (0.4 Torr) [lit.¹⁹⁵, 190°C (10 Torr)]: N-secbutyl-cyclohexylamine (Method B(ii), 75%) b.p. 109 - 111°C (lit.¹⁹⁸, 110.6°C): N-isopropyl-(α-methyl)benzylamine (Method B(i), 61%) b.p. 95°C (28 Torr) [lit.¹⁹⁹, 92°C (20 Torr)]: N-isopropyl-aniline (Method A, 76%) b.p. 54°C (0.3 Torr) [lit.²⁰⁰, 209°C (712 Torr)]: dicycloheptylamine (Method B(i), 83%) b.p. 135°C (15 Torr) (previously prepared as hydrochloride, m.p. 230°C²⁰¹): 1,2-dihydrophenanthridine (Method B, 70%) m.p. 89-90°C (from ethanol)(lit.²⁰², 92°C): 1-methyl-tetrahydroisoquinoline (Method B, 64%) b.p. 228°C [lit.²⁰³, 233°C (745 Torr)]: 1-phenyl-tetrahydroisoquinoline (Method B, 95%) m.p. 94 - 96°C (from toluene) (lit.²⁰³, 97°C).

Both enantiomers of N-isopropyl-(α-methyl)benzylamine were prepared from (+) and (-) α-methyl-benzylamine respectively (Method A, 60 and 65%). Resolution of the

tetrahydroisoquinolines was effected by formation of the (+)tartrate in an ether/acetone solution and recrystallisation from water until constant m.p. This gave 1-phenyltetrahydroisoquinoline $[\alpha]_D^{25} -47.5$ (c 2.8 in CCl_4) (lit.²⁰³, -47.6) and 1-methyltetrahydroisoquinoline $[\alpha]_D^{25} -83.1$ (c. 0.9 in CCl_4) (lit.²⁰³, -79.9).*

PREPARATION OF 5-AMINOMETHYLIDENE-2,2-DIMETHYL-1,3-DIOXANE-4,6-DIONES

Method A¹¹⁰ A solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's Acid) (25 mmol) in triethylorthoformate (25 mls) was heated under reflux for 2 h. The appropriate secondary amine (50 mmol) was added and heating was continued for a further 2h. The product crystallised when the solution was cooled or on partial removal of solvent.

Method B A solution of 2,2-dimethyl-5-methoxymethylene-1,3-dioxane-4,6-dione¹¹⁰ (10 mmol) and the appropriate amine (11 mmol) in cyclohexane (20 mls) was heated under reflux for 2 h. The product was obtained on evaporation of solvent.

Method C A solution of 2,2-dimethyl-5-methoxymethylene-1,3-dioxane-4,6-dione¹¹⁰ (10 mmol) and the appropriate amine (11 mmol) in acetonitrile (10 ml) was left at room temperature for 30 minutes. The product was

* Literature m.p. of tartrate 92°C,²⁰³ found 124°C.

obtained as a precipitate from the solution or on removal of solvent.

Method D Sodium hydride (50% suspension in oil, 0.24 g, 5 mmol) was washed three times with light petroleum (40/60) and then dried at a vacuum pump. The appropriate 5-(N-monosubstituted-aminomethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.5 mmol) was dissolved in dimethylsulphoxide (10 ml) and the pre-washed sodium hydride was added in portions. Methyl iodide (0.8 ml, 12.5 mmol) was added and the reaction mixture was stirred, at room temperature overnight. (For examples using labelled methyl iodide a 2x excess of alkylating agent gave greater than 90% reaction, provided only a 1.5x excess of sodium hydride was used). The mixture was then poured into methanol (10 ml) and water (20 ml) was added. The aqueous solution was extracted with methylene chloride (3 x 30 ml) and the combined organic layers were back extracted with water (3 x 50 ml). The organic layer was then dried (MgSO_4) and the solvent was removed in vacuo to give the desired product.

This reaction could not be extended to allow the preparation of derivatives with other alkyl substituents, possibly due to formation of the corresponding alkene occurring more readily than alkylation. Quantitative recovery of starting material was observed. Similarly, starting material was recovered from attempts to generate

the anion with lithium diisopropylamide in tetrahydrofuran. It was thought that this may be due to the formation of lithium complexes but changing the solvent to dimethoxyethane or the addition of tetramethylethylenediamine, which would be expected to release the anion, still resulted in recovered starting material.

The use of acetyl chloride instead of an alkylating agent in the dimethylsulphoxide-sodium hydride method apparently resulted in reaction of the chloride with the solvent. In tetrahydrofuran a water soluble solid was obtained. It is thought this was sodium chloride produced by reaction of the acetyl chloride to give ketene under the basic conditions.

The following derivatives of 5-aminomethylidene-2,2-dimethyl-1,3-dioxane-4,6-dione were prepared: 5-(N,N-diisopropyl-)⁷⁰ (Method A, 60%) m.p. 120°C (from cyclohexane) (Found: C, 61.45; H, 8.5; N, 5.65. $C_{13}H_{21}NO_4$ requires C, 61.2; H, 8.25; N, 5.5%); δ_H (80 MHz) 8.21 (1H, s), 4.84 (1H, m), 3.82 (1H, m), 1.69 (6H, s), 1.39 (6H, d, ^3J 6.7 Hz), and 1.31 (6H, d, ^3J 6.7 Hz); δ_C (20 MHz) 163.46(q), 155.83, 102.19(q), 83.18(q), 55.76, 49.15, 26.40, 23.82 and 20.04; m/z 255 (M^+ , 21%), 198(63), 197(100), 182(53), 154(66), 153(34), 138(44), 127(61) and 124(75): 5-(N,N-diethyl-). (Method C, 86%) m.p. 57-58°C (from ethanol) (Found: C, 58.4; H, 7.7; N, 6.15. $C_{11}H_{17}NO_4$ requires C, 58.15; H, 7.5; N, 6.15%);

δ_H (80 MHz) 8.02 (1H, s), 5.49 (2H, q, ^3J 7.2 Hz), 3.84 (2H, q, ^3J 7.2 Hz), 1.61 (6H, s), 1.28 (3H, t, ^3J 7.2 Hz), and 1.15 (3H, t, ^3J 7.2 Hz); δ_C (20 MHz) 163.3(q), 157.9, 102.8(q), 83.89(q), 47.16, 42.54, 26.27, 14.37 and 12.34; m/z 227 (M^+ , 5%), 170(35), 169(100), 155(20), 125(90), 114(37), 110(63), and 97(40):

5-(N,N-dicycloheptyl-) (Method A, 52%) m.p. 125°C (from cyclohexane) (Found: C, 69.45; H, 9.35; N, 3.75.

$C_{21}H_{33}NO_4$ requires C, 69.4; H, 9.1; N, 3.85%); δ_H (80 MHz) 8.01 (1H, s), 4.3-4.7 (1H, m), 3.1-3.6 (1H, m), 1.58 (6H, s) (clearly superimposed on methylene signals), and 1.0-2.0 (24H, m); δ_C (20 MHz) 163.50(q), 156.27, 102.06(q), 82.73(q), 65.92, 61.63, 37.19, 32.83, 26.79 (2 signals superimposed), 26.39, 24.90 and 24.77; m/z 363 (M^+ , 10%) 305(87), 287(100), 218(22), 164(27), and 124(24):

5-(N,N-dibenzyl) (Method A, 62%) m.p. 152°C (from ethanol)

(Found: C, 71.65; H, 5.95; N, 3.9. $C_{21}H_{21}NO_4$ requires

C, 71.8; H, 6.0; N, 4.0%) δ_H (80 MHz) 8.38 (1H, s),

7.03-7.46 (10H, m), 6.69 (2H, s), 4.61 (2H, s) and

1.47 (6H, s); δ_C (20 MHz) (quaternary signal missing)

159.06, 133.93(q), 133.52(q), 129.13, 128.77, 128.46,

128.04, 127.81, 127.66, 102.80(q), 86.12(q), 63.90,

55.71 and 26.12; m/z 351 (M^+ , <1%), 293(100), 202(75),

158(95), 130(20) and 115(44): 5-(N,N-di-(α -methyl)-

benzylamine) (Method A, 29%) m.p. 206°C (from ethanol)

(Found: C, 72.9; H, 6.5; N, 3.85. $C_{23}H_{25}NO_4$ requires

C, 72.8; H, 6.6; N, 3.7%); δ_H (80 MHz) 8.36 (1H, s),

7.32 (6H, m), 7.15 (2H, m), 6.5 (2H, m), 6.42 (1H, q, ^3J 7.0 Hz), 4.67 (1H, q, ^3J 7.0 Hz), 1.86 (3H, d, ^3J 7.0 Hz), 1.70 (3H, d, ^3J 7.0 Hz), and 1.69 (6H, s); δ_C (50 MHz) 163.34(q), 156.93, 138.28(q), 137.34(q), 128.42 (2 peaks superimposed), 128.26 (2 peaks superimposed), 127.94, 126.68, 102.21(q), 84.44(q), 61.43, 57.97, 26.40, 23.06, and 16.45; m/z 379 (M^+ <1%), 321(55), 216(100), 172(90), and 105(90): 5-(N-ethyl-N-cyclohexyl) (Method A, 48%) m.p. 92°C (from cyclohexane) (Found: C, 64.25; H, 8.4; N, 4.9. $C_{15}H_{23}NO_4$ requires C, 64.05; H, 8.2; N, 5.0%); δ_H (80 MHz) 8.09 (1H, s), 3.87 (2H, q, ^3J 7.0 Hz), 3.0-3.5 (1H, m), 1.0-2.0 (10H, m), 1.62 (6H, s) (clearly superimposed on methylene signals), and 1.11 (3H, t, ^3J 7.0 Hz); δ_C (50 MHz) 159.12(q), 155.94, 102.18(q), 83.92(q), 68.68, 46.62, 32.38, 26.32, 25.26, 24.63, and 12.97; m/z 281 (M^+ , 13%), 223(64), 205(41), 180(18), 179(20), 150(46), 84(87), and 56(100): 5-(N-isopropyl-N-cyclohexyl) (Method A, 32%) m.p. 103°C (from cyclohexane) (Found: C, 65.0; H, 8.75; N, 4.65. $C_{16}H_{25}NO_4$ requires C, 65.1; H, 8.45; N, 4.75%); δ_H (80 MHz) (peaks of second rotamer given in brackets) 8.02 (8.01) (1H, s), 4.63 (3.73) (1H, m), 4.0-4.5 (3.05-3.5) (1H, m), 1.0-2.0 (10H, m), 1.52 (6H, s) (clearly superimposed on methylene signals), and 1.21 (1.13) (6H, d, ^3J 6.7 Hz); δ_C (50 MHz) (peaks of second rotamer given in brackets) 163.61 (163.50) (q), 156.48 (155.93), 102.25 (102.25), 83.19 (82.87), 64.09 (57.72), 55.84 (50.37), 34.48 (30.71), 26.50 (26.50), 25.64 (25.26), 25.03 (24.59), and 23.86 (20.20).

m/z 295 (M^+ , 21%), 237(100), 219(87), 164(47), 150(34), and 127(66): 5-(N-isopropyl-N-phenyl) (Method A, 63%) m.p. 166-67°C (from ethanol) (Found: C, 66.2; H, 6.45; N, 4.5. $C_{16}H_{19}NO_4$ requires C, 66.45; H, 6.55; N, 4.85%); δ_H (80 MHz) (peaks of minor rotamer given in brackets) 8.35 (8.12) (1H, s), 7.0-7.5 (5H, m), 5.10 (5.35) (1H, m), 1.58 (1.72) (6H, s), and 1.40 (1.21) (6H, d); δ_C (20 MHz) (peaks of major rotamer only) 160.08(q), 156.05, 143.13(q), 129.04, 127.98, 124.97, 102.61(q), 86.50(q), 62.79, 26.63, and 22.28; m/z 289 (M^+ , 9%), 232(22), 231(100), 186(19), 158(50), 144(34), and 118(56): 5-(N-ethyl-N-phenyl) (Method A, 49%) m.p. 163-165°C (from ethanol) (Found: C, 65.35; H, 6.15; N, 5.05. $C_{15}H_{17}NO_4$ requires C, 65.45; H, 6.2; N, 5.1%); δ_H (80 MHz) (peaks of minor rotamer given in brackets) 8.22 (8.27) (1H, s), 7.0-7.5 (5H, m), 4.32 (3.88) (2H, q, ^3J 7.1 Hz), 1.71 (1.59) (6H, s), and 1.23 (1.24) (3H, t, ^3J 7.1 Hz); δ_C (20 MHz) (peaks of major rotamer only, quaternary signal missing) 158.05, 145.87(q), 129.65, 128.26, 123.52, 102.80(q), 86.87(q), 49.87, 26.62, and 12.84; m/z 275 (M^+ , 12%), 217(100), 173(20), 172(25), 145(18), 144(53), 130(34), and 104(25): 5-(N-benzyl-N-phenyl) (Method C, 40%) m.p. 161°C (from ethanol) (Found: C, 70.9; H, 5.45; N, 4.1. $C_{20}H_{19}NO_4$ requires C, 71.2; H, 5.65; N, 4.15%); δ_H (80 MHz) 8.35 (1H, s), 7.0-7.5 (10H, m), 5.65 (2H, s), and 1.27 (6H, s); δ_C (20 MHz) 165.29(q), 159.51(q), 155.93, 147.65(q), 134.34(q), 129.62,

128.70 (2 peaks superimposed), 127.73, 127.07, 122.51, 102.84(q), 90.16(q), 57.79, and 25.72; m/z 337 (M^+ , <1%), 280(41), 279(100), 250(69), 235(14), 234(14), 206(90), 193(15), 181(15), and 180(12): 5-(N-benzyl-N-methyl) (Method A, 55%) m.p. 107.5-109°C (from ethanol) (Found: C, 65.0; H, 6.45; N, 4.85. $C_{15}H_{19}NO_4$ requires C, 65.0; H, 6.85; N, 5.05%); δ_H (80 MHz) (peaks of minor rotamer given in brackets) 8.32 (8.16) (1H, s), 7.0-7.5 (5H, m), 4.64 (5.07) (2H, s), 3.19 (3.32) (3H, s), and 1.69 (1.50) (6H, s); δ_C (20 MHz) (peaks of minor rotamer given in brackets, quaternary signal missing) 160.40 (159.53), 133.19 (133.88) (q), 129.13 (128.84), 128.16 (128.50), 127.49 (127.81), 102.82 (102.82) (q), 84.52 (85.29) (q), 65.23 (58.15), 41.56 (47.38), and 26.47 (26.17); m/z 275 (M^+ , <1%), 217(70), 188(45), 144(35), and 91(100): 5-(N-benzyl-N-isopropyl) (Method A, 50%) m.p. 111.5-112°C (from ethanol) (Found: C, 67.25; H, 6.75; N, 4.4. $C_{17}H_{21}NO_4$ requires C, 67.35; H, 6.95; N, 4.6%) δ_H (80 MHz) 8.26 (1H, s), 7.0-7.5 (5H, m), 5.09 (2H, s), 3.88 (1H, m), 1.39 (6H, d, ^3J 6.7 Hz), and 1.29 (6H, s); δ_C (20 MHz) 160.5(q), 155.90, 134.31(q), 128.66, 127.73, 127.41, 102.58(q), 86.00(q), 61.04, 54.03, 25.85, and 21.68; m/z 303 (M^+ , <1%), 246(40), 245(100), 230(23), 216(70), 202(23), 201(27), 186(17), 175(23), 173(17), 159(27), and 158(83): 5-(N-sec-butyl-N-cyclohexyl) (Method A, 34%) m.p. 113-115°C (from cyclohexane) (Found: C, 65.85; H, 8.7; N, 4.3.

$C_{17}H_{26}NO_4$ requires C, 66.0; H, 8.75; N, 4.55%); δ_H (80 MHz) (peaks for second rotamer given in brackets) 8.26 (8.13) (1H, s), 4.60 (3.50) (1H, m), 4.4 (3.3) (1H, m), 1.69 (1.68) (6H, s) (clearly superimposed on methylene signals), and 0.75-2.0 (18H, m); δ_C (20 MHz) (peaks for second rotamer given in brackets) 163.56 (163.28) (q), 157.01 (156.13), 102.14 (second resonance superimposed) (q), 82.94 (83.09) (q), 61.79 (63.70), 58.01 (56.07), (the following CH_2 resonances were not assigned to individual rotamers) 35.61, 33.31, 31.26, 30.90, 30.68, 27.44, 25.70 (two peaks superimposed), 25.40, 25.26, 25.06, 24.64, 26.53 (two peaks superimposed), 17.91 (21.70), and 11.17 (10.87); m/z 309 (M^+ , 16%), 252(47), 251(100), 222(60), 205(84), and 178(60): 5-[N-isopropyl-N-(α -methyl)benzyl] (Method A, 44%) (chiral derivatives were prepared by Method B, 80 and 88%) m.p. 90-91°C (from cyclohexane) (Found: C, 68.3; H, 7.25; N, 4.3. $C_{18}H_{23}NO_4$ requires C, 68.15; H, 7.25; N, 4.4%); δ_H (200 MHz) 8.30 (1H, s) 7.2-7.4 (5H, m), 6.23 (1H, q, ^3J 6.8 Hz), 3.57 (1H, m), 1.77 (3H, d, ^3J 6.8 Hz), 1.74 (6H, s), 1.33 (3H, d, ^3J 6.8 Hz), and 0.91 (3H, d, ^3J 6.7 Hz); δ_C (20 MHz) 163.84 (q), 155.91, 137.70 (q), 128.56, 128.33, 127.51, 102.49 (q), 83.96 (q), 61.56, 51.37, 26.57, 24.96, 22.47, and 16.07; m/z 317 (M^+ , <1%), 259(100), 216(35), 172(47), 154(29), and 148(59): 5-(N-tert-butyl-N-methyl) (Method A, 41%; Method B, 81%; Method D, 56%) m.p. 152-154°C (from cyclohexane) ($N-[^2H_3]$ methyl derivative was prepared using $C[^2H_3]I$, Method D, 55%) (Found: C, 60.0; H, 7.9;

N, 5.9. $C_{12}H_{19}NO_4$ requires C, 59.75; N, 7.9; H, 5.8%); δ_H (80 MHz) 8.43 (1H, s), 3.19 (3H, s), 1.71 (6H, s); and 1.47 (9H, s); δ_C (20 MHz) (one quaternary signal missing) 157.49, 102.42(q), 83.62(q), 62.49(q), 38.16, 28.26, and 26.28; m/z 241 (M^+ , 25%), 184(36), 183(100), 168(61), 128(54), 127(46), 124(33), 110(51), and 99(46):

5-[N-p-(tert-butyl)phenyl] (Method C, 95%) m.p. 140-142°C (from methanol) (Found: C, 65.6; H, 6.95; N, 4.6.

$C_{17}H_{21}NO_4 \cdot 0.5H_2O$ requires C, 65.4; H, 7.05; N, 4.5%); δ_H (80 MHz) 11.19 (1H, bd, ^3J 14.5 Hz) 8.60 (1H, d, ^3J 14.5 Hz), 7.43 (2H, d, ^3J 8.9 Hz), 7.15 (2H, d, ^3J 8.9 Hz) 1.73 (6H, s), and 1.31 (9H, s); δ_C (200 MHz) 165.09(q), 163.03(q), (carbonyls of ring observed as separate signals) 152.26, 149.81(q), 135.14(q), 126.52, 117.49, 104.52(q), 86.69(q), 34.23(q), 30.88, and 26.66; m/z 303 (M^+ , 30%), 245(33), 186(19), 158(10), 144(100), and 117(11):

5-[N-p-tert-butylphenyl)-N-methyl] (Method D, 69%)

m.p. 154-155°C (from methanol) (Found: C, 66.3; H, 7.25;

N, 4.45. $C_{18}H_{23}NO_4 \cdot 0.5H_2O$ requires C, 66.25; H, 7.35; N, 4.3%); δ_H (200 MHz) 8.33 (1H, s), 7.43 (2H, d, ^3J 8.8 Hz), 7.24 (2H, d, ^3J 8.8 Hz), 3.70 (2H, s), 1.75 (6H, s), and 1.32 (9H, s); δ_C (50 MHz) (quaternary signal missing) 158.65, 151.45(q), 144.18(q), 126.42, 121.99, 102.75(q), 87.14(q), 43.35(q), 30.92, and 26.52; m/z 317 (M^+ , 36%), 259 (81), 244(100), 214(26), 200(17), 170(21), 158(69), 144(25), and 131(16): 5-(N-tert-butyl) (Method A, 87%)

m.p. 151-153°C (from cyclohexane) (Found: C, 58.05; H, 7.55; N, 6.15. $C_{11}H_{17}NO_4$ requires C, 58.15; H, 7.5;

N, 6.15%); δ_H (80 MHz) 9.7 (1H, bd), 8.04 (1H, d, ^3J 15.2 Hz), 1.53 (6H, s) and 1.26 (9H, s); δ_C (20 MHz) 165.27(q), 163.82(q), 155.07, 104.10(q), 83.54(q), 54.69(q), 29.13, 26.39; m/z 227 (M^+ , 100%), 170(33), 154(80), 125(85), 114(50) and 110(60); 5-(N-methyl-N-phenyl) (Method A, 61%; Method B, 94%) m.p. 121-122°C (lit.¹¹⁰, 124°C, (N-[^{13}C]methyl derivative was prepared using [^{13}C]methyl iodide, Method D, 90%): 5-(N-cyclohexyl-N-methyl) (Method A, 84%) m.p. 132°C (from cyclohexane) (lit.¹¹⁰, 130.5-131.5°C): 5-(N-phenyl) (Method B, 76%) m.p. 156-158°C (from ethanol) (lit.¹¹⁰, 157°C):

5-(N,N-dimethyl) (Method C, 56%) (in this case the amine was added slowly as an acetonitrile solution; the reaction is very exothermic) m.p. 152°C (lit.¹¹², 153-154.5°C).

The following derivatives of 2,2-dimethyl-1,3-dioxane-4,6-dione were prepared: 5-[1-(2,6-dimethyl)-piperidinyl]-methylidene (Method A, 11%) m.p. 101°C (from cyclohexane) (Found: C, 63.1; H, 8.15; N, 5.25. $C_{14}H_{21}NO_4$ requires C, 62.9; H, 7.85; N, 5.25%); δ_H (200 MHz) 7.99 (1H, s), 4.80 (1H, m), 3.86 (1H, m), 1.10-1.81 (6H, m), 1.55 (6H, s), 1.35 (3H, d, ^3J 7.0 Hz) and 1.31 (3H, d, ^3J 7.0 Hz) (singlet and doublets clearly superimposed on methylene signals); δ_C (50 MHz) 163.74(q), 159.13, 102.29(q), 83.34(q), 62.41, 53.96, 30.44, 29.81, 26.42, 22.14, 20.88, and 12.72; m/z 267 (M^+ , 4%), 210(22), 209(56), 165(10), 150(20), 137(24), 136(100) and 122(22): 5-[5-(5,6-dihydro-phenanthridyl)]methylidene (Method A, 88%) m.p. 220°C

(from ethanol) (Found: C, 71.4; H, 4.95; N, 4.0.

$C_{20}H_{17}NO_4$ requires C, 71.6; H, 5.05; N, 4.2%);

δ_H (80 MHz) 8.40 (1H, s), 7.0-8.0 (8H, m), 5.10 (2H, s) and 1.78 (6H, s); δ_C (20 MHz) (quaternary signal missing) 165.28(q), 160.47(q), 156.52, 138.66(q), 131.38(q), 129.16, 128.61, 128.53, 128.41, 127.44(q), 126.17, 123.67, 123.13, 122.30, 103.34(q), 89.29(q), 58.09, 54.63, and 26.80; m/z 335 (M^+ , <1%), 277(58), 249(13) 248(39), 205(52), 204(100), 180(26) and 179(48):

5-[-2-(1-methyl-tetrahydroisoquinolinyl)]-methylenidene

(Method C, 85%) (chiral derivative was prepared by Method C, 88%) m.p. 134-135°C (from methanol) (Found: C, 67.7; H, 6.3; N, 4.65. $C_{17}H_{19}NO_4$ requires C, 67.8; H, 6.3, N, 4.65%) δ_H (200 MHz) (peaks of minor rotamer given in brackets) 8.35 (8.20) (1H, s), 7.0-7.35 (7.0 - 7.35) (4H, m), 4.88 (6.16) [1H, q, ^3J 7.0 Hz (7.0 Hz)], 4.5 - 4.6 (3.9 - 4.0) (2H, m), 2.9 - 4.0 (2.9 - 4.0) (2H, m), 1.71 (1.71) (6H, s) and 1.68 (1.70) [3H, d, ^3J 7.0 Hz (7.0 Hz)]; δ_C (50 MHz) (peaks of minor rotamer given in brackets; quaternary signal missing) 157.84 (157.57), 135.60 (136.59) (q), 132.30 (131.04) (q), 127.27 (128.59), 128.42 (2 peaks superimposed), 126.73 (126.54), 125.77 (126.41), 102.38 (102.45) (q), 83.74 (84.23) (q), 63.85 (56.64), 45.23 (51.41), 28.60 (29.40), 26.37 (2 peaks superimposed) and 23.70 (22.79); m/z 301 (M^+ , <1%), 275 (14), 243(58), 228(25), 184(22), 170(100) and 126(88): 5-[2-(1-phenyl)tetrahydroisoquinolinyl]-

methylidene (Method C, 77%) m.p. 221-222°C (from acetonitrile) (chiral derivative was prepared by Method C, 91%) (Found: C, 73.1; H, 5.85; N, 4.10. $C_{18}H_{15}NO_4$ requires C, 72.7; H, 5.8; N, 3.85%); δ_H (200 MHz) (peaks for minor rotamer given in brackets) 8.56 (8.22) (1H, s), 5.90 (7.69) (1H, s), 7.0 - 7.4 (9H, m), 3.7 - 4.4 (2H, m), 2.8 - 3.3 (2H, m), and 1.69 (1.58) (6H, s); δ_C (50 MHz) (peaks for minor rotamer given in brackets, some aromatic peaks superimposed and not assigned) 172.88 (q) (second resonance not observed), 158.33 (157.27), 138.65 (140.40) (q), 133.78 (132.35) (q), 133.43 (133.94) (q), 128.83, 128.60, 128.52, 128.44, 128.14, 128.07, 127.64, 127.54, 127.31, 126.89, 126.60, 102.69 (102.74), 84.40 (85.55), 71.70 (63.08), 46.07 (53.18), 29.63 (28.42), and 26.55 (second resonance superimposed); m/z 363 (M^+ , <1%), 305(36), 277(100), 232(43), and 219(50).

PYROLYSES OF 5-AMINOMETHYLIDENE-2,2-DIMETHYL-
1,3-DIOXANE-4,6-DIONES

Large scale pyrolyses were carried out as described in Section B and the entire pyrolysate was removed from the trap by dissolving the pyrolysate in acetone. After removal of the acetone in vacuo, the product was purified by bulb-to-bulb distillation. Where two isomers or diastereomers resulted from pyrolysis, these were separated by column chromatography on alumina with a 60:40 mixture of ethyl acetate:light petroleum.

The 1-phenyl- and 2,2-dimethyl-1-isopropyl-1,2-dihydro-3H-pyrrol-3-ones were prepared repeatedly on large scales (up to 7 g) and the following points should be noted: (i) it is important that the inlet temperature does not greatly exceed the required sublimation temperature as this leads to an alternative radical cleavage of the C-N bond and significant amounts of the parent amine are obtained. N-Methylaniline, in particular, is difficult to remove; (ii) the large trap (see Section B) is required to prevent blockage of the system by solid acetone; (iii) prolonged heating to remove acetone during work up decreases yields, and (iv) large scale distillation of the 1-phenyl-1,2-dihydro-3H-pyrrol-3-one is not successful; if a small amount of acetone is used to remove the product from the trap, reasonably pure material can be simply filtered off.

The following 1,2-dihydro-3H-pyrrol-3-ones were prepared by pyrolysis. The 5-aminomethylidene-2,2-dimethyl-1,3-dioxane-4,6-dione substrate and pyrolysis parameters are quoted. 2,2-dimethyl-1-isopropyl⁷⁰, [5-(N,N-diisopropyl-), 600°C, 120-130°C, 1.25 h] (64%) m.p. 70-72°C (from hexane) (Found: C, 67.2; H, 9.9; N, 8.95. C₉H₁₅NO requires C, 67.4; H, 9.9; N, 8.95%); δ_H (80 MHz) 7.86 (1H, d, ³J 3.3 Hz), 5.02 (1H, d, ³J 3.3 Hz), 3.59 (1H, m, ³J 6.7 Hz), 1.26 (6H, d, ³J 6.7 Hz) and 1.19 (6H, s); δ_C (20 MHz) 204.68 (q), 158.78, 94.28, 67.56 (q), 45.23, 23.73 and 21.71; m/z 153 (M⁺, 100%), 138(50) and 110(90); 1-ethyl-2-methyl, [5-(N,N-diethyl-), 600°C, 120-135°C, 2h] (77%) b.p. 123-124°C (0.3 Torr) (Found, M⁺ 125.084. C₇H₁₁NO requires M⁺, 125.084); δ_H (200 MHz) (two tautomers present in chloroform - see Discussion Section, keto tautomer quoted) 7.71 (1H, d, 3.3 Hz), 4.92 (1H, d, 3.3 Hz), 3.44 (1H, q, 7.3 Hz), 3.27 (2H, q, 7.2 Hz), 1.22 (3H, d, ³J 7.3 Hz) and 1.13 (3H, t, ³J 7.2 Hz); δ_C (50 MHz) 203.91 (q), 163.93, 96.46, 61.85, 42.37, 14.24 and 14.03; m/z 125 (M⁺, 100%), 124(56), 110(39), 98(35) and 96(48); 1-cycloheptyl-2,2-hexamethylene, [5-(N,N-dicycloheptyl-), 600°C, 155-175°C, 2h, 5%], (64%) m.p. 125°C (from hexane), (Found: C, 78.0; H, 10.55; N, 5.55. C₁₇H₂₇NO requires C, 78.15; H, 10.35; N, 5.35%); δ_H (80 MHz) 7.78 (1H, d, ³J 3.3 Hz), 4.93 (1H, d, ³J 3.3 Hz), 3.0-3.75 (1H, m) and 1.0-2.5 (24H, m);

δ_C (20 MHz) 205.89(q), 158.86, 93.59, 71.86 (q), 56.19, 36.96, 34.71, 31.47, 27.20, 24.75 and 22.62; m/z 261 (M^+ , 100%), 192(95), 164(49), and 55(54): 1-benzyl-2-phenyl [5-(N,N-dibenzyl-), 600°C, 170-195°C, 2.5 h, 14%] (51%) b.p. 180-182°C (0.3 Torr), (Found: C, 81.85; H, 6.25; N, 5.45. $C_{17}H_{15}NO$ requires C, 81.95; H, 6.0; N, 5.6%); δ_H (two tautomers present in chloroform - see discussion section, keto tautomer quoted) 8.18 (1H, d, ^3J 3.4 Hz), 6.8-7.7 (10H, m), 5.55 (1H, d, ^3J 13.0 Hz), 5.15 (1H, d, ^3J 3.4 Hz), 4.43 (1H, s), and 4.20 (1H, d, ^3J 13.0 Hz); δ_C (20 MHz) 201.31(q), 166.13, 125-140 (complex pattern of aromatic signals) 97.30, 69.89 and 52.25; m/z 249 (M^+ , 34%), 160(40), 158(12), 134(32), 105(17), and 91(100): 600°C, 1-(α -methyl)benzyl-2-methyl-2-phenyl [5-(N,N-(α -methyl)benzyl), 600°C, 175 - 190°C, 2.5 h, 6.5%] (two diastereomers were isolated by column chromatography and available data for the minor isomer is given in brackets, [9% (3.5%)] m.p. 114.5-115°C (from hexane), (Found: C, 82.25; H, 6.8; N, 5.15. $C_{19}H_{19}NO$ requires C, 82.3; H, 6.85; N, 5.05%); δ_H (80 MHz) 8.03 (8.32) [1H, d, ^3J 3.4 Hz (3.5 Hz)], 6.8 - 7.6 (10H, m), 5.14 (5.19) [1H, d, ^3J 3.4 Hz (3.5 Hz)], 4.43 (4.35) [1H, q, ^3J 7.0 Hz (7.0 Hz)], 1.79 (1.35) (3H, s), and 1.61 (1.50) [3H, d, ^3J 7.0 Hz (7.0 Hz)]; δ_C (50 MHz) (m signals of both isomers and o signals of major isomer superimposed) 204.04 (203.64) (q), 161.82 (161.33), 140.57 (142.71) (q), 136.70 (137.24) (q),

128.35 (128.75), 127.89 (127.87), 127.61 (127.61),
 126.63 (125.89), and 126.63 (125.72), 95.53 (94.80),
 72.85 (73.31), 54.54 (55.18), 22.07 (23.26) and 20.03
 (22.92); m/z 277 (M^+ , 23%), 174(59), 173(100), 146(41),
 and 144(59): 1-isopropyl-2,2-pentamethylene [5-(N-
 isopropyl-N-cyclohexyl-), 600°C, 140°C, 1 h, 6%] (22%)
 m.p. 75-76°C (from hexane) (Found: C, 74.5; H, 9.85;
 N, 7.4. $C_{12}H_{19}NO$ requires C, 74.35; H, 9.9; N, 7.0%);
 δ_H (80 MHz) 7.84 (1H, d, ^3J 3.4 Hz), 4.99 (1H, d,
 ^3J 3.4 Hz), 3.65 (1H, m, ^3J 6.7 Hz), 1.0-2.5 (10H, m),
 and 1.25 (6H, d, ^3J 6.7 Hz) (clearly superimposed on
 methylene signals); δ_C (20 MHz) 205.56(q), 157.94,
 94.60, 68.04(q), 44.35, 30.20, 24.29, 23.72 and 19.40;
 m/z 193 (M^+ , 100%), 150(85) and 138(95), separated
 by chromatography from 1-cyclohexyl-2,2-dimethyl [5-(N-
 isopropyl-N-cyclohexyl-), 600°C, 140°C, 1h, 6%] (21.5%)
 m.p. 81-83°C (from hexane). (Found: C, 74.35; H, 9.9;
 N, 7.0. $C_{12}H_{19}NO$ requires C, 74.35; H, 9.9; N, 7.0%);
 δ_H (80 MHz) 7.86 (1H, d, ^3J 3.4 Hz), 5.04 (1H, d, ^3J
 3.4 Hz), 3.1 (1H, m), 1.0-2.0 (10H, m) and 1.22 (6H, s)
 (clearly superimposed on methylene signals); δ_C (20 MHz)
 204.61(q), 159.22, 94.02, 67.61(q), 53.54, 34.68, 25.80,
 24.29 and 21.85; m/z 193 (M^+ , 100%), 150(90) and
 110(90): 2,2-dimethyl-1-phenyl [5-(N-isopropyl-N-phenyl-),
 600°C, 140-160°C, 1.5 h, 10%] (64%) m.p. 84-87°C (from
 hexane), δ_H (80 MHz) 8.10 (1H, d, ^3J 3.6 Hz), 7.25 -
 7.75 (5H, m), 5.37 (1H, d, ^3J 3.6 Hz) and 1.54 (6H, s);

δ_C (20 MHz) 205.73(q), 160.19, 139.88(q), 129.39, 125.47, 121.99, 99.11, 68.65(q) and 23.04; m/z 187 (M^+ , 59%), 172(15), 158(26), 144(37) and 118(100): 2-methyl-1-phenyl [5-(N-ethyl-N-phenyl-), 160°C, 155°C, 1.25 h] (73%), b.p. approx. 140°C (0.3 Torr), this compound was occasionally obtained as a yellow solid directly on pyrolysis but could not generally be satisfactorily distilled or recrystallised due to its rapid oxidation. Boiling point was inconsistent on attempted distillation. (Found, M^+ , 173.084. $C_{11}H_{11}NO$ requires M^+ , 173.084); δ_H (200 MHz) 8.30 (1H, d, ^3J 3.6 Hz), 7.0-7.5 (5H, m), 5.42 (1H, d, ^3J 3.6 Hz), 4.15 (1H, q, ^3J 7.2 Hz) and 1.41 (3H, d, ^3J 7.2 Hz); δ_C (20 MHz) 202.92(q), 158.59, 138.76(q), 129.67, 123.55, 117.09, 101.41, 61.08 and 15.29; m/z 173 (M^+ , 100%), 147(83), 130(33), 119(27), 104(53) and 77(80): 1,2-diphenyl [5-(N-benzyl-N-phenyl-), 600°C, 180°C, 2.5 h] (56%) b.p. 190°C (0.5 Torr), (Found: M^+ , 235.099. $C_{16}H_{13}NO$ requires M^+ , 235.100); δ_H (80 MHz) (two tautomers present in chloroform solution: see Discussion Section. Keto tautomer quoted) 8.62 (1H, d, ^3J 3.7 Hz), 6.8 - 7.8 (10H, m), 5.45 (1H, d, ^3J 3.7 Hz) and 5.04 (1H, s); δ_C (20 MHz) 199.81(q), 159.60, 123-138 (complex pattern of aromatic signals), 101.26 and 69.39; m/z 235 (M^+ , 64%), 206(20), 146(50), 105(23), 104(27), 103(18), 91(23) and 77(100): 1-methyl-2-phenyl [5-(N-benzyl-N-methyl-), 600°C, 180°C, 1.5 h] (80%)

b.p. 170°C (0.05 Torr) (Found: C, 74.5; H, 6.2; N, 7.85. $C_{11}H_{11}NO \cdot 0.250$ requires C, 74.55; H, 6.2; N, 7.9%); δ_H (80 MHz) (two tautomers present in chloroform solution - see Discussion Section, keto tautomer quoted) 7.86 (1H, d, ^3J 3.2 Hz), 7.0-7.5 (5H, m), 5.08 (1H, d, ^3J 3.2 Hz), 4.34 (1H, s), and 2.97 (3H, s); δ_C (keto tautomer not sufficient for determination - see Discussion Section for enol parameters); m/z 173 (M^+ , 100%): 1-isopropyl-2-methyl-2-phenyl- {5-[N-isopropyl-N-(α -methyl)benzyl]}, 600°C, 170°C, 1 hr}, (55%) m.p. 65-67°C (from hexane) (Found: C, 78.0; H, 7.65; N, 6.25. $C_{14}H_{17}NO$ requires C, 78.1; H, 7.9; N, 6.5%); δ_H (80 MHz) 8.08 (1H, d, ^3J 3.3 Hz), 7.0-7.5 (5H, m), 5.11 (1H, d, ^3J 3.3 Hz), 3.39 (1H, m, ^3J 6.7 Hz), 1.67 (3H, s), 1.25 (3H, d, ^3J 6.7 Hz), and 1.10 (3H, d, ^3J 6.7 Hz); δ_C (50 MHz) 203.50(q), 160.73, 137.03(q), 128.41, 127.67, 125.98, 94.34, 72.69(q), 46.47, 23.95, 22.92, and 19.78; m/z 215 (M^+ , 100%), 200(33), 186(33), 172(95), 171(60), 144(50), 130(23), 105(40), 104(53), and 103(80): 1-tert-butyl [5-(N-tert-butyl-N-methyl-), 600°C, 135°C, 1.5 h] (62%) b.p. 115-17°C (0.4 Torr) (Found: C, 66.65; H, 9.2; N, 9.5. $C_8H_{13}NO \cdot 0.25$ O requires C, 67.0; H, 9.1; N, 9.8%); δ_H (80 MHz) 7.93 (1H, d, ^3J 4.0 Hz), 5.09 (1H, d, ^3J 4.0 Hz), 3.95 (2H, d, ^4J 0.8 Hz), and 1.54 (9H, s); δ_C (50 MHz) 199.76(q), 162.58, 99.13, 54.80(q), 54.19(q), and 28.32; m/z 139 (M^+ , 40%), 124(16) and 83(100): 1-p-tert-butyl-

phenyl [5-(N-p-tert-butylphenyl-N-methyl-), 600°C, 200°C (metal inlet), 3 h.] (35%) m.p. 95-97°C (from hexane) (Found: C, 77.3; H, 7.85; N, 6.4. $C_{14}H_{17}NO \cdot 0.125 O$ requires C, 77.4; H, 7.85; N, 6.45%); δ_H (80 MHz) 8.38 (1H, d, ^3J 3.5 Hz), 7.36 (2H, d, 8.9 Hz), 6.94 (2H, d, ^3J 8.9 Hz), 5.43 (1H, d, ^3J 3.5 Hz), 4.10 (2H, s) and 1.29 (9H, s); δ_C (50 MHz) 198.73(q), 158.52, 146.28(q), 137.10(q), 126.48, 114.68, 103.38, 55.90, 34.10(q) and 31.11; m/z 215 (M^+ , 53%) and 200(100): 1-phenyl [5-(N-methyl-N-phenyl-), 600°C, 120-150°C, 1.5 h, 13%] (63%) m.p. 80-81°C (from methanol), b.p. 157-158°C (0.5 Torr) (Found: C, 73.8; H, 5.4; N, 8.2. $C_{10}H_9NO \cdot 0.25 O$ requires C, 73.6; H, 5.5; N, 8.55%); δ_H (80 MHz), 8.40 (1H, d, ^3J 3.6 Hz), 6.9-7.5 (5H, m), 5.46 (1H, d, ^3J 3.6 Hz) and 4.10 (2H, d, ^4J 0.6 Hz); δ_C (50 MHz), 198.71(q), 158.31, 139.28(q), 129.62, 122.97, 114.67, 103.81 and 55.65; m/z 159 (M^+ , 100%), 131(95), 105(73) and 104(87); 1-phenyl-2-[^{13}C] [5-(2-[^{13}C]methyl-2-phenyl-), 600°C, 180°C, 1 h.] (40%); δ_H (80 MHz), 8.41 (1H, dd, ^3J 3.7 Hz and 3.8 Hz), 6.9-7.4 (5H, m), 5.47 (1H, dd, ^3J 3.7 Hz and 4.6 Hz), 4.11 (2H, d, ^1J 14.3 Hz).

The following bicyclic and tricyclic compounds were also prepared from 2,2-dimethyl-1,3-dioxane-4,6-dione derivatives: 5,8a-dimethyl-4,5,6,7,8,8a-hexahydro-indolizin-1H-1-one{5-[1-(2,6-dimethyl)piperidinyl]}

methylidene, 600°C, 155°C, 2.25 h.}. [Two diastereomers were isolated by column chromatography and the relative stereochemistry of each determined by n.o.e. experiments (see Discussion Section)], 5,8a-cis-dimethyl (23%) m.p. 72-73°C (from hexane) (Found: C, 72.5; H, 9.3; N, 8.65. $C_{10}H_{14}NO$ requires C, 72.75; H, 9.1; N, 8.5%); δ_H (80 MHz) 7.64 (1H, d, ^3J 3.1 Hz), 4.82 (1H, d, ^3J 3.1 Hz), 3.75-4.0 (1H, m), 1.3-2.0 (6H, m), 1.19 (3H, d, ^3J 6.8 Hz), and 1.20 (3H, s); δ_C (50 MHz) 206.89(q), 162.70, 93.99, 65.28(q), 53.77, 32.36, 31.80, 21.16, 20.42, and 15.19; m/z 165 (M^+ , 100%), 150(14), 136(71), and 122(77); 5,8a-trans-dimethyl (9%), b.p. 136°C (0.5 Torr), (Found: C, 72.5; H, 9.25; N, 8.55.

$C_{10}H_{14}NO$ requires C, 72.75; H, 9.1; N, 8.5%); δ_H (80 MHz), 7.76 (1H, d, ^3J 3.4 Hz), 4.99 (1H, d, ^3J 3.4 Hz), 3.3-3.6 (1H, m), 1.4-2.0 (6H, m), 1.32 (3H, d, ^3J 6.5 Hz), and 1.20 (3H, s); δ_C (50 MHz), 206.87(q), 156.90, 94.18, 66.35(q), 50.07, 36.59, 32.36, 20.06, 17.84, and 17.60; m/z 165 (M^+ , 100%), 150(14), 136(71), and 122(77):

10b-methyl-1,5,6,10b-tetrahydro-4H-pyrrolo[2,1-a]-isoquinolin-1-one {5-[2-(1-methyl)tetrahydroisoquinolyl]-methylidene, 600°C, 200°C (metal inlet), 1 h, 6%} (82%), b.p. 164°C (0.2 Torr), (Found: M^+ , 199.0997 $C_{13}H_{13}NO$ requires M^+ 199.0997); δ_H (200 MHz), 7.89 (1H, d, ^3J 3.3 Hz), 7.88 (1H, d, 1.2 Hz), 7.0-7.3 (3H, m), 5.25 (1H, d, ^3J 3.3 Hz), 3.5-3.8 (2H, m), 2.8-3.0 (2H, m), and 1.59 (3H, s); δ_C (50 MHz), 203.11 (q), 163.96, 135.67(q),

131.67(q), 128.17, 127.00, 126.63, 126.51, 100.15, 66.92(q), 43.62, 31.18, and 25.42; m/z 199 (M^+ , 100%), 144(72), 128(33), 115(52), 103(29), and 77(37):

10b-phenyl-1,5,6,10b-tetrahydro-4H-pyrrolo[2,1-a]-isoquinolin-1-one {5-[2-(1-phenyl)tetrahydroisoquinolyl]-methylidene, 600°C, 210°C (metal inlet), 1.5 h} (86%)

m.p. 162-163°C (from methanol), (Found: C, 82.4; H, 5.65; N, 5.4. $C_{18}H_{15}NO$ requires C, 82.75; H, 5.75; N, 5.35%); δ_H (200 MHz), 8.04 (1H, d, ^3J 3.3 Hz), 7.89-7.95 (1H, m), 7.0-7.3 (8H, m), 5.32 (1H, d, ^3J 3.3 Hz), 3.5-3.7 (2H, m), and 2.85-3.0 (2H, m); δ_C (50 MHz) (two aromatic peaks superimposed) 202.38(q), 164.93, 140.27(q), 133.45(q), 133.10(q), 128.33, 128.25, 127.96, 127.69, 127.47, 127.28, 126.49, 99.98, 72.66(q), 43.32, and 30.18; m/z 261 (M^+ , 45%), and 232(100).

A number of small scale pyrolyses were carried out without isolation of the products which were identified by ^1H n.m.r. spectroscopy. The following derivatives of 5-aminomethylidene-2,2-dimethyl-1,3-dioxane-4,6-dione were pyrolysed. The pyrolysis parameters and 1,2-dihydro-3H-pyrrol-3-one(s) produced are recorded; where two isomers were produced the ratio is given after the second product: N,N-dimethyl, 600°C, 125°C, 25 min., 1-methyl δ_H (two tautomers present, keto: enol, 75:25, enol tautomer quoted in brackets) 7.68 (1H, d, ^3J 3.1 Hz), 5.05 (1H, d, ^3J 3.1 Hz), 3.65 (2H, d, ^4J 0.7 Hz), and 3.64 (3H, s), [6.75 (1H, m), 6.2 (2H, m)

and 3.47 (3H, s)]; δ_H ($[^2H_4]MeOH$) (two tautomers present, keto:enol, 60:40, C2-H proton(s) exchanged) 8.16 (1H, d, ^3J 2.9 Hz), 5.10 (1H, d, ^3J 2.9 Hz) and 3.28 (3H, d, ^4J 0.4 Hz), [6.37 (1H, d, ^3J 2.7 Hz), 5.70 (1H, d, ^3J 2.7 Hz), and 3.58 (3H, d, ^4J 0.3 Hz)]:

5-(N-benzyl-N-isopropyl-), 600°C, 175°C, 20 min., 1-isopropyl-2-phenyl, δ_H (two tautomers present, keto:enol, 1:9, enol tautomer quoted in brackets) 8.07 (1H, d, ^3J 3.3 Hz), 7.0-7.5 (5H, m), 5.12 (1H, d, ^3J 3.3 Hz), 4.53 (1H, s), 3.51 (1H, m, ^3J 6.6 Hz), 1.31 (3H, d, ^3J 6.6 Hz), and 1.14 (3H, d, ^3J 6.6 Hz), [7.0-7.5 (5H, m), 6.58 (1H, d, ^3J 3.0 Hz), 5.91 (1H, d, ^3J 3.0 Hz), 4.25 (1H, m), and 1.31 (6H, d, ^3J 6.6 Hz)]:

5-(N-cyclohexyl-N-methyl-), 600°C, 130°C, 20 min., 1-cyclohexyl, δ_H (80 MHz) 7.83 (1H, d, ^3J 3.2 Hz), 5.06 (1H, d, ^3J 3.2 Hz), 3.68 (2H, s), 3.0-3.3 (1H, m), and 1.0-2.0 (10H, m); 1-methyl-2,2-pentamethylene, δ_H (80 MHz) 7.62 (1H, d, ^3J 3.2 Hz), 4.94 (1H, d, ^3J 3.2 Hz), 3.02 (3H, s), and 1.0-2.0 (10H, m) (39:11):

5-(N-cyclohexyl-N-ethyl-), 600°C, 150°C, 20 min., 1-cyclohexyl-2-methyl, δ_H (80 MHz) (only olefinic signals quoted) 7.82 (1H, d, ^3J 3.2 Hz), and 5.00 (1H, d, ^3J 3.2 Hz);

1-ethyl-2,2-pentamethylene, δ_H (80 MHz) (only olefinic signals quoted) 7.73 (1H, d, ^3J 3.3 Hz), and 4.93 (1H, d, ^3J 3.3 Hz) (29:21): 5-(N-cyclohexyl-N-isopropyl),

600°C, 135°C, 25 min., 1-cyclohexyl-2,2-dimethyl,

δ_H (see preparative section), 1-isopropyl-2,2-pentamethylene,

δ_H (see preparative section) (28:22): 5-(N-sec-butyl-

-N-isopropyl), 600°C, 140°C, 20 min., 1-sec-butyl-2,2-pentamethylene, δ_H (80 MHz) 7.76 (1H, d, ^3J 3.4 Hz), 4.98 (1H, d, ^3J 3.4 Hz), 3.33 (1H, m), 1.5-2.5 (15H, m) (doublet centred at 1.20 clearly superimposed on methylene signals), and 0.88 (3H, t, ^3J 7.0 Hz), 1-cyclohexyl-2-ethyl-2-methyl, δ_H (80 MHz) 7.94 (1H, d, ^3J 3.4 Hz), 5.06 (1H, d, ^3J 3.4 Hz), 2.75-3.25 (1H, m), 1.0-2.0 (15H, m) (singlet at 1.21 clearly superimposed on methylene signals), and 0.63 (3H, t, ^3J 7.0 Hz) (30:20).

A small scale pyrolysis was also carried out on a chiral 5-[2-(α -methyl)benzyl-2-isopropyl-] derivative (400°C, 170°C, 30 min.) and starting material was recovered in order to check for racemisation (see Discussion Section).

A preparative pyrolysis was carried out on the dihydrophenanthridyl methylidene derivative but this did not lead to a 1,2-dihydro-3H-pyrrol-3-one (3-hydroxypyrrole) structure. G.c. and ^1H n.m.r. analysis of the white solid obtained showed it to be phenanthridine. This was presumably formed by radical cleavage of the C-N bond. Pyrolysis of 0.2 g of the derivative, 600°C, 205°C, 30 min. gave phenanthridine (40 mg, 43%).

PREPARATION AND PYROLYSIS OF 5-(1-ALKYL-1-AMINO-METHYLIDENE)-2,2-DIMETHYL-1,3-DIOXANE-4,6-DIONE

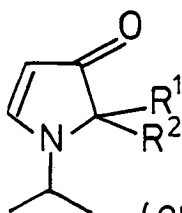
Attempts to prepare the title compounds using the route described in Section C(2), Method A, by replacement of triethylorthoformate with triethylorthoacetate were unsuccessful, as were most attempts to replace it with triethylorthopropionate. However, reaction with the propionate followed by addition of N-methylbenzylamine gave a low yield of 5-[1-ethyl-1-(N-methyl-N-benzyl)aminomethylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione (26%), m.p. 176-177°C (from methanol) (Found: C, 67.2; H, 6.9; N, 4.7. $C_{17}H_{21}NO_4$ requires C, 67.3; H, 6.95; N, 4.6%), δ_H (200 MHz) (signals of second rotamer given in brackets where observable) 7.15-7.45 (5H, m), 4.85 (4.66) (2H, s), 3.28 (2H, q, ^3J 7.5 Hz), 3.21 (3.07) (3H, s), 1.70 (1.68) (6H, s) and 1.20 (1.27) (3H, t, ^3J 7.5 Hz); δ_C (50 MHz) (signals of second rotamer given in brackets where observable) 184.0(q), 162.30(q), 132.69 (133.42) (q), 128.95, 128.60, 128.32 (126.37), 101.60(q), 82.08(q), 57.08 (62.63), 44.85 (38.16), 26.67 (27.29), 26.18 and 11.91 (10.86); m/z 303 (M^+ , 18%), 245(16), 201(23), 172(22), 120(16), 118(16), 104(15), and 91(100).

Pyrolysis of this compound led to a number of products with no evidence for the 5-ethyl-pyrrolone (C4-H signal expected at $\sim 5.2^{39}$ - no signals between 4.65 and 7.0, and no clear ethyl group), and was not further investigated.

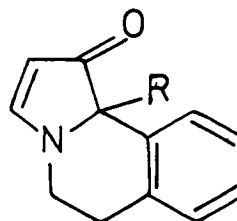
Derivatives of this type have been previously prepared by condensation of 2,2-dimethyl-1,3-dioxane-4,6-dione with activated N,N-dialkylamides²⁰⁴ such as N,N-dimethylacetamide and N-methylpyrrolidinone.

THE USE OF CHIRAL SHIFT REAGENTS

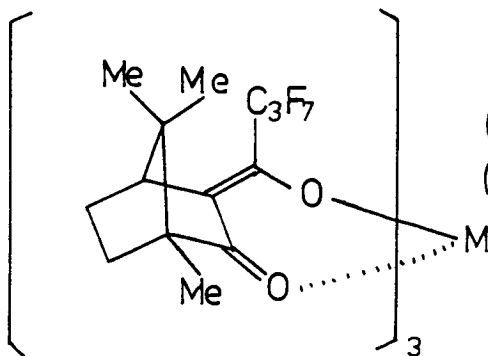
Chiral lanthanide shift reagents²⁰⁵ were used to determine the enantiomeric excess in 1-isopropyl-2-methyl-2-phenyl-1,2-dihydro-3H-pyrrol-3-ones (97) and 10b-substituted-1,5,6,10b-tetrahydro-4H-pyrrolo[2,1-a]-isoquinolin-1-ones (91 and 92) by ¹H n.m.r. spectroscopy. The tris[3-(heptafluoropropylhydroxymethylene)-(+) - canphorato], europium (III) derivative (229) was found most suitable for the analysis because of the shift of signals to more deshielded positions. The equivalent praseodymium derivative (230) shifted signals to more shielded positions which made the spectra more complex, and a chiral alcohol (231) required the addition of considerably more reagent (approximately ten equivalents) to fully separate peaks.



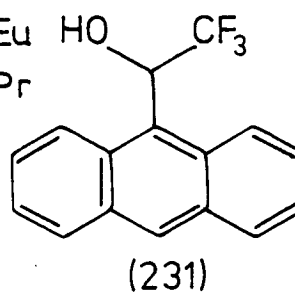
(97) $R^1 = \text{Me}, R^2 = \text{Ph}$
 (232) $R^1 = \text{Me}, R^2 = \text{Et}$



(91) $R = \text{Me}$
 (92) $R = \text{Ph}$



(229) $M = \text{Eu}$
 (230) $M = \text{Pr}$



(231)

All attempts to separate enantiomers of (232, $R^1 = \text{Me}$, $R^2 = \text{Et}$) were unsuccessful. The methyl and ethyl groups are apparently not sufficiently different for the signals of the diastereomeric complexes to be resolved.

When chiral shift reagents are used for analysis it is important to prepare samples carefully. Samples can be prepared satisfactorily without the use of a dry box but the reagent should be kept free from moisture and air, if stored. Best results are obtained using

only small quantities of substrate (5-10 mg) since these require less shift reagent to fully resolve the enantiomeric signals. The reagent contains small amounts of insoluble material and samples must be filtered (at least through a cotton wool plug, and better through celite) to remove these, or the resolution of the spectra becomes very poor. The quantity of reagent required to give baseline separation of peaks varies from sample to sample, possibly because of the presence of insoluble material. It was therefore found that the best method involved addition of increments of shift reagent (approximately 0.25 equivalents) and recording the spectra until the required separation was achieved.

Spectra of (91), (92) and (97) from chiral precursors, the chiral precursor of (97), (75) (d form) before and after pyrolysis at 400°C, and the product of repyrolysis of the optically active mixture of (97), were obtained.

D. STRUCTURE, PHYSICAL AND SPECTROSCOPIC PROPERTIES
OF 1,2-DIHYDRO-3H-PYRROL-3-ONES (3-HYDROXY-
PYRROLES)

The preparations of all 1,2-dihydro-3H-pyrrol-3-ones are described in the sections concerning the pyrolyses of 5-aminomethylene-2,2-dimethyl-1,3-dioxane-4,6-dione derivatives or the alkylation of some of the pyrolysis products. The 2,2-[$^2\text{H}_2$]- and 2,2,4-[$^2\text{H}_3$]-1-substituted examples were obtained by exchange in [$^2\text{H}_4$]methanol solution. When exchange was complete (as determined by ^1H n.m.r. spectroscopy) the methanol was removed in vacuo and the labelled material was dissolved immediately in [^2H]chloroform or [$^2\text{H}_6$]-dimethylsulphoxide as appropriate. Attempts to specifically label the 4-position were unsuccessful as the label rapidly equilibrated between the 2- and 4-positions when in solution.

PREPARATION OF 1-PHENYL-3-HYDROXY PYRROLE FOR
CRYSTAL STRUCTURE DETERMINATION

A small quantity of the pyrrole (≈ 20 mg) was dissolved in methanol at room temperature. The solution was kept at -20°C until crystallisation occurred (generally overnight). The solution was filtered rapidly at room temperature to give crystals suitable for X-ray studies.

E. THE REACTIVITY OF 1,2-DIHYDRO-3H-PYRROL-3-ONES

PROTONATION

Preparation of Samples for N.M.R. Spectroscopy

The appropriate pyrrol-3-one was dissolved in trifluoroacetic acid and spectra were recorded using an external [$^2\text{H}_2$]water lock. Tetramethylsilane was added to give a reference peak. The deuterium exchange of the protonated form was observed using [^2H]trifluoroacetic acid, again with tetramethylsilane added.

Preparation of Picrates

The pyrrol-3-one (0.5 mmol) was dissolved in ethanol (4 ml) and an excess of a saturated solution of picric acid in ethanol was added. The salts precipitated when the side of the flask was scratched with a glass rod. In neutral solutions a rapid equilibrium between the free base and protonated forms exists which gives rise to unresolved peaks in the ^1H n.m.r. spectra. Proton spectra of the salts were therefore obtained in acid solution. The following pyrrolium picrates were prepared: 1-tert-butyl-3-hydroxy-1,2-dihydro (175 mg, 95%), m.p. 80-82°C (from ethanol) (Found: C, 45.55; H, 4.1; N, 15.2. $\text{C}_{14}\text{H}_{16}\text{N}_4\text{O}_8$ requires C, 45.65; H, 4.35; N, 15.2%) δ_{H} (80 MHz) (trifluoroacetic acid) 9.32 (2H, s), 8.56 (1H, apparent q, ^3J and ^4J 2.0 Hz),

5.94 (1H, d, ^3J 2.1 Hz), 4.75 (2H, d, ^4J 1.9 Hz);

3-hydroxy-1-phenyl-1,2-dihydro (145 mg, 75%), m.p. 102-104°C (decomposed on attempts to recrystallise) (Found: C, 48.6; H, 3.05; N, 13.4. $C_{16}H_{12}N_4O_8 \cdot 0.5 H_2O$, requires C, 48.35; H, 3.25; N, 14.1%), δ_H (80 MHz) (trifluoroacetic acid) 9.32 (2H, s), 8.94 (1H, dd, ^3J 2.6 Hz and ^4J 1.8 Hz), 7.4-7.7 (5H, m), 6.30 (1H, d, ^3J 2.6 Hz) and 5.29 (2H, d, ^4J 1.8 Hz): 2,2-dimethyl-3-hydroxy-1-isopropyl-1,2-dihydro (120 mg, 63%), m.p. 135-136°C (from methanol) (Found: C, 47.5; H, 4.75; N, 14.6. $C_{15}H_{18}N_4O_8$ requires C, 47.1; H, 4.7; N, 14.65%); δ_H (80 MHz) (trifluoroacetic acid) 9.32 (2H, s), 8.64 (1H, d, ^3J 2.0 Hz), 6.00 (1H, d, ^3J 2.0 Hz), 4.23 (1H, m), 1.69 (6H, s) and 1.60 (6H, d, ^3J 6.7 Hz).

REACTIONS WITH ELECTROPHILES

Preparation of 2,2-Dimethyl-3-ethoxy-1-isopropyl-1,2-dihydro-pyrrolium Tetrafluoroborate

The pyrrolone (0.6 g, 4 mmol) was dissolved in methylene chloride (15 ml) and a solution of triethyl-oxonium tetrafluoroborate²⁰⁶ in methylene chloride (0.83 M, 5.5 ml) was added dropwise while the mixture was stirred, and cooled, in an ice bath. The reaction mixture was allowed to warm to room temperature and left to stand for 30 min. The methylene chloride was then removed

in vacuo and ether was added to the oily residue. It was stored at -20°C overnight and this yielded the salt as a solid which was purified by dissolving it in the minimum quantity of acetone and addition of ether until precipitation of the pure alkylated salt occurred: (0.75 g, 70%) m.p. $70-72^{\circ}\text{C}$ (from acetone), (Found: C, 48.85; H, 7.25; N, 5.05. $\text{C}_{11}\text{H}_{20}\text{BF}_4\text{NO}$ requires C, 49.05; H, 7.45; N, 5.2%); δ_{H} (200 MHz), 8.93 (1H, d, ^3J 2.4 Hz), 6.03 (1H, d, ^3J 2.4 Hz), 4.34 (2H, q, ^3J 7.1 Hz), 4.14 (1H, m, ^3J 6.7 Hz), 1.53 (6H, s), 1.50 (6H, d, ^3J 6.7 Hz), and 1.46 (3H, t, ^3J 7.1 Hz); δ_{C} (20 MHz) 190.24(q), 168.28, 95.14, 73.78(q), 70.61, 49.50, 23.24, 20.69, and 13.59; no reasonable mass spectrum could be obtained.

Preparation of 2-Phenylhydrazo-1,2-dihydro-3H-pyrrol-3-ones

A solution of benzenediazonium chloride (1 mmol) in water (0.75 ml) was added to a stirred solution of the pyrrol-3-one (1 mmol) in methanol (5 ml) at room temperature, and was stirred for 20 min. The 1-phenyl compound precipitated from solution and was collected. The 1-tert-butyl product was obtained by extraction of the reaction mixture with methylene chloride (3 x 15 ml), drying (MgSO_4), evaporation of the solvent in vacuo and bulb-to-bulb distillation of the residue. The

2-phenylhydrazo-1,2-dihydro-3H-pyrrol-3-ones were

obtained: 1-phenyl (158 mg, 60%), m.p. 159-160°C (from methanol) (Found: C, 72.85; H, 4.85; N, 15.8.

$C_{16}H_{13}N_3O$ requires C, 73.0; H, 4.95; N, 15.95%);

δ_H (80 MHz) 13.57 (1H, b), 7.87 (1H, d, ^3J 4.0 Hz), 6.9-7.6 (10H, m), and 5.66 (1H, d, ^3J 4.0 Hz); δ_C (50 MHz) 179.25(q), 149.44, 142.60(q), 137.51(q), 133.38(q), 129.29, 129.22, 126.10, 123.07, 122.69, 114.29, and 101.29;

m/z 263 (M^+ , 100%), 234(16), 206(10), 186(16), 171(61), 158(52), 146(58), 145(42), 130(45), 117(48), and 104(74):

1-tert-butyl (172 mg, 71%), m.p. 70-72°C (from methanol)

(Found: C, 68.85; H, 6.75; N, 17.05. $C_{14}H_{17}N_3O$ requires C, 69.15; H, 7.0; N, 17.3%); δ_H (80 MHz)

7.63 (1H, d, ^3J 3.9 Hz), 6.8-7.4 (5H, m), 5.33 (1H, d, ^3J 3.9 Hz), and 1.59 (9H, s); δ_C (20 MHz) 178.86(q), 148.93, 142.89(q), 134.48(q), 129.26, 122.58, 114.04, 97.47, 56.69(q), and 28.89; m/z 243 (M^+ , 90%), 187(100), 110(37), 95(67), and 93(49).

Preparation of Aryldiazonium Tetrafluoroborates

The phenyl- and p-nitrophenyl-diazonium tetrafluoroborates²⁰⁷ were prepared by literature methods.

The p-carboxyphenyldiazonium tetrafluoroborate was prepared as follows: 4-aminobenzoic acid (6.85 g, 50 mmol) was dissolved in fluoroboric acid (40%, 43.5 ml, 200 mmol) and water (50 ml). The solution was heated until the aniline was completely dissolved and then was cooled

on ice (some precipitation of solid occurred). Sodium nitrite (3.65 g, 53 mmol) in water (10 ml) was added dropwise while the solution was stirred. The reaction mixture was allowed to warm to room temperature and water was removed from the clear solution in vacuo at room temperature. The solution was concentrated to approximately half its original volume, which led to precipitation of some of the diazonium salt. However, the salt is very water soluble and the reaction mixture was cooled on ice before filtration in order to obtain a reasonable yield. The solid diazonium salt (9.7 g, 89%) was washed with ether and dried in vacuo.

Preparation of 4-Arylazo-2,2-dimethyl-1-isopropyl-1,2-dihydro-3H-pyrrol-3-ones

The pyrrol-3-one (80 mg, 0.52 mmol) was dissolved in acetonitrile (5 ml) and was cooled to 0°C. The appropriate aryldiazonium tetrafluoroborate (0.52 mmol) was added in portions and the reaction mixture was then allowed to warm to room temperature. Evaporation of the solvent in vacuo gave the phenylazo derivative as a dark oil which was purified by chromatography on alumina with ethyl acetate:hexane (4:1) as eluant, but it could not be obtained in crystalline form. Evaporation of solvent gave the *p*-nitro- and *p*-carboxyphenylazo derivatives as their tetrafluoroborate salts. The free bases were

obtained by careful neutralisation of a solution of the salts with potassium hydroxide solution and extraction with methylene chloride. For the p-carboxyphenylazo case it was necessary to avoid the addition of excess base as the acid function then prevented extraction of the compound. The following azo derivatives were obtained: 4-phenylazo- (104 mg, 66%) (Found: $\underline{M}^+$, 257.1528 . $C_{15}H_{19}N_3O$ requires $\underline{M}^+$, 257.1528); δ_H (80 MHz) 8.66 (1H, s), 7.25-8.0 (5H, m), 3.83 (1H, m, ^3J 6.7 Hz), 1.43 (6H, d, ^3J 6.7 Hz), and 1.41 (6H, s); δ_C (20 MHz) 193.99(q), 154.22, 153.42(q), 128.93(q), 128.36, 128.26, 121.38, 71.04(q), 46.55, 23.52, and 21.65; $\underline{m/z}$ 257 ($\underline{M}^+$, 100%), 186(28), 180(90), and 110(59); 4-p-nitrophenylazo- (97 mg, 62%), m.p. 228-229°C (from ethanol) (Found: C, 59.6; H, 5.95; N, 18.55. $C_{15}H_{18}N_4O_3$ requires C, 59.8; H, 6.0; N, 18.45%); δ_H (80 MHz) 8.72 (1H, s), 8.22 (2H, d, ^3J 9.1 Hz), 7.78 (2H, d, ^3J 9.1 Hz), 3.84 (1H, m, ^3J 6.6 Hz), 1.45 (6H, d, ^3J 6.6 Hz), and 1.41 (6H, s); δ_C (50 MHz), 193.13(q), 157.60(q), 156.02, 146.82(q), 130.08(q), 124.34, 121.89, 71.84(q), 47.24, 23.78, and 21.85; $\underline{m/z}$ 302 ($\underline{M}^+$, 100%), 231(23), 180(66), 122(33), and 110(60); 4-p-carboxyphenylazo (119 mg, 76%), m.p. 189-191°C (from toluene) (Found: C, 63.8; H, 6.15; N, 13.6. $C_{16}H_{19}N_3O_3$ requires C, 63.8; H, 6.3; N, 13.95%); δ_H (200 MHz) ($[^2H_6]$ dimethylsulphoxide) 9.28 (1H, s), 8.01 (2H, d, ^3J 8.4 Hz), 7.64 (2H, d, ^3J 8.4 Hz),

3.98 (1H, m), 1.38 (6H, d, ^3J 6.7 Hz) and 1.31 (6H, s);
 δ_C (20 MHz) ($[^2H_6]$ dimethylsulphoxide) 193.14(q),
167.12(q), 157.21, 156.46(q), 130.43, 129.76(q),
129.36(q), 120.79, 70.98(q), 46.96, 23.21 and 21.34;
 m/z 301 (M^+ , 36%), 217(27), 180(17), 143(20), 137(90)
and 120(100).

Preparation of 4-Amino-2,2-dimethyl-1-isopropyl-
1,2-dihydro-3H-pyrrol-3-one

The 4-carboxyphenylazopyrrol-3-one (described above),
as its tetrafluoroborate salt (390 mg, 1 mmol), was
added in portions to a solution of tin(II)chloride
dihydrate (1.33 g, 6 mmol) in concentrated hydrochloric
acid (8 ml) and the reaction mixture was stirred at
room temperature until the solution became opaque
(approximately 2 h). The mixture was then cooled on ice
and was basified with potassium hydroxide solution.
Methylene chloride (50 ml) was added and the resulting
two-phase system was filtered through celite. The
organic layer was separated and the aqueous layer was
extracted with methylene chloride (4 x 50 ml). The
combined organic layers were dried ($MgSO_4$) and the
solvent was removed in vacuo, at the minimum required
temperature. The residue was purified by bulb to
bulb distillation to give the amine: (120 mg, 72%),
b.p. 145°C (0.3 Torr), δ_H (80 MHz), 7.65 (1H, s), 3.56
(1H, m, ^3J 6.6 Hz), 1.22 (6H, d, ^3J 6.6 Hz) and 1.19

(6H, s); δ_C (50 MHz) 197.97(q), 149.79, 115.28(q), 66.57(q), 44.52, 23.34 and 21.60; m/z 168 (M^+ , 36%), 153(59), 107(82) and 106(100). Alternatively, prior to distillation, the amine was dissolved in ethanol and an excess of a saturated solution of picric acid in ethanol was added to give 4-amino-2,2-dimethyl-3-hydroxy-1-isopropyl pyrrolium picrate: (290 mg, 73%, from azo salt), m.p. 158°C (decomp.) (from dimethylformamide) (Found: C, 44.8; H, 5.1; N, 17.6. $C_{15}H_{19}N_5O_8$ requires C, 44.9; H, 4.75; N, 17.45%); δ_H (80 MHz) ($[^2H_6]$ -acetone) 8.82 (1H, s), 8.72 (2H, s), 4.02 (1H, m, ^3J 6.7 Hz), 3.5-4.2 (2H, b), 1.39 (6H, d, ^3J 6.7 Hz), and 1.36 (6H, s); δ_C (50 MHz) ($[^2H_6]$ dimethylsulphoxide) 194.91(q), 160.84(q), 155.42, 141.89(q), 125.14, 124.36(q), 99.73(q), 68.34(q), 45.68, 23.25, and 21.17.

Preparation of 4-Acetylamino-2,2-dimethyl-1-isopropyl-1,2-dihydro-3H-pyrrol-3-one

The 4-carboxyphenylazopyrrolone (base) (301 mg, 1 mmol) was dissolved in acetic acid (2 ml) and was added to a solution of tin(II)chloride dihydrate (2 g, 9 mmol) in acetic acid (20 ml) at 80°C. The reaction mixture was maintained at 80°C and was stirred for 2 h. The mixture was then poured into potassium hydroxide solution (20%, 25 ml), the basic solution was extracted with methylene chloride (3 x 30 ml) and the combined organic layers were washed again with potassium hydroxide

solution, dried (MgSO_4) and the solvent was removed in vacuo to give the 4-acetyl compound as a yellow solid: (86 mg, 41%), m.p. 192°C (from methanol)

(Found: C, 61.6; H, 8.3; N, 13.0. $\text{C}_{11}\text{H}_{18}\text{N}_2\text{O}_2 \cdot 0.25 \text{H}_2\text{O}$ requires C, 61.5; H, 8.6; N, 13.05%); δ_{H} (200 MHz) 8.81 (1H, s), 7.98 (1H, bs), 3.62 (1H, m, ^3J 6.7 Hz), 2.08 (3H, s), 1.29 (6H, d, ^3J 6.7 Hz), and 1.23 (6H, s); δ_{C} (50 MHz) 194.83(q), 166.83(q), 150.31, 110.42(q), 66.13(q), 45.45, 23.56, 22.86, and 21.77; m/z 210 (M⁺, 100%), 195(68), 168(43), 153(64), and 84(54).

Preparation of 2,2-dimethyl-1-isopropyl-1,2-dihydro-3H-pyrrol-3-one-4-diazonium chloride and its coupling to β -naphthol

The amine (85 mg, 0.5 mmol) was dissolved in dilute hydrochloric acid (0.6 ml) and the solution was cooled to 0°C . A solution of sodium nitrite (40 mg, 0.55 mmol) in water (0.3 ml) was added dropwise. A solution of β -naphthol (90 mg, 0.6 mmol) in sodium hydroxide (2M, 1 ml) was then added in one portion to the cooled solution. The deep red precipitate which resulted was filtered, dissolved in base and extracted with methylene chloride (3 x 1.0 ml). The combined extracts were dried and the solvent was removed in vacuo to give 4-[1-(2-naphtholazo)]-2,2-dimethyl-1-isopropyl-1,2-dihydro-3H-pyrrol-3-one (53 mg, 33%) (Found: M⁺, 323.163

$C_{19}H_{21}N_3O_2$ requires M^+ , 323.163); δ_H (200 MHz) 8.74 (1H, d, ^3J 9.5 Hz), 8.71 (1H, s), 7.2-7.75 (5H, m), 3.84 (1H, m), 1.48 (6H, d, ^3J 6.8 Hz), 1.44 (6H, s); δ_C (50 MHz) 194.08(q), 151.31, 151.23(q), 132.30(q), 131.74, 129.62, 128.30(q), 127.80, 127.03(q), 126.84, 123.72, 121.82, 119.96, 71.09(q), 46.92, 23.94 and 22.06; m/z 324 (35%), 323 (M^+ , 24%), 221(24), 167(42), 143(56), 115(36), 97(30) and 69(100). This could not be satisfactorily recrystallised and attempted recrystallisation from methanol gave a solid which analysed reproducibly as C, 64.8; H, 6.6; N, 10.8. $C_{19}H_{21}N_3O_2$ requires C, 70.6; H, 6.5; N, 13.0%. The analysis is also inconsistent with any simple salt or hydrate.

Preparation and Pyrolysis of 2,2-dimethyl-5-(3-hydroxy-1-phenyl-2-pyrrolylmethylidene)-1,3-dioxane-4,6-dione

(a) 2,2-Dimethyl-5-methoxymethylidene-1,3-dioxane-4,6-dione (0.93 g, 5 mmol) was dissolved in acetonitrile (10 ml) and 1-phenyl-1,2-dihydro-3H-pyrrol-3-one (0.8 g, 5 mmol) was added in portions. The reaction mixture was stirred at room temperature overnight which led to some precipitation of product. The solvent was removed at room temperature in vacuo and the solid residue was recrystallised from toluene to give the -ylidenedioxane-dione (1.57 g, 62%), m.p. 160-162°C (from toluene) (Found: C, 65.0; H, 4.8; N, 4.45. $C_{17}H_{15}NO_5$ requires C, 65.2; H, 4.8; N, 4.45%); δ_H (200 MHz) 10.92 (1H, s),

8.10 (1H, s), 7.2-7.6 (5H, m), 7.47 (1H, d, ^3J 2.9 Hz), 6.12 (1H, d, ^3J 2.9 Hz), and 1.74 (6H, s); δ_C (50 MHz) 167.04(q), 163.57(q), 163.04(q), 139.49, 139.34, 137.45(q), 129.79, 128.91, 126.52, 121.09(q), 103.86(q), 102.24, 95.17(q), and 26.78; m/z 313 (M^+ , 55%), 255(100), 256(60), 212(50), 211(95), 183(95), and 182(80).

(b) Large scale pyrolysis of the derivative prepared in (a) above, was carried out using the following pyrolysis parameters: 550°C, 180°C, 30 min. This gave a mixture of two related products - an acid and its decarboxylated analogue. These were separated by dissolving the mixture in sodium hydrogen carbonate which precipitated the acid as its sodium salt. The salt was filtered, dissolved in dilute hydrochloric acid (15 ml) and the acid solution was extracted with methylene chloride (3 x 20 ml). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated in vacuo to give the acid product. The sodium hydrogencarbonate solution above was extracted with methylene chloride (3 x 20 mls) and the combined extracts were dried ($MgSO_4$) and the solvent was evaporated in vacuo to give the decarboxylated product. Small scale pyrolysis at a furnace temperature of 600°C showed greater than 99% of the decarboxylated product in the total pyrolysate. The following compounds were obtained: 5-oxo-1-phenyl-1,5-dihydro-pyrano[3,2-b]pyrrole-6-carboxylic acid (175 mg, 27%),

m.p. 204-205°C (from acetonitrile) (Found: C, 65.8; H, 3.5; N, 5.7. $C_{14}H_9NO_4$ requires C, 65.9; H, 3.55; N, 5.5%); δ_H (200 MHz) 8.71 (1H, d, ^5J 0.8 Hz), 7.52 (1H, d, ^3J 3.1 Hz), 7.3-7.5 (5H, m) and 6.47 (1H, dd, ^3J 3.1 Hz and ^5J 0.8 Hz); δ_C (20 MHz) 165.68(q), 164.39(q), 151.88(q), 137.65, 136.55(q), 133.01, 130.26, 129.05, 124.40, 118.06(q), 104.53(q), and 98.18; m/z 255 (M^+ , 100%), 183(41), 182(37), 154(41), 129(48), 128(52), and 103(37), and 1-phenyl-1,5-dihydro-pyrano[3,2-b]pyrrol-5-one (201 mg, 38%), m.p. 108-109°C (from acetone) (Found: C, 73.7; H, 4.25; N, 6.75. $C_{13}H_9NO_2$ requires C, 73.95; H, 4.25; N, 6.65%); δ_H (200 MHz) 7.58 (1H, dd, ^3J 9.7 Hz and ^5J 0.8 Hz), 7.3-7.55 (5H, m), 7.13 (1H, d, ^3J 3.2 Hz); 6.28 (1H, dd, ^3J 3.2 Hz and ^5J 0.8 Hz), and 6.01 (1H, d, ^3J 9.7 Hz); δ_C (20 MHz) 162.52(q), 148.68(q), 137.81(q), 131.92, 129.80, 127.71, 125.79, 123.88, 116.12(q), 107.16, and 97.64; m/z 211 (M^+ , 100%), 183(40), 182(37), 154(41), 129(48), 128(52), and 103(37).

Preparation of 2,2-Dimethyl-5-[1,2-dihydro-2,2-dimethyl-1-isopropyl-3-oxo-(4-3H-pyrrolylmethylidene)]-1,3-dioxane-4,6-dione and its reaction with sodium methoxide

(a) 2,2-Dimethyl-5-methoxymethylidene-1,3-dioxane-4,6-dione (1.02 g, 5.5 mmol) was dissolved in acetonitrile (10 ml) and 2,2-dimethyl-1-isopropyl-1,2-dihydro-3H-pyrrol-3-one (0.85 g, 5.5 mmol) was added. The reaction

mixture was stirred at room temperature for 2 h. and then the solvent was removed in vacuo to give a thick oil. Trituration with toluene yielded a yellow solid which was recrystallised from toluene to give the title compound: (1.23 g, 73%), m.p. 188-190°C (from toluene) (Found: C, 64.7; H, 7.1; N, 4.2. $C_{16}H_{21}NO_5 \cdot 0.25 C_7H_8$ requires C, 64.55; H, 6.95; N, 4.25%); δ_H (200 MHz) 9.79 (1H, s), 7.89 (1H, s), 3.70 (1H, m, ^3J 6.7 Hz), 1.35 (6H, s), 1.15 (6H, d, ^3J 6.7 Hz), and 1.06 (6H, s); δ_C (20 MHz) 199.95(q), 165.91, 164.23(q), 163.18(q), 145.31, 107.58(q), 103.30(q), 99.83(q), 70.35(q), 47.25, 27.00, 23.60, and 21.58; m/z 307 (M^+ , 100%), 249(50), 221(45), 206(90), and 193(30).

(b) The derivative prepared in (a) above (1 g, 3.25 mmol) was dissolved in methanol (10 ml) and sodium methoxide [from sodium (150 mg, 6.5 mmol) in methanol (5 ml)] was added. The reaction mixture was stirred at room temperature for 1 h. and was then poured into water (15 ml) and acidified with hydrochloric acid. The acid solution was extracted with methylene chloride (4 x 20 ml) and the combined organic layers were dried ($MgSO_4$), and the solvent was removed in vacuo to give methyl-1,2-dihydro-2,2-dimethyl-1-isopropyl-3-oxo-(4-3H-pyrrolylmethylidene)malonate (1.2 g, 100%, crude product); δ_H (200 MHz) 10.14 (1H, s), 8.19 (1H, s), 3.81 (3H, s), 3.81 (1H, m), 1.40 (6H, d, ^3J 6.7 Hz),

and 1.30 (6H, s); δ_C (50 MHz) 200.57(q), 172.26(q), 166.77(q), 166.36, 143.79, 106.49(q), 103.47(q), 69.83(q), 52.54, 47.63, 23.52, and 21.58; m/z 281 (M^+ , 58%), 237(15), 236(30), 221(15), 220(19), 219(19), 205(100), 193(23), 188(54), and 166(30). Bulb-to-bulb distillation gave a solid decarboxylated product, the methyl-3-[1,2-dihydro-2,2-dimethyl-1-isopropyl-3-oxo-(4-3H-pyrrolyl)]-propenoate (1.5 g, 65%), m.p. 105-107°C (from cyclohexane) (Found: C, 65.8; H, 8.2; N, 6.1. $C_{13}H_{19}NO_3$ requires C, 65.8; H, 8.0; N, 5.9%); δ_H (80 MHz), 8.00 (1H, s), 7.32 (1H, d, ^3J 15.5 Hz), 6.53 (1H, d, ^3J 15.5 Hz), 3.67 (4H, s and superimposed m), 1.32 (6H, d, ^3J 6.8 Hz), and 1.24 (6H, s); δ_C (50 MHz) 199.78(q), 168.47(q), 159.61, 134.84, 110.08, 104.97(q), 69.78(q), 45.91, 23.24, and 21.36; m/z 237 (M^+ , 100%), 222(31), 206(38), 194(62), 166(85), and 154(46).

(c) Alternatively, the methanol was removed in vacuo from the sodium methoxide solution prepared in (b) above, and the residual anion was dissolved in dimethylformamide (10 ml). Potassium carbonate (0.9 g, 6.5 mmol) and methyl iodide (100 μ l, 16 mmol) were added and the reaction mixture was stirred at room temperature overnight. The mixture was filtered and the filtrate was added to water (10 ml). The product could not be extracted into ether so it was extracted into methylene chloride (3 x 10 ml), the extracts were dried ($MgSO_4$)

and the methylene chloride and dimethylformamide were removed in vacuo. This yielded the dimethyl 1,2-dihydro-2,2-dimethyl-1-isopropyl-3-oxo-(4-3H-pyrrolylmethylidene)-malonate (0.48 g, 50%), m.p. 116-117°C (from methanol) (Found: C, 61.05; H, 7.25; N, 4.85. $C_{15}H_{21}NO_5$ requires C, 61.0; H, 7.1; N, 4.75%); δ_H (200 MHz) 8.89 (1H, s), 7.59 (1H, s), 3.74 (3H, s), 3.68 (1H, m, ^3J 6.9 Hz), 3.66 (3H, s), 1.31 (6H, d, ^3J 6.9 Hz), and 1.21 (6H, s); δ_C (50 MHz) 199.92(q), 167.61(q), 166.29(q), 161.40, 136.22, 113.13(q), 104.28(q), 69.24(q), 51.52 (ester methyl resonances accidentally equivalent), 46.73, 23.61, and 21.63; m/z 295 (M^+ , 90%), 264(46), 251(25), 224(41), 220(78), 180(84), and 153(100).

Reaction of p-Nitrobenzaldehyde with 1,2-dihydro-3H-pyrrol-3-ones

The 1-phenyl-1,2-dihydro-3H-pyrrol-3-one (112 mg, 0.7 mmol) was dissolved in methanol (3 ml) and a solution of p-nitrobenzaldehyde (105 mg, 0.7 mmol) in methanol (3 ml) was added. The reaction mixture was stirred at room temperature for two hours during which time a solid precipitated. The mixture was filtered and the solid was washed with ether (2 x 3 ml). This gave a creamy solid (85 mg) which was very insoluble in most organic solvents. ^1H n.m.r. spectra were obtained in $[^2H_6]$ dimethylsulphoxide solution and these

showed that the product began to decompose in solution over a period of 1 h.; it was also found that the product could not be successfully recrystallised. The following ^1H n.m.r. signals were found: δ_{H} (200 MHz) ($[\text{}^2\text{H}_6]$ dimethylsulphoxide) 8.70 (d, J 3.8 Hz), 8.12 (d, J 8.8 Hz), 7.3-7.5 (m), 7.05-7.15 (m), 6.09 (d, J 4.5 Hz), 5.26 (m), 5.20 (d, J 3.8 Hz), 4.89 (d, J 2.3 Hz), and 3.31 (s); m/z 292 (<5%), 245 (<5%), 159(100), 150(66), and 77(50). Elemental analysis gave C, 59.1; H, 4.1; N, 8.1. $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_6$ requires C, 59.6; H, 4.1; N, 8.2%. This corresponds to the addition of H_2O and O_2 to the expected condensation product (see Discussion Section).

The 1-tert-butyl-1,2-dihydro-3H-pyrrol-3-one (35 mg, 0.25 mmol) was dissolved in $[\text{}^2\text{H}_4]$ methanol (0.3 ml) and a solution of p-nitrobenzaldehyde (38 mg, 0.25 mmol) in $[\text{}^2\text{H}_4]$ methanol (0.3 ml) was added. The reaction mixture was monitored by ^1H n.m.r. spectroscopy. A number of new peaks became evident immediately but these are thought to be due to acetal formation: δ_{H} (200 MHz) ($[\text{}^2\text{H}_4]$ methanol) 8.32 (2H, d, ^3J 9.1 Hz), 7.80 (2H, d, ^3J 9.1 Hz), 5.69 (1H, s) (methyl signal masked by water peak). There is no evidence for reaction of the pyrrolone after 8 h. at reflux.

Other Attempted Reactions with Electrophiles

Nitration: Attempted nitration of 2,2-dimethyl-1-isopropyl-1,2-dihydro-3H-pyrrol-3-one using concentrated nitric acid under the conditions of Lloyd,²⁰⁸ Barnett²⁰⁹ and of Kucera and Arnold²¹⁰, led only to decomposition.

Bromination: Attempted bromination of 1-phenyl-1,2-dihydro-3H-pyrrol-3-one with N-bromosuccinimide under the conditions described for 2,2-disubstituted compounds led to decomposition. Initial reaction at -78°C had the same result. Reaction with molecular bromine at -78°C resulted in no change in the U.V. spectrum of aliquots, removed from the mixture and diluted, after the addition of 3 equivalents of bromine, while the ¹H n.m.r. spectrum of the N-bromosuccinimide reaction mixture showed only starting material on warming from -60°C to room temperature. After 30 minutes at room temperature this solution became black and the ¹H n.m.r. spectrum was uninterpretable.

Preparation of 2,2-Dimethyl-4-halogeno-1-isopropyl-1,2-dihydro-3H-pyrrol-3-ones

Method A The pyrrolone (80 mg, 0.52 mmol) was dissolved in methanol (8 ml) and was cooled on an ice bath. The appropriate N-halogenosuccinimide²¹¹ (0.52 mmol)

was added in portions to the stirred solution and the reaction mixture was allowed to warm to room temperature and stirred overnight. The mixture was then poured into methylene chloride (15 ml) and was washed with sodium hydrogen carbonate solution (20%, 3 x 15 ml). The organic layer was dried (MgSO_4) and the solvent was removed in vacuo to give the 4-halogeno compounds as crystalline solids.

Method B The pyrrolone (80 mg, 0.52 mmol) was dissolved in methanol (8 ml) and a solution of bromine (80 mg, 0.5 mmol) in methanol (2 ml) was added. Potassium carbonate (~1 g) was added and the mixture was stirred at room temperature overnight and then poured into water (10 ml). The solution was extracted with methylene chloride (3 x 15 ml), dried (MgSO_4) and the solvent was removed in vacuo to give the 4-bromo compound. The following 2,2-dimethyl-1-isopropyl-1,2-dihydro-3H-pyrrol-3-ones were prepared: 4-bromo- (Method A, 106 mg, 88%; Method B, 99 mg, 82%) m.p. 114-115°C (from methanol) (Found: C, 46.7; H, 5.85; N, 5.85. $\text{C}_9\text{H}_{14}\text{BrNO}$ requires C, 46.55; H, 6.0; N, 6.0%); δ_{H} (80 MHz), 7.92 (1H, s), 3.64 (1H, m, ^3J 6.8 Hz), 1.30 (6H, d, ^3J 6.8 Hz), and 1.26 (6H, s); δ_{C} (50 MHz) 196.82(q), 158.38, 83.61(q), 68.48(q), 46.09, 23.73, and 21.94; m/z 233, 231 (M^+ , 33 and 31%), 163(19), 161(25), 149(25), 148(20), 147(25), 146(20), 124(50), 110(50), and 99(100):

4-chloro- (Method A, 89 mg, 91%), m.p. 130-131°C (from methanol), [Found: C, 55.1; H, 7.7; N, 6.8.

$C_9H_{14}ClNO \cdot 0.5 H_2O$ requires C, 54.95; H, 7.65; N, 7.1% (analyses reproducibly as partial hydrate)]; δ_H (200 MHz) 7.89 (1H, s), 3.63 (1H, m, ^3J 6.7 Hz), 1.28 (6H, d, ^3J 6.7 Hz), and 1.25 (6H, s); δ_C (50 MHz) 196.21(q), 156.35, 98.43(q), 68.80(q), 45.94, 23.80, and 22.00; m/z 189, 187 (M^+ , 100 and 25%), 174(31), 172(8), 144(10), 124(50), and 84(75): 4-iodo- (Method A, 110 mg, 76%), m.p. 127-129°C (from methanol) (Found: C, 39.05; H, 4.85; N, 5.0. $C_9H_{14}INO$ requires C, 38.7; H, 5.0; N, 5.0%); δ_H (80 MHz) 7.96 (1H, s), 3.67 (1H, m, ^3J 6.7 Hz), 1.32 (6H, d, ^3J 6.7 Hz), and 1.27 (6H, s); δ_C (50 MHz) 200.11(q), 162.19, 67.75(q), 50.74(q), 23.91, and 22.04; m/z 279 (M^+ , 90%), 264(20), 236(37), 195(23), 194(27), 152(43), and 110(100).

Reaction of 2,2-Dimethyl-4-halogeno-1-isopropyl-1,2-dihydro-3H-pyrrol-3-ones with sodium methoxide

The pyrrolone (0.1 mmol) was dissolved in [$^2H_4$]-methanol (0.2 ml) and sodium methoxide [from sodium (5 mg, 0.2 mmol) in [$^2H_4$]methanol (0.3 ml)] was added carefully. The reaction mixture was placed in an n.m.r. tube and was heated by immersion in methanol at reflux. The reaction was followed to completion by periodic examination of the ^1H n.m.r. spectrum. It was then

poured into water (5 ml), acidified (HCl) and extracted with methylene chloride (3 x 10 ml). The combined organic layers were dried (MgSO₄) and the solvent was removed to give the following 5-[²H]-2,2-dimethyl-1-isopropyl-1,2-dihydro-3H-pyrrol-3-ones: 4-bromo (91%) (²H) (30 MHz) (CHCl₃) 8.04; m/z 234, 232 (M⁺, 36 and 39%), 219(14), 217(14), 191(16), 189(18), 164(20), 162(20), 125(50), 111(43), and 84(100): 4-iodo (93%) δ(²H) (30 MHz) (CHCl₃) 8.09; m/z 280 (M⁺, 89%), 153(61), and 111(100). An experiment in which approximate rate constants for this reaction for the 4-chloro, 4-bromo, 4-iodo and parent compounds were determined was also carried out as follows: the four starting materials were added sequentially to [²H₄]methanol and ¹H n.m.r. spectra obtained between each addition in order to assign the C5-H resonance for each [δ_H (200 MHz, LB-1, GB 0.3) 8.60 (bromo), 8.59 (chloro), 8.57 (iodo), and 8.44 (parent)]. Sodium methoxide [from sodium (two equivalents) in [²H₄]methanol] was added. The reaction mixture was placed in an n.m.r. tube and heated to 55°C in the probe of the spectrometer. The ¹H n.m.r. spectrum of the reaction mixture was monitored at intervals.

Reaction of 2,2-Dimethyl-4-halogeno-1-isopropyl-
1,2-dihydro-3H-pyrrol-3-ones with triphenylphosphine

The pyrrolone (0.5 mmol) was dissolved in methanol (5 ml) and triphenylphosphine (130 mg, 0.5 mmol) was added. The reaction was followed to completion (approximately 30 min. for 4-iodo- and 16 h for 4-bromo-compounds) by t.l.c. on alumina plates with ethyl acetate:hexane (50:50) as eluant. Methanolic hydrochloric acid (~2M, 10 ml) was added and the hydrochloride salt which was obtained was washed with ether. The salt was then dissolved in sodium hydroxide (10%, 15 ml) and was extracted with methylene chloride (3 x 15 ml). The combined organic fractions were dried (MgSO₄), the solvent was removed in vacuo and the product was recrystallised from hexane to give the 4-unsubstituted compound. Melting point and mixed melting point for both examples: 70-71°C (from hexane).

Reactions of 4-Chloro-1,2-dihydro-2,2-dimethyl-1-
isopropyl-3H-pyrrol-3-one with lithium diisopropylamide

All apparatus was dried overnight before use. A solution of diisopropylamine (560 µl, 4 mmol) in dry tetrahydrofuran (20 ml) was cooled to -78°C and was stirred using a magnetic stirrer in a 3-necked flask equipped with a rubber septum. Butyl lithium (1.5M, 2.7 ml, 4 mmol) was added by syringe and the mixture was

stirred for 15 min. The pyrrolone (187 mg, 1 mmol) in tetrahydrofuran (5 ml) was added and again stirring was continued for 15 min. The electrophile was added and the mixture was stirred for a further 15 min. and then allowed to warm to room temperature. The reaction mixture was then poured into hydrochloric acid (2M, 30 ml) and the acid solution was extracted with methylene chloride (3 x 30 ml), the combined organic layers were dried (MgSO_4) and the solvent was removed in vacuo to give mixtures of products as shown by t.l.c. These mixtures were separated by column chromatography on alumina using ethyl acetate:hexane (60:40) as eluant.

(a) Quenching with water: chromatography yielded starting material (40 mg, 22%), a second product (60 mg) as an oil which decomposed on attempted distillation (although a small amount of starting material was recovered) and a mixed fraction (30 mg).

(b) Quenching with [$^2\text{H}_2$]water: chromatography yielded the 5- ^2H -pyrrolone (51 mg, 27%), and a second toffee-like material (77 mg). The second material produced two peaks on analysis by g.c. using a 5% S.E. 30 column at 180°C.

(c) Quenching with methyl iodide: chromatography yielded a creamy solid (130 mg) and a dark oil (20 mg) which appeared to be solely hexane residues. The creamy solid was shown by ^1H - and ^{13}C -spectroscopy to

contain two products. The major one was obtained in pure form by repeated recrystallisation and identified as 4-chloro-2,2-dimethyl-5-ethyl-1-isopropyl-1,2-dihydro-3H-pyrrol-3-one: (Found: $\underline{M}^+$, 217.103 and 215.109. $C_{11}H_{18}ClNO$ requires $\underline{M}^+$, 217.105 and 215.108); δ_H (200 MHz) 3.82 (1H, m), 2.71 (2H, q, ^3J 7.6 Hz), 1.41 (6H, d, ^3J 7.1 Hz), 1.28 (3H, t, ^3J 7.6 Hz), and 1.27 (6H, s); δ_C (50 MHz) 194.09(q), 174.45(q), 98.03(q), 69.09(q), 46.74, 23.27, 22.27, 20.97, and 11.11; m/z 217, 215 ($\underline{M}^+$, 6 and 30%), 202(13), 172(13), 152(38), 143(16), 110(38), and 84(100).

ATTEMPTED ANION FORMATION

The appropriate pyrrol-3-one was dissolved in [$^2H_6$]dimethylsulphoxide or [$^2H_8$]tetrahydrofuran and the solution was added to sodium hydride (50% dispersion in oil, two times excess). An immediate deep red colour ensued. The mixture was shaken for a few minutes and was then filtered through a cotton wool plug. ^1H and ^{13}C n.m.r. showed marked changes which are considered in the Discussion Section. The 1-phenyl-1,2-dihydro-3H-pyrrol-3-one could be readily reprotonated by the addition of [$^2H_4$]acetic acid which resulted in a lightening of the coloured solution. The ^1H n.m.r. spectrum of the reprotonated material showed it to be the anticipated 2-[^2H]-3-hydroxypyrrole δ_H (dimethylsulphoxide) 7.0-7.5 (5H, m), 6.95 (1H, d, 3.1 Hz), and 5.84 (1H, d, ^3J 3.1 Hz).

ALKYLATION AND ACYLATION

Preparative Alkylations and Acylations

Method A: Sodium hydride (50% dispersion in oil, 190 mg, ≈ 4 mmol) was washed three times with light petroleum and then dried at 0.1 Torr. The required pyrrol-3-one (1 mmol) was dissolved in tetrahydrofuran (10 ml) and the prewashed sodium hydride was added while the solution was stirred at room temperature. Stirring was continued for 10 min. and then the appropriate alkylating or acylating agent (5-10 mmol) was added and the reaction mixture was stirred for a further 30 min. The mixture was then poured into methanol (10 ml) and water (20 ml) was added. The aqueous solution was extracted with methylene chloride (3 x 25 ml), the combined organic layers were dried (MgSO_4) and the solvent was removed in vacuo. In some cases this gave a mixture of 3-alkoxypyrrole and 2,2-disubstituted pyrrol-3-one which were separated by column chromatography on alumina using ethyl acetate:hexane (50:50) as eluant. 2-Unsubstituted examples gave a small amount of C-alkylated-3-alkoxypyrroles which were inseparable from the 3-alkoxypyrroles. All products were purified by bulb-to-bulb distillation.

Method B: The same procedure as described for Method A was carried out using dimethylsulphoxide as solvent except that the combined organic extracts were

back extracted with water (3 x 50 ml) before they were dried, in order to remove the dimethylsulphoxide.

Method C: The anion was prepared again in the manner of Method A but methyl tosylate (1 mmol) was added as the alkylating agent. The reaction mixture was heated to reflux for 16 h. and then cooled and the work up described in Method A was followed. The products of alkylation are now reported with a record of the method used preparatively, the pyrrol-3-one used as starting material, and the alkylating agent. The following 1,2-dihydro-3H-pyrrol-3-ones were prepared:

1,2-diphenyl-2-methyl (Method B, 1,2-diphenyl-, methyl-iodide) (48% after chromatography), m.p. 104-106°C (from cyclohexane) (Found: C, 79.4; H, 6.25; N, 5.3. $C_{17}H_{15}NO \cdot 0.5 H_2O$ requires C, 79.05; H, 6.2; N, 5.45%); δ_H (200 MHz) 8.57 (1H, d, ^3J 3.7 Hz), 6.8-7.5 (10H, m), 5.44 (1H, d, ^3J 3.7 Hz), and 1.75 (3H, s); δ_C (20 MHz) (C2 quaternary not observed - possibly superimposed on solvent peaks) 203.50(q), 159.16, 133.73(q), 129.33, 128.89, 128.06(q), 127.66, 125.23, 123.95, 118.33, 99.36, and 20.32; m/z 249 (M^+ , 46%), 220(38), 206(17), 180(29), 105(42), and 77(100): 1,2-dimethyl-2-phenyl- (Method B, 1-methyl-2-phenyl-, methyl iodide) (32%, after chromatography), m.p. 81-82°C (from toluene) (Found: C, 74.95; H, 7.0; N, 7.15. $C_{12}H_{13}NO \cdot 0.5 H_2O$ requires C, 74.6; H, 7.1; N, 7.25%); δ_H (80 MHz), 7.87 (1H, d, ^3J 3.3 Hz), 7.1-7.5 (5H, m), 5.05 (1H, d, ^3J 3.3 Hz),

2.94 (3H, s), and 1.64 (3H, s); δ_C (200 MHz), 203.67(q), 164.80, 139.49(q), 128.64, 127.57, 125.60, 94.47, 67.45(q), 32.58, and 19.34; m/z 187 (M^+ , 100%), 158(91), and 118(50): 1-benzyl-2-methyl-2-phenyl- (Method B, 1-benzyl-2-phenyl-, methyl iodide) (14%, after chromatography), m.p. 66.5-68°C (from toluene), (Found: C, 82.1; H, 6.55; N, 5.4. $C_{18}H_{17}NO$ requires C, 82.15; H, 6.45; N, 5.3%); δ_H (200 MHz), 7.78 (1H, d, ^3J 3.4 Hz), 7.0-7.4 (10H, m), 5.03 (1H, d, ^3J 3.4 Hz), 4.32 (1H, d, ^2J 14.2 Hz), 4.19 (1H, d, ^2J 14.2 Hz), and 1.59 (3H, s); δ_C (200 MHz) 203.53(q), 163.56, 136.48(q), 134.87(q), 128.45, 128.41, 128.32, 127.81, 127.49, 125.66, 94.80, 71.96(q), 49.59, and 19.57; m/z 263 (M^+ , 20%), 211(10), 134(14), 127(31), 99(60), and 91(100): 1-tert-butyl-2,2-dimethyl- (Method B, 1-tert-butyl, methyl iodide) (28%, after chromatography), m.p. 114-115°C (from hexane) (Found: C, 72.1; H, 10.2; N, 8.1. $C_{10}H_{17}NO$ requires C, 71.85; H, 10.2; N, 8.4%); δ_H (80 MHz) 7.99 (1H, d, ^3J 3.5 Hz), 5.03 (1H, d, ^3J 3.5 Hz), 1.40 (9H, s), and 1.34 (6H, s); δ_C (50 MHz) 204.68(q), 161.05, 94.34, 69.56(q), 57.05(q), 30.77, and 24.52; m/z 167 (M^+ , 24%), 152(10), 111(26), 110(100), 83(20), 82(27), 68(12), and 57(31): 2,2-dimethyl-1-phenyl (Method A, 2-methyl-1-phenyl, methyl iodide (85%), (structure confirmed by comparison of g.c. retention time and spectra with those of authentic prepared directly by pyrolysis). The

following 3-alkoxypyrroles were prepared: 1,2-diphenyl-3-methoxy (Method B, 1,2-diphenyl, methyl iodide) (48%, after chromatography), m.p. 68-69°C (from toluene) (Found: C, 81.9; H, 6.2; N, 5.3. $C_{17}H_{15}NO$ requires C, 81.95; H, 6.0; N, 5.6%); δ_H (80 MHz) 6.8-7.5 (10H, m), 6.73 (1H, d, ^3J 3.2 Hz), 6.19 (1H, d, ^3J 3.2 Hz), and 3.82 (3H, s); δ_C (20 MHz) 146.93(q), 140.54(q), 129.34(q), 128.73 (two peaks superimposed), 127.61, 125.96, 125.28, 124.94, 120.43, 116.91(q), 97.29, and 58.18; m/z 249 (M^+ , 50%), 234(41), and 173(40); 1-benzyl-3-methoxy-2-phenyl- (Method B, 1-benzyl-2-phenyl, methyl iodide) (54%, after chromatography), m.p. 33-34°C (from toluene) (Found: C, 81.6; H, 6.55; N, 5.3. $C_{18}H_{17}NO$ requires C, 82.15; H, 6.45; N, 5.3%); δ_H 7.2-7.75 (10H, m), 6.78 (1H, d, ^3J 3.1 Hz), 6.38 (1H, d, ^3J 3.1 Hz), 5.25 (2H, s), and 3.99 (3H, s); δ_C (50 MHz), 145.22(q), 138.30(q), 130.94(q), 129.01, 128.03, 127.74, 126.74, 126.06, 125.85, 118.84, 118.03(q), 96.05, 57.85, and 50.49; m/z 263 (M^+ , 22%), 211(11), 137(30), 99(66), and 91(100%); 3-methoxy-1-methyl-2-phenyl- (Method B, 1-methyl-2-phenyl, methyl iodide) (38%, after chromatography) b.p. 105°C (0.3 Torr) (Found: M^+ , 187.0995. $C_{12}H_{13}NO$ requires M^+ , 187.0997); δ_H (200 MHz) 7.1-7.5 (5H, m), 6.47 (1H, d, ^3J 3.0 Hz), 5.97 (1H, d, ^3J 3.0 Hz), 3.72 (3H, s) and 3.55 (3H, s); δ_C (50 MHz), 145.48(q), 131.34(q), 129.17, 128.05, 126.02, 119.53,

118.44(q), 95.52, 58.43, and 35.19; m/z 187 (M^+ , 100%), 173(89), 172(89), 144(67), 131(47), 118(33), 105(27), and 103(35): 3-methoxy-2-methyl-1-phenyl (Method C, 2-methyl-1-phenyl, methyl tosylate) (34%), b.p. 101°C (0.3 Torr) (Found: M^+ , 187.1003. $C_{12}H_{13}NO$ requires M^+ , 187.1000); δ_H (80 MHz) 7.25-7.65 (5H, m), 6.68 (1H, d, ^3J 3.2 Hz), 6.18 (1H, d, ^3J 3.2 Hz), 3.91 (3H, s), and 2.27 (3H, s); δ_C (200 MHz) 145.42(q), 140.41(q), 128.75, 126.17, 124.95, 116.75, 112.93(q), 97.21, 58.59, and 8.82; m/z 187 (M^+ , 73%), 172(100), 104(10) and 77(30): 3-methoxy-1-phenyl (Method C, 1-phenyl, methyl tosylate) (59%) b.p. 125°C (0.3 Torr) (Found: M^+ , 173.0841. $C_{11}H_{11}NO$ requires M^+ , 173.0841)[†] δ_H (200 MHz) 7.0-7.5 (5H, m), 6.95 (1H, dd, ^3J 3.1 Hz and ^4J 2.4 Hz), 6.73 (1H, dd, ^4J 2.4 and 2.0 Hz), 6.14 (1H, dd, ^3J 3.1 Hz and ^4J 2.0 Hz), and 3.83 (3H, s); δ_C (50 MHz) 150.83(q), 140.83(q), 129.35, 124.82, 119.39, 116.99, 100.86, 100.32, and 57.69; m/z 173 (M^+ , 50%), 172(87), 159(57), 158(100), and 104(60): 1-tert-butyl-3-methoxy- (Method C, 1-tert-butyl, methyl tosylate) (54%) b.p. 52°C (0.3 Torr) (Found: M^+ , 153.1153 . $C_{10}H_{17}NO$ requires 153.1153)[†]; δ_H (80 MHz) 6.57 (1H, apparent t, ^3J and ^4J 2.8 Hz), 6.39 (1H, apparent t, ^3J and ^4J 2.4 Hz), 5.82 (1H, dd, ^3J 2.9 Hz and ^4J 2.2 Hz), 3.72 (3H, s), and 1.48 (9H, s); δ_C (20 MHz) 148.36(q),

[†] Contaminated with small amounts of O,C-dialkylated product.

115.04, 99.76, 95.80, 57.65, 54.50(q), and 30.29;

m/z 153 (M⁺, 47%), 111(13), 97(100), and 82(68):

3-ethoxy-1-phenyl (Method C, 1-phenyl-, triethyloxonium tetrafluoroborate) (72%) b.p. 111°C (0.3 Torr) (Found:

M⁺, 187.0998. C₁₂H₁₃NO requires M⁺, 187.1000); δ_H (80 MHz) 7.0-7.5 (5H, m), 6.90 (1H, apparent t, ³J and ⁴J 2.8 Hz), 6.69 (1H, apparent t, ³J and ⁴J 2.2 Hz), 6.09 (1H, dd, ³J 3.1 Hz and ⁴J 2.0 Hz), 3.99 (2H, q, ³J 7.0 Hz), and 1.42 (3H, t, ³J 7.0 Hz); δ_C (50 MHz)

149.61(q), 140.82(q), 129.37, 124.76, 119.31, 116.84, 101.49, 100.78, 66.01, and 14.86; m/z 187 (M⁺, 100%),

159(46), 158(93), 104(33), and 77(46): 3-isopropyloxy-1-phenyl (Method B, 1-phenyl-, isopropyl bromide) (68%)

(Found: C, 75.90; H, 7.55; N, 6.7. C₁₃H₁₅NO requires C, 77.6; H, 7.5; N, 6.95%)[†]; δ_H (80 MHz) 7.0-7.5 (5H, m), 6.88 (1H, dd, ³J 3.1 Hz and ⁴J 2.6 Hz), 6.67 (1H, dd, ⁴J 2.6 and 2.0 Hz), 6.05 (1H, dd, ³J 3.1 Hz and ⁴J 2.0 Hz), 4.26 (1H, m, ³J 6.1 Hz), and 1.35 (6H, d, ³J 6.1 Hz); δ_C (20 MHz) 147.79(q),

140.66(q), 129.32, 124.74, 119.31, 116.62, 102.98, 101.57, 72.69, and 21.95; m/z 201 (M⁺, 86%), 186(21), 160(27), 159(100), 158(41), 130(35), and 104(72):

3-acetyloxy-1-phenyl (Method A, 1-phenyl, acetyl chloride) (88%) (m.p. 31-32°C (from cyclohexane) (Found: C, 72.1; H, 5.6; N, 7.25. C₁₂H₁₁NO₂ requires C, 71.65; H, 5.45;

[†] Contaminated with small amounts of O,C-dialkylated product.

N, 6.95%); δ_{H} (80 MHz) 7.0-7.5 (5H, m), 7.16 (1H, dd, ^4J 2.6 and 1.8 Hz), 6.90 (1H, dd, ^3J 3.2 Hz and ^4J 2.6 Hz), 6.19 (1H, dd, ^3J 3.2 Hz and ^4J 1.8 Hz), and 2.24 (3H, s); δ_{C} (50 MHz) 168.23(q), 140.43(q), 139.11(q), 129.39, 125.54, 119.99, 116.44, 108.60, 103.25, and 20.66; m/z 201 (M^+ , 100%), 159(78), 131(40), 130(83), 104(83), and 93(75): 3-acetyloxy-1-tert-butyl- (Method A, 1-tert-butyl, acetyl chloride) (75%) (Found: C, 66.0; H, 8.5; N, 7.5. $\text{C}_{10}\text{H}_{15}\text{NO}_2$ requires C, 66.3; H, 8.3; N, 7.75%); δ_{H} (200 MHz) 6.86 (1H, dd, ^4J 2.6 and 1.9 Hz), 6.63 (1H, apparent t, ^3J and ^4J 2.9 Hz), 5.98 (1H, dd, ^3J 3.2 Hz and ^4J 1.9 Hz), 2.19 (3H, s), and 1.49 (9H, s); δ_{C} 168.29(q), 136.82(q), 114.38, 106.81, 99.73, 54.69(q), 30.15, and 20.59; m/z 181 (M^+ , 86%), 139(100), and 124(20).

Comparative Alkylations: In order to evaluate the effect of substrate substitution patterns, alkylating agents and solvents, a number of alkylations were carried out using the same general procedure while one of the above variables was changed. The method used was as follows: Sodium hydride (50% dispersion in oil, 45 mg, ~ 1 mmol) was washed three times with hexane and was then dried at a vacuum pump. The pyrrol-3-one (0.33 mmol) was dissolved in solvent (4 ml) and the prewashed sodium hydride was added in portions while the solution was stirred at room temperature. The alkylating agent was

added (3 mmol, except for methyl tosylate, 0.33 mmol) and the reaction mixture was stirred for a further 20 min., except for methyl tosylate, which was heated to reflux for 16 h. The mixture was then added to methanol (3 ml) and water (10 ml) was added. The aqueous solution was extracted with methylene chloride (3 x 10 ml). The combined organic layers were back extracted with water (3 x 15 ml) for reactions in dimethylsulphoxide. The organic layer was then dried (MgSO_4) and the solvent was removed in vacuo. The total residue was then dissolved in $[\text{}^2\text{H}]\text{chloroform}$ and the ^1H n.m.r. spectrum was obtained. Some 3-alkoxypyrroles were identified by comparison with related examples and were not fully characterised. In these cases the C4-H and C5-H resonances were assigned unambiguously since the examples all involved additional 2-alkylation and therefore gave rise to simple doublets whereas the alternative non-alkylated product exhibited further coupling. The following 3-alkoxypyrroles were observed: 1-tert-butyl-3-methoxy-2-methyl δ_{H} (200 MHz) 6.56 (1H, d) and 5.81 (1H, d): 3-ethoxy-2-ethyl-1-phenyl δ_{H} (200 MHz) 6.52 (1H, d) and 6.04 (1H, d): 1-tert-butyl-3-ethoxy-3-ethyl- 6.45 (1H, d) and 5.67 (1H, d): 3-isopropoxy-2-isopropyl-1-phenyl δ_{H} (200 MHz) 6.45 (1H, d) and 6.02 (1H, d).

Other Methods of Alkylation: Attempted alkylation using methyl iodide and potassium carbonate in dimethylformamide resulted in quantitative recovery of starting material as did an attempt using methyl iodide and potassium hydroxide in dimethylsulphoxide.²¹² An experiment carried out in an n.m.r. tube indicates that generation of the anion using methanolic sodium methoxide is feasible but C-alkylation is the major result under these conditions. Attempts to use trimethylsilylchloride as the alkylating agent, with sodium hydride in tetrahydrofuran as base, also produced only starting material (possibly due to hydrolysis of the product). Using sodium hydride in dimethylsulphoxide with trimethylsilyl chloride as the electrophile the only products appeared to have resulted from reaction with solvent. Reaction of the neutral species with triethyloxonium tetrafluoroborate in methylene chloride at room temperature, and subsequent washing with base produced alkylated products, but the reaction was not clean and a mixture of O- and C-alkylated products was still produced.

Other Attempted Reactions with Nucleophiles

Attempted reaction of 2,2-dimethyl-1-isopropyl-1,2-dihydro-3H-pyrrol-3-one with anilinium perchlorate by heating in ethanol at reflux for 4 h. resulted in recovered starting material (70%) as did heating a solution of the pyrrolone

and methoxycarbonylmethylene-triphenylphosphinate in ethanol at reflux for 24 h. Attempted reaction of the above pyrrolone with butyl lithium in benzene²¹³ at 0°C gave no reproducible results.

Attempted reduction of the same pyrrolone using lithium aluminium hydride by heating to reflux in ether or tetrahydrofuran, surprisingly led to a quantitative recovery of starting material, in contrast to the results of Eicher.²⁴

REACTIONS WITH RADICALS

Preparation of 2-Hydroxy-2-methyl-1-phenyl-1,2-dihydro-3H-pyrrol-3-one [1-(N-phenylamino)pent-1-ene-3,4-dione]

2-Methyl-1-phenyl-1,2-dihydro-3H-pyrrol-3-one (crude material from pyrolysis, 5 mmol of starting material were pyrolysed) was dissolved in an ethanol:water (50:50) mixture (20 ml). Potassium ferricyanide (3.3 g, 10 mmol) was added and the mixture was stirred at room temperature for 3 h. The aqueous solution was then extracted with methylene chloride (3 x 25 ml), the combined organic layers were dried (MgSO₄) and the solvent was removed in vacuo. Bulb-to-bulb distillation [130°C (10 Torr)] yielded the title compound as a yellow solid (308 mg, 40% from pyrolysis substrate) m.p. 68-70°C [sublimed at 155°C (0.3 Torr) (Found: $\underline{M}^+$, 189.079. C₁₁H₁₁NO₂ requires $\underline{M}^+$, 189.079); δ_{H} (200 MHz) (open-chain tautomer - see Discussion Section) 12.03 (1H,

b), 7.63 (1H, dd, ^3J 7.5 and 12.8 Hz), 7.0-7.55 (5H, m), 6.04 (1H, d, ^3J 7.5 Hz), and 2.42 (3H, s); δ_C (20 MHz) (one carbonyl resonance not observed) 184.89(q), 147.93, 139.21(q), 129.72, 124.78, 116.77, 90.56, and 23.96; m/z 189 (M^+ , 11%), 147(10), 146(100), and 93(10).

Reaction of the 1-(N-phenylamino)pent-1-ene-3,4-dione with 1,2-diaminobenzene

The dione (95 mg, 0.5 mmol) was dissolved in ethanol (2 ml) and the diamine (54 mg, 0.5 mmol) in ethanol (2 ml) was added and the mixture was heated to reflux for 15 min. Water (5 ml) was added to give an orange precipitate (118 mg). The simple quinoxaline would give $C_{17}H_{15}N_3$; product thought to include amine exchange (see Discussion Section) (Found: C, 76.1; H, 5.7; N, 17.0. $C_{17}H_{15}N_3 \cdot 0.4 C_{17}H_{16}N_4$ requires C, 76.9; H, 5.7; N, 17.3%), δ_H (200 MHz), 12.95 (bd), 12.40 (bd), 7.89 (m), 6.75-7.65 (m), 5.78 (d), 5.62 (d), 5.60 (d) and 2.73 (s) (not fully reproducible; ratio of integral values for doublets varies); δ_C (50 MHz) 153.20(q), 152.56 (q), 146.02 (q), 141.35 (q), 138.54 (q), 136.95, 129.49, 128.86, 128.49, 128.32, 128.09, 126.80, 126.53, 121.88, 115.19, 29.46, 22.75 and 18.20 (additional minor peaks between δ_C 128-132); m/z 261 (M^+ , 100), 246(87), 169(98), 158(52), 118(38), 117(61), 93(27), 77(35) and 76(27).

Electron Spin Resonance Spectra of 2-Unsubstituted-
1,2-dihydro-3H-pyrrol-3-ones

E.s.r. spectra of the product from 1-phenyl-1,2-dihydro-3H-pyrrol-3-one and its 2,2-[$^2\text{H}_2$]-, 2-[^{13}C]-, and 1-p-tert-butyl phenyl analogues were obtained. Samples of pyrrolone (approx. 20 mg) in tert-butylbenzene (250 μl) and di-tert-butylperoxide (50 μl) were degassed by two, or three, freeze, pump, thaw cycles and photolysed as previously described. Analysis of the spectra was carried out with the aid of computer simulations (see Discussion Section).

F. ELECTROPHILIC SUBSTITUTION REACTIONS OF 2,2-DIMETHYL-
5-METHOXYMETHYLIDENE-1,3-DIOXANE-4,6-DIONE

PREPARATION OF 2,2-DIMETHYL-5-METHOXYMETHYLIDENE-
1,3-DIOXANE-4,6-DIONE

The title compound was prepared by the method of Bihlmayer et al¹¹⁰ and the crystalline compound which was obtained was washed with ether. It appears to be subject to decomposition to the 5-hydroxymethylidene compound even when stored at -20°C . Contamination by the hydroxy compound does not affect the reactions with amines but for reactions with less reactive nucleophiles it is best to use freshly prepared starting material.

REACTION WITH AMINES

A number of N-mono- and N,N-disubstituted 5-amino-methylidene-2,2-dimethyl-1,3-dioxane-4,6-diones were prepared in the manner described in Section C, Method C, from the methoxymethylidene derivative and the appropriate primary or secondary amine. During the course of the other work in this laboratory the method has been used for a wide variety of amines and appears to be very general.

REACTION WITH AROMATIC AND HETEROAROMATIC COMPOUNDS

The title compound (5 mmol) was dissolved in acetonitrile and the nucleophile (5.5 mmol) was added. The reaction mixture was either stirred at room temperature [in which case a minimum amount of solvent (8 ml) was used] or heated to reflux (16 ml solvent). The precise reaction conditions are given with individual examples. The products precipitated and were filtered, or were obtained by evaporation of solvent. Evaporation of solvent in some cases led to oils which could be crystallised by trituration with toluene. The reaction with 3-hydroxy-1-phenylpyrrole is described in Section E. The following 2,2-dimethyl-1,3-dioxane-4,6-diones were prepared: 5-(p-N,N-dimethylamino)benzylidene (from N,N-dimethyl aniline at reflux for 2 h) (74%), m.p. 172-174°C (from methanol) (lit.^{156a}, 175°C): 5-(pyrrol-2-methylidene) (from pyrrole, overnight at room temperature

(73%) m.p. 179-181°C (from ethanol) (lit.^{156a}, 182°C):
5-(indolyl-3-methylidene) (from indole, at reflux for
40 min. (68%), m.p. 245-246°C (from ethanol) (lit.^{156a},
246°C).

Reaction with a number of other substrates was also
attempted but the following yielded only starting material
in quantitative recovery: anisole (at reflux, overnight),
dimethoxybenzene (at reflux, 78 h.), furan (at reflux,
overnight), thiophene (room temperature, overnight) and
N-methylpyrrole (at reflux, 5 h).

REACTION WITH ENAMINONES

Reactions were carried out as described above.
The reaction with 2,2-dimethyl-1-isopropyl-1,2-dihydro-
3H-pyrrol-3-one is described in Section E. The following
2,2-dimethyl-1,3-dioxane-4,6-diones were prepared:
5-[2-(1-N,N-dimethylamino-5,5-dimethyl-3-oxo-cyclo-
hex-1-ene)methylidene] (from 5,5-dimethyl-3-N,N-dimethyl-
amino-2-cyclohexen-1-one, at reflux for 3 h) (52%),
m.p. 218-220°C (from methanol) (Found: C, 63.6; H, 7.3;
N, 4.45. C₁₇H₂₃NO₅ requires C, 63.55; H, 7.15; N, 4.35%);
 δ_{H} (80 MHz) 8.84 (1H, s), 3.08 (6H, s), 2.72 (2H, s),
2.30 (2H, s), 1.70 (6H, s), and 1.09 (6H, s); δ_{C} (50 MHz)
(quaternary signal missing) 194.01(q), 178.31(q),
164.53 (q), 161.08 (q), 150.36, 109.61 (q), 102.57 (q),

95.74 (q), 50.54, 45.55, 43.32, 29.59, and 26.88; m/z , 321 (M^+ , 100%), 264(56), 248(27), 236(27), and 219(90): 5-[2-(3-N,N-dimethylaminopropenal)methylidene] (from 3-N,N-dimethylaminopropenal, room temperature for 6 h) (6%), m.p. 203°C (from toluene) (Found: C, 56.75; H, 6.0; N, 5.65. $C_{12}H_{15}NO_5$ requires C, 56.9; H, 5.95; N, 5.55%); δ_H (200 MHz) 9.20 (1H, s), 8.60 (1H, bs), 8.24 (1H, s), 3.59 (3H, s), 3.22 (3H, s), and 1.69 (6H, s); δ_C (50 MHz), 187.14, 168.03, 164.35 (q), 163.40 (q), 156.73, 109.59 (q), 102.99 (q), 94.60 (q), 48.22, 43.70, and 26.82; m/z 253 (M^+ , <5%), 225(42), 195(100), 167(53), 152(19), 151(28), and 139(90): 5- { N[-2-(4-oxo-pent-2-ene)]aminomethylidene } (from 2-aminopent-2-en-4-one, room temperature, overnight) (60%) m.p. 185-187°C (from methanol) (Found: C, 56.9; H, 5.95; N, 5.6. $C_{12}H_{15}NO_5$ requires C, 56.9; H, 5.95; N, 5.55%); δ_H (80 MHz) 13.7-14.0 (1H, bs), 8.32 (1H, d, ^3J 14.0 Hz), 5.71 (1H, bs), 2.23 (3H, s), 2.19 (3H, d, ^4J 0.9 Hz), and 1.25 (6H, s); δ_C (50 MHz) 198.45 (q), 163.13 (q), 162.37 (q), 150.43, 148.08 (q), 109.33, 104.57 (q), 90.55 (q), 30.37, 26.90, and 17.63; m/z 253 (M^+ , 40%), 195(100), 167(20), 149(85), 136(40), and 135(30): 5- {N-[1-(5,5-dimethyl-3-oxocyclohex-1-ene)]-aminomethylidene } (from 1-amino-5,5-dimethyl-cyclohex-1-en-3-one, room temperature, overnight) (45%) m.p. 202-203°C (from ethanol), δ_H (200 MHz) 10.91 (1H, bd, ^3J 13.8 Hz),

8.34 (1H, d, ^3J 13.8 Hz), 5.85 (1H, s), 2.43 (2H, s), 2.34 (2H, s), 1.67 (6H, s), and 1.08 (6H, s); δ_C (50 MHz) (1 quaternary signal not observed), 164.56 (q), 162.23 (q), 152.19 (q), 150.40, 111.95, 105.36 (q), 90.54 (q), 50.38 (q), 38.82, 32.73, 28.12, and 26.96; m/z 293 (M^+ , 66%), 236(29), 235(100), 217(54), 191(71), 189(73), and 188(24).

Attempted reaction with 1-(N-phenylamino)-5,5-dimethyl-cyclohex-1-en-3-one (at reflux for 6 h) resulted only in recovered starting material.

REACTION WITH OTHER NUCLEOPHILES

Reaction was carried out as described in (3) above. Reaction with the pyrrolidino enamine of cyclohexanone (any excess pyrrolidine was removed by evaporation using a rotary pump) may have given 5-[1-(2-pyrrolidino)-cyclohex-1-ene]methylidene-2,2-dimethyl-1,3-dioxane-4,6-dione (37%) (Found: C, 65.6; H, 7.5; N, 4.85. $C_{17}H_{23}NO_4$ requires C, 66.9; H, 7.55; N, 4.85%), m/z 305 (M^+ , 36%) and 203(100). The ^1H and ^{13}C n.m.r. spectra of this compound are broad and temperature dependant. The compound decomposes to a sticky material on storage at room temperature and the properties (reaction with base and pyrolysis) are not as would be predicted from those of analogous compounds.

Attempted reaction with dimedone (room temperature, overnight), tropolone (at reflux, overnight) and acetamide (at reflux, overnight) resulted only in recovered starting material. Reaction with basic substrates resulted in formation of 5-hydroxymethylidene-2,2-dimethyl-1,3-dioxane-4,6-dione. Thus, attempts to react phenoxide anion, a diazepine and imidazole resulted in the formation of the hydroxy compound, m.p. 93-94°C (from methanol) (lit.¹¹⁰, 95-96°C), or its salt.

REACTIONS OF PRODUCTS

The pyrolysis of the 3-hydroxy-1-phenylpyrrole derivative and the reaction of the 2,2-dimethyl-1-isopropyl-3H-pyrrol-3-one with base are reported in Section E.

The following pyrolyses of other derivatives reported in this section were carried out. The derivative pyrolysed is reported and the following information quoted: pyrolysis parameters, purification method, product(s) (yield). The following 2,2-dimethyl-1,3-dioxane-4,6-diones were pyrolysed 5-[N-[1-(5,5-dimethyl-3-oxo-cyclohex-1-en)amine methylidene]; 600°C, 195°C, 3 h., bulb-to-bulb distillation, 7,7-dimethyl-7,8-dihydro-1H-,6H-quinolin-4,5-dione (83%), m.p. 191-192°C (from ethanol) (Found: C, 68.0; H, 6.9; N, 7.25. C₁₁H₁₃NO.0.2 H₂O requires C, 67.8; H, 6.9; N, 7.2%); analyses reproducibly as a partial hydrate; δ_H (80 MHz) 8.36 (1H, d, ³J 5.9 Hz), 6.73 (1H, d, ³J 5.9 Hz), 2.93 (2H, s),

2.55 (2H, s), and 1.10 (6H, s); δ_C (20 MHz) 186.52 (q), 168.00 (q), 164.32 (q), 154.76, 113.12 (q), 111.41, 51.56, 46.18, 32.79 (q), and 28.00; m/z 191 (M^+ , 41%), 176(26), 163(12), 135(100), and 125(35): 5-[N-2-(4-oxo-pent-2-ene)]aminomethylidene, 600°C, 190°C, 2.5 h., pyrolysate was removed in two fractions (the first, consisting of volatile material from the liquid nitrogen level in the trap and the second from the trap entrance). The first fraction was purified by bulb to bulb distillation to yield 4-acetyloxy-2-methylpyridine (20%), b.p. 84°C (0.2 Torr) (Found; M^+ , 151.062. $C_8H_9NO_2$ requires M^+ , 151.063); δ_H (200 MHz), 8.42 (1H, d, ^3J 5.4 Hz), 6.91 (1H, s with unresolved fine coupling), 6.86 (1H, dd, ^3J 5.6 Hz and ^4J 1.8 Hz), 2.51 (3H, s), and 2.25 (3H, s); δ_C (50 MHz), 167.67 (q), 160.27 (q), 157.64 (q), 150.16, 115.88, 113.79, 23.94, and 20.73; m/z 151 (M^+ , 15%), 109(100), and 58(90).

The second fraction consisted of two crystalline compounds after distillation, one of which was very insoluble and was obtained in pure form by recrystallisation from ethanol. This was 2-methyl-1H-pyridin-4-one (25%), m.p. 179-180°C (from ethanol) (lit.²¹⁴, b.p. 350-360°C); δ_H (200 MHz), 7.52 (1H, d, ^3J 7.1 Hz), 6.29 (1H, dd, ^3J 7.1 Hz and ^4J 2.4 Hz), 6.22 (1H, bs), and 2.31 (3H, s); δ_C (50 MHz) ($[^2H_6]$ dimethylsulphoxide) 176.38 (q), 148.95 (q), 138.85, 115.14, 114.20, and 19.22;

m/z 109 (M^+ , 8%), 108(100), 79(10), and 70(16). The second compound was obtained by solution of the mixture in water (10 ml) and extraction with methylene chloride (3 x 15 ml) to give 3-acetyl-2-methyl-1H-pyridin-4-one (10%), m.p. 164-165°C; δ_H (200 MHz), 7.88 (1H, d, ^3J 9.6 Hz), 6.44 (1H, d, ^3J 9.6 Hz), 2.70 (3H, s), and 2.47 (3H, s); δ_C (50 MHz), 195.39 (q), 164.66 (q), 152.62 (q), 142.15, 116.42 (q), 115.79, 28.60, and 20.04; m/z 151 (M^+ , 60), 136(100), 109(13), and 108(13).

A small scale pyrolysis (600°C, 180°C, 20 min.) was carried out and the crude products were examined by ^1H n.m.r. spectroscopy. The ratio of 4-acetyloxy-2-methylpyridine to 3-acetyl-2-methyl-1H-pyridin-4-one to 2-methyl-1H-pyridin-4-one was 5:1:5.

5-[2-(1-N,N-dimethylamino-5,5-dimethyl-3-oxo-cyclohex-1-ene)]; 600°C, 220°C, 2 h, 10%, column chromatography on alumina using ethyl acetate:hexane (75:25) as eluant, 8,8-dimethyl-2,3,6,7,8,9-hexahydro-1H-benzazepin-3,6-dione (45%), m.p. 119-120°C (from toluene) (Found: C, 71.25; H, 7.9; N, 6.6. $C_{13}H_{17}NO_2$ requires C, 71.25; H, 7.75; N, 6.4%); δ_H (200 MHz) 7.75 (1H, d, ^3J 11.5 Hz), 6.13 (1H, d, ^3J 11.5 Hz), 3.59 (2H, s), 3.22 (3H, s), 2.56 (2H, s), 2.25 (2H, s), and 1.03 (6H, s); δ_C (50 MHz) 194.48 (q), 182.40 (q), 164.66 (q), 140.45, 122.12,

112.00 (q), 64.69, 49.82, 42.13, 40.49, 30.70 (q), and 28.34; m/z 219 (M^+ , 50%), 191(21), 190(100), 188(12), and 186(12).

A small scale pyrolysis of 2,2-dimethyl-5-[2-(3-N,N-dimethylaminopropenal)methylidene]-1,3-dioxane-4,6-dione (500°C, 200°C, 30 min) was carried out. The ^1H n.m.r. spectrum of the pyrolysate was consistent with the formation of 6-formyl-1-methyl-1,2-dihydro-3H-azepin-3-one; δ_H (200 MHz) 9.28 (1H, s), 7.52 (1H, s), 7.43 (1H, d, ^3J 13.0 Hz, additional fine coupling also observed), 6.27 (1H, d, ^3J 11.6 Hz), 3.85 (2H, s), and 3.43 (3H, s).

G. INVESTIGATION OF THE MECHANISM OF PYROLYSIS OF VINYLOGOUS 2,2-DIMETHYL-1,3-DIOXANE-4,6-DIONES

PREPARATION OF ENAMINALS

3-(N,N-Dimethylamino)prop-2-enal was obtained commercially[†] or was prepared by a literature method.²¹⁵ It was found that extraction of the product from the aqueous alkaline medium of the final hydrolysis step was not complete after six extractions and the use of a continuous extractor may increase the yield of this preparation.

[†] It is best to distill this before use.

Other N,N-disubstituted-prop-2-enals were prepared as follows:^{157a} the appropriate secondary amine (30 mmol) was added to a solution of propargyl alcohol (2.9 ml, 25 mmol) in benzene (40 ml). The reaction mixture was cooled on an ice bath and manganese dioxide (12.5 g, 140 mmol) (6.25 g, 70 mmol was later found to be sufficient) was added in portions, over a period of 30 min., to the stirred solution. The suspension was then allowed to warm to room temperature and was stirred overnight. The remaining solid was removed by filtration and the solvent was removed from the filtrate in vacuo. The residue was purified by bulb-to-bulb distillation. In cases where the starting amine was involatile, care was required during the distillation to give reasonable separation. The amount of amine which remained as contaminant could be calculated from the ¹H n.m.r. spectrum and this material was used without further purification. The following prop-2-enals were prepared: 3-(N,N-diisopropyl-) (55%) m.p. 75-76°C (lit.²¹⁶, 75-78°C); 3-(N-methyl-N-phenyl-) (49%), b.p. 130°C (0.3 Torr) (lit.²¹⁷, 144°C (0.8 Torr)): 3-(N-benzyl-N-methyl-) (49%), b.p. 167°C (0.3 Torr) (Found: C, 74.3; H, 7.45; N, 7.8. C₁₀H₁₁NO.0.15 H₂O requires C, 74.3; H, 7.5; N, 7.9%); δ_H (200 MHz) 9.12 (1H, d, ³J 8.1 Hz), 7.05-7.45 (6H, m), 5.23 (1H, m), 4.40 (2H, bs), and 2.74 (3H, bs); δ_C (50 MHz) 188.95, 159.13, 135.28 (q), 128.78, 128.00, 127.17, 101.75, 61.27, and 35.59

(methylene and methyl signals very broad due to restricted rotation); m/z 175 (M^+ , 17%), 158(10), 149(27), 134(12), 92(12), and 91(100): 3-(N-benzyl-N-phenyl-) (47%) m.p. 130-131°C (from cyclohexane), (Found: C, 80.7; H, 6.1; N, 5.9. $C_{16}H_{15}NO$ requires C, 81.0; H, 6.35; N, 5.9%); δ_H (200 MHz), 9.23 (1H, d, ^3J 8.0 Hz), 7.61 (1H, d, ^3J 13.2 Hz), 7.1-7.5 (10H, m), 5.39 (1H, dd, ^3J 8.0 and 13.2 Hz), and 4.88 (2H, s); δ_C (50 MHz) 190.04, 155.60, 145.31 (q), 135.15 (q), 129.62, 128.76, 127.60, 126.43, 125.68, 121.28, 106.37, and 54.92; m/z 238 (M^++1 , 12%) 237(72), 220(23), 208(11), 91(100), and 77(12).

5-(N,N-dimethylamino-)pent-2,4-dienal was prepared by the method of Malhorta and Whiting to give an orange solid (56%), m.p. 59-60°C (lit.^{157b}, 59°C).

PREPARATION OF 5-(AMINOPROPENYLIDENE)-2,2-DIMETHYL-1,3-DIOXANE-4,6-DIONES

2,2-Dimethyl-1,3-dioxane-4,6-dione (2.2 g, 15 mmol) was dissolved in pyridine (10 ml)⁹⁶ and a solution of the appropriate aldehyde (15 mmol) in pyridine (5 ml) was added. The reaction mixture rapidly became a deep red colour and was stirred overnight at room temperature. This produced the condensation product as a precipitate which was filtered and recrystallised. In order to obtain a reasonable yield of the dialkylamino examples, the filtrate was concentrated in vacuo and the residue was

trituated with ethanol to yield a further quantity of product. The condensation could not be accomplished using the method generally applied to aldehydes which uses benzene as solvent with catalytic amounts of piperidine and acetic acid.⁹⁶

The following 5-[(3-N,N-disubstituted-amino)-propenylidene]-2,2-dimethyl-1,3-dioxane-4,6-diones were prepared: N,N-dimethyl- (57%) m.p. 173-175°C (from ethanol) (Found: C, 58.8; H, 6.75; N, 6.05. $C_{11}H_{15}NO_4$ requires C, 58.65; H, 6.65; N, 6.2%); δ_H (200 MHz) 7.94 (1H, d, ^3J 13.2 Hz), 7.29 (1H, d, ^3J 12.1 Hz), 6.88 (1H, dd, ^3J 12.1 and 13.2 Hz), 3.11 (3H, s), 3.26 (3H, s), and 1.67 (6H, s); δ_C (50 MHz) 165.20 (q), 163.19 (q), 162.97, 158.36, 102.94 (q), 101.95, 94.38 (q), 45.11, 38.12, and 26.86; m/z 225 (M^+ , 83%), 168 (25), 139 (12), 123 (13), 108 (25), and 94 (100); N,N-diisopropyl- (66%) m.p. 257-258°C (from ethanol) (Found: C, 63.6; H, 8.3; N, 4.95. $C_{15}H_{23}NO_4$ requires C, 64.0; H, 8.2; N, 4.9%); δ_H (200 MHz), 7.93 (1H, d, ^3J 13.0 Hz), 7.35 (1H, d, ^3J 12.2 Hz), 7.03 (1H, apparent t, ^3J and ^3J 12.6 Hz), 4.26 (1H, m, ^3J 6.7 Hz), 3.72 (1H, m, ^3J 6.7 Hz), 1.63 (6H, s), 1.265 (6H, d, ^3J 6.7 Hz), and 1.260 (6H, d, ^3J 6.7 Hz); δ_C (20 MHz) 165.51 (q), 163.36 (q), 158.88, 158.51, 102.92 (q), 102.09, 93.38 (q), 51.02, 48.91, 26.85, 23.41, and 19.65; m/z 281 (M^+ , 42%), 224 (16), 136 (79), 122 (21), 98 (53), 96 (100), and 94 (68): N-methyl-N-phenyl (93%), m.p. 218-219°C (from ethanol) (Found:

C, 67.0; H, 5.95; N, 5.15. $C_{16}H_{17}NO_4$ requires C, 66.9; H, 5.9; N, 4.9%); δ_H (200 MHz) 8.07 (1H, d, ^3J 12.9 Hz), 7.66 (1H, d, ^3J 12.3 Hz), 7.0-7.5 (6H, m) (central olefinic resonance superimposed on aromatics), 3.52 (3H, s), and 1.67 (6H, s); δ_C (20 MHz) 164.74 (q), 162.78 (q), 159.11, 158.64, 145.43 (q), 129.85, 126.89, 120.89, 104.23, 103.34 (q), 98.19 (q), 38.12, and 27.06; m/z 287 (M^+ , 73%), 230(27), 184(80), 159(40), 158(67), 157(40), 156(100), 144(27), 132(60), and 131(60): N-benzyl-N-methyl (56%) m.p. 172-173°C (from ethanol) (Found: C, 67.5; H, 6.4; N, 4.7. $C_{17}H_{19}NO_4$ requires C, 67.75; H, 6.3; N, 4.65%); δ_H (200 MHz) (minor rotamer quoted in brackets, where observable) 7.53 (1H, d, ^3J 13.1 Hz), 7.01 (1H, d, ^3J 12.2 Hz), 6.7-7.0 (5H, m), 6.49 (1H, dd, ^3J 12.2 and 13.1 Hz, 4.08 (4.14) (2H, s), 2.58 (2.72) (3H, s), and 1.23 (1.69) (6H, s); δ_C (50 MHz) 165.14 (q), 163.76 (q), 163.02, 158.42, 133.43 (q), 128.71, 128.37, 127.36, 102.68 (q), 102.01, 93.78 (q), 62.10, 57.25, and 26.36; m/z 301 (M^+ , 45%), 254(24), 170(17), and 91(100): N-benzyl-N-phenyl (80%), m.p. 201-202°C (from acetonitrile) (Found: C, 72.3; H, 5.75; N, 4.0. $C_{22}H_{21}NO_4$ requires C, 72.7; H, 5.8; N, 3.85%); δ_H (80 MHz) 8.09 (1H, d, ^3J 12.9 Hz), 7.76 (1H, d, ^3J 12.7 Hz), 7.15-7.45 (11H, m) (olefinic resonance superimposed on aromatics), 5.10 (2H, s), and 1.70 (6H, s); δ_C (50 MHz) 164.62 (q), 162.48 (q), 159.24, 158.24, 145.50 (q), 134.20 (q), 129.93 (two

signals superimposed), 128.97, 128.14, 127.04, 121.58, 104.73, 103.28 (q), 99.25 (q), 54.57 and 27.11; m/z 363 (M^+ , 23%), 260(6), 183(38), 91(100) and 77(21).

PYROLYSES OF 5-AMINOPROPENYLIDENE-2,2-DIMETHYL-1,3-DIOXANE-4,6-DIONES

Large scale pyrolyses were carried out and the desired product was separated from the small amount of cyclopentadienone dimer formed when necessary (see Discussion Section). The separation was carried out by chromatography on an alumina column with ethyl acetate: hexane (75:25) as eluant. The following 1,2-dihydro-3H-azepin-3-ones were prepared. The [5-(3-aminopropenylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione substrate and pyrolysis parameters are reported. 1-methyl [N,N-dimethyl, 500°C, 200°C (metal inlet), 2.5 h], (64%), b.p. 92°C (0.3 Torr) (Found: M^+ , 123.068. C_7H_9NO requires M^+ , 123.068); δ_H (200 MHz), 6.84 (1H, dd, ^3J 9.1 and 11.0 Hz), 6.72 (1H, d, ^3J 7.2 Hz), 6.17 (1H, d, ^3J 11.0 Hz), 5.17 (1H, dd, ^3J 7.2 and 9.0 Hz), 3.57 (2H, s), and 3.20 (3H, s); δ_C (50 MHz) 180.21 (q), 147.19, 142.01, 123.33, 99.41, 62.65, and 44.04; m/z 123 (M^+ , 61%), 95(12), and 94(100); 1-phenyl [N-methyl-N-phenyl, 500°C, 210°C, 5 h) (75%), m.p. 79-81°C (from methanol) (Found: C, 77.9; H, 5.95; N, 7.25. $C_{12}H_{11}NO$ requires C, 77.85; H, 5.95; N, 7.55%); δ_H (200 MHz), 7.05-7.35 (5H, m), 6.99 (1H, d, ^3J 8.0 Hz), 6.89 (1H, dd, ^3J 11.2 and 8.6 Hz), 6.34 (1H, d, ^3J 11.2 Hz),

5.49 (1H, apparent t, ^3J 8.4 Hz), and 4.14 (2H, s); δ_C (50 MHz), 182.87 (q), 144.11 (q), 141.54, 140.16, 129.18, 126.71, 124.73, 119.77, 103.86, and 59.38; m/z 185 (M^+ , 67%), 156(100), 105(53), and 77(40): 1,2-diphenyl [N-benzyl-N-phenyl, 500°C, 225°C (metal inlet), 2 h., 10%) (32%), b.p. 205°C (0.5 Torr). (Found: M^+ , 261.1153. $C_{18}H_{15}NO$ requires M^+ , 261.1154); δ_H (200 MHz), 7.1-7.5 (10H, m), 6.90 (1H, d, ^3J 8.3 Hz), 6.64 (1H, dd, ^3J 8.5 and 11.3 Hz), 6.44 (1H, d, ^3J 11.3 Hz), 5.95 (1H, s), and 5.32 (1H, apparent t, ^3J 8.4 Hz), (further fine coupling also observed - see Discussion Section); δ_C (50 MHz) 184.74 (q), 147.23 (q), 139.88, 139.13, 134.41 (q), 129.42, 127.92, 127.64, 125.64, 125.50, 125.39, 121.49, 104.64, and 73.92; m/z 261 (M^+ , 9%), 232(23), 183(35), 182(29), 180(34), 156(52), 115(25), 104(53), 91(85), and 77(100). 2,2-dimethyl-1-isopropyl (N,N-diisopropyl, 500°C, 200°C, 4 h) (29%) b.p. 108°C (0.2 Torr), m.p. 141.5-142°C (from hexane) (Found: C, 73.2; H, 9.6; N, 7.75. $C_{11}H_{17}NO$ requires C, 73.7; H, 9.5; N, 7.8%), δ_H (200 MHz) 6.63 (1H, d, ^3J 8.2 Hz), 6.61 (1H, dd, ^3J 8.5 and 11.4 Hz), 6.08 (1H, d, ^3J 11.4 Hz), 5.31 (1H, apparent triplet, ^3J 8.3 Hz), 3.83 (1H, m, ^3J 6.7 Hz), 1.26 (6H, s), and 1.13 (6H, d, ^3J 6.7 Hz) (further fine coupling observed - see Discussion Section); δ_C (50 MHz), 184.11 (q), 138.11, 137.50, 121.67, 102.68, 63.76 (q), 49.24, 23.62, and 21.62; m/z 179 (M^+ , 56%), 136(36), 98(35), 96(100), 94(64), and 78(27).

Pyrolysis of a derivative with non-equivalent potential sites for hydrogen transfer produced the two possible azepinones which were not separated: 1-methyl-2-phenyl- and 1-benzyl (N-benzyl-N-methyl, 500°C, 180°C, 4 h) (51% combined yield, 4:1 mixture, respectively) b.p. 154-172°C (0.3 Torr), δ_{H} 200 MHz (assigned by comparison with other examples) 7.1-7.4 (5H, m, both isomers), 6.8-7.0 (2H, m, minor isomer), 6.74 (1H, d, ^3J 7.8 Hz, major isomer), 6.57 (1H, dd, ^3J 9.0 and 11.4 Hz, major isomer), 6.38 (1H, d, minor isomer), 6.25 (1H, d, 11.2 Hz, major isomer, 5.25 (1H, apparent t, minor isomer), 5.03 (2H, m, superimposed dd and s, major isomer), 4.47 (2H, s, minor isomer) 3.58 (2H, s, minor isomer), and 3.42 (3H, s, major isomer); δ_{C} (50 MHz) (D.E.P.T. assigned by comparison with other examples) major isomer - 144.76, 140.72, 127.78, 127.53, 125.58, 121.75, 100.16, 75.26, and 46.84; minor isomer, methylene signals - 60.71 and 46.84.

A second large scale pyrolysis of the dimethylamino-derivative was carried out at 600°C in order to isolate the cyclopentadienenone dimer which was produced as a by-product (see Discussion Section). It was obtained using the chromatographic conditions described above: [N,N-dimethyl, 200°C (metal inlet), 2 h] (24%), m.p. and mixed m.p. 99-100°C (from hexane) (lit.¹⁵⁸, 101°C), δ_{H} 7.34 (1H, dd, ^3J 5.7 and 2.7 Hz), 6.1-6.3 (3H, m), 3.43-3.5 (1H, m), 3.3-3.38 (1H, m), 3.12-3.17 (1H, m)

and 2.85 (1H, t, ^3J 5.5 Hz); δ_C (50 MHz) 206.06 (q), 199.14 (q), 160.19, 141.07, 129.54, 128.91, 49.92, 49.03, 43.13, and 41.38.

A number of small scale pyrolyses were also carried out and the 5-(3-aminopropenylidene)-2,2-dimethyl-1,3-dioxane-4,6-diones pyrolysed are now reported with the following information: pyrolysis parameters, identifiable products (ratio). (The series of pyrolyses showing the temperature dependance of the reaction were carried out on similar amounts of material which allowed a qualitative estimate of absolute yields - see Discussion Section). N,N-dimethyl, 500°C, 200°C, 1.5 h., 1-methyl-1,2-dihydro-3H-azepin-3-one, cyclopentadienone dimer, (3:1): N,N-dimethyl, 600°C, 200°C, 1 h., 1-methyl-1,2-dihydro-3H-azepin-3-one, cyclopentadienone dimer, (2:1): N,N-dimethyl, 700°C, 200°C, 1 h., 1-methyl-1,2-dihydro-3H-azepin-3-one, cyclopentadienone dimer, (<1:3): N-benzyl-N-phenyl, 500°C, 225°C, 45 min., 1,2-diphenyl-1,2-dihydro-3H-azepin-3-one, cyclopentadienone dimer, benzylidene aniline (shown to be present by g.c. comparison with and 'spiking' of n.m.r. solution with an authentic sample (6:1:1): N-benzyl-N-phenyl, 600°C, 225°C, 30 min., 1,2-diphenyl-1,2-dihydro-3H-azepin-3-one, cyclopentadienone dimer, benzylidene aniline (1:3:3): N-benzyl-N-methyl, 500°C, 220°C, 45 min., 1-methyl-2-phenyl-1,2-dihydro-3H-azepin-3-one, 1-benzyl-1,2-dihydro-3H-azepin-3-one (2:1).

PREPARATION OF AUTHENTIC SAMPLES

The cyclopentadienone dimer was prepared by a literature method¹⁵⁸ (15%) m.p. 100-101°C (lit.¹⁵⁸, 101°C). This gave a 50:50 mixture of exo and endo adducts by g.c. analysis while the pyrolysis conditions lead to considerably more of one adduct.

Benzylidene aniline was prepared by reaction of aniline and benzaldehyde in ethanol.

PREPARATION AND PYROLYSIS OF 5-(DIMETHYLAMINO-PENTADIENYLIDINE)-2,2-DIMETHYL-1,3-DIOXANE-4,6-DIONE

The title compound was prepared as described earlier in Section F from N,N-dimethylaminopentadienal and 2,2-dimethyl-1,3-dioxane-4,6-dione: (72%), m.p. 215°C (from methanol) (Found: C, 62.5; H, 6.85; N, 5.85. $C_{13}H_{17}NO_4$ requires C, 62.15; H, 6.75; N, 5.6%); δ_H 7.81 (1H, d ^3J 12.7 Hz), 7.1-7.4 (3H, m), 5.58 (1H, t, ^3J 11.8 Hz), 3.18 (3H, b), 2.96 (3H, b) and 1.62 (6H, s); δ_C (20 MHz) 165.16 (q), 162.77 (q), 162.51, 158.08, 157.25, 103.18, 102.81, 95.74 (q), 92.93 (q), 45.2, 37.6 (methyl carbon atom signals are broad due to restricted rotation), and 26.84; m/z 251 (M^+ , 68%), 164(12), 121(28), 120(24), and 105(100).

A large scale pyrolysis yielded N,N-dimethylbenzamide [600°C, 210°C, 1h., 25%] (72%) b.p. 125°C (12 Torr) [lit.²¹⁸, 132-133°C (15 Torr)]. An authentic sample was obtained commercially which gave identical spectra and g.c. retention time. δ_H (200 MHz) 7.30 (5H, s) and 2.94 (6H, s); δ_C (50 MHz) 171.01 (q), 135.96 (q), 128.91, 127.76, 126.47, 38.75 and 34.70 (methyl carbon atom signal broadened due to restricted rotation). Analysis by n.m.r. spectroscopy of the pyrolysate of a small scale pyrolysis (350°C, 195°C, 25 min.) also indicated the presence of the benzamide along with starting material.

H. THE REACTIVITY OF 1,2-DIHYDRO-3H-AZEPIN-3-ONES

PROTONATION

N.m.r. spectra of protonated species were recorded in trifluoroacetic acid in the same manner as described for the 1,2-dihydro-3H-pyrrol-3-ones.

REACTIONS WITH ELECTROPHILES

Reaction with Triethyloxonium Tetrafluoroborate and Reaction of the Salt with Base

The 1-methyl-1,2-dihydro-3H-azepin-3-one (60 mg, 0.50 mmol) was dissolved in methylene chloride and a solution of triethyloxonium tetrafluoroborate²⁰⁶ in methylene

chloride (0.67M, 0.53 mmol) was added. Solid potassium carbonate (75 mg, 0.55 mmol) was also added and the solution was stirred at room temperature overnight. The reaction mixture was filtered and the solvent was evaporated from the filtrate in vacuo to give the alkylated salt as an orange oil which could not be obtained in crystalline form. In the absence of potassium carbonate a small amount of the protonated salt was also observed. Thus, 3-ethoxy-1-methyl-1,2-dihydro-azepinium tetrafluoroborate was prepared: (100 mg, 79%); δ_H (200 MHz) ($[^2H_6]$ acetone) 8.41 (1H, d, ^3J 4.7 Hz), 7.70 (1H, dd, ^3J 11.3 and 7.7 Hz), 6.69 (1H, dd, ^3J 11.3 and 4.8 Hz), 6.38 (1H, d, ^3J 7.7 Hz), 4.19 (2H, q, ^3J 7.0 Hz), 4.17 (2H, s), 3.86 (3H, s), and 1.37 (3H, t, ^3J 7.0 Hz); δ_C (50 MHz) (D.E.P.T.) 160.31, 148.93, 115.91, 104.49, 66.81, 56.40, 46.41, and 12.64; no reasonable mass spectrum could be obtained.

The tetrafluoroborate salt (30 mg, 0.14 mmol) was dissolved in $[^2H_4]$ methanol (0.3 ml) and an ^1H n.m.r. spectrum was recorded. A solution of sodium (12 mg, 0.52 mg) in $[^2H_4]$ methanol (0.2 ml) was added while the mixture was cooled on ice. The ^1H n.m.r. of the reaction mixture was recorded and showed instantaneous changes (see Discussion Section).

Reaction with N-Halogenosuccinimides

A number of reactions were carried out with N-halogenosuccinimides (NXS). All reactions were carried out by addition of a solution of the appropriate NXS in methanol (8 ml) to a solution of the azepinone (1 mmol) in methanol (10 ml) cooled on an ice bath. The reactions were stirred at 0°C for 10 minutes in all cases and further reaction conditions are listed with individual examples. The reaction mixture was then poured into methylene chloride (20 ml) and washed with sodium hydrogen carbonate solution (20%, 3 x 20 ml). The organic layer was then dried (MgSO_4) and the solvent was removed in vacuo at room temperature. Chlorinated products were then purified by dry-flash column chromatography using methylene chloride as eluant. The dibromo compound was similarly purified or was obtained as a crystalline solid when two equivalents of NBS were used. All products were very sensitive to heat, and solvent was therefore removed at room temperature and the products could not be purified by distillation or conventional recrystallisation. Solids were dissolved in the minimum possible quantity of methanol and kept at -20°C overnight; crystalline, analytically pure solids were thus obtained. The crystals obtained were filtered rapidly under vacuum. The dibromo compound was particularly sensitive and decomposed to a black insoluble material when left in solution at ~30°C.

The following halogeno-1,2-dihydro-3H-azepin-3-ones were obtained: 4,6-dichloro-1-phenyl (from the 1-phenyl azepinone and 2.1 equivalents NCS, room temperature for 45 min.) (110 mg, 44%), m.p. 105-108°C (decomp.) (from methanol (Found: C, 55.7; H, 3.5; N, 5.45. $C_{12}H_9Cl_2NO \cdot 0.25 H_2O$ requires C, 55.7; H, 3.65; N, 5.4%); δ_H (200 MHz) 7.46 (1H, d, ^4J 0.9 Hz), 7.25 (1H, q, ^4J and ^5J 0.9 Hz), 7.1-7.45 (5H, m), and 4.29 (2H, d, ^5J 0.9 Hz); δ_C (50 MHz) 175.44 (q), 142.60 (q), 139.55, 139.08, 130.08 (q), 129.66, 126.06, 120.13, 109.49 (q), and 58.55; m/z 257, 255, 253 (M^+ , 10, 33 and 50%), 226(17), 224(25), and 105(100): 4-chloro-1-phenyl (from the 1-phenyl azepinone and 1 equivalent NCS, 0°C for 45 min. (90 mg, 41%), m.p. 66-67°C (from methanol) (Found: C, 64.6; H, 4.6; N, 6.25. $C_{12}H_{10}ClNO \cdot 0.25 H_2O$ requires C, 64.3; H, 4.7; N, 6.25%); δ_H (200 MHz) 7.1-7.4 (6H, m) (olefinic proton superimposed on aromatics) 7.10 (1H, d, ^3J 7.5 Hz), 5.52 (1H, dd, ^3J 7.5 Hz and 9.8 Hz), and 4.27 (2H, s); δ_C (50 MHz) 176.06 (q), 143.74 (q), 141.90, 138.88, 129.80 (q), 129.57, 125.71, 120.36, 103.07, and 58.68; m/z 221, 219 (M^+ , 29 and 70%), 192(18), 190(47), 156(35), 105(100), and 77(47): 4-chloro-1-methyl (from 1-methyl azepinone and 1 equivalent NCS, 0°C for 45 min.) (80 mg, 51%) (Found: M^+ , 157.0288. C_7H_8ClNO requires M^+ , 157.0228); δ_H (200 MHz), 7.21 (1H, d, ^3J 10.0 Hz), 6.83 (1H, d, ^3J 6.9 Hz), 5.20 (1H, dd, ^3J 6.9 Hz and 10.0 Hz), 3.63 (2H, s), and 3.20 (3H, s); δ_C (50 MHz)

173.42 (q), 147.37, 140.62, 125.85 (q), 98.15, 61.31, and 43.88; m/z 159, 157 (M^+ , 26 and 79%), 130(30), 128(100), and 94(72): 4,6-dibromo-1-methyl [from 1-methyl azepinone and 2.1 equivalents NBS, 5 min. at 0°C (also from 1-methyl azepinone and 1 equivalent NBS, 5 min. at 0°C)], [168 mg, 60% (23 mg, 8%)], m.p. 140-141°C (decomp.) (from methanol) (Found: C, 30.4; H, 2.7; N, 5.15. $C_7H_7Br_2NO$ requires C, 29.9; H, 2.5; N, 5.0%); δ_H (200 MHz) 7.72 (1H, s), 7.12 (1H, s), 3.71 (2H, s) and 3.19 (3H, s); δ_C (^{13}C n.m.r. spectrum could not be obtained due to the facile decomposition of the compound in solution); m/z 282, 281, 280 (M^+ , 36, 71 and 36%), 253(16), 252(32), 251(16), 202(50), 200(50), 174(18), 172(18), 159(20), 157(20), and 40(100).

From the reaction with one equivalent of NBS and the 1-methyl azepinone, a fraction was collected with the following well defined n.m.r. spectrum:
 δ_H (200 MHz) 7.59 (1H, d, J 4.9 Hz), 7.46 (1H, d, J 10.0 Hz), 6.87 (1H, d, J 6.9 Hz), 6.06 (1H, d, J 10.7 Hz), 5.19 (1H, dd, J 10.0 and 6.9 Hz), 4.67 (1H, dd, J 4.9 and 10.6 Hz), 3.71 (2H, s), 3.22 (3H, s), 2.78 (3H, s), and 2.47 (2H, s). This contained only 11 mg from 60 mg of starting material and it was not clear whether one or two components were present (see Discussion Section).

PERICYCLIC REACTIONS

(a) Preparation of 2-Aza-2-phenyl-bicyclo[3.2.0]-hept-6-en-4-one: 1-Phenyl-1,2-dihydro-3H-azepin-3-one (280 mg, 1.5 mmol) was dissolved in acetone (4 ml) and the solution was irradiated at room temperature, using a 125 Watt lamp and a quartz vessel. After 48 h. only a trace of starting material remained as shown by t.l.c. [on silica with ethyl acetate:methylene chloride (50:50) as eluant], and ^1H n.m.r. spectroscopy. The solvent was removed in vacuo at room temperature and the residue was purified by dry flash column chromatography using methylene chloride:ethyl acetate mixtures as eluant. The initial eluant was 100% methylene chloride and the amount of ethyl acetate was increased by 5% every second fraction. This gave the product as an orange solid. Attempts to distil or recrystallise the solid led only to recovered azepinone. Thus, the title compound was prepared (180 mg, 64%) (Found: $\underline{M}^+$, 185.0843. $\text{C}_{12}\text{H}_{11}\text{NO}$ requires $\underline{M}^+$, 185.0840); δ_{H} (200 MHz) 7.29 (2H, dd, ^3J 7.4 and 8.8 Hz), 6.85 (1H, t, ^3J 7.3 Hz), 6.68 (2H, d, ^3J 8.9 Hz), 6.60 (1H, d, ^3J 2.7 Hz), 6.33 (1H, d, ^3J 2.7 Hz), 4.99 (1H, d, ^3J 3.2 Hz), 4.04 (2H, m), and 3.80 (1H, d, ^3J 3.2 Hz) (further fine coupling is also observed - see Discussion Section); δ_{C} (50 MHz) 207.92 (q), 145.84 (q), 141.06, 137.13, 129.29, 118.08, 112.37, 60.23, 55.14, and 54.55; $\underline{m/z}$ 185 ($\underline{M}^+$, 18%), 159(20),

158(22), 130(27), 105(40) and 104(30).

An investigation of the thermal reversion of the photolytic cyclisation just described was carried out by n.m.r. spectroscopy. A solution of 2-aza-2-phenyl-bicyclo[3.2.0]hept-6-en-4-one in [$^2\text{H}_8$]toluene was kept in a sample tube in the probe of the spectrometer at the required temperature. Anthracene was used as an internal standard and the disappearance of the bicyclic product monitored to allow calculation of rate constants at both 78 and 84.5°C.

(b) Reactions of 1,2-Dihydro-3H-azepin-3-ones with olefinic dienophiles

(a) Maleic Anhydride. The azepinone (1 mmol) was dissolved in benzene and maleic anhydride (100 mg, 1 mmol) was added. The reaction mixture was stirred at room temperature until reaction was complete as shown by t.l.c. [on silica with ethyl acetate:methylene chloride (50:50) as eluant]. The reactions were also carried out on a small scale in [$^2\text{H}_6$]benzene and monitored by ^1H n.m.r. spectroscopy to give an indication of the rate of reaction. The use of other solvents (e.g. chloroform, acetonitrile) seemed to have no effect on the reaction. The solvent was removed in vacuo to give the Diels-Alder adducts as crystalline solids. The N-phenyl compound was purified by recrystallisation, but all attempts to purify the

the N-methyl analogue by recrystallisation resulted in the formation of an insoluble material of undetermined structure. The following 2-aza-4-oxo-bicyclonon-8-ene-endo-6,7-dicarboxylic anhydrides were prepared:

2-phenyl (48 h. at room temperature) (192 mg, 68%), m.p. 157-158°C (from methanol) [Found: C, 66.7; H, 4.6; N, 5.05. $C_{16}H_{13}NO_4 \cdot 0.25 H_2O$ requires C, 66.8; H, 4.7; N, 4.85% (recrystallises reproducibly as a partial hydrate)]; δ_H (360 MHz) ($[^2H_6]$ acetone) 7.31 (2H, apparent t, ^3J 7.5 Hz of d, ^4J 2.0 Hz), 7.02 (2H, d, ^3J 8.0 Hz), 6.88 Hz (1H, t, ^3J 7.3 Hz), 6.63 (2H, m), 5.12 (1H, m), 4.32 (1H, d, ^3J 16.0 Hz), 4.09 (1H, dd, ^3J 8.9 Hz and ^4J 2.4 Hz), 4.02 (1H, d, ^3J 16.0 Hz), 3.83 (1H, dd, ^3J 9.0 Hz and ^4J 2.0 Hz), and 3.72 (1H, m); δ_C (50 MHz) 198.84 (q), 170.92 (q), 170.52 (q), 147.57 (q), 130.56, 129.85, 128.73, 119.30, 115.32, 55.92, 54.14, 49.68, 45.05, and 42.11; m/z 284 (19%), 283 (M^+ , 90%), 260(95), 185(90), 156(82), 105(100), 93(31), and 77(48):

2-methyl (2 h. at room temperature) (180 mg, 81%), m.p. 184-188°C (decomp.) (crude product) (Found: C, 59.3; H, 5.3; N, 6.6. $C_{11}H_{11}NO_4$ requires C, 59.75; H, 5.0; N, 6.35%); δ_H (200 MHz) 6.36 (2H, m), 4.01 (1H, d, ^3J 5.8 Hz of apparent t, ^4J 2.1 Hz), 3.79 (1H, dd, ^3J 9.2 Hz and ^4J 2.3 Hz), 3.60 (1H, d, ^3J 5.8 Hz of apparent t, ^4J 2.2 Hz), 3.49 (1H, dd, ^3J 11.4 Hz and ^4J 2.9 Hz), 3.44 (1H, d, ^2J 15.2 Hz), 3.20 (1H, d, ^2J 15.2 Hz), and 2.46 (3H, s); δ_C (50 MHz) 199.94 (q), 170.89 (q),

170.64 (q), 130.20, 129.62, 63.09, 57.71, 49.22, 44.78, 44.13, and 42.50; m/z 221 (M^+ , <1%), 193(40), and 123(100).

(b) Tetracyanoethylene. The 1-phenyl-1,2-dihydro-3H-azepin-3-one (30 mg, 0.17 mmol) was dissolved in methanol (1 ml) and a solution of the alkene (21 mg, 0.17 mmol) in methanol (1 ml) was added at room temperature. This gave immediate precipitation of a yellow solid which was practically insoluble in normal organic solvents. A small amount of the material was dissolved in [$^2H_6$]-dimethylsulphoxide to give a bright red solution and the ^1H n.m.r. spectrum which was obtained immediately on making up the solution showed only starting material. It is thought that the solid is a charge transfer complex of the diene and dienophile: (76%) m.p. 120-125°C (decomp.) (Found: C, 68.2; H, 3.45; N, 22.2. $C_{18}H_{11}N_5O$ requires C, 69.0; H, 3.5; N, 22.35%), (crude product - all attempts at recrystallisation resulted in bright red solutions from which no solid could be obtained); ν_{max} 1615 cm^{-1} (extended amide).

(c) Other Dienophiles. A number of attempts were made to form adducts with other olefinic dienophiles. These reactions were carried out on a small scale and monitored by ^1H n.m.r. spectroscopy. Heating solutions to the temperature of acetonitrile at reflux (82°C) for

extended periods of time led to apparent decomposition [1-methyl-azepinone and ethyl acrylate or 1,2-bis(phenylsulphonyl)ethene, 1-phenyl-azepinone and 2-(3,3-dimethyl-1,2,4-triazen-1-yl)benzoic acid], or to no apparent change [1-phenylazepinone and 2-chloroacrylonitrile, diethyl fumarate or 1,2-bis(phenylsulphonyl)ethene]. Addition of a Lewis Acid catalyst (borontrifluoride etherate) apparently leads to decomposition of the azepinone.

(c) Reactions of 1-Methyl-1,2-dihydro-3H-azepin-3-one with Acetylenic Dienophiles

The azepinone (30 mg, 0.25 mmol) was dissolved in [$^2\text{H}_3$]acetonitrile and the appropriate acetylene derivative (0.25 mmol) was added. The reaction was monitored by ^1H n.m.r. spectroscopy and found to give substituted benzene derivatives. Thus, reaction with ethyl propiolate (16 h. at reflux) followed by removal of solvent in vacuo, and bulb-to-bulb distillation, gave ethyl benzoate (30 mg, 80%), b.p. 98°C (13 Torr), δ_{C} (50 MHz, D.E.P.T.) 132.62, 129.35, 128.13, 60.77, and 14.15; g.c. retention time and ^{13}C n.m.r. spectrum identical to those of an authentic sample: dimethyl acetylenedicarboxylate (six days, room temperature) gave dimethyl phthalate (35 mg, 73%), b.p. 110°C (0.2 Torr), δ_{C} (55 MHz, D.E.P.T.) 130.92, 128.68 and 52.43; g.c. retention time and ^{13}C n.m.r. spectrum identical to those of an authentic sample.

Preparation of 4,6-[²H₂]-1-Methyl-1,2-dihydro-3H-azepin-3-one

The azepinone (45 mg, 0.36 mmol) was dissolved in [²H₄]methanol (0.4 ml) and [²H]trifluoroacetic acid (30 μl, 0.38 mmol) was added. After 30 min. the ¹H n.m.r. spectrum indicated that exchange at the 4- and 6-positions was practically complete, [²H₂]water (5 ml) was added and the solution was basified with solid potassium carbonate. The basic solution was extracted with methylene chloride (4 x 6 ml), the combined organic layers were dried (MgSO₄) and the solvent was removed in vacuo to give the title compound (12%).

Reaction of 4,6-[²H₂]-1-Methyl-1,2-dihydro-3H-azepin-3-one with Ethyl Propiolate

The small amount of deuteriated azepinone obtained as above was dissolved in [²H]chloroform (0.3 ml) and ethyl propiolate (4.6 μl, 0.05 mmol) was added. The solution was heated at 60°C and was monitored by ¹H n.m.r. spectroscopy. The reaction yielded ethyl-3,5-[²H₂]benzoate; δ_H (200 MHz) 8.04 (s), δ(²H) (30 MHz) 7.46 (s).

Pyrolysis of 2-Aza-4-oxo-2-phenyl-bicyclonon-8-ene-
endo-6,7-dicarboxylic anhydride

A small scale pyrolysis was carried out on the title compound (600°C, 150°C, 15 min.). ^1H n.m.r. spectroscopy and g.c. analysis showed the pyrolysate to consist of 1-phenyl-1,2-dihydro-3H-azepin-3-one and maleic anhydride.

REACTIONS WITH BASE

(a) Reaction of 1,2-Dihydro-3H-azepin-3-ones with
Sodium Methoxide

The azepinone (0.25 mmol) was dissolved in $[\text{}^2\text{H}_4]$ -methanol (0.3 ml) and a solution of sodium methoxide [from sodium (12 mg, 0.5 mmol)] in $[\text{}^2\text{H}_4]$ methanol (0.3 ml) was added. The reaction was monitored by ^1H n.m.r. spectroscopy; the products were found to be N-substituted-2-aminophenols. The reaction mixture of 1-methyl-1,2-dihydro-3H-azepin-3-one was heated to reflux for 24 h. and was then neutralised with potassium carbonate and the product was shown to be 2-(N-methylamino)phenol by g.c.; the retention time of the only major peak was identical to that of an authentic sample.²¹⁹ A D.E.P.T., ^{13}C n.m.r. spectrum of the basic reaction mixture was identical to the spectrum of the authentic sample of the phenol in sodium methoxide solution. δ_{C} (50 MHz) ($[\text{}^2\text{H}_4]$ -methanol/methoxide) 118.13, 115.44, 113.28, 110.21, and 30.62.

The methanol was removed from the reaction mixture of 1-phenyl-1,2-dihydro-3H-azepin-3-one after 16 h. at room temperature and the residue was dissolved in dimethylformamide (4 ml). Potassium carbonate (70 mg, 0.5 mmol) and methyl iodide (95 μ l, 1.5 mmol) were added and the reaction mixture was stirred overnight at room temperature. The potassium carbonate was removed by filtration and the filtrate was added to water (10 ml). The aqueous solution was extracted with ether (3 x 15 ml) and the combined organic extracts were back extracted with water (3 x 20 ml). The organic fraction was dried (MgSO_4) and the solvent was removed in vacuo to give 2-phenylaminoanisole (33 mg, 66%), b.p. 92°C (0.12 Torr), [lit.²²⁰, 120°C (0.2 Torr)]; δ_{H} (80 MHz) 6.85-7.45 (9H, m), 6.14 (1H, b) and 3.89 (3H, s).

(b) Reaction of 1,2-Dihydro-3H-azepin-3-ones with Other Bases

The ^1H n.m.r. spectrum of the 1-methyl azepinone was completely unchanged after treating a solution in [$^2\text{H}_6$]dimethylsulphoxide with sodium hydride.

After reaction with lithium diisopropylamide in tetrahydrofuran at -78°C, the mixture was quenched with water and warmed to room temperature, but the results were inconclusive. A small amount of starting material was recovered but when [$^2\text{H}_2$]water was used as the quenching agent there was no evidence for deuterium incorporation.

REFERENCES

- (1) (a) J.A. Joule and G.F. Smith, 'Heterocyclic Chemistry', Van Nostrand Reinhold, 1978, p. 211.
(b) T.L. Gilchrist, 'Heterocyclic Chemistry', Pitman, London, 1985, p. 139.
- (2) (a) R.A. Jones and G.P. Bean, 'The Chemistry of Pyrroles', Academic Press, 1977, p. 379.
(b) K. Schofield, 'Pyrroles and Pyridines', Butterworths, London, 1967, p. 104.
- (3) N.N. Gerber, CRC Crit.Rev.Microbiol., 1975, 469.
- (4) H.J. Gordon, J.C. Martin and H. McNab, J.Chem.Soc., Chem.Comm., 1983, 957.
- (5) R. Kuhn and G. Osswald, Chem.Ber., 1956, 89, 1423.
- (6) H. Rapoport and C.D. Willson, J.Am.Chem.Soc., 1962, 84, 630.
- (7) E. Campaigne and G.M. Schutske, J. Heterocycl.Chem., 1974, 11, 929.
- (8) J. Patjens, R. Ghaffiri-Tabrizi and P. Margaretha, Helv.Chim.Acta, 1986, 69, 905.
- (9) A.R. Mattocks, J.Chem.Soc., Perkin Trans. 1, 1978, 896.
- (10) T. Momose, T. Tanaka and T. Yokota, Heterocycles, 1977, 6, 1821.
- (11) T. Momose, T. Tanaka, T. Yokota, N. Nagamoto and K. Yamada, (a) Chem. Pharm.Bull., 1978, 26, 2224;
(b) 1979, 27, 1448.

- (12) I.T. Kay and N. Punja, J.Chem.Soc.(C), 1970, 2409.
- (13) R. Fuks and H.G. Viehe, Tetrahedron, 1969, 25, 5721.
- (14) A. Treibs and A. Ohorodnik, Justus Leibigs Ann. Chem., 1958, 611, 139.
- (15) H. Bauer, Justus Leibigs Ann. Chem., 1970, 736, 1.
- (16) S.K. Gupta, Synthesis, 1975, 726.
- (17) E. Benary and B. Silbermann, Chem. Ber., 1913, 46, 1363.
- (18) E. Benary and W. Lau, Chem. Ber., 1923, 56, 591.
- (19) J. Davoll, J. Chem. Soc., 1953, 3802.
- (20) T. Wieland and T. Severin, Z. Lebensm-Unters. Forsch., 1973, 153, 201.
- (21) E. Benary and R. Konrad, Chem. Ber., 1923, 56, 44.
- (22) R. Chong and P.S. Clezy, Aust. J. Chem., 1967, 20, 935.
- (23) T. Eicher and J.L. Weber, Tetrahedron Lett., 1974, 1381.
- (24) T. Eicher, J.L. Weber and G. Chatila, Justus Liebigs Ann. Chem., 1978, 1203.
- (25) M. Takahashi, N. Inaba, H. Kiriara and S. Watanabe, Bull. Chem. Soc. Jpn., 1978, 51, 3312.
- (26) T. Eicher, F. Abdesaken, G. Franke and J.L. Weber, Tetrahedron Lett., 1975, 3915.
- (27) M. Takahashi, T. Funaki, H. Honda, Y. Yokoyama and H. Takimoto, Heterocycles, 1982, 19, 1921.
- (28) H. Yoshida, S. Sogame, Y. Takishata and T. Ogata, Bull.Chem.Soc.Jpn., 1983, 56, 2438.
- (29) H. Yoshida, S. Bando, S. Nakajima, T. Ogata and K. Matsumoto, Bull.Chem.Soc.Jpn., 1984, 57, 2677.

- (30) H. Yoshida, S. Sogame, S. Bando, S. Nakajimo, T. Ogata, K. Matsumoto, Bull.Chem.Soc.Jpn., 1983, 56, 3849.
- (31) B. Chantegrat and S. Gelin, J. Heterocycl.Chem., 1978, 15, 1215.
- (32) J.P. Freeman and M.K. Fettes-Fields, Heterocycles, 1985, 23, 1073.
- (33) G. Bianchi, A. Gamba-Invernizzi and R. Gandolfi, J.Chem.Soc., Perkin Trans. 1, 1974, 1757.
- (34) R.R. Schmidt, W.J.W. Mayer and H.U. Wagner, Justus Liebigs Ann.Chem., 1973, 2010.
- (35) D.A. Lightner and L.K. Low, J.Heterocycl.Chem., 1975, 12, 793.
- (36) J.P. Freeman and M.J. Haddadin, Tetrahedron Lett., 1979, 4813.
- (37) R.A.Y. Jones and N. Sadighi, J.Chem.Soc., Perkin Trans 1, 1976, 2259.
- (38) T. Severin, W. Supp and G. Manninger, Chem.Ber., 1979, 112, 3013.
- (39) E.R. Talaty, A.R. Claque, M.O. Agha, M.N. Deshpande, P.M. Courtney, D.H. Burger and E.F. Roberts, J.Chem.Soc., Chem.Comm., 1980, 889.
- (40) (a) F.S. Babichev and Yu.M. Volovenko, Ukr.Khim.Zh. (Russ.Ed.), 1977, 43, 711.
(b) F.S. Babichev, Yu.M. Volovenko and L. Gofmann, Dopov.Akad.Nauk.Ukr. RSR, Ser. B Geol.Khim.Biol. Nauki, 1978, 7, 619.

- (41) G. Kresze, M. Morper and A. Bijev, Tetrahedron Lett., 1977, 2259.
- (42) (a) K.S. Kochhar and H.W. Pinnick, J.Org.Chem., 1984, 49, 3222.
(b) L. Bonaccina, P. Mencarelli and F. Stegel, J.Org.Chem., 1979, 44, 4420.
- (43) N. Bodor, M.J.S. Dewar and A.J. Harget, J.Am.Chem.Soc., 1970, 92, 2929.
- (44) A. Karpfen, P. Schuster and H. Berner, J.Org.Chem., 1979, 44, 374.
- (45) H. Bauer, Angew.Chem.Int.Ed.Eng., 1968, 7, 734.
- (46) B. Capon and Fu-Chiu Kwok, Tetrahedron Lett., 1986, 27, 3275.
- (47) R.S. Atkinson and E. Bullock, Can.J.Chem., 1963, 41, 625.
- (48) G. Pfeiffer and H. Bauer, Justus Liebigs Ann. Chem., 1980, 564.
- (49) J.V. Greenhill, Chem.Soc.Rev., 1977, 277.
- (50) R.S. Atkinson and E. Bullock, Can.J.Chem., 1964, 42, 1524.
- (51) G. Pfeiffer, W. Otting and H. Bauer, Angew.Chem.Int.Ed.Eng., 1976, 15, 52.
- (52) R.A.Y. Jones and N. Sadighi, J.Chem.Soc., Perkin Trans 1, 1976, 2259.
- (53) H.G. Viehe, Z. Janousek, R. Merenyi and L. Stella, Acc.Chem.Res., 1985, 18, 148.
- (54) M. Takahashi, N. Inaba, H. Kirihaara and S. Watanabe, Bull.Chem.Soc.Jpn., 1978, 51, 3312.

- (55) E. Campaigne and G.M. Schutske, J. Heterocycl. Chem., 1974, 11, 929.
- (56) E.P. Kohler, F. Westheimer and M. Tieshler, J.Am.Chem.Soc., 1936, 58, 264.
- (57) G.A. Russell and G. Kaupp, J.Am.Chem.Soc., 1969, 91, 3851.
- (58) H. Bauer, Chem.Ber., 1971, 104, 259.
- (59) E. Campaigne and G.M. Schutske, J. Heterocycl. Chem., 1975, 12, 67.
- (60) T. Momose, T. Tanaka, T. Yokota, N. Nagamoto, H. Kobayashi and S. Takomo, Heterocycles, 1981, 15, 843.
- (61) E. Campaigne and G.M. Schutske, J.Heterocycl.Chem., 1975, 12, 1047.
- (62) A. Treibs and A. Ohorodnik, Justus Liebigs Ann.Chem., 1958, 611, 149.
- (63) A.R. Mattocks, J.Chem.Soc., Perkin Trans. 1, 1978, 896.
- (64) T. Momose, T. Tanaka, T. Yokota, N. Nagamoto and K. Yamada, Chem.Pharm.Bull., 1978, 26, 3521.
- (65) R. Ghaffiri-Tabrizi, P. Margaretha and H.W. Schmidt, Helv.Chim.Acta., 1984, 67, 1957.
- (66) A. Hassner, A.S. Millar and M.J. Haddadin, J.Org.Chem., 1972, 37, 2682.
- (67) E. Campaigne and G.M. Schutske, J. Heterocycl.Chem., 1975, 12, 317.
- (68) R. Chong and P.S. Clezy, Aust.J.Chem., 1967, 20, 951.
- (69) R. Ghaffiri-Tabrizi and P. Margaretha, Helv.Chim.Acta, 1982, 65, 1029.

- (70) E. Anklam, R. Ghaffiri-Tabrizi, H. Hombrecher, S. Lau and P. Margaretha, Helv.Chim.Acta, 1984, 67, 1402.
- (71) M. Beyer, R. Ghaffiri-Tabrizi, M. Jung and P. Margaretha, Helv.Chim.Acta, 1984, 67, 1535.
- (72) R.F.C. Brown, 'Pyrolytic Methods in Organic Chemistry', Academic Press, New York, 1980.
- (73) J.I.G. Cadogan, C.L. Hickson and H. McNab, Tetrahedron, 1986, 42, 2135.
- (74) U.E. Wiersum, Aldrichimica Acta, 1984, 17, 31.
- (75) G. Schaden, J.Anal.Appl.Pyr., (a) 1982, 4, 83; (b) 1985, 8, 135.
- (76) M.C. Lasne and J.P. Ripoll, Synthesis, 1985, 121.
- (77) C. Wentrup, Adv.Heterocycl.Chem., 1981, 28, 231.
- (78) H. McNab, Chem.Soc.Rev., 1978, 7, 345.
- (79) E. Ott, Justus Liebigs Ann.Chem., 1913, 401, 159.
- (80) R.F.C. Brown, F.W. Eastwood and K.J. Harrington, Aust.J.Chem., 1974, 27, 2373.
- (81) R.F.C. Brown and F.W. Eastwood in 'The Chemistry of Ketenes and Allenes', Ed. S. Patai, Wiley, New York, 1980, p. 757.
- (82) C. Wentrup, G. Gross, H.-M. Berstermann and P. Lorencak, J.Org.Chem., 1985, 50, 2877.
- (83) R.F.C. Brown, F.W. Eastwood and G. McMullen, Aust.J.Chem., 1977, 30, 179.
- (84) R.D. Brown, P.D. Godfrey, R. Champion and D. McNaughton, J.Am.Chem.Soc., 1981, 103, 5711.

- (85) R.D. Brown, R. Champion, P.S. Elmes and P.D. Godfrey, J.Am.Chem.Soc., 1985, 107, 4109.
- (86) A. Kormonicki, G.E. Dykstra, M.A. Vincent and L. Radom, J.Am.Chem.Soc., 1981, 103, 1652.
- (87) L. Farnell and L. Radom, Chem.Phys.Lett., 1982, 91, 373.
- (88) G.A. Baxter, R.F.C. Brown, F.W. Eastwood and G. McMullen, Aust.J.Chem., 1977, 30, 459.
- (89) R.F.C. Brown and G. McMullen, Aust.J.Chem., 1974, 27, 2385.
- (90) G.A. Baxter, R.F.C. Brown and G. McMullen, Aust.J.Chem., 1974, 27, 2605.
- (91) D.W.M. Benzies, P.M. Fresneda, R.A. Jones and H. McNab, J.Chem.Soc., Perkin Trans. 1, 1986, 1651.
- (92) G.A. Baxter and R.F.C. Brown, Aust.J.Chem., 1975, 28, 1551.
- (93) R.F.C. Brown and C.M. Jones, Aust.J.Chem., 1980, 33, 1817.
- (94) H. McNab, J.Org.Chem., 1981, 46, 2809.
- (95) H. McNab, J.Chem.Soc., Perkin Trans. 1, (in press).
- (96) H. McNab and I. Stobie, J.Chem.Soc., Perkin Trans. 1, 1982, 1845.
- (97) H.J. Gordon, J.C. Martin and H. McNab, J.Chem.Soc., Perkin Trans. 1, 1984, 2129.
- (98) H. Briel, A. Lukosch and C. Wentrup, J.Org.Chem., 1984, 49, 2772.

- (99) J.P. Célérier, G. Lhomme and P. Maitte,
Tetrahedron Lett., 1981, 22, 963.
- (100) I. Hermecz, A. Horvath, L. Vasvari-Debreczy
and Z. Meszaros, Synthesis, 1983, 195.
- (101) P. Matyus, E. Kasztreiner, G. Szilagyi and M. Soti,
Heterocycles, 1983, 20, 2225.
- (102) R. Cassis, R. Tapia and J.A. Valdorrana, Synth.
Commun., 1985, 15, 125.
- (103) H. Dihmane, J.C. Pommelet, J. Chuche, G. Lhomme,
M.G. Richaud and M. Haddad, Tetrahedron Lett.,
1985, 26, 833.
- (104) P. Lorencak, J.C. Pommelet, J. Chuche and
C. Wentrup, J.Chem.Soc., Chem.Comm., 1986, 369.
- (105) H. McNab and L.C. Monahan, J.Chem.Soc., Chem.Comm.,
1985, 213.
- (106) C.L. Hickson, E.M. Keith, J.C. Martin, H. McNab,
L.C. Monahan and M.D. Walkinshaw, J.Chem.Soc.,
Perkin Trans. 1, 1986, 1465.
- (107) R.F.C. Brown, F.W. Eastwood, K.J. Harrington and
G. McMullen, Aust.J.Chem., 1974, 27, 2393.
- (108) R.J. Armstrong, R.F.C. Brown, F.W. Eastwood and
M.E. Ramyn, Aust.J.Chem., 1979, 32, 1767.
- (109) J. Scharp and U.E. Wiersum, J.Chem.Soc., Chem.
Commun., 1983, 629.

- (110) G.A. Bihlmayer, G. Derflinger, J. Derkosch and O. Polansky, Monatsh. Chem., 1967, 98, 564.
- (111) (a) L.M. Jackmann in "Dynamic N.m.r. Spectroscopy", ed. L.M. Jackmann and F.A. Cotton, Academic Press, New York, 1975.
(b) E.A. Murray, Ph.D. Thesis, p. 125.
- (112) U. Kölle, B. Kolb and A. Mannschreck, Chem.Ber., 1980, 113, 2545.
- (113) H. McNab (unpublished results).
- (114) M. Meier and C. Rüchardt, Tetrahedron Lett., 1984, 25, 3441.
- (115) H. McNab and E.A. Murray, J.Chem.Soc., Chem.Comm., 1981, 722.
- (116) W.D. Crow and H. McNab, Aust.J.Chem., 1979, 32, 123.
- (117) C.L. Hickson and H. McNab (unpublished results).
- (118) J. Dabrowski and K. Kamienska-Trela, Spectrochim. Acta, 1966, 22, 211.
- (119) K.-H. Klaska, O. Jarchov, T. Eicher and H. Preut, Acta Crystallogr., Sect. B, 1979, 35, 2788.
- (120) C. Barnett, H.P. Cleghorn, G.E. Cross, D. Lloyd and D.R. Marshall, J.Chem.Soc.(C), 1966, 93.
- (121) L.M. Jackmann and S. Sternhall, "Applications of Nuclear Magnetic Resonance Spectroscopy", Pergamon, Braunschweig, 1969.
- (122) A.L. Weis and R. Vishkautsan, Chem.Lett., 1984, 1773.
- (123) T.J. Batterham, "N.m.r. Spectra of Simple Heterocycles", Wiley, New York, 1973.

- (124) R.J. Cushley, R.J. Sykes, C.-K. Shaw and H.H. Wassermann, Can.J.Chem., 1975, 53, 148.
- (125) H. McNab, J.Chem.Soc., Perkin Trans. II, 1981, 1283.
- (126) S. Danishefsky and J.F. Kerwin, J.Org.Chem., 1982, 47, 3183.
- (127) G.C. Levy, R.L. Lichter and G.L. Nelson, "Carbon-13 N.m.r. Spectroscopy", Wiley, New York, 1980.
- (128) J. Schreurs, C.A.H. Van Norden Mudde, J.L.M. Van de Ven, J.W. de Haan, Org.Mag.Reson., 1980, 13, 354.
- (129) E.B. Whipple and Y. Chiang, J.Am.Chem.Soc., 1963, 85, 2763.
- (130) Ref. 2(a), p. 117.
- (131) R. Gassner, E. Krumbholz and F.W. Steuber, Justus Liebigs Ann. Chem., 1981, 879.
- (132) (a) G.H. Alt and A.J. Speziale, J.Org.Chem., 1965, 30, 1407.
(b) N.J. Leonard and J.A. Adamcik, J.Am.Chem.Soc., 1959, 81, 593.
- (133) H.E.A. Kramer, Justus Liebigs Ann. Chem., 1966, 696, 15.
- (134) For example, (a) H. McNab, J.Chem.Soc., Perkin Trans.II, 1981, 1287.
(b) H. Seel and H. Günther, J.Am.Chem.Soc., 1980, 102, 7051.
- (135) R.J. Abraham, E. Bullock and S.S. Mitra, Can.J.Chem., 1959, 37, 1859.

- (136) G.A. Olah, J.S. Staral, G. Asensio, G. Liang, D.A. Forsyth and G.D. Matees, J.Am.Chem.Soc., 1978, 100, 6299.
- (137) M.H. Palmer, "The Structure and Reactions of Heterocyclic Chemistry", Clowes, London, 1967.
- (138) P.A.S. Smith, "Open-Chain Nitrogen Compounds", Benjamin, New York, 1965.
- (139) For example, H. McNab, J.Chem.Soc., Perkin Trans. I, 1978, 1023.
- (140) C.A. Buehler and D.E. Pearson, "Survey of Organic Syntheses", Wiley, New York, 1977, p. 417.
- (141) B.T. Newbold in "The Chemistry of Hydrazo, Azo and Azoxy Compounds, Part 2", ed. S. Patai, Wiley, London, 1975.
- (142) J.J. Lyons and H. McNab (in press).
- (143) I. Jirkovsky, Can.J.Chem., 1974, 52, 55.
- (144) D. Lloyd, H.P. Cleghorn and D.R. Marshall, Adv. Heterocycl. Chem., 1974, 17, 1.
- (145) D. Lloyd, R.K. Mackie, G. Richardson and D.R. Marshall, Angew.Chem., Int. Ed. Eng., 1981, 20, 190.
- (146) H.G. Richey, Jr., in "The Chemistry of Alkenes", Ed. J. Zabicky, Wiley, London, 1970, p. 49.
- (147) A.J. Burn and J.I.G. Cadogan, J.Chem.Soc., 1963, 5788.
- (148) P. Patel and J.A. Joule, J.Chem.Soc., Chem.Comm., 1985, 1021.
- (149) For example, G.W. Gribble and M.G. Saulnier, Tetrahedron Lett., 1980, 21, 4137.

- (150) W.J. Le Noble, Synthesis, 1970, 1.
- (151) R.G. Pearson, J. Chem. Ed., 1968, 45, 581 and 643.
- (152) H. Tse-Lok, Tetrahedron, 1985, 41, 3.
- (153) G.J. Heiswolf and H. Kloosterziel, J.Chem.Soc.,
Chem.Comm., 1966, 51.
- (154) G. Hunter and H. McNab, (unpublished results).
- (155) S. Patai and Z. Rappoport, in "The Chemistry of Alkenes", Ed. J. Zabicky, Wiley, London, 1970, p.469.
- (156) P. Schuster, O.E. Polansky, F. Wessely,
(a) Monatsh.Chem., 1963, 95, 53; (b) Monatsh.Chem.,
1967, 99, 1246.
- (157) (a) S.M. Makin, V.V. Yastrebov and A.A. Ismail, Dokl.
Vses.Conf.Khim. Atsetilena 4th, 1972, 1, 260
(Chem. Abs., 1973, 79, 17974z).
(b) S.S. Malhorta and M.C. Whiting, J.Chem.Soc.,
1960, 3812.
- (158) K. Hafner and K. Goliasch, Chem.Ber., 1961, 94, 2909.
- (159) W. Klop and L. Brandsma, J.Chem.Soc., Chem.Comm.,
1983, 988.
- (160) F. Texier, R. Carrié and J. Jaz, J.Chem.Soc., Chem.
Commun., 1972, 199.
- (161) T. Gray and H. McNab, (unpublished results).
- (162) A.R. Katritzky, J. Arrowsmith, Z. bin Bahari,
C. Jayarem, T. Siddiqui, and S. Vassilatos, J.Chem.
Soc., Perkin Trans I., 1980, 2851.
- (163) P. Bamfield and P.F. Gordon, Chem.Soc.Rev., 1984,
13, 441.

- (164) B.R. Penfold, Acta Crystallogr., 1953, 6, 591-600.
- (165) E. Breitmaier and W. Voelter, "¹³C N.m.r. Spectroscopy", Verlag, New York, 1978, p. 73.
- (166) L.A. Paquette in "Non-Benzenoid Aromatics, Volume 1", ed. J.P. Snyder, Academic Press, New York, 1969, p. 249.
- (167) H. Tieckelmann in "Pyridine and its Derivatives, Supplement, Part 3", ed. R.A. Abramovitch, Wiley-Interscience, New York, 1974, p. 597.
- (168) R.A. Abramovitch and J.G. Saha, Adv. Heterocycl.Chem., 1966, 6, 229.
- (169) A. El-Anani, J. Bauger, G. Bianchi, S. Clementi, C.D. Johnson and A.R. Katritzky, J.Chem.Soc., Perkin Trans. II, 1973, 1065.
- (170) Y. Kawazoe and Y. Yoshioka, Chem. Pharm. Bull., 1968, 16, 715.
- (171) A.H. Berrie, G.T. Newbold and F.S. Spring, J.Chem.Soc., 1951, 2590.
- (172) W.H. Mills and S.T. Widdows, J.Chem.Soc., 1908, 1372.
- (173) L.A. Paquette and W.C. Farley, J.Org.Chem., 1967, 32, 2725.
- (174) E.C. Taylor, R.O. Kan and W.W. Paudler, J.Am.Chem.Soc., 1961, 83, 4484.
- (175) E.J. Corey and J. Streith, J.Am.Chem.Soc., 1964, 86, 950.
- (176) B.S. Thyagarajan and K. Rajagopalan, Tetrahedron, 1963, 19, 1483.
- (177) B.S. Thyagarajan, K. Rajagopalan and P.V. Gopalakrishnan, J.Chem.Soc.(B), 1968, 300.

- (178) H. Tomisawa and H. Hongo, Chem. Pharm. Bull., 1970, 18, 941.
- (179) L. Bauer, C.L. Bell and G.E. Wright, J. Heterocycl. Chem., 1966, 3, 393.
- (180) (a) E. Vogel, R. Erb, G. Lenz and A.A. Bothner-By, Justus Liebigs Ann. Chem., 1965, 682, 1.
(b) O.L. Chapman and E.D. Hoganson, J. Am. Chem. Soc., 1964, 86, 498.
(c) L.A. Paquette, J. Am. Chem. Soc., 1964, 86, 500.
- (181) L.A. Paquette, J. Org. Chem., 1963, 28, 3590.
- (182) R. Radeaglia, M. Wähnert, S. Dähne and H. Bögel, J. Prakt. Chem., 1978, 320, 539.
- (183) L.A. Paquette, J. Am. Chem. Soc., 1964, 86, 4096.
- (184) J.E. Stothers and P.C. Lauterbur, Can. J. Chem., 1964, 42, 1563.
- (185) S.T. Reid, Adv. Heterocycl. Chem., 1970, 11, 30.
- (186) D.N. Reinhoudt, Adv. Heterocycl. Chem., 1977, 21, 300.
- (187) L.A. Paquette and D.E. Kuhla, J. Org. Chem., 1969, 34, 2885.
- (188) J.M. Holovka and P.D. Gardner, J. Am. Chem. Soc., 1967, 89, 6390.
- (189) H. Hofmann and B. Meyer, Tetrahedron Lett., 1972, 4597.
- (190) K.E. Wilzbach and D.J. Rausch, J. Am. Chem. Soc., 1970, 92, 2178.
- (191) I. Fleming, "Frontier Orbitals and Organic Chemical Reactions", Wiley, London, 1976, p. 133.

- (192) Reference 1(b), p. 341.
- (193) K. Hafner, Angew. Chem., Int. Ed. Eng., 1964, 3, 165.
- (194) L.M. Harwood, Aldrichimica Acta, 1985, 18, 25.
- (195) C.L. Hickson, Ph.D. Thesis, p. 113., University of Edinburgh, 1983
- (196) J.H. Billman and K. Tai, J. Org. Chem., 1958, 23, 535.
- (197) M. Kitamoto, K. Hiroi, S. Tarashimo and S. Yamoda, Chem. Pharm. Bull., 1974, 32, 459.
- (198) D.G. Norton, V.E. Hawry, F.C. Davis, L.J. Mitchell and S.A. Ballard, J. Org. Chem., 1954, 19, 1054.
- (199) M.C. De Leeuw, Recl. Trav. Chim. Pays-Bas, 1911, 30, 246.
- (200) A. Pictet and P. Crepieux, Chem. Ber., 1888, 21, 1109.
- (201) G.S. Fonken, M.E. Herr, H.C. Murray and L.M. Reineke, J. Org. Chem., 1968, 33, 3182.
- (202) A. Pictet and H.J. Akersmit, Justus Liebigs Ann. Chem., 1891, 266, 151.
- (203) W. Leithe, Monatsh. Chem., 1929, 53-54, 956.
- (204) J.P. Célérier, M.G. Richaud and G. Lhommet, Synthesis, 1983, 113, 195.
- (205) G.R. Sullivan, Topics in Stereochemistry, 1978, 10, 287.
- (206) H. Meerwein, Org. Synth. Coll. Vol. V, 1080.
- (207) E.B. Starkey, Org. Synth. Coll. Vol. II, 1943, 225.
- (208) A.M. Gorringer, D. Lloyd and D.K. Marshall, J. Chem. Soc. (C), 1970, 617.
- (209) C. Barnett, J. Chem. Soc. (C), 1967, 2436.

- (210) J. Kucera and Z. Arnold, Collect. Czech. Chem. Commun., 1967, 32, 1704.
- (211) Y.D. Vankar and G. Kumaraud, Tetrahedron Lett., 1984, 25, 233.
- (212) (a) C.L. Hickson, Ph.D. Thesis, p. 133., *University of Edinburgh*, 1983
(b) E.A. Murray, Ph.D. Thesis, p. 166., *University of Edinburgh*, 1985
- (213) A.J. Meyer and S. Singh, Tetrahedron Lett., 1967, 5319.
- (214) J.N. Collie and G. Bishop, J.Chem.Soc., 1925, 127, 963.
- (215) H. McNab, J.Chem.Res.(M), 1979, 1448.
- (216) J. Dabrowski and K. Kamińska-Trela, J.Am.Chem.Soc., 1976, 98, 2826.
- (217) J. Fiana and H. Normant, Bull. Chim. Soc. Fr., 1964, 1294.
- (218) J. Braun, Chem. Ber., 1903, 36, 3525.
- (219) J. B. Husband, Ph.D. Thesis, p. 78., *University of Edinburgh*, 1982.
- (220) K. Shudo, T. Ohta and T. Okamoto, J.Am.Chem.Soc., 1981, 103, 645.

PUBLICATIONS

3-Hydroxypyrroles [Pyrrol-3(2H)-ones]

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Simple 3-hydroxypyrroles are obtained by pyrolysis of appropriate aminomethylene Meldrum's acid derivatives: the unusual reactions of these compounds with acids, bases, and electrophiles is discussed.

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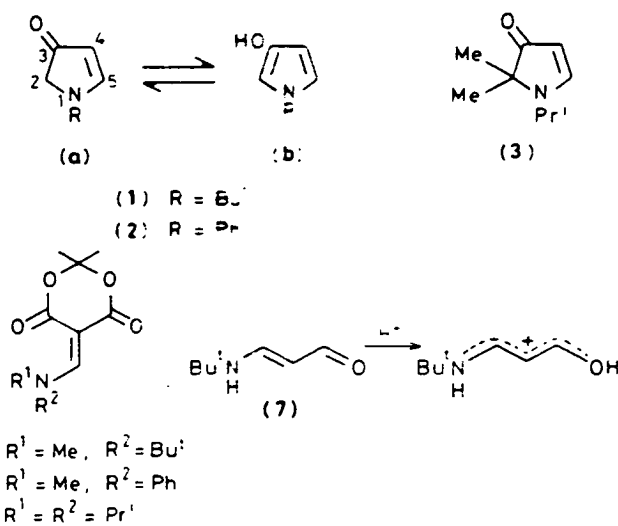
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Simple 3-hydroxypyrroles are obtained by pyrolysis of appropriate aminomethylene Meldrum's acid derivatives: the unusual reactions of these compounds with acids, bases, and electrophiles is discussed.

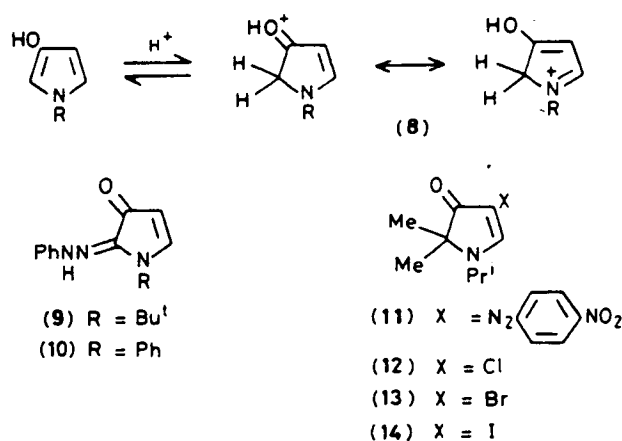
Despite the great importance in heterocyclic chemistry of the hydroxy (or oxo) function, simple examples in the pyrrole series are rare. Indeed, the only 3-hydroxypyrroles [pyrrol-3(2H)-ones] to be investigated in detail¹⁻³ are substituted at the potentially reactive 4- and 5-positions, and in just one study of C-unsubstituted derivatives the products were obtained only on a small scale, and were described as 'extremely unstable'.^{4,5} In this paper, we extend our Meldrum's acid method⁶ to the synthesis of (2),4,5-unsubstituted 3-hydroxypyrroles on a multi-gram scale and report some chemical properties of this fundamental heterocyclic system.

Thus, the *N*-alkyl compound (1) and the *N*-aryl compound (2)⁵ are readily available in 38 and 63% yield respectively by flash vacuum pyrolysis (600°C; 10⁻² Torr) of the Meldrum's acid derivatives (4) and (5).[†] Although both hydroxypyrroles are somewhat sensitive to oxygen, they can be stored for long periods at -20°C, and can be manipulated in air, without special precautions. For comparison, the 2,2-disubstituted

compound (3)⁷ is indefinitely stable in air at room temperature.



[†] All new compounds are characterised by their spectra and by elemental analysis.

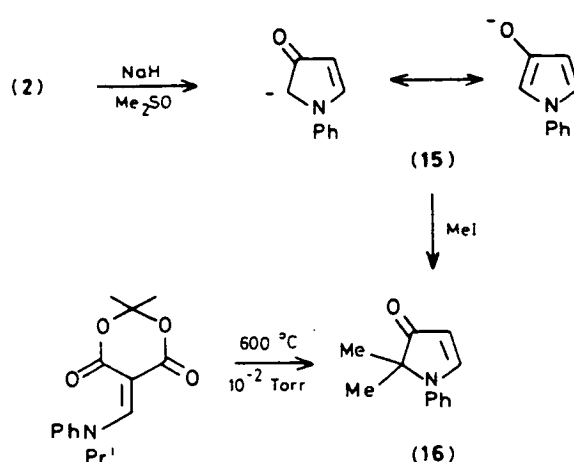


In accord with earlier work we have found that both (1) and (2)^{4,5} exclusively adopt the keto tautomeric form (a) in non-polar solvents (e.g. CDCl₃), although in both cases the enol form (b) is predominant in polar solvents (e.g. CD₃SOCD₃) to the extent of 85–95%.

Pyrroles are notoriously sensitive to acids. In contrast, the hydroxypyrroles (1) and (2) dissolve in trifluoroacetic acid to give solutions which are unchanged after many days at room temperature. The ¹H and ¹³C n.m.r. parameters of these solutions [and of the 2,2-dimethyl compound (3)] follow identical trends to those of the enamine (7), which is known⁶ to undergo *O*-protonation in acid. In the present case, such protonation generates a Wheland intermediate (8) for electrophilic substitution of the 3-hydroxypyrrole system, which is accordingly a stable species and directly observable under mild conditions. Its dynamic equilibrium with the neutral molecule is demonstrated by deuterium exchange reactions which show rapid incorporation at position 2 [(1): *t*_{1/2} < 10 min]. Remarkably, the exchange at position 4 is even faster (*t*_{1/2} < 1 min), whereas reaction at position 5 could not be detected at all, even after 24 h at 20 °C. This behaviour is reminiscent of the properties of the similar conjugated systems found in enamines⁷ and in 2,3-dihydro-1,4-diazepines.¹⁰

Other electrophilic reagents also react at positions 2 and 4. Thus (1) and (2) yield the 2-hydrazones (9) and (10) (50–60%) on treatment with benzenediazonium salts (cf. ref. 2). When this site is blocked, pyrrol-3(2*H*)-ones smoothly undergo diazo-coupling reactions to give 4-azo derivatives [e.g. (11) (63%)]. Similarly, the 4-halogeno-derivatives (12)–(14) are readily formed in 85–90% yield by reaction with *N*-halogenosuccinimides in methanol solution.

The reactions of 3-hydroxypyrroles with bases are complex, and result in reversible spectroscopic changes which are still



Scheme 1

under investigation. However, treatment of the *N*-phenyl derivative (2) with sodium hydride in dimethyl sulphoxide, then with an excess of iodomethane gave the 2,2-dimethyl derivative (16) as the major product (Scheme 1). Clearly, under these conditions, deprotonation of the hydroxypyrrole generates an anion (15) which behaves as an enolate rather than as an analogue of phenoxide. In agreement with this interpretation, 3-hydroxypyrroles are recovered unchanged after treatment with iodomethane–potassium carbonate in dimethylformamide, conditions which lead to quantitative *O*-alkylation of phenols.

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References

- 1 H. Bauer, *Liebigs Ann. Chem.*, 1970, **736**, 1.
- 2 H. Bauer, *Chem. Ber.*, 1971, **104**, 259.
- 3 G. Pfeiffer and H. Bauer, *Liebigs Ann. Chem.*, 1980, **563**.
- 4 T. Momose, T. Tanaka, and T. Yokota, *Heterocycles*, 1977, **6**, 1827.
- 5 T. Momose, T. Tanaka, T. Yokota, N. Nagamoto, and K. Yamada, *Chem. Pharm. Bull.*, 1979, **27**, 1448.
- 6 H. J. Gordon, J. C. Martin, and H. McNab, *J. Chem. Soc., Chem. Commun.*, 1983, 957.
- 7 E. Anklam, R. Ghaffari-Tabrizi, H. Hombrecher, S. Lau, and P. Margaretha, *Helv. Chim. Acta*, 1984, **67**, 1402.
- 8 H. McNab, *J. Chem. Soc., Perkin Trans. 2*, 1981, 1287.
- 9 J. V. Greenhill, *Chem. Soc. Rev.*, 1977, **6**, 277.
- 10 D. Lloyd, H. P. Cleghorn, and D. R. Marshall, *Adv. Heterocycl. Chem.*, 1974, **17**, 1.

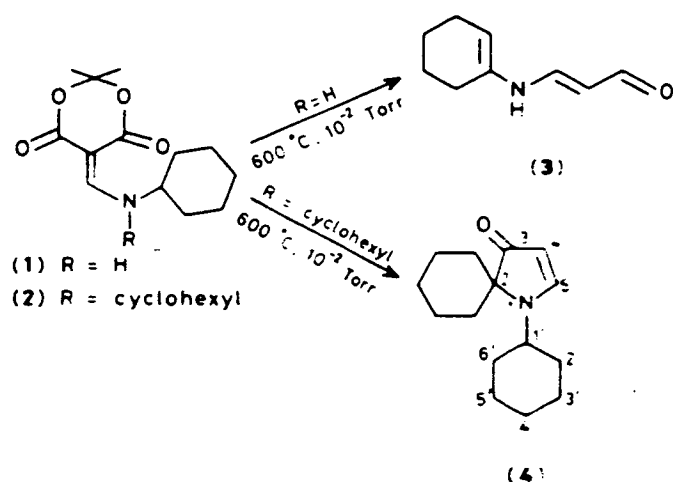
3-Hydroxypyrroles and 1*H*-Pyrrol-3(2*H*)-ones. Part 1. Formation and X-Ray Crystal and Molecular Structure of 1-Cyclohexyl-2,2-pentamethylene-1*H*-pyrrol-3(2*H*)-one

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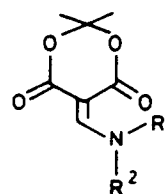
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The title compound (4) is formed by flash vacuum pyrolysis of a dicyclohexylaminomethylene derivative of Meldrum's acid, (2), and its structure was determined by X-ray crystallography. Deuterium-labelling studies show that the reaction mechanism involves a specific, intramolecular, rate-determining hydrogen transfer from the 1-position of a cyclohexyl ring to form the 4-hydrogen atom in the product.

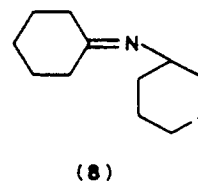
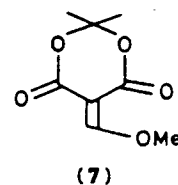
In a preliminary communication,¹ we have described the diverse thermal behaviour of *N*-alkylaminomethylene derivatives of Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione). Secondary derivatives [e.g. (1)] give open-chain compounds [e.g. (3)] after a sequence of hydrogen shifts in a methyleneketene² intermediate, initiated by tautomerism to an iminoketene^{3,4} (Scheme). Tertiary derivatives cannot undergo this behaviour, and instead an unusual hydrogen-transfer-cyclisation process takes place to give an efficient synthesis of 1*H*-pyrrol-3(2*H*)-ones (Scheme).^{1,5-7} In this paper, we give details of a typical example of this reaction, together with a full structural characterisation of the product by X-ray crystallography. In addition, we describe the results of experiments which relate to the mechanism of the hydrogen-transfer step.



Scheme.



(5) R¹ = cyclohexyl, R² = [1-²H]cyclohexyl
(6) R¹ = Ph, R² = Pr¹



mass spectroscopy. In general, the mass spectra of Meldrum's acid derivatives exhibit sequential loss of acetone, CO₂, and CO from the molecular ion,^{9,10} and this pattern is followed by the *N*-isopropyl-*N*-phenyl compound (6). The spectrum of the *N*,*N*-dicyclohexyl compound (2) is anomalous, since the most intense peak in the high-mass range is due to loss of H₂O following the cleavage of acetone [Found: *m/z* 259.1568; (*M* - C₃H₆O - H₂O)⁺ (C₁₆H₂₁NO₂) requires *m/z* 259.1572]. Significantly the corresponding monodeuteriated compound (5) shows a corresponding doublet at *m/z* 260 and 259, which indicates that one N-CH hydrogen atom is lost in this process, though the structure of the ion formed is unclear at this stage.

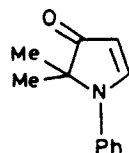
Flash vacuum pyrolysis of the Meldrum's acid derivative (2) at 600 °C (10⁻² Torr) gave a good yield of a crystalline material, which condensed at the exit point of the furnace. It was shown by mass spectroscopy to be derived from compound (2) by loss of acetone and carbon dioxide. ¹H N.m.r. spectroscopy shows two mutually coupled protons in the alkene region, whose chemical shifts are widely separated [δ_H 7.82 (d) and 4.97 (d)], suggesting an enone (or enamino) system, and whose coupling constant (³J 3.4 Hz) is typical of a five-membered ring. Whereas the starting material (2) has two C-N methine carbon atoms, the ¹³C n.m.r. spectrum of the product shows just one methine carbon atom and one quaternary carbon atom in this region (δ_C 52.56 and 67.96 respectively). A C-N methine group is therefore the source of the second alkene hydrogen atom (above). These data serve to establish the structure of the

The precursors (2), (5), and (6) were synthesised by the standard 'one-pot' method⁸ from Meldrum's acid triethyl orthoformate, and the appropriate amine at reflux temperature. However, the yield (based on the amine) could be improved significantly by treatment of the methoxymethylene derivative (7)⁸ with a slight excess of the amine, in acetonitrile at room temperature. [1-²H]-Labelled dicyclohexylamine, required for the preparation of the deuteriated compound (5), was obtained by reduction (LiAl[²H]₄) of the imine (8).

Characterisation of the Meldrum's acid derivatives (2), (5), and (6) was effected by n.m.r. [which typically shows a sharp singlet at δ_H 8.0–8.5 (1 H) due to the methylene proton] and

product as the 1*H*-pyrrol-3(2*H*)-one (4), and are supported by a u.v. absorption maximum (λ_{max} , 328 nm) typical of such systems.¹¹

As a second example, the *N*-phenylpyrrolone (9) was formed in 64% yield from the Meldrum's acid derivative (6).



(9)

Because of the scarcity of information on 1*H*-pyrrol-3(2*H*)-ones with small and/or non-polar substituents the structure of compound (4) was determined by *X*-ray crystallography (Tables 1 and 2, and Figures 1 and 2). The five-membered ring is

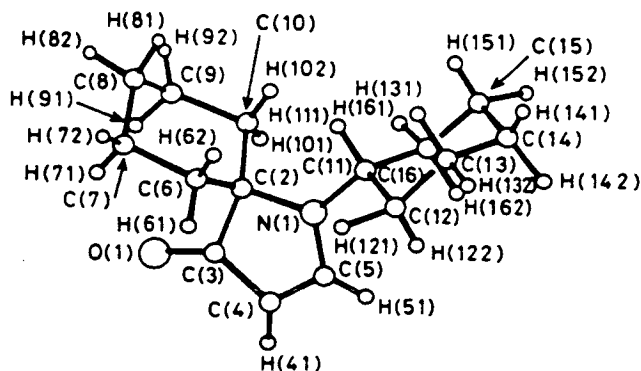


Figure 1. A view of the 1*H*-pyrrol-3(2*H*)-one (4), showing the crystallographic numbering scheme

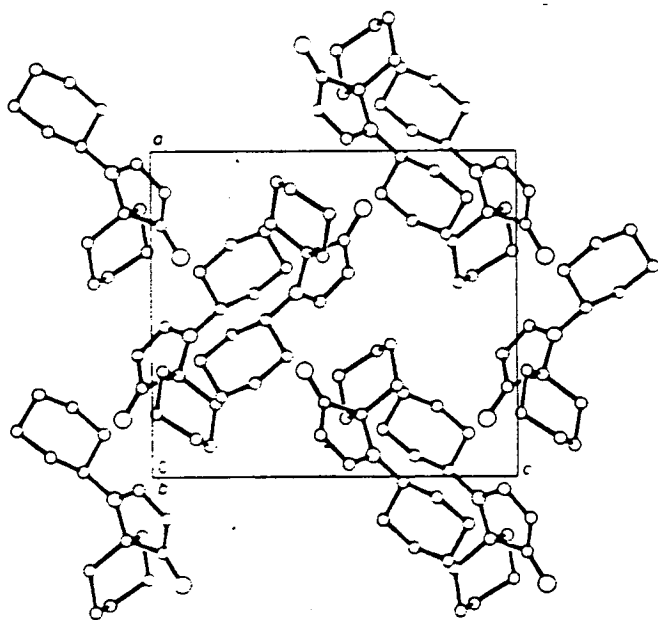


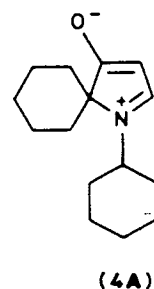
Figure 2. Packing diagram of the 1*H*-pyrrol-3(2*H*)-one (4)

essentially planar, with a maximum intra-ring torsion angle of 1.4°; angles round N(1) and C(3) add to 359.8 and 360.0° respectively and indicate planar co-ordination. The delocalisa-

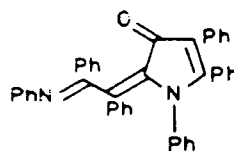
Table 1. Fractional atomic co-ordinates of non-hydrogen atoms of compound (4) with standard deviations in parentheses

x	y	z	
O(1)	0.175 8(6)	0.380 1(5)	0.918 5(5)
N(1)	0.435 2(6)	0.408 9(6)	1.103 6(5)
C(2)	0.311 5(7)	0.456 2(7)	1.072 4(7)
C(3)	0.274 0(9)	0.369 5(8)	0.971 8(7)
C(4)	0.374 0(10)	0.285 7(8)	0.960 3(8)
C(5)	0.462 0(10)	0.314 5(8)	1.038 1(9)
C(6)	0.222 0(9)	0.442 8(10)	1.172 2(9)
C(7)	0.095 0(10)	0.505 8(11)	1.155 1(11)
C(8)	0.115 8(14)	0.636 8(11)	1.117 5(15)
C(9)	0.192 3(11)	0.643 5(10)	1.011 0(11)
C(10)	0.323 1(8)	0.588 9(7)	1.029 8(9)
C(11)	0.517 7(7)	0.466 0(7)	1.188 1(7)
C(12)	0.562 8(9)	0.375 0(8)	1.280 0(7)
C(13)	0.643 1(8)	0.438 9(8)	1.368 4(7)
C(14)	0.754 3(10)	0.500 1(11)	1.310 4(10)
C(15)	0.714 4(10)	0.587 1(10)	1.218 7(9)
C(16)	0.631 1(9)	0.525 2(10)	1.131 4(8)

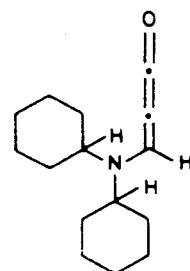
tion of the enaminone system, implicit in the canonical form (4A), is demonstrated by the lengths of the C(3)–C(4) and N(1)–C(5) bonds (1.416 and 1.317 Å) which are significantly shorter than in the analogous structure (10)¹² (1.462 and 1.40 Å respectively) in which exocyclic delocalisation can compete. Both cyclohexane rings adopt a chair conformation with similar structural parameters. All C–H bonds refine to between 0.8 and 1.16 Å. The low crystal density of 1.14 g cm⁻³ is explained by the packing pattern, which leaves unfilled channels throughout the crystal. The only notable non-bonded intermolecular contacts involve the carbonyl oxygen atom, and are O(1)···C(5) (3.17 Å), and also H(91)···H(121) (2.16 Å).



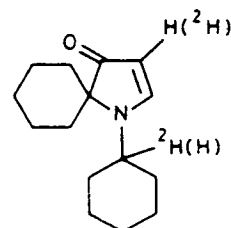
(4A)



(10)



(11)



(12)

Table 2. Bond lengths, bond angles, and torsion angles of compound (4) with standard deviations in parentheses

(a) Bond lengths

O(1)-C(3)	1.221(11)	C(7)-C(8)	1.519(19)
N(1)-C(2)	1.464(10)	C(8)-C(9)	1.481(19)
N(1)-C(5)	1.317(12)	C(9)-C(10)	1.535(15)
N(1)-C(11)	1.458(10)	C(11)-C(12)	1.537(12)
C(2)-C(3)	1.557(12)	C(11)-C(16)	1.524(13)
C(2)-C(6)	1.507(13)	C(12)-C(13)	1.508(12)
C(2)-C(10)	1.544(12)	C(13)-C(14)	1.520(14)
C(3)-C(4)	1.416(13)	C(14)-C(15)	1.491(16)
C(4)-C(5)	1.339(14)	C(15)-C(16)	1.508(15)
C(6)-C(7)	1.535(16)		

(b) Bond angles

C(2)-N(1)-C(5)	109.4(7)	C(2)-C(6)-C(7)	114.6(9)
C(2)-N(1)-C(11)	123.9(6)	C(6)-C(7)-C(8)	109.6(10)
C(5)-N(1)-C(11)	126.5(7)	C(7)-C(8)-C(9)	111.5(11)
N(1)-C(2)-C(3)	101.5(6)	C(8)-C(9)-C(10)	111.4(10)
N(1)-C(2)-C(6)	110.3(7)	C(2)-C(10)-C(9)	109.9(8)
N(1)-C(2)-C(10)	110.0(6)	N(1)-C(11)-C(12)	112.0(7)
C(3)-C(2)-C(6)	110.6(7)	N(1)-C(11)-C(16)	111.9(7)
C(3)-C(2)-C(10)	111.1(6)	C(12)-C(11)-C(16)	109.1(7)
C(6)-C(2)-C(10)	112.9(7)	C(11)-C(12)-C(13)	110.2(7)
O(1)-C(3)-C(2)	122.7(8)	C(12)-C(13)-C(14)	110.4(8)
O(1)-C(3)-C(4)	131.4(9)	C(13)-C(14)-C(15)	112.0(9)
C(2)-C(3)-C(4)	105.9(7)	C(14)-C(15)-C(16)	110.9(9)
C(3)-C(4)-C(5)	108.2(9)	C(11)-C(16)-C(15)	111.8(8)
N(1)-C(5)-C(4)	114.9(9)		

(c) Torsion angles

C(5)-N(1)-C(2)-C(3)	-1.3(8)
C(5)-N(1)-C(2)-C(6)	116.0(8)
C(5)-N(1)-C(2)-C(10)	-118.9(8)
C(11)-N(1)-C(2)-C(3)	174.2(7)
C(11)-N(1)-C(2)-C(6)	-68.6(9)
C(11)-N(1)-C(2)-C(10)	56.5(9)
C(2)-N(1)-C(5)-C(4)	0.7(11)
C(11)-N(1)-C(5)-C(4)	-174.6(8)
C(2)-N(1)-C(11)-C(12)	128.2(7)
C(2)-N(1)-C(11)-C(16)	-106.9(8)
C(5)-N(1)-C(11)-C(12)	-57.2(11)
C(5)-N(1)-C(11)-C(16)	63.7(11)
N(1)-C(2)-C(3)-O(1)	-178.2(8)
N(1)-C(2)-C(3)-C(4)	1.4(8)
C(6)-C(2)-C(3)-O(1)	64.8(11)
C(6)-C(2)-C(3)-C(4)	-115.7(9)
C(10)-C(2)-C(3)-O(1)	-61.3(10)
C(10)-C(2)-C(3)-C(4)	118.2(8)
N(1)-C(2)-C(6)-C(7)	171.7(8)
C(3)-C(2)-C(6)-C(7)	-76.8(10)
C(10)-C(2)-C(6)-C(7)	48.2(11)
N(1)-C(2)-C(10)-C(9)	-173.2(7)
C(3)-C(2)-C(10)-C(9)	75.3(9)
C(6)-C(2)-C(10)-C(9)	-49.6(10)
O(1)-C(3)-C(4)-C(5)	178.5(10)
C(2)-C(3)-C(4)-C(5)	-1.1(9)
C(3)-C(4)-C(5)-N(1)	0.2(12)
C(2)-C(6)-C(7)-C(8)	-5.5(13)
C(6)-C(7)-C(8)-C(9)	56.8(14)
C(7)-C(8)-C(9)-C(10)	-61.7(14)
C(8)-C(9)-C(10)-C(11)	5.5(12)
N(1)-C(11)-C(12)-C(13)	-177.8(7)
C(16)-C(11)-C(12)-C(13)	57.8(7)
N(1)-C(11)-C(16)-C(15)	178.4(7)
C(12)-C(11)-C(16)-C(15)	-57.0(10)
C(11)-C(12)-C(13)-C(14)	-57.7(10)
C(12)-C(13)-C(14)-C(15)	56.6(11)
C(13)-C(14)-C(15)-C(16)	-55.0(12)
C(14)-C(15)-C(16)-C(11)	55.9(11)

Table 3. Isotope effects (k_H/k_D) in the formation of spiropyrrolone (12) from dioxanedione (5)

Pyrolysis temperature (°C)	Equation 1	Equation 2	Equation 3	Average
500	1.98 ± 0.14	1.69 ± 0.14	—	1.84
550	1.81 ± 0.07	1.67 ± 0.10	1.83	1.77
600	2.15 ± 0.13	1.71 ± 0.15	1.86	1.91
650	2.08 ± 0.15	1.69 ± 0.13	2.01	1.93

The mechanism of the formation of 1*H*-pyrrol-3(2*H*)-ones from aminomethylene Meldrum's acid derivatives probably involves a methyleneketene² intermediate, [cf. (11)], which has been observed spectroscopically in some related examples.¹³ Subsequent steps require the transfer of a C-hydrogen atom from a site adjacent to nitrogen, followed by the final cyclisation to form the five-membered ring. The hydrogen-transfer step is of particular interest, since it allows specific thermal functionalisation at a site *x* to a *non-activated* nitrogen atom. Although some related reactions have been reported recently^{14,15} the present example is especially suited for detailed study because of the ready availability of the precursors, and the absence of complicating side-reactions.¹⁴

First, we have established the specificity of the hydrogen transfer, by the pyrolysis of the monodeuterated compound (5), in which a protium atom and a deuterium atom are located at the two sites of potential reaction. Investigation of the product by ¹H and ²H n.m.r. spectroscopy reveals that the transferred deuterium atom is located exclusively at C(4) and, as expected, unchanged deuterium remains at the 1-position of the *N*-cyclohexyl ring, (12). Further, the mass spectrum of this material, formed by competitive transfer of protium and deuterium, shows the absence of dideuterated and undeuterated species, which strongly suggests that the reaction is intramolecular. This conclusion was confirmed by a coprolysis of compounds (5) and (6): no cross-over incorporation of deuterium into product (9) could be detected by ¹H n.m.r. spectroscopy of the product mixture. We therefore conclude that the hydrogen transfer is a highly specific intramolecular process, though the present results give no indication of the mechanism of the transfer, which may be diradical,¹ dipolar,¹ or concerted with the cyclisation.¹⁶ We hope to comment on these possibilities in a later Part of this series.

The distribution of protium and deuterium in compound (12), as formed from dione (5), gives a direct measure of the isotope effect for the transfer process. Little work has been carried out on isotope effects under flash vacuum pyrolysis conditions though small values of k_H/k_D (ca. 1.5–3.0 at 400–800 °C) have been reported in cases in which the hydrogen shift is clearly rate determining.^{17–19} In addition, isotope effects are expected to decrease with temperature,²⁰ though the interpretation of certain anomalous features in this context is a matter of recent debate.^{21,22} In the present case, we have studied the isotope effect (k_H/k_D) over the maximum temperature range (500–650 °C) at which a significant yield of product was obtained. The results were calculated from the integral values of peaks in three ways [equations (1)–(3)], which allows a direct assessment of their consistency (Table 3).

$$^1\text{H n.m.r.: } k_H/k_D = \frac{^1\text{H}(4)}{^1\text{H}(5)} = \frac{^1\text{H}(4)}{^1\text{H}(1)} \quad (1)$$

$$k_H/k_D = \frac{^1\text{H}(4)}{^1\text{H}(1)} \quad (2)$$

$$^2\text{H n.m.r.: } k_H/k_D = \frac{^2\text{H}(1)}{^2\text{H}(4)} \quad (3)$$

[The numbering scheme is as shown in structure (4)].

The results (Table 3) show a small but significant isotope effect (k_H/k_D ca. 1.9) with only reasonable consistency (± 5 –10%). By comparison with the literature data^{17–19} it therefore seems likely that the hydrogen transfer is rate determining. Under our conditions and at our level of accuracy, the isotope effect is apparently independent of temperature, though the wider mechanistic implications of this result must await related studies on other hydrogen-transfer processes.

Experimental

Unless otherwise stated, ^1H , ^2H , and ^{13}C n.m.r. spectra were recorded at 80, 30, and 20 MHz respectively, on Bruker WP80, Bruker WP200, and Varian CFT 20 spectrometers. Chemical shifts are reported relative to SiMe_4 .

N-[1- ^2H]Cyclohexylcyclohexylamine.—(a) *N*-Cyclohexylidene-cyclohexylamine (8). A solution of cyclohexylamine (20 g, 0.2 mol) and cyclohexanone (20 g, 0.2 mol) in toluene (200 ml) containing toluene-*p*-sulphonic acid (0.4 g) was heated under reflux for 3 h, using a Dean-Stark trap to remove the water which was formed. The solvent was evaporated off under reduced pressure and the residue was distilled (Kugelrohr) to give the imine (8) (18.7 g, 52%), b.p. 120–130 °C (1.0 Torr) [lit.,²³ 135–137 °C (20 Torr)]; $\delta_{\text{C}}(\text{CDCl}_3)$ 170.04 (q), 57.39, 39.77, 33.70, 28.55, 27.42, 27.12, 25.75, 25.21, and 24.59.

(b) *N*-[1- ^2H]Cyclohexylcyclohexylamine. A solution of the above imine (5.03 g, 28 mmol) in dry ether (50 ml) was added under dry nitrogen to a suspension of [$^2\text{H}_4$]lithium aluminium hydride (1.0 g, 23 mmol) in dry ether (150 ml). The mixture was heated under reflux for 35 min, cooled, and the excess of hydride was carefully decomposed with wet ether (20 ml) and water (30 ml). After the successive addition of aqueous potassium sodium tartrate (20%; 80 ml) and aqueous sodium hydroxide (10%; 30 ml), the organic layer was separated, and the aqueous layer was extracted with ether (2 $\times$ 100 ml). The combined organic layers were dried (MgSO_4), concentrated, and distilled (Kugelrohr) to give the title labelled amine (3.96 g, 78%), b.p. 140–145 °C (30 Torr), [lit.,²⁴ 136–138 °C (26 Torr) for undeuteriated compound].

5-(2,2-Disubstituted-2-azaethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione Derivatives.—Method A.^{3,8} A solution of Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) (1.44 g, 10 mmol) in triethyl-orthoformate (12 ml) was heated under reflux for 2 h. The appropriate secondary amine (12.5 mmol) was added, and the mixture was heated for a further 2 h. The product crystallised when the solution was cooled, or after partial evaporation of the solvent.

Method B. A solution of 5-methoxymethylene-2,2-dimethyl-1,3-dioxane-4,6-dione (7)⁸ (10 mmol) and the appropriate amine (11 mmol) in acetonitrile (10 ml) was set aside at room temperature for 5 min. Evaporation of the solvent under reduced pressure gave the product as a crystalline solid.

The following derivatives were made by these methods: 5-(2,2-Dicyclohexyl-2-azaethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (2). (Method A, 67%; Method B, 99%). m.p. 170–171 °C (from ethanol) (Found: C, 67.8; H, 8.45; N, 4.3. $\text{C}_{16}\text{H}_{26}\text{N}_2\text{O}_4$ requires C, 68.05; H, 8.05; N, 4.2%). $\delta_{\text{H}}(\text{CDCl}_3)$ 8.15 (1 H, s), 4.36 (1 H, br s), 3.29 (1 H, br s), 1.0–2.1 (20 H, m), and 1.67 (6 H, s); $\delta_{\text{C}}(\text{CDCl}_3)$ (50 MHz) 163.47 (br q), 156.35, 102.08 (q), 83.03 (q), 63.89, 58.74, 34.40, 30.74, 26.43, 25.54, 25.21, 24.94, and 24.59; m/z 335 (M^+ , 1%), 277 (11), 259 (22), 204 (14), 150 (14), 110 (19), 98 (24), 83 (43), 67 (31), and 55 (100).

5-(2-[1- ^2H]Cyclohexyl-2-cyclohexyl-2-azaethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (5) (Method A, 46%). m.p. 166–168 °C; δ (^2H) (CHCl_3) 4.35 (s) and 3.30 (s); m/z 336 (M^+ , 10%), 278 (70), 260 (100), 205 (38), 204 (33), and 55 (83).

5-(2-Isopropyl-2-phenyl-2-azaethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (6) (Method A, 63%). m.p. 166–167 °C (from ethanol) (Found: C, 66.2; H, 6.45; N, 4.5. $\text{C}_{16}\text{H}_{19}\text{NO}_4$ requires C, 66.45; H, 6.55; N, 4.85%). $\delta_{\text{H}}(\text{CDCl}_3)$ (peaks of minor rotamer given in parenthesis) 8.35 (8.12) (1 H, s), 7.0–7.5 (5 H, m), 5.10 (5.35) (1 H, m), 1.58 (1.72) (6 H, s), and 1.40 (1.21) (6 H, d); $\delta_{\text{C}}(\text{CDCl}_3)$ (major rotamer only) 160.08 (q), 156.05, 143.13 (q), 129.04, 127.98, 124.97, 102.61 (q), 86.50 (q), 62.79, 26.63, and 22.28; m/z 289 (M^+ , 9%), 232 (22), 231 (100), 186 (19), 158 (50), 144 (34), and 118 (56).

1*H*-Pyrrol-3(2*H*)-ones (General Method).—The appropriate Meldrum's acid derivative was sublimed at 10^{-2} – 10^{-3} Torr through a furnace tube (35 $\times$ 2.5 cm) which was maintained at 600 °C. The product was collected in a U-tube which was cooled by liquid nitrogen, and situated at the exit point of the furnace. The following 1*H*-pyrrol-3(2*H*)-ones were prepared.

1-Cyclohexyl-2,2-pentamethylene-1*H*-pyrrol-3(2*H*)-one (4) [from the 2,2-dicyclohexyl derivative (2.0 g, 6 mmol); sublimation temperature 180–200 °C; pyrolysis time 5 h] (1.02 g, 73%), m.p. 200–202 °C (from toluene) (Found: C, 77.05; H, 9.9; N, 6.1. $\text{C}_{15}\text{H}_{23}\text{NO}$ requires C, 77.2; H, 9.95; N, 6.0%). $\delta_{\text{H}}(\text{CDCl}_3)$ 7.82 (1 H, d, $^3J_{4,5}$ 3.4 Hz), 4.97 (1 H, d, $^3J_{4,5}$ 3.4 Hz), 3.14 (1 H, m), and 1.0–2.3 (20 H, m); $\delta_{\text{C}}(\text{CDCl}_3)$ 205.61 (q), 158.39, 94.23, 67.96 (q), 52.56, 34.61, 30.31, 25.77, 24.90, 24.69, and 19.42; m/z 233 (M^+ , 97%), 178 (100), 150 (48), 122 (27), 95 (28), 81 (35), and 55 (58); λ_{max} 328 nm (ϵ 12 400).

2,2-Dimethyl-1-phenyl-*H*-pyrrol-3(2*H*)-one [from the 2-isopropyl-2-phenyl derivative (0.60 g, 2.1 mmol); sublimation temperature 140–160 °C; pyrolysis time 1.5 h] (0.25 g, 64%), m.p. 85–87 °C (from hexane) (Found: C, 76.8; H, 7.15; N, 7.3. $\text{C}_{12}\text{H}_{13}\text{NO}$ requires C, 77.0; H, 6.95; N, 7.5%). $\delta_{\text{H}}(\text{CDCl}_3)$ 8.10 (1 H, d, $^3J_{4,5}$ 3.6 Hz), 7.0–7.5 (5 H, m), 5.37 (1 H, d, $^3J_{4,5}$ 3.6 Hz), and 1.36 (6 H, s); $\delta_{\text{C}}(\text{CDCl}_3)$ 205.73 (q), 160.19, 139.88 (q), 129.39, 125.47, 121.99, 99.11, 68.65 (q), and 23.04; m/z 187 (M^+ , 59%), 172 (15), 158 (26), 144 (37), and 118 (100).

Pyrolyses of 5-(2-[1- ^2H]Cyclohexyl-2-cyclohexyl-2-azaethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (5). (a) 600 °C Pyrolysis. A sample of the [^2H]-labelled compound (0.10 g) was pyrolysed under the standard conditions at 600 °C (5– 10×10^{-3} Torr). The pyrrolone product (0.04 g, 58%) had $\delta_{\text{H}}(\text{CDCl}_3)$ 7.80 (1 H, superimposed s and d), 4.95 (<1 H, d), 3.10 (<1 H, br s), and 1.0–2.3 (20 H, m); δ (^2H) (CHCl_3) 4.98 and 3.10; m/z 234 (M^+ , 100%) and 179 (83); significant ($M + 1$) and ($M - 1$) peaks were absent.

(b) *Co-pyrolysis with the 2-isopropyl-2-phenyl derivative* (6). Samples of the [^2H]-labelled compound (5) (0.057 g, 0.16 mmol) and the 2-isopropyl-2-phenyl derivative (6) (0.064 g, 0.24 mmol) were sublimed at 155 °C and 10^{-3} Torr during 15 min into the furnace, which was maintained at 600 °C. Problems of differential volatility were overcome by placing the former compound on a foil boat, and the latter in a small test-tube, within the inlet heater. The mixture of pyrrolones so obtained, analysed by ^1H n.m.r. spectroscopy, showed clean doublets at δ_{H} 8.13 and 5.40 (integral ratio 1:1) due to the 2,2-dimethyl-1-phenyl compound (9), and a more intense superimposed doublet and singlet (δ_{H} 7.80) and a doublet (δ_{H} 4.94) (integral ratio 1:0.56) corresponding to the labelled 1-cyclohexyl-2,2-pentamethylene derivative (4). No scrambling of deuterium could be detected.

(c) *Measurement of isotope effect for the hydrogen transfer.* Problems of reproducibility were encountered, partly because of ready back-exchange of deuterium from the 4-position, and partly because of the requirement for very accurate peak integration. Control experiments at the optimum temperature (600 °C) showed that recrystallisation of the product from

toluene gave much better spectra without significant alteration of the relative areas, and so this procedure was adopted at all temperatures used (500, 550, 600, and 650 °C; only low yields of pyrrolone were obtained at temperatures below 500 and above 650 °C). In practice, pyrolysis of 150–300 mg generally gave a sample (40–80 mg) of purified material, which was divided into two portions and was analysed by ^1H and ^2H n.m.r. spectroscopy. The results are given in Table 3.

Crystal Data for 1-Cyclohexyl-2,2-pentamethylene-1H-pyrrol-3(2H)-one.— $\text{C}_{15}\text{H}_{23}\text{NO}$, $M_r = 233.4$, orthorhombic, space group $P2_12_12_1$, $a = 10.672(4)$, $b = 10.986(4)$, $c = 11.581(4)$ Å, $v = 1357.8$ Å ^{3} , $Z = 4$, $D_c = 1.141$ g cm $^{-3}$, $\lambda(\text{Mo-K}_\alpha) = 0.71069$ Å, $\mu = 0.66$ cm $^{-1}$, $F(000) = 512$, $T = 293$ K. Final $R = 0.055$ from 693 observed reflections.

A clear crystal of dimensions $0.2 \times 0.2 \times 0.2$ mm was used; intensities of 1300 unique reflections were measured out to θ 25° using a Nonius CAD-4 diffractometer with graphite monochromator; 693 reflections with $I > 2.5\sigma(I)$ were used in refinement; the structure was solved by direct methods.²⁵ All hydrogen atoms except the methylene hydrogens on C(13) were located on difference Fourier maps, and positional and isotropic thermal parameters were refined. H(131) and H(132) were included in their calculated position with fixed thermal parameters. Non-hydrogen atoms were refined anisotropically. The maximum ratio of least-squares fit to error was 0.11. Maximum and minimum peak heights in the final difference map are 0.19 and 0.17 e Å $^{-3}$. The weighting scheme was $w = 1/[\sigma^2(F) + 0.0008F^2]$ which gave a final R 0.055 and R_w 0.058.

Fractional co-ordinates for all atoms are given in Table 1. Bond lengths, bond angles, and selected torsion angles are given in Table 2. Thermal parameters have been deposited as Supplementary Publication No. SUP 56565 (3 pp.).* A labelled drawing of the molecule is given in Figure 1 and a packing diagram in Figure 2.

* For details of the Supplementary Publications Scheme, see Instructions for Authors (1986), *J. Chem. Soc., Perkin Trans. 1*, 1986, issue 1. Structure factor tables are available from the editorial office on request.

References

- 1 H. J. Gordon, J. C. Martin, and H. McNab, *J. Chem. Soc., Chem. Commun.*, 1983, 957.
- 2 J. Besida and R. F. C. Brown, *Aust. J. Chem.*, 1982, **35**, 1385, and earlier papers in the series.
- 3 H. J. Gordon, J. C. Martin, and H. McNab, *J. Chem. Soc., Perkin Trans. 1*, 1984, 2129.
- 4 H. Briel, A. Lukosch, and C. Wentrup, *J. Org. Chem.*, 1984, **49**, 2772.
- 5 H. McNab and L. C. Monahan, *J. Chem. Soc., Chem. Commun.*, 1985, 213.
- 6 E. Anklam, R. Ghaffari-Tabrizi, H. Hombrecht, S. Lau, and P. Margärelth, *Helv. Chim. Acta*, 1984, **67**, 1402.
- 7 H. Dhimane, J. C. Pommelet, J. Chuche, G. Lhomme, M. G. Richaud, and M. Haddad, *Tetrahedron Lett.*, 1985, **26**, 833.
- 8 G. A. Bihlmayer, G. Derflinger, J. Derkosch, and O. E. Polansky, *Monatsh. Chem.*, 1967, **98**, 564.
- 9 H. Egger, *Monatsh. Chem.*, 1967, **98**, 1245.
- 10 H. McNab and I. Stobie, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1845.
- 11 For example, J. Davoll, *J. Chem. Soc.*, 1953, 3802.
- 12 K.-H. Klaska, O. Jarchow, T. Eicher, and H. Preut, *Acta Crystallogr., Sect. B*, 1979, **35**, 2788.
- 13 H. Briel and C. Wentrup, unpublished work, quoted in footnote 29 of ref. 4.
- 14 H. McNab and E.-A. Murray, *J. Chem. Soc., Chem. Commun.*, 1981, 722, and unpublished results.
- 15 W. Klop and L. Brandsma, *J. Chem. Soc., Chem. Commun.*, 1983, 988.
- 16 Cf. A. Viola, J. J. Collins, and N. Filipp, *Prepn. Div. Pet. Chem., Am. Chem. Soc.*, 1979, **24**, 206.
- 17 C. H. De Puy and R. W. King, *Chem. Rev.*, 1960, **60**, 431.
- 18 W. S. Trahanovsky and C. C. Ong, *J. Am. Chem. Soc.*, 1970, **92**, 7174.
- 19 W. S. Trahanovsky and M. E. Scribner, *J. Am. Chem. Soc.*, 1984, **106**, 7976.
- 20 K. Wiberg, *Chem. Rev.*, 1955, **55**, 713.
- 21 H. Kwart, *Acc. Chem. Res.*, 1982, **15**, 401.
- 22 D. J. McLennan and P. M. W. Gill, *J. Am. Chem. Soc.*, 1985, **107**, 2971.
- 23 Shell Devel. Co., U.S.P. 2 418 173 (1944), quoted in 'Beilstein,' drittes Ergänzungswerk, 1972, vol. 12, p. 32.
- 24 G. S. Hiers and R. Adams, *Chem. Ber.*, 1926, **59**, 162.
- 25 G. Sheldrick, SHELX 84, Program for Crystal Structure Solution, University of Göttingen, 1984.

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