MECHANISTIC STUDIES

OF

THE REACTION OF UREA WITH SELECTED DIKETONES

A Thesis

presented for the degree of

DOCTOR OF PHILOSOPHY

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by

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ABSTRACT

Although urea is often considered to be an unreactive molecule, it will react very readily with certain diketones. The reactions of urea, N-methylurea and N, N'-dimethylurea with a β -diketone and three different α -diketones were investigated. In all cases, the spectral changes of the reaction were examined and, where appropriate, the variation of the rate constants with the urea, acid and alkali concentrations was investigated. The products were also prepared and, whenever possible, identified.

Pyrimidin-2(1H)-ones result from the reaction of the ureas with pentane-2, 4-dione in the presence of acid. Results showed that the mechanism involves slow attack of the protonated keto-enol tautomer of pentane-2, 4-dione by protonated urea followed by rapid cyclisation.

The reaction of benzil with urea was investigated under alkaline and acidic conditions. In the presence of alkali, urea and N-methylurea result in 5, 5-diphenylhydantoins while N, N'-dimethylurea forms a cyclic diol. Reaction was found to be the slow attack of benzil by the urea anion followed by rapid cyclisation to yield cyclic diols. The hydantoins result from a slow benzilic acid type rearrangement of the diols but the N, N'-dimethylurea diol is unable to undergo this rearrangement.

In the presence of acid, three different products result from the reaction of benzil with urea, N-methylurea and N, N'-dimethylurea. The kinetic evidence suggested that similar cyclic diol intermediates result in all three cases

from the slow attack of protonated benzil by the unprotonated urea followed by rapid cyclisation. The urea and N-methylurea intermediates are subsequently attacked by a second urea molecule to yield two different diureides. The N, N'-dimethylurea diol undergoes a pinacol-pinacolone type rearrangement to yield a hydantoin.

The reactions of urea with butane-2, 3-dione and 1-phenylpropane-1, 2-dione in the presence of acid proved to be more complex than that with benzil. Products similar to those obtained with benzil were isolated from urea and N-methylurea but these products apparently undergo further reaction in the presence of acid to yield intensely coloured products. In spite of much work, the identity of these coloured products remained a mystery and little could be said about the mechanism of the reactions with these two diketones. What is evident is that the presence of a methyl group adjacent to at least one of the carbonyl groups results in colour formation. Benzil, with no adjacent methyl groups, does not form any intense colours during reaction with urea.

DECLARATION

I declare that this thesis is based on the results of experiments carried out by me, that it is my own composition, and that it has not previously been presented for a Higher Degree.

This thesis describes the results of research carried out in the Department of Chemistry of the University of St. Andrews, under the supervision of Dr. A.R. Butler, between October 1974 and June 1977.

CERTIFICATE

I hereby certify that Elizabeth Leitch has spent twelve terms at research work under my supervision, has fulfilled the conditions of Ordinance General No. 12 and Resolution of the University Court 1967, No. 1, and is qualified to submit the accompanying thesis in application for the degree of Doctor of Philosophy.

Director of Research

ACKNOWLEDGEMENTS

I would like to thank Dr. A. R. Butler for suggesting this topic of research and for his help and encouragement throughout this work.

My thanks also go to members of the Chemistry Department for helpful discussion and assistance, to Mrs. E. J. West for her careful typing of this thesis and to my husband for his encouragement.

Finally, I gratefully acknowledge a studentship from the University of St. Andrews.

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CHAPTER I

INTRODUCTION

Friedrich Wöhler 1800-1882

General

Urea is of historical interest in the development of organic chemistry. At the beginning of the nineteenth century it was widely believed that organic compounds, as distinct from inorganic compounds, could only be produced under the influence of a 'vital force'. In 1828, the German chemist Friedrich Wöhler[1] reported the synthesis of organic urea from inorganic starting materials (cyanogen and ammonia). Wöhler's synthesis of urea is often regarded today as the first synthesis of an organic compound and that it brought about the end of the 'vitalistic theory'. This has been shown by Berrie[2] and others[3,4] to be an erroneous view.

For instance, in 1812 John Davy[5] apparently prepared urea from the reaction of phosgene with ammonia but he did not realise the product of the reaction as such. The following extract relates what happened :

> "(When phosgene was) mixed with ammonical gas, a rapid condensation took place, a white salt was formed, and much heat was produced.
>
> The compound of this gas and ammonia was a perfect neutral salt, neither changing the colour of turmeric or litmus ; it had no perceptible odour, but a pungent saline taste ; it was deliquescent, and of course very soluble in water; ....."[5].

If Davy cannot claim the credit for the first organic synthesis as he did not identify the product, the credit must then to to Wöhler not for the synthesis of urea but of oxalic acid. In 1824, Wöhler[6] prepared oxalic acid by the

hydrolysis of cyanogen gas in aqueous ammonia. Urea was also prepared in the same reaction but was not recognised at that time by him. Oxalic acid was, at that time, well known as an organic compound and Wöhler's synthesis was reported, but the significance of this synthesis in relation to the 'vitalistic theory' was apparently not recognised[2].

When he reported the synthesis of urea in 1828, Wöhler realised the implications of his discovery. He wrote to Berzelius on 22nd February 1828 :

> "I cannot, so to speak, hold my chemical water ...
> I can make urea without the necessity of a kidney .."[7]

However, in the very same letter, Wöhler admitted that his experiment did not necessarily disprove the 'vitalistic theory' as some might conclude that 'vitalism' was still present in the starting materials which were themselves of animal origin.

Wöhler's experiment attracted much interest[2] at that time, partly because of its being an example of the synthesis of an organic compound from inorganic compounds and partly because of it having demonstrated the isomeric properties[1] of urea and ammonium cyanate. However, as Berrie[2] has shown, the theory of 'vitalism' continued to be widely held for a variety of reasons. Some scientists, like Wöhler, pointed out that the starting materials were of animal origin. Others stated that urea was an excretion product or a product of degradation and that as such it could not be classed as a true organic substance. It was only through the continued accumulation of further

Figure 1. Mesomeric structure of urea

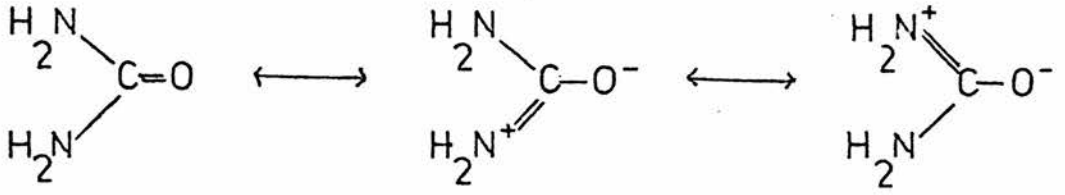
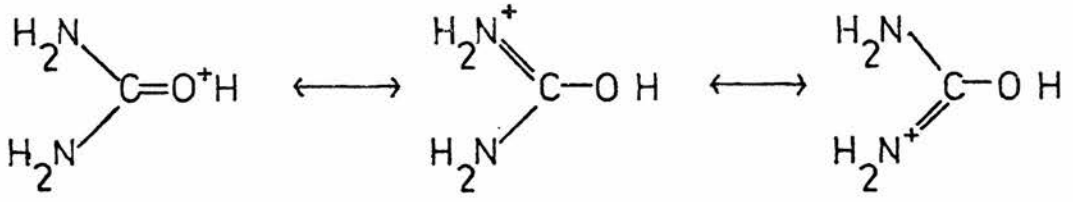


Figure 2. Mesomeric structure of O-protonated urea cation



chemical knowledge over several decades that belief in 'vitalism' gradually declined.

As early as 1830, urea was recognised by Dumas[8] as being the amide of carbonic acid but even a hundred years after Wöhler's synthesis, the fine structure of urea was still a matter of debate. No less than eight structures have been proposed for urea[9]. Today X-ray data, dielectric constant measurements and other evidence are strongly in favour of a mesomeric structure where the dipolar form makes a significant contribution[8]. (Figure 1).

Protonation of urea.

The site of protonation of urea and other amides has also been a matter of controversy. There is an excellent review[10] on the subject and some of the main evidence is considered here. The mesomeric structures for urea suggest that O-protonation is more likely than N-protonation. O-protonation would result in a cation that is itself resonance-stabilised (Figure 2). However, those in favour of N-protonation either suggest that the mesomeric structures are not important or that the stabilisation arising from the resonance is not enough to outweigh the effect of the greater basicity of the nitrogen atom over the oxgen atom.

The evidence in favour of N-protonation comes principally from I. R. data. It has been suggested that the carbonyl stretch frequencies for amides should be lower for O-protonated cations and higher for N-protonated

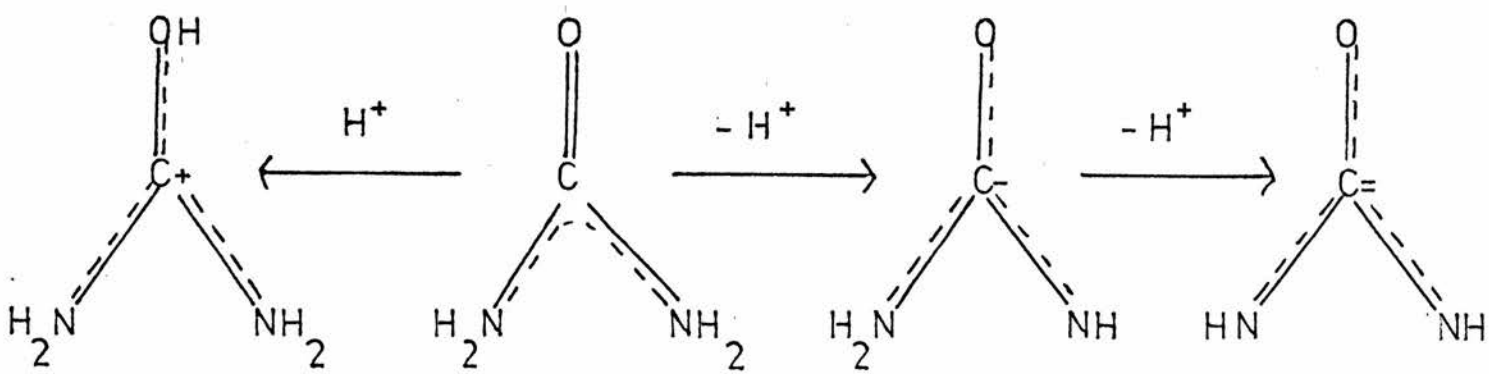
cations than for the unprotonated amide. Several instances have been reported where strong bands (assumed to be carbonyl bands) have been found for amide cations at frequencies higher than those recorded for the carbonyl bands of the parent amides. For example, Davies and Hopkins[11], in a study of urea nitrate, found that the cation had a band at 1670 cm^{-1} as compared to the carbonyl band of urea itself at 1610 cm^{-1}. They also suggested that the bands observed at 3260 and 3200 cm^{-1} were characteristic of NH_3^+. Similar conclusions were reached by Spinner[12] in a I. R. study of the hydrochlorides of urea, thiourea and acetamide.

These conclusions were, however, challenged by the work of Stewart and Muenster[13] who prepared O^{18}-labelled dicyclohexylurea and its toluene-p-sulphonate salt. The carbonyl band of the labelled urea showed the expected shift to a lower frequency due to isotopic substitution. But in the salt the band at 1669 cm^{-1}, often attributed to carbonyl stretching in amide salts, showed no such isotopic shift. It is thus evident that such bands had previously been wrongly attributed to carbonyl stretching.

Proton n.m.r. studies of amides have been overwhelmingly consistent with O-protonation[14,15]. Redpath and Smith[16] also came to the conclusion that urea is O-protonated in their proton n.m.r. study of urea salts at low temperatures.

Overall, the evidence is seen to be strongly in favour of O-protonation. This, however, does not exclude the possibility that a small proportion of N-protonated urea may still exist and that it may even be the

Figure 3. 'Y-delocalisation' in urea[18]



reactive species undergoing reaction in some reactions of urea under acid conditions. Fraenkel and Franconi[14], for instance, have detected a very small amount of N-protonation in their proton n.m.r. study of certain amides. However, in the present study of the reactions of urea with diketones under acid conditions, it has been assumed that urea is O-protonated.

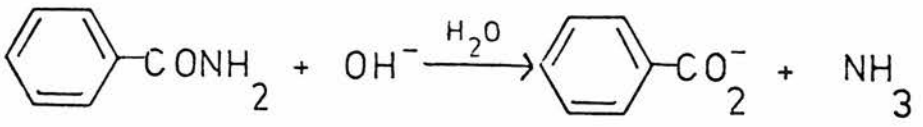
The urea anion.

As well as their behaviour as bases, amides behave as very weak acids by losing a proton from the amino group. Hine and Hine[17], among others, have deduced several pK_a values for amides as acids, but there appears to be no reported value for urea itself. In the coming study of the reaction of urea with benzil under alkaline conditions, it will be seen that there are grounds for believing that it is the urea anion that undergoes reaction.

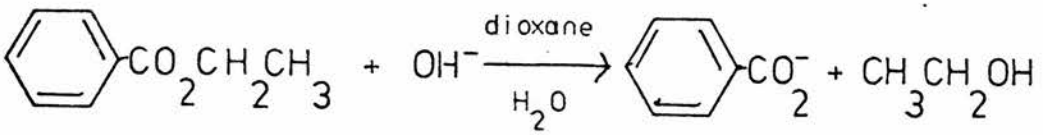
Hydrolysis of urea and other amides.

A look can now be taken into the reactions of urea and amides in general. Urea is often considered to be an unreactive molecule. Its stability has even been attributed to a type of aromaticity known as 'Y-delocalisation' (Figure 3)[18]. Like amides, urea is resistant to non-enzymatic hydrolysis. The relative stability of amides towards hydrolysis is illustrated by comparing the rates of hydrolysis of an amide with a similar ester under comparable conditions (Scheme 1)[19]. The ester is seen to undergo hydrolysis at a rate of almost 10^3 times faster than the amide.

Scheme 1. Hydrolysis of an amide and an ester



$k^{40^{o}} = 4.0 \times 10^{-5}$ l mol^{-1}s^{-1}



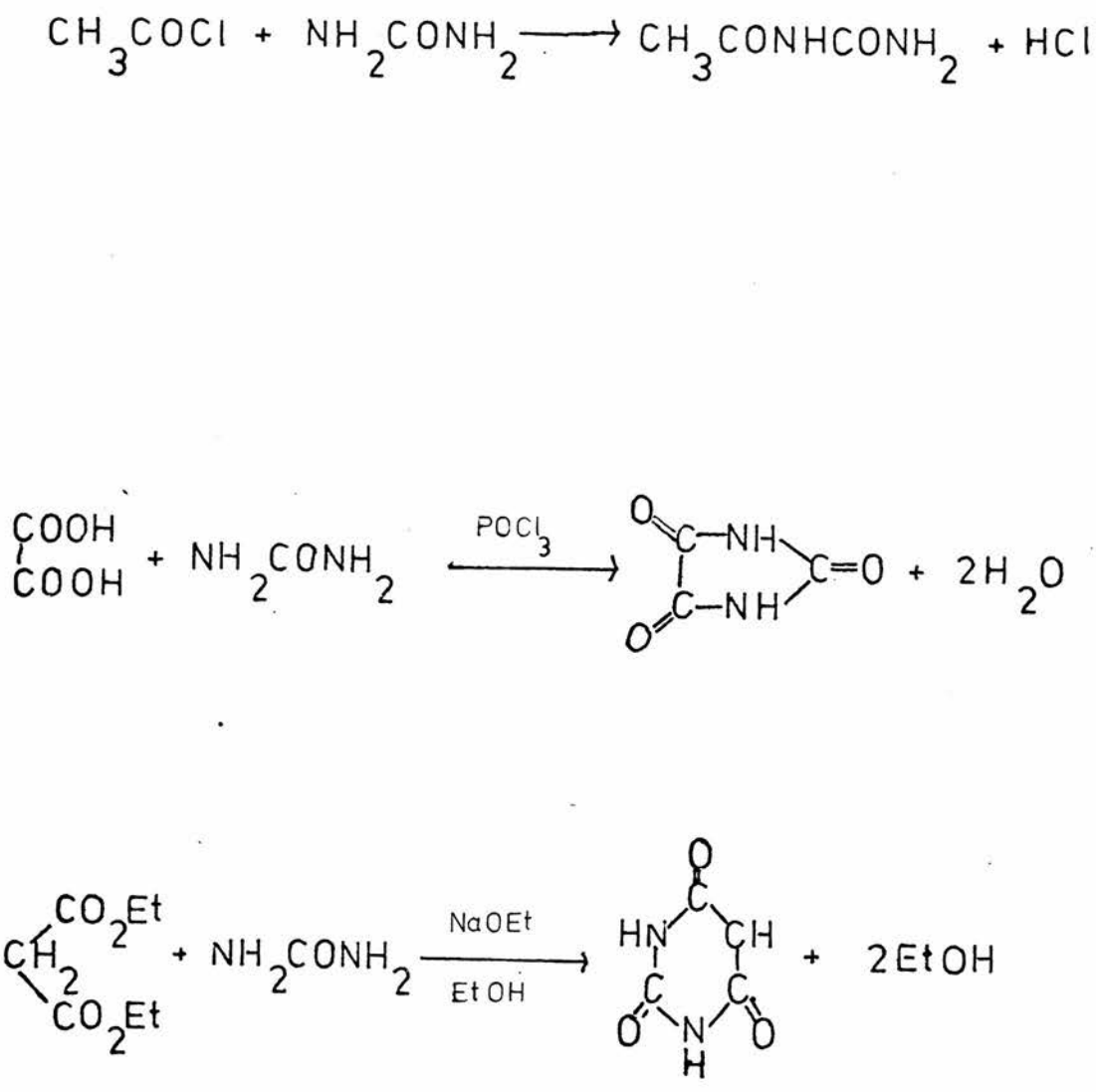
$k^{40^{o}} = 2.58 \times 10^{-2}$ l mol^{-1}s^{-1}

Although both urea and amides are resistant to hydrolysis, the hydrolysis of urea apparently differs in several respects from the hydrolysis of simple amides[8]. Analysis of the mechanism of hydrolysis of urea is complicated by the fact that, in aqueous solution, urea is in equilibrium with ammonium cyanate, and the cyanate ion is very readily hydrolysed by acids (and less so by alkalis). There are several mechanistic studies of the hydrolysis of urea[20,21].

The reverse reaction - the formation of urea from ammonium cyanate - has also been a subject of much study. Frost and Pearson[22] have written an excellent review on the mechanism of this reaction. More recently, there has also been a kinetic investigation of the formation of urea from amines and cyanic acid[23].

Urea is very readily hydrolysed into ammonium carbonate by the enzyme urease which was first isolated from jack beans by Sumner[24]. The catalytic power of urease can be seen by comparing the relative rates of enzymatic and non-enzymatic hydrolysis[25]. The hydrolysis of urea, when catalysed by urease at 20.8^{o} at pH 8.0, has a first-order rate constant of 3×10^{4} sec^{-1}. Non-enzymatic hydrolysis has a first-order rate constant of 4.15×10^{-5} sec^{-1} at 100^{o} which, if extrapolated back, is equal to about 3×10^{-10} sec^{-1} at 20.8^{o}. Urease therefore accelerates the rate of hydrolysis by a factor of 10^{14}. Urease was thought by Sumner[26] to be completely specific for urea, but hydroxyurea[27], dihydroxyurea[28] and semicarbazide[26] have all

Scheme 2. Some displacement reactions of urea[29]



been reported as substrates for urease.

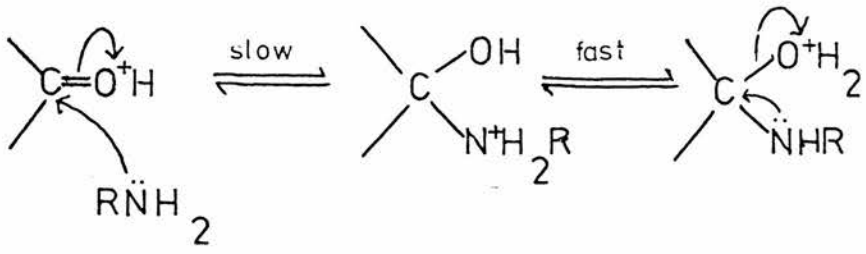
Reactions of urea with other organic compounds.

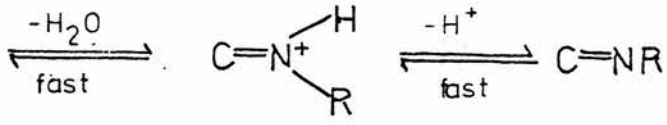
Urea appears to react with few other organic compounds, but it does undergo a few displacement reactions[29]. Acid chlorides and acid anhydrides will react to form ureides. Dicarboxylic acids also react with urea in the presence of phosphoryl chloride to form cyclic ureides. Reaction is also known with diesters, notably with malonic ester which was used in one of the first methods of preparing barbituric acid. These reactions are illustrated in Scheme 2. It will be seen in these examples that reaction involves the displacement of a good leaving group by the urea molecule rather than attack on the carbonyl group. However, urea does show a surprising readiness to react with certain carbonyl compounds, particularly with α- and β-dicarbonyl compounds. In this thesis, the result of an investigation into the mechanism and kinetics of the reactions of urea with selected diketones is presented.

Reaction of the amino group with carbonyl compounds.

Before discussing the results of the work carried out in this thesis, it is worthwhile to review the reactions of compounds containing an amino group with carbonyl compounds. The presence of a pair of non-bonded electrons on the nitrogen of the amino group makes it an excellent nucleophile to attack the polarised carbonyl group. Thus the reactions of ammonia, amines,

Scheme 3. Reaction of amines with carbonyl group





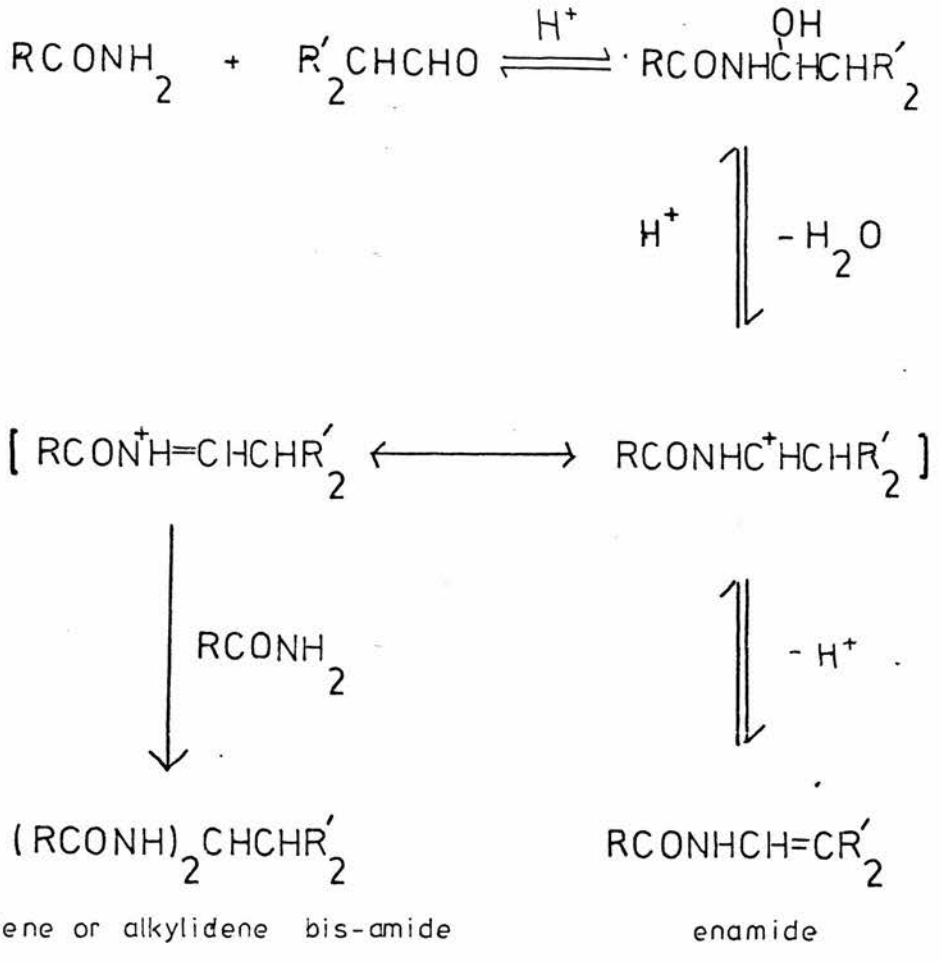
hydroxylamine, hydrazines and semicarbazides with carbonyl compounds are well known.

Reaction with ammonia often results in the formation of polymeric products as the carbon-nitrogen bond formed has no particular stabilisation[30,31]. With N-substitution, products become more stable and reaction usually results in the formation of a carbon-nitrogen bond via the dehydration of the initial carbinolamine intermediate.

The kinetics of the formation of Schiff bases[32,33], oximes[34,35], semicarbazones[34,35,36], and phenylhydrazones[35,37] in aqueous solution have all been extensively investigated. The general mechanism for this type of reactions is usually depicted as in Scheme 3[38]. The reactions are generally first order in the carbonyl compound and in the nitrogen base and are subject to general acid catalysis. Reactions normally proceed in two main steps : a) formation of the carbinolamine intermediate and b) dehydration of the intermediate. The rate-determining step is pH dependent. In neutral solutions the rate-determining step is the dehydration of the carbinolamine intermediate. However, at low pH dehydration becomes fast and also the concentration of free amine decreases so that the first step becomes rate-limiting. This pH dependent behaviour results in bell-shaped curves for pH-rate profiles which are characteristic of this type of reactions.

The isolation of the carbinolamines is difficult as these intermediates are generally not stable, but there are a few reported instances where stable

Scheme 4. Reaction of amides with carbonyl group[42]



carbinolamine intermediates have been successfully prepared[39,40]. Strong evidence for a two step mechanism comes from the observation of the U.V. spectra of certain carbonyl compounds before and immediately after the addition of the nitrogen base. For example the addition of hydroxylamine, O-methylhydroxylamine or semicarbazide to a solution of furfural at neutral pH results in a rapid drop in the absorption due to furfural and is due to the formation of the carbinolamine intermediate[34]. Dehydration of the intermediate results in the slow formation of a new absorbance at almost the same wavelength as that of furfural. Similar results were observed in the reaction of hydroxylamine with p-chlorobenzaldehyde at pH 8[41].

These spectral changes are of interest because spectral changes of a similar nature were observed in the study of the reaction of urea with benzil which will be discussed in this thesis.

Like amines, amides also add to carbonyl compounds and the initial product is usually a carbinolamine which is stable in neutral and mildly basic solutions. In the presence of acid, dehydration and further reaction can occur and two types of products are possible. Further coupling may occur with the amide to give a alkylidene or arylidene bis-amide product. Also for carbonyl compounds with at least one α-hydrogen atom, elimination of water may result in an enamide (Scheme 4)[42].

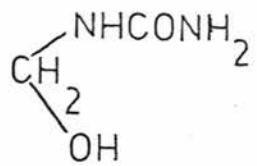
The second step of the reaction of amides with carbonyl compounds thus differs from the usual elimination of water to produce a carbon-nitrogen double bond observed with amines. The presence of a carbonyl group adjacent

to the attacking amino group makes the nitrogen atom less basic. Because of this weak nucleophilic property of amides, catalysis becomes more important. Reaction also often requires more activated carbonyl compounds and relatively high temperatures[42].

The following examples are illustrative of the situation. Under neutral and mildly basic conditions aldehydes such as formaldehyde and chloral (with electron-withdrawing substituents) will react with a variety of amides at temperatures of 100° or above to yield carbinolamine type products[43,44]. Acetamide will react with a number of aldehydes at 100° to give the bis-amides[45].

Ketones are generally less reactive than aldehydes and only a few examples of addition to ketones are known. Newallis and Rumanowski[46] have prepared a number of carbinolamine products from the reaction of a variety of amides with halogenated derivatives of acetone. Because of the highly activated nature of the carbonyl compounds reaction occurs quite readily at temperatures of 50° or below. An enamide N-(1-cyclohexenyl)-phenylacetamide has been prepared from the reaction of phenylacetamide with cyclohexanone[47], but high temperature and long reaction time were required for the product to be formed.

Most of the kinetic investigation of the reactions of amides with carbonyl compounds have been in studies of hydroxymethylation (reaction with formaldehyde). The aqueous base-catalysed addition of acetamide and benzamide to formaldehyde has been investigated by Crowe and Lynch[48]. They suggest that base catalysis is assosiated with the formation of amide



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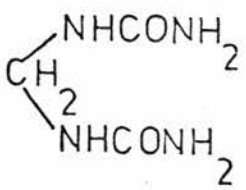


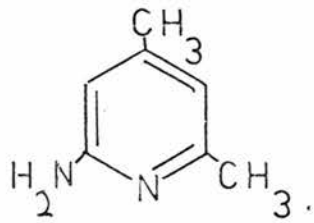
III

anion which attacks the formaldehyde. The acid catalysed reaction with formaldehyde has also been investigated by Imoto and Kobayashi[49] for a series of alkylamides and substituted benzamides. They propose that the rate-determining step is the attack of protonated formaldehyde on the neutral amide.

The above two kinetic investigations are of interest because in both the base and acid catalysed reactions evidence is put forward for the nature of the reactive species. In the study of the reactions of urea with diketones described in this thesis, the same pairs of reactive species are proposed for base and acid catalysed additions.

Reaction of urea with the carbonyl group.

Like other amides, urea will condense with a number of aldehydes. Urea as an amide is further complicated by the presence of an extra amino group which may also undergo reaction. One of the best known reactions of urea is that with formaldehyde which subsequently results in the formation of urea-formaldehyde resins[50]. The simplest product obtained from the reaction of urea with formaldehyde is monomethylolurea (I) but this may undergo further reaction, either with another molecule of formaldehyde to give the dimethylolurea(II), or with another molecule of urea to give methylene diurea (III). Further reaction under suitable conditions results in polymeric products. The kinetics of the formation of mono- and di-methylolurea have been investigated by de Jong and de Jonge[51]. The reactions are similar and are both acid and base



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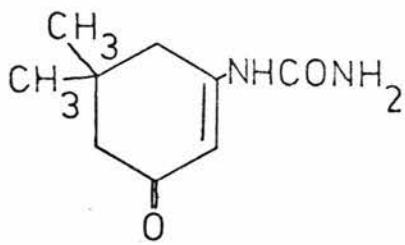


V

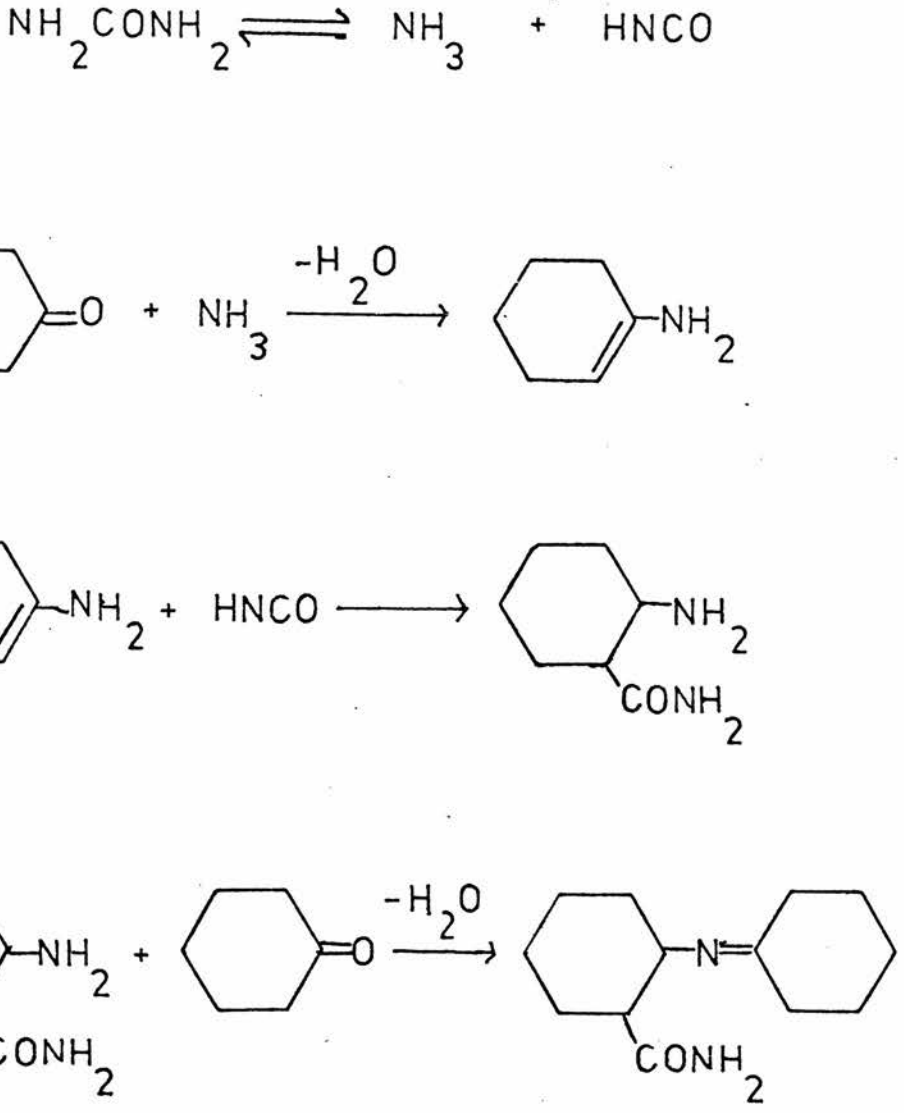
catalysed. As in the reactions of other amides it is believed that acid catalysis involves the free urea attacking the protonated formaldehyde, and base catalysis involves the urea anion attacking the free formaldehyde.

The condensation of urea with other aliphatic aldehydes has also been reported[52, 53]. The products of the reactions are principally alkylidene-diureas, though other products are possible. Kinetic studies of the reaction[52, 53] show that the reactions between urea and aliphatic aldehydes follow a mechanism similar to that suggested for formaldehyde. The rate determining step is the reaction of urea with the aldehyde to form the alkylolurea intermediate. The reaction of urea with benzaldehyde was carried out by Schiff[54]. As well as a benzodiureide ($C_9H_{12}N_4O_2$), other polymeric products were obtained.

As with amides, there are few examples of reactions of urea with monoketones. Riehm[55] apparently obtained a pyrimidine (IV) form the reaction of a molecule of urea with two molecules of acetone. Weinschenk[56] reported the condensation of urea hydrochloride with acetone which resulted in a product ($C_{11}H_{20}N_4O_2$) involving the reaction of three molecules of acetone with every two molecules of urea. More recently, the reaction of ureas with fluorinated and chlorinated acetone derivatives has been reported[46]. The products of the reaction were 1:1 carbinolamine-type adducts. Only ureas with primary amidic groups (such as urea, N-methylurea and N,N-dimethylurea) underwent reaction.

An enamide product (V) has been obtained by heating urea with

Scheme 5. Reaction of urea with cyclohexanone[58]

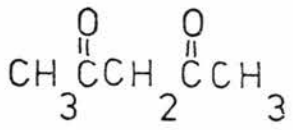


5, 5-dimethyl-1, 3-cyclohexanedione[57]. A more unusual product results from the reaction of urea with cyclohexanone under alkaline conditions[58]. Reaction is thought to involve the splitting of the urea molecule into ammonia and isocyanic acid, and the suggested mechanism is shown in Scheme 5.

Reactions of urea with monocarbonyl compounds therefore tend to be with more activated carbonyl compounds where polarisation of the carbonyl group is increased. Aldehydes are generally more reactive than ketones because the presence of a hydrogen atom rather than an alkyl group has less electron-repelling effect and increases the polarisation of the carbonyl group. Similarly, the presence of electron - withdrawing groups adjacent to the carbonyl group (as in the case of fluorinated acetone) will increase the polarisation of the carbonyl group. In other cases, reaction may require more drastic conditions such as elevated temperatures.

Reactions of urea with diketones.

Urea reacts very readily with certain diketones, particularly α- and β -diketones. This thesis is concerned with a study of the reactions of urea with selected diketones : pentane-2, 4-dione (VI), benzil (VII), butane-2, 3-dione (VIII), 1-phenylpropane-1, 2-dione (IX) and some of their substituted derivatives. Pentane-2, 4-dione is a β -diketone while the other three are α -diketones. The reactions of all four diketones were investigated under acidic conditions and that of benzil was also examined under alkaline conditions.



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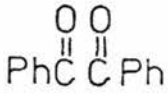

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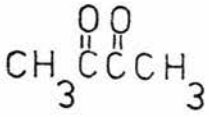
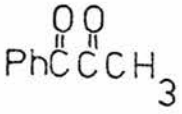


VIII



IX

With α-diketones it appears that reaction is favourable because the polarisation of the carbonyl groups is enchanced by their being adjacent to each other. The reason for the reactivity of β-diketones such as pentane-2,4-dione is probably due to the substantial amount of keto-enol and keto-keto tautomerism that they exhibit. As it will be seen from the work with pentane-2,4-dione, it is the keto-enol tautomer that undergoes reaction. Under acidic conditions, the enol group becomes protonated and forms an excellent leaving group when attacked by the urea molecule.

Acetone itself exhibits very little enol form and this helps to account for the fact it is not easy to obtain reaction between urea and acetone. It seems likely that acetonylacetone (hexane-2,5-dione) where the two carbonyl groups are separated by two methylene carbons also exists predominately in the keto-keto form. This would explain why no reaction was observed between acetonylacetone and urea when an attempt was made to react them together. As carbonyl groups of diketones become more separated, they are more likely to behave independently of each other.

The proximity of the carbonyl groups in α- and β-diketones makes intramolecular cyclisation possible after the initial reaction of a molecule of urea with the first carbonyl group. In this work it was found that in many cases intramolecular cyclisation did occur and that this second reaction was faster than the first reaction because of the entropy factors being more favourable for intramolecular reaction rather than intermolecular reaction. As the second reaction was much faster than the first, it was never possible to

isolate any product with only one carbonyl group reacted. In cases where a cyclic product was not isolated, the evidence shows that it seems probable that a cyclic intermediate is formed, but that this cyclic intermediate is attacked by another molecule of urea with ring-opening, especially if an excess of urea is present. Sometimes the cyclic intermediate will undergo rearrangement to give a more stable cyclic product and this was found to be the case with some of the benzil reactions.

The results of this work show that reaction between urea and diketones in acidic medium is the attack of the protonated diketone by the free urea which is consistent with the results observed for the reaction of other amino-group containing compounds with carbonyl compounds. Under basic conditions (as for the work with benzil) there are grounds for believing that reaction is between the urea anion and the free diketone.

Some surprising results were observed with α-diketones. Benzil reacts with urea and N-methylurea in a fairly simple manner under acidic conditions to yield white and readily identifiable diurea compounds. However, the replacement of one or both phenyl groups by methyl groups (as in 1-phenylpropane-1,2-dione and butane-2,3-dione) makes the reaction far more complex. It was possible to isolate white diurea products similar to those obtained with benzil, but in the presence of acid these diurea products undergo further reaction to produce very intense colours. It was not possible to isolate, or characterise fully, these coloured products and the structure of these coloured products is still a mystery. What is evident is that the presence

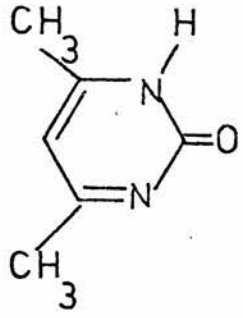
of at least one methyl group adjacent to one of the carbonyl groups will result in the formation of these colours.

These reactions of urea, N-methylurea and N,N'-dimethylurea with the diketones were investigated. Sometimes the reaction was tried out with N,N-dimethylurea but it was found that it either did not undergo reaction or if it did react, it reacted in a different way from the other ureas and it was not possible to isolate a product. There are two possible reasons for the behaviour of N,N-dimethylurea. One is that the more nucleophilic methylated end of the molecule tries to attack the diketone but is unable to react as there are no hydrogens on the nitrogen atom. The other possibility is that the hydrogenated end of the molecule may undergo reaction but that stabilisation of the intermediate by, say, cyclisation is not possible because of the two methyl groups. As expected, N,N,N',N'-tetramethylurea did not react at all with any of the diketones.

The next five chapters examine in detail the reaction of urea with each of the diketones used. Chapter II looks at the reaction with pentane-2,4-dione; chapters III and IV deal with the reactions with benzil under alkaline and acidic conditions and the last two chapters deal with butane-2,3-dione and 1-phenylpropane-1,2-dione.

CHAPTER II

REACTION WITH PENTANE-2, 4-DIONE



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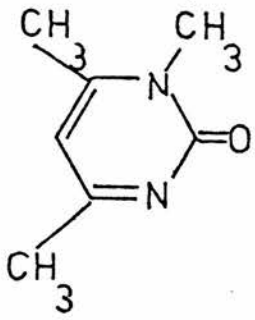

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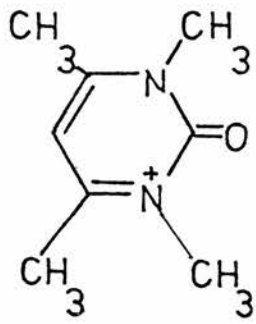

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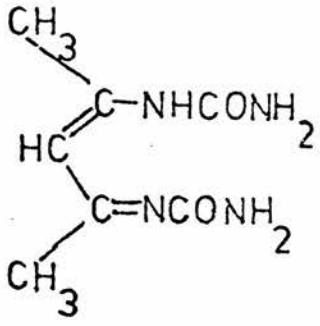

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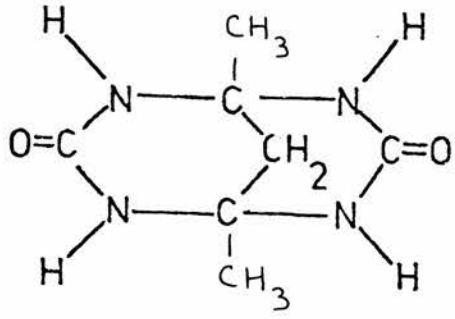

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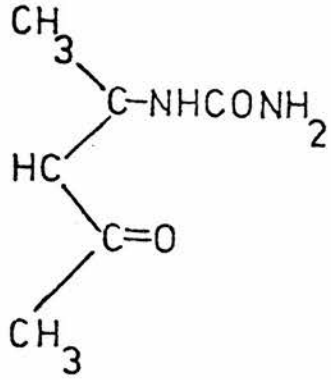


XV

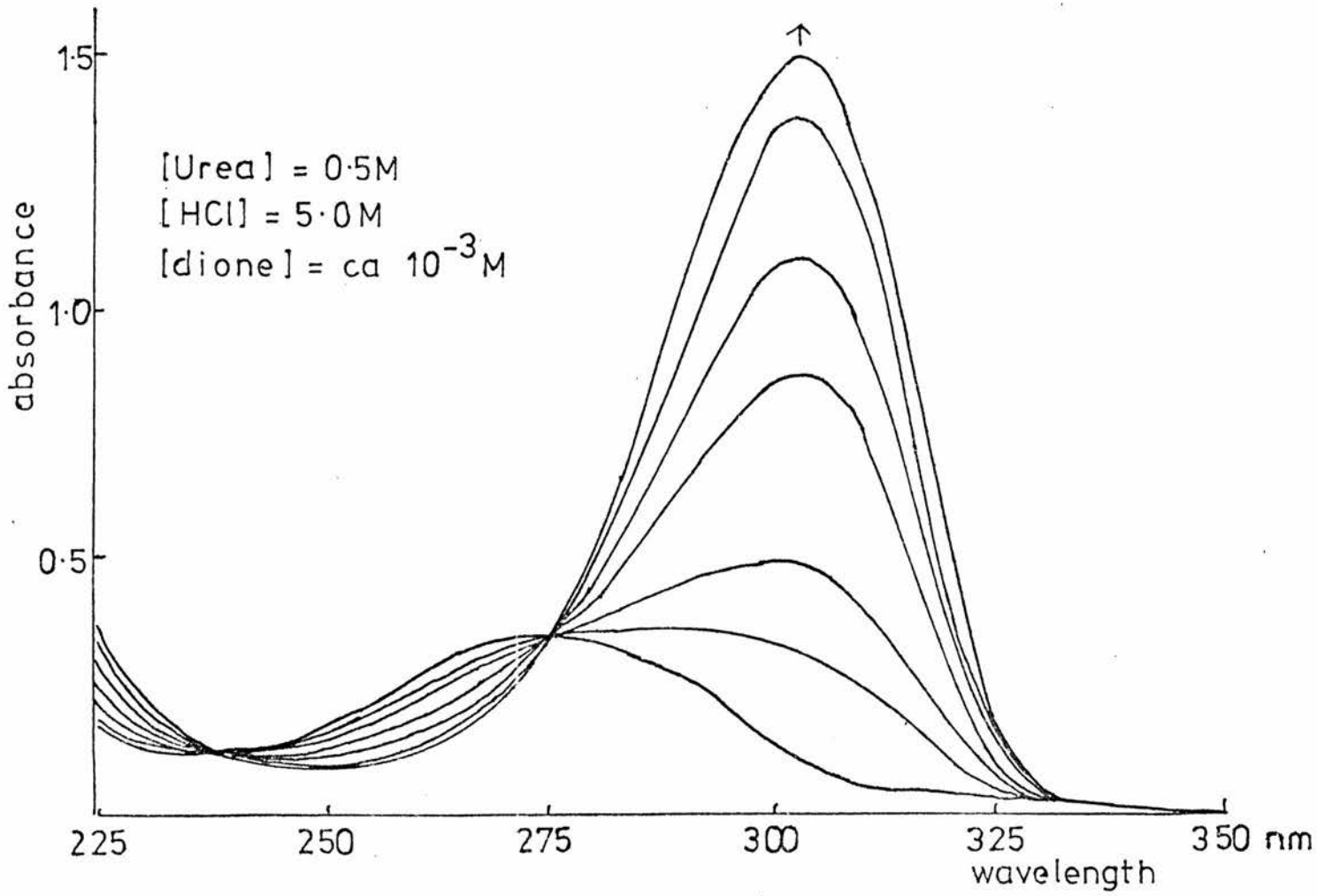
INTRODUCTION

Urea, N-methylurea and N,N'-dimethylurea react with pentane-2,4-dione (acetylacetone, VI) in the presence of acid to give pyrimidin-2(1H)-ones (X, XI and XII). By varying the reaction conditions it was also possible to isolate a diurea product (XIII or XIV) but this was not found to play any significant role in the mechanism of the reaction.

An investigation was undertaken into these reactions to gain some insight into the mechanism of the reactions of ureas with β-diketones. The results showed that the slow step of the reaction of urea with pentane-2,4-dione is the attack of the protonated pentane-2,4-dione by unprotonated urea. This is followed by rapid cyclisation to give X.

Further work with 3-methyl and 3,3-dimethylpentane-2,4-diones and fluorinated pentane-2,4-diones suggested that the protonated keto-enol tautomer of pentane-2,4-dione is the reactive species.

Figure 4. Spectral changes of reaction between urea and pentane-2,4-dione at ca. 0, 15, 30, 70, 120, 240 and 690 min ($40^{o}C$)



RESULTS AND DISCUSSION

Preparation of the products.

The salt of 4, 6-dimethylpyrimidin-2(1H)-one (X) was prepared by the reaction of urea with pentane-2, 4-dione in ethanol in the presence of hydrochloric acid[59]. 1, 4, 6-Trimethyl- and 1, 3, 4, 6-tetramethyl-pyrimidin-2(1H)-ones (XI and XII) were also prepared in a similar manner from N-methylurea and N, N'-dimethylurea. The structures were confirmed by mass spectra, elemental analysis and proton n. m. r. The products are often known as 2-hydroxy-4, 6-dimethylpyrimidines, but Marshall and Walker[60] have shown that 2-hydroxy pyrimidines exist primarily in the oxo form. Although N, N-dimethylurea appears to undergo reaction it was not possible to isolate the product of the reaction.

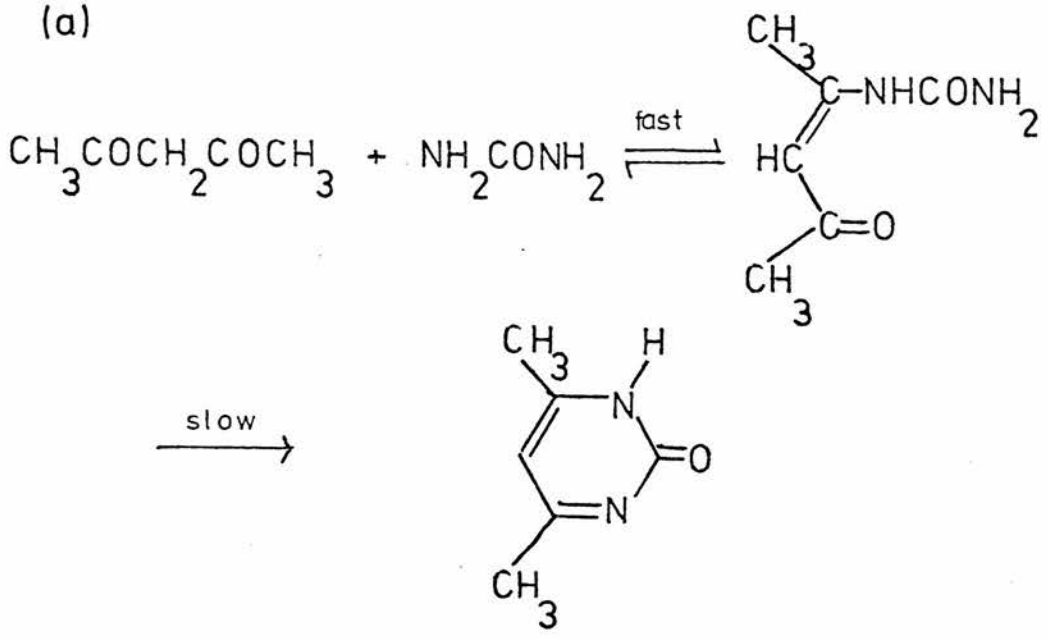
By varying the reaction conditions, the diurea product of pentane-2, 4-dione was isolated. Two different structures XIII and XIV are possible for this product. XIII was proposed by Evans[61] and XIV by de Haan[62]. XIV is favoured here on the basis of mass spectral evidence. The mass spectrum does not record any peaks whatsoever corresponding to m/e = 85 or 99 which would be expected for the fragments obtained from splitting the molecule into two across the bond between the 2- and 3- carbon atoms.

Spectral changes during reaction.

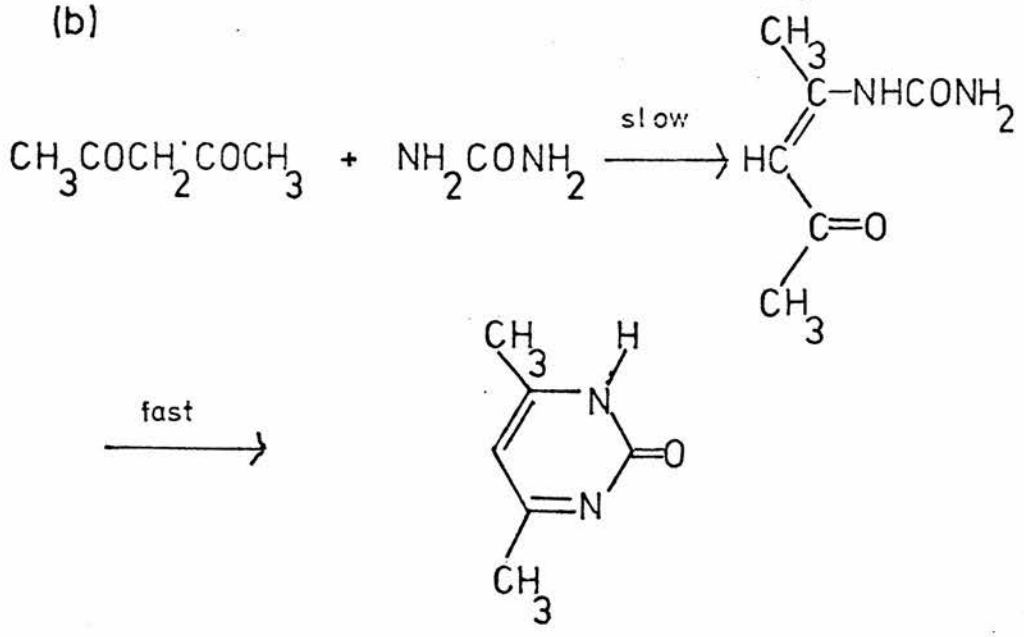
A solution of pentane-2, 4-dione in aqueous hydrochloric acid shows an absorbance at 275 nm in the ultra-violet region of the spectrum.

Scheme 6.

(a)



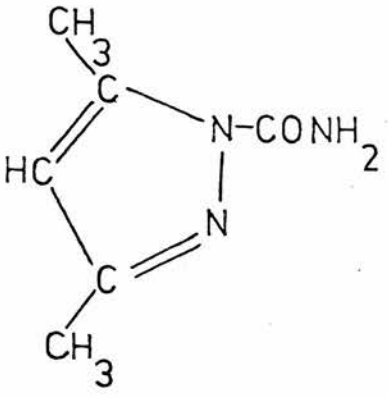
(b)



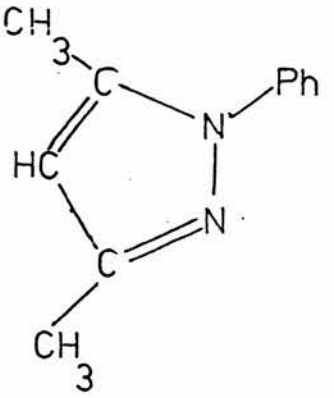
This absorbance decreases slightly on standing over several hours. In the presence of urea, the pentane-2,4-dione absorbance falls, and simultaneously a new peak is formed at 300 nm. Two tight isosbestic points are observed at 240 and 275 nm. Similar spectral changes are observed with N-methylurea (peak formed at 307 nm, isosbestic points at 240 and 278 nm) and with N,N'-dimethylurea (peak at 310 nm, isosbestic points at 240 and 285nm). Typical spectral changes are illustrated in Figure 4.

The final spectrum of the reaction of urea with pentane-2,4-dione was found to be identical to the spectra of X. The diurea compound (XIV), when dissolved in acid shows no U.V. absorption initially, but if the solution is allowed to stand for several hours an absorbance corresponding to the cyclic compound (X) eventually appears. However, it appears that the diurea compound only forms under preparative conditions as it is precipitated because of its low solubility.

Reaction must therefore occur via two main steps : reaction of urea with one carbonyl group of the pentane-2,4-dione, followed by cyclisation to give X. The presence of isosbestic points in the spectral changes indicate that there is only one slow step in the overall process. The absorbance due to penta-2,4-dione disappears as that due to X appears, so that the mechanism cannot be rapid formation of XV followed by slow cyclisation. This leaves two possibilities : (a) rapid equilibrium formation of XV at low concentration followed by slow cyclisation or (b) slow formation of XV followed by rapid



XVI



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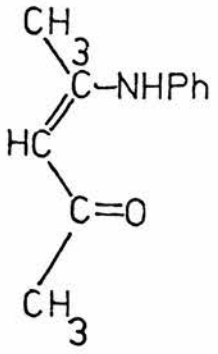

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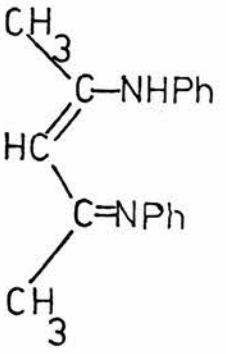

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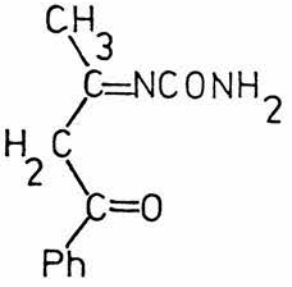

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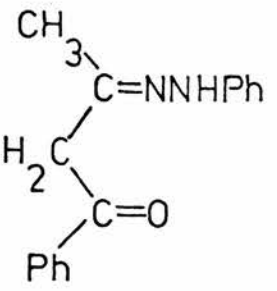


XXI

cyclisation (Scheme 6). The latter process is favoured because of the entropy changes involved. Bruice and Benkovic[63] have shown that when a reaction changes from intermolcular to intramolcular, the intramolecular reaction becomes more favourable because of the decrease in the magnitude of the entropy change.

In several other instances where cyclisation can occur, the intermediate product has not been isolated. For example, pentane-2,4-dione reacts with semicarbazide to give 3,5-dimethylpyrazole-1-carboxamide (XVI)[64] and with 2,4-dinitrophenylhydrazine to give 1-(2,4-dinitrophenyl)-3,5-dimethylpyrazole (XVII)[65]. However, when cyclisation is not possible the intermediate 1:1 adduct has been isolated although it may undergo further reaction. For example, aniline will react with pentane-2,4-dione to give XVIII which, in turn, reacts with more aniline to give XIX[66].

It is of interest to note that with benzoylacetone it is possible to isolate the intermediate products. Evans[61,67] reports that benzoylacetone and urea condense in the presence of acid to give XX which, on treatment with alkali, undergoes cyclisation. This reaction with benzoylacetone does not occur as readily as it does with pentane-2,4-dione. The isolation of the 1:1 phenylhydrazone adduct (XXI) with benzoylacetone has also been reported[68]. The presence of a deactivating phenyl group obviously plays a significant part in these reactions and makes reaction with the adjacent carbonyl groups more difficult. In the above two instances, it has been the carbonyl group adjacent

to the methyl group of benzoylacetone that undergoes reaction first.

Kinetics of the reaction.

The kinetics of the reaction of pentane-2,4-dione with urea were examined by monitoring the increase of the peak corresponding to the formation of the cyclic product, and the variation of rate with urea concentration was investigated. The reaction of pentane-2,4-dione with N-methylurea was similarly examined. The rate constants obtained are shown in Table 1 and the plots of the observed rate constant k_{obs} against the stoicheiometric urea concentration $[U]_{st}$ are shown in Figure 5. A linear relationship is observed between k_{obs} and $[U]_{st}$ for both urea and N-methylurea. A single rate constant was obtained for the reaction of pentane-2,4-dione with N,N'-dimethylurea (Table 1) but the variation of k_{obs} with the dimethylurea concentration was not investigated. In view of the similarity of the spectral changes observed with urea, N-methylurea and N,N'-dimethylurea, it seems highly probable that k_{obs} would vary with the dimethylurea concentration in a similar manner.

To analyse the results, one must consider the acid-base equilibrium of urea and N-methylurea. There has been much discussion[10] on the site of protonation of the urea molecule, but it is now generally accepted on the basis of I.R., U.V. and n.m.r. data that urea is O-protonated[13]. The unprotonated and protonated urea concentrations and the acidity can be expected to vary with the stoicheiometric urea concentration. It is possible to calculate these quantities from a knowledge of the pK_a values of both urea[69]

Table 1.

Kinetics of the reaction of urea, N-methylurea and N,N'-dimethylurea with pentane-2,4-dione at 40°

Urea

[HCl] = 5.0M

[Urea] M	1.5	2.0	2.5	3.0	3.5
$10^4 k_{obs} s^{-1}$	4.67	6.35	7.12	8.10	9.53

N-Methylurea

[HCl] = 5.0M

[Methylurea] M	0.5	1.0	1.5	2.0	2.5
$10^3 k_{obs} s^{-1}$	0.94	1.37	1.66	2.69	3.51

N,N'-Dimethylurea

[HCl] = 5.0M

[Dimethylurea] M 2.0

$10^4 k_{obs} s^{-1}$ 5.10

[Pentane-2,4-dione] = ca. 10^{-3}M

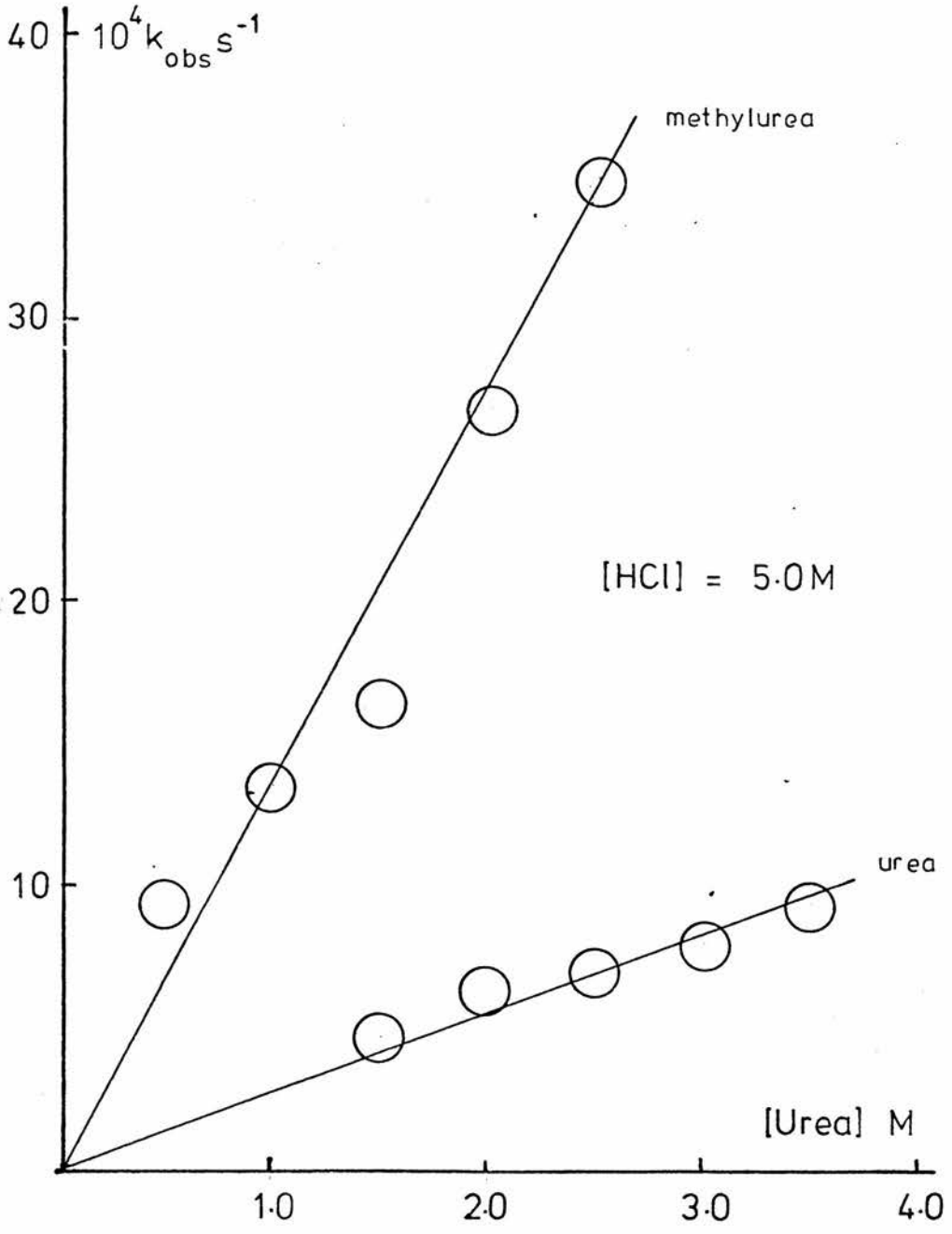


Figure 5. Variation of k_{obs} with stoichiometric urea and methylurea concentrations in reaction with pentane-2,4-dione at 40°

and N-methylurea[69a]. However, the use of these calculated quantities would not be justified in view of the fact that the acidity of the solution is much greater than the stoicheiometric acid concentration (5 M HCl) at which the kinetics were investigated. Instead the use of acidity functions must be considered and this makes the analysis of the protonation of urea more complex.

In a study of the hydrolysis of urea in sulphuric acid/water mixtures. Moodie et al.[70] were able to analyse their kinetic data by assuming that the protonation of urea follows the acidity scale h_o. In another investigation, Barnett and O'Connor[71] determined the basicity constants of phenylureas in sulphuric acid and showed that the protonation of phenylureas followed the h_A acidity scale much better than the h_o scale. Yates and Riordan[72] give the h_o and h_A acidity scales for hydrochloric acid at 25° and it can be seen that up to about 5 M HCl acid there is little to choose between the two scales (Figure 6). Only above 5 M HCl do the two scales begin to differ significantly. So for the purpose of this study the choice of the acidity scale is not important, and for the sake of convenience it will be assumed here that the protonation of urea follows the h_A acidity scale.

Thus in the equilibrium

$$NH_2CONH_2 + H^+ \underset{}{\overset{K_A}{\rightleftharpoons}} NH_2COH^+NH_2$$

where

$$K_A = \frac{[U][H^+]}{[UH^+]} \qquad (1)$$

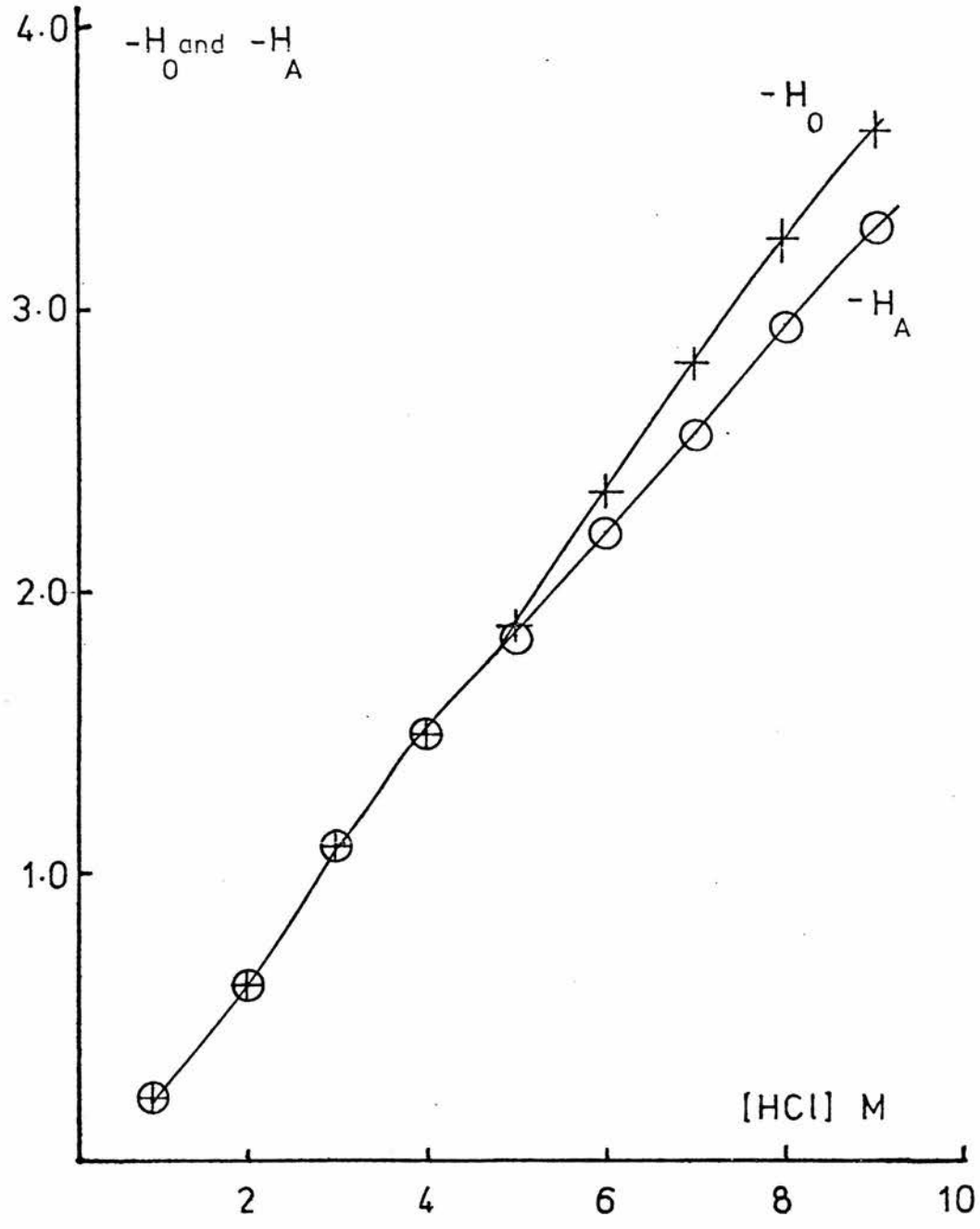


Figure 6. Plot of $-H_O$ and $-H_A$ against molarity of HCl[72]

we now have

$$K_A = \frac{[U]\,h_A}{[UH^+]} \qquad (2)$$

Calculations using K_A and h_A show that all urea is essentially protonated so that $[UH^+]$ is the same as the stoicheiometric concentration of urea $[U]_{st}$. The low concentration of unprotonated urea is therefore given by

$$[U] = \frac{K_A\,[U]_{st}}{h_A} \qquad (3)$$

Little is known about the acid-base equilibrium of diketones, so it is assumed here that the protonation of pentane-2,4-dione follows an unspecified acidity scale h. Thus in the equilibrium

$$CH_3COCH_2COCH_3 + H^+ \underset{}{\overset{K'_A}{\rightleftharpoons}} CH_3COH^+CH_2COCH_3$$

where

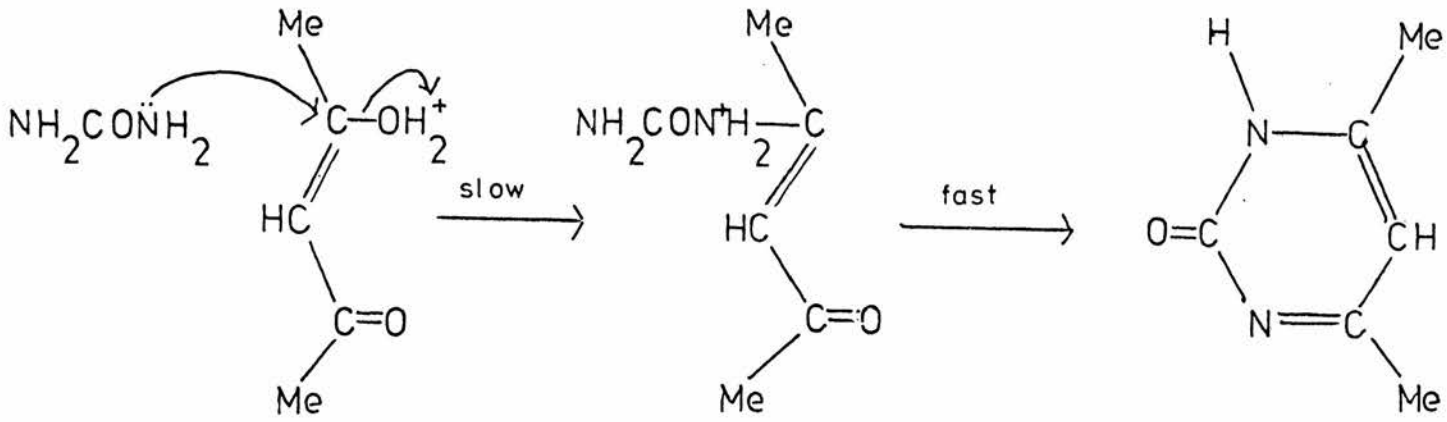
$$K'_A = \frac{[P]\,[H^+]}{[PH^+]} \qquad (4)$$

and P is the pentane-2,4-dione, we now have

$$K'_A = \frac{[P]\,h}{[PH^+]} \qquad (5)$$

There is little protonation of pentane-2,4-dione so that $[P]$ is effectively the same as the stoicheiometric concentration of pentane-2,4-dione $[P]_{st}$. The low concentration of the protonated diketone is therefore given by

Scheme 7. Reaction of urea with pentane-2,4-dione



$$[PH^+] = \frac{[P]_{st}\, h}{K'_A} \qquad (6)$$

The variation of k_{obs} with the urea concentration and hence with the change in acidity suggests that reaction is between one protonated and one unprotonated species. It is difficult to visualise O-protonated urea attacking the polarised carbonyl group of the diketone when reaction involves the nitrogen atom of the urea. So the most likely reaction is that of unprotonated urea with the protonated pentane-2,4-dione followed by rapid cyclisation as illustrated in Scheme 7. The rate equation is thus given as

$$\text{rate} = k\,[U]\,[PH^+] \qquad (7)$$

where k is the rate constant. Substitution of (3) and (6) for $[U]$ and $[PH^+]$ into the rate equation gives

$$\text{rate} = \frac{k\,K_A\,h\,[U]_{st}\,[P]_{st}}{K'_A\,h_A} \qquad (8)$$

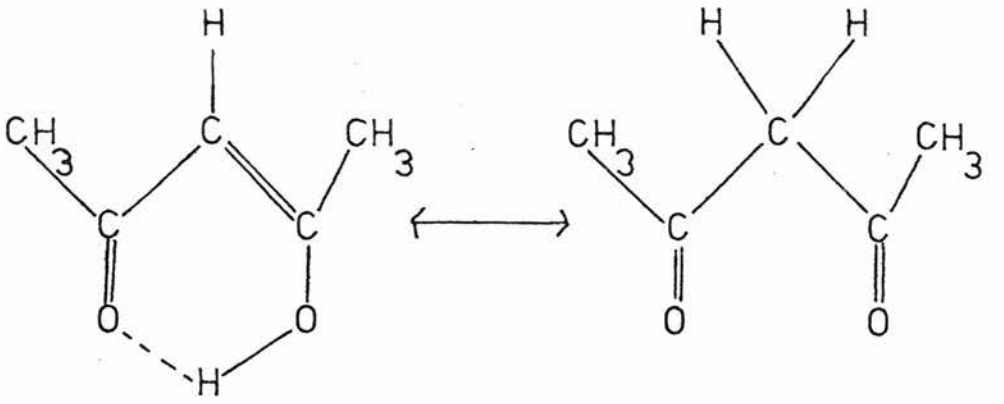
In the kinetics the rate is observed for the formation of the cyclic product. This is the same as the rate of disappearance of pentane-2,4-dione which is first order in the diketone so that

$$\text{rate} = k_{obs}\,[P]_{st} \qquad (9)$$

Combining (8) with (9) gives an expression for the observed rate constant

$$k_{obs} = \frac{k\,K_A\,h\,[U]_{st}}{K'_A\,h_A} \qquad (10)$$

Figure 7. Tautomeric forms of pentane-2, 4-dione

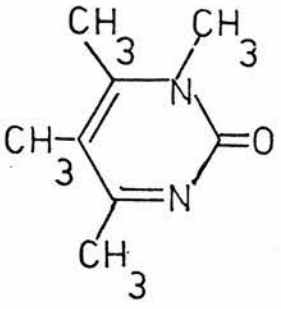


If h is similar to h_A, as in in moderately dilute solutions acidity functions are similar, then k_{obs} becomes a linear function of the stoicheiometric urea concentration. This is in agreement with the plot of k_{obs} against $[U]_{st}$ as shown in Figure 5 and therefore the kinetics are consistent with the proposed scheme.

The presence of a methyl group in the methylurea molecule makes it more nucleophilic and hence it will attack the pentane-2,4-dione more readily than urea. This is consistent with the observation that N-methylurea reacts faster than urea. For the same reason one would also expect N,N'-dimethylurea to react even faster than the other two ureas but N,N'-dimethylurea was found to react more slowly than urea. This slower behaviour may be due to steric factors.

Keto-enol tautomerism of pentane-2,4-dione.

As proton and C-13 n.m.r. studies have shown, pentane-2,4-dione has two tautomeric forms : the keto-enol and the keto-keto forms (Figure 7). The question as to which form is the reactive species arises. Neat pentane-2,4-dione is approximately 76% keto-enol[73] but in water the proportion decreases to 16%[74]. In the neat liquid the keto-enol form is stabilised by internal hydrogen bonding. In the presence of water the solvent molecules are also competing for hydrogen bonding with the carbonyl groups of the keto-keto tautomer so that the ratio of the two tautomers changes. Schwarzenbach and Wittwer[75] have shown that, in acid solutions, the ratio of the two



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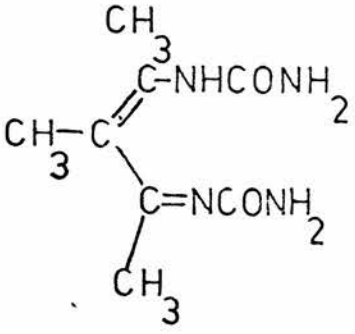

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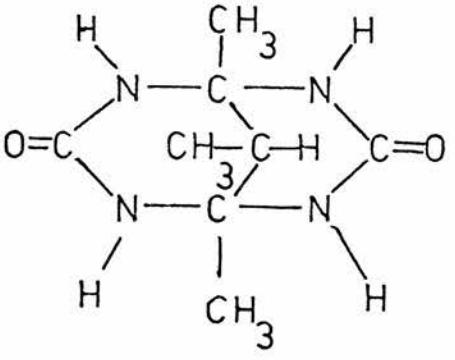
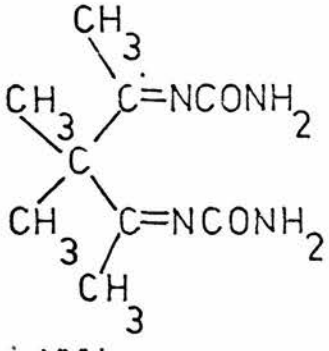
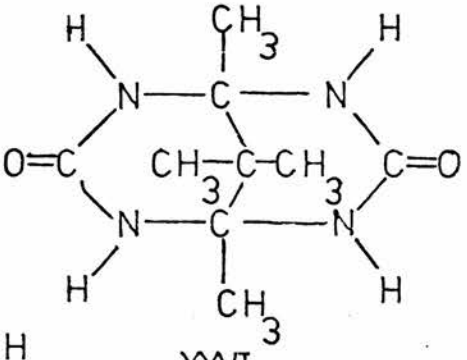


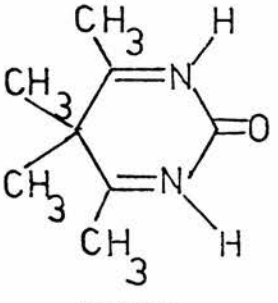
XXIV



XXV



XXVI



XXVII

tautomeric forms varies with the pH. From their work it can be seen that, under present experimental conditions, the keto-keto tautomer is the dominant form. However keto-enol tautomerism is faster than the rate of reaction of urea[76], and either form can still undergo reaction with urea. Both forms can be protonated and Schwarzenbach and Wittwer[75] give pK_a values of -5.0 and -6.1 for the keto-enol and keto-keto forms respectively. These pK_a values show that the keto-enol tautomer is the more basic one. There are reasons for believing that it is the protonated keto-enol form that undergoes reaction with urea and support for this belief comes from the following examination of the reactions of urea with 3-methyl- and 3,3-dimethyl-pentane-2,4-diones and with fluorinated pentane-2,4-diones.

Reaction with 3-methylpentane-2,4-dione.

3-Methylpentane-2,4-dione was prepared[77] and was found to show a weak absorbance at ca. 295 nm. The spectral charges of its reaction with urea, N-methylurea and N,N'-dimethylurea were examined and, in all three cases, were found to be similar to those observed with pentane-2,4-dione. The formation of the following peaks and isosbestic points were observed with urea (315 nm; 248 and 272 nm.), methylurea (320 nm; 252 and 275 nm.) and dimethylurea (325 nm; 255 and 297 nm.).

The products of the reaction were prepared by the method of Kosalapoff and Roy[59] used for pentane-2,4-dione. N-Methylurea yielded the expected cyclic product (XXII), but a diurea product was, surprisingly,

obtained with urea. The diurea product gave a rather poor mass spectrum, so it was not possible to decide which structure (XXIII or XXIV) it might possess. As it has already been noted in the case of pentane-2,4-dione, it seems that the diurea product forms because of its high insolubility so that it is precipitated out, and that it shows very little U.V. absorption. It was not possible to isolate the N,N'-dimethylurea product.

In view of the similarity of the spectral changes to those observed with pentane-2,4-dione, it is reasonable to suggest that 3-methylpentane-2,4-dione reacts by the same mechanism. Rate constants were obtained for the reaction of 3-methylpentane-2,4-dione with the three ureas and these are shown in Table 2. The introduction of a 3-methyl groups in pentane-2,4-dione reduces the rate of reaction with urea by a factor of three. This could be due to the steric effect or may reflect the smaller proportion of the keto-enol form which is 28% for the neat liquid[78].

Reactions with 3,3-dimethylpentane-2,4-dione.

3,3-Dimethylpentane-2,4-dione was prepared[79] so that the effect of replacing the enolisable hydrogens of the 3-position of pentane-2,4-dione could be examined. 3,3-Dimethylpentane-2,4-dione has an absorbance at ca. 280 nm. and the spectral changes of its reaction with urea, N-methylurea and N,N'-dimethylurea were examined. The spectral changes were found to differ in some respects from those observed with 3-methylpentane-2,4-dione. With urea and N-methylurea, peaks were formed at 302 and 307 nm. respectively,

Table 2.

Kinetics of the reaction of urea, N-methylurea and N,N'-dimethylurea with 3-methylpentane-2,4-dione at 40°

[HCl] = 5.0M

[Urea] 0.5M

$10^5 k_{obs} s^{-1}$ 4.5

[Methylurea] 0.5M

$10^4 k_{obs} s^{-1}$ 2.2

[Dimethylurea] 0.5M

$10^5 k_{obs} s^{-1}$ 9.5

[Diketone] = ca. 10^{-3}M

but the absorbances were much weaker than those observed with 3-methylpentane-2,4-dione. The methylurea product absorbance, for example, was weaker by a factor of about a hundred. N,N'-Dimethylurea barely showed the formation of a peak at ca. 313 nm. Also, in each case, only one isosbestic point was observed (275, 281 and 291 nm. for urea, methylurea and dimethylurea respectively), and the 3,3-pentane-2,4-dione absorbance did not decrease very much.

Rate constants obtained for the reaction of N-methylurea with 3,3-dimethylpentane-2,4-dione (Table 3) showed that the presence of two 3-methyl groups reduced the rate of reaction by a factor of four.

Only the diurea product (XXV or XXVI) was isolated via the method of Kosalapoff and Roy[59]. Attempts made to isolate the other products were unsuccessful.

The different spectral changes and a different product indicate a change of mechanism resulting from the absence of enolisable hydrogen atoms in the 3-position. A similar change of product has been reported by Drewes and Coleman[80] for the reaction of O-phenylenediamine with pentane-2,4-dione and with 3,3-dimethylpentane-2,4-dione. However the presence of the two methyl groups could also prevent proton transfer to give a cyclic product of the type XXVII, so the evidence for the keto-enol form as a reactive species is not entirely conclusive.

Table 3.

Kinetics of the reaction of N-methylurea with 3,3-dimethylpentane-2,4-dione at 40^{o}

[HCl] = 5.0M

[Methylurea] M	0.5	2.0
$10^{4}k_{obs}s^{-1}$	1.99	6.30

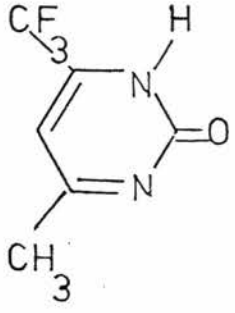
[Diketone] = ca. 10^{-4}M

Reaction with fluorinated pentane-2,4-diones.

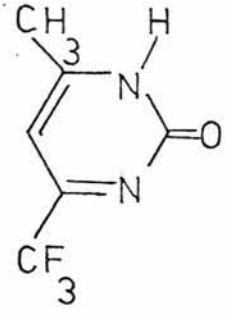
If the reaction is the nucleophilic attack of the protonated keto-enol form of pentane-2,4-dione by urea as illustrated in Scheme 7, then water forms the leaving group. Some confirmation of this comes from a study of the reactions of urea with fluorinated pentane-2,4-diones.

If reaction involves addition across the carbonyl double bond of the keto form, then 1,1,1,5,5,5-hexafluoropentane-2,4-dione should react faster than pentane-2,4-dione as the fluorine atoms will increase polarisation of the carbonyl group. However no reaction occurs as evident from the complete absence of spectral changes. Fluorination increases the proportion of the keto-enol form so that neat hexafluoropentane-2,4-dione is 100% keto-enol[78] but this proportion will be substantially reduced when dissolved in water. In addition, the presence of fluorine atoms will have a large effect on the protonation of the hydroxy group of the keto-enol form so that elimination of water as a leaving group will be much more difficult. Thus the lack of reactivity can be understood in terms of the proposed mechanism.

1,1,1-Trifluorpentane-2,4-dione reacts with both urea and N-methylurea to give somewhat similar spectral changes. Peaks are formed at 316 and 319 nm. for urea and methylurea respectively, but no isosbestic points are recorded. The absence of isosbestic points is due to the fact that trifluoropentane-2,4-dione shows no U.V. absorbance in aqueous hydrochloric acid.



XXVIII



XXIX

Difficulty was encountered in the preparation of products from trifluoropentane-2,4-dione, but a sample of the fluorinated cyclic product (XXVIII or XXIX) was eventually isolated from urea.

Rate constants (Table 4) obtained for both urea and N-methylurea show that the rate of reaction of trifluoropentane-2,4-dione is considerably slower than the unfluorinated diketone. This is again consistent with the proposal of the protonated keto-enol form as the reactive species. A set of rate constants plotted against the methylurea concentration gave a linear plot similar to that obtained for pentane-2,4-dione in Figure 8, and provided confirmation that the mechanism of the rection remained unchanged.

Table 4.

Kinetics of the reaction of N-methylurea with 1,1,1-trifluoropentane-2,4-dione at 40°

[HCl] = 5.0M

[Methylurea] M	0.5	1.5	2.0	2.5
$10^4 k_{obs} s^{-1}$	1.20	2.58	2.99	4.39

[Diketone] = ca. 10^{-4}M

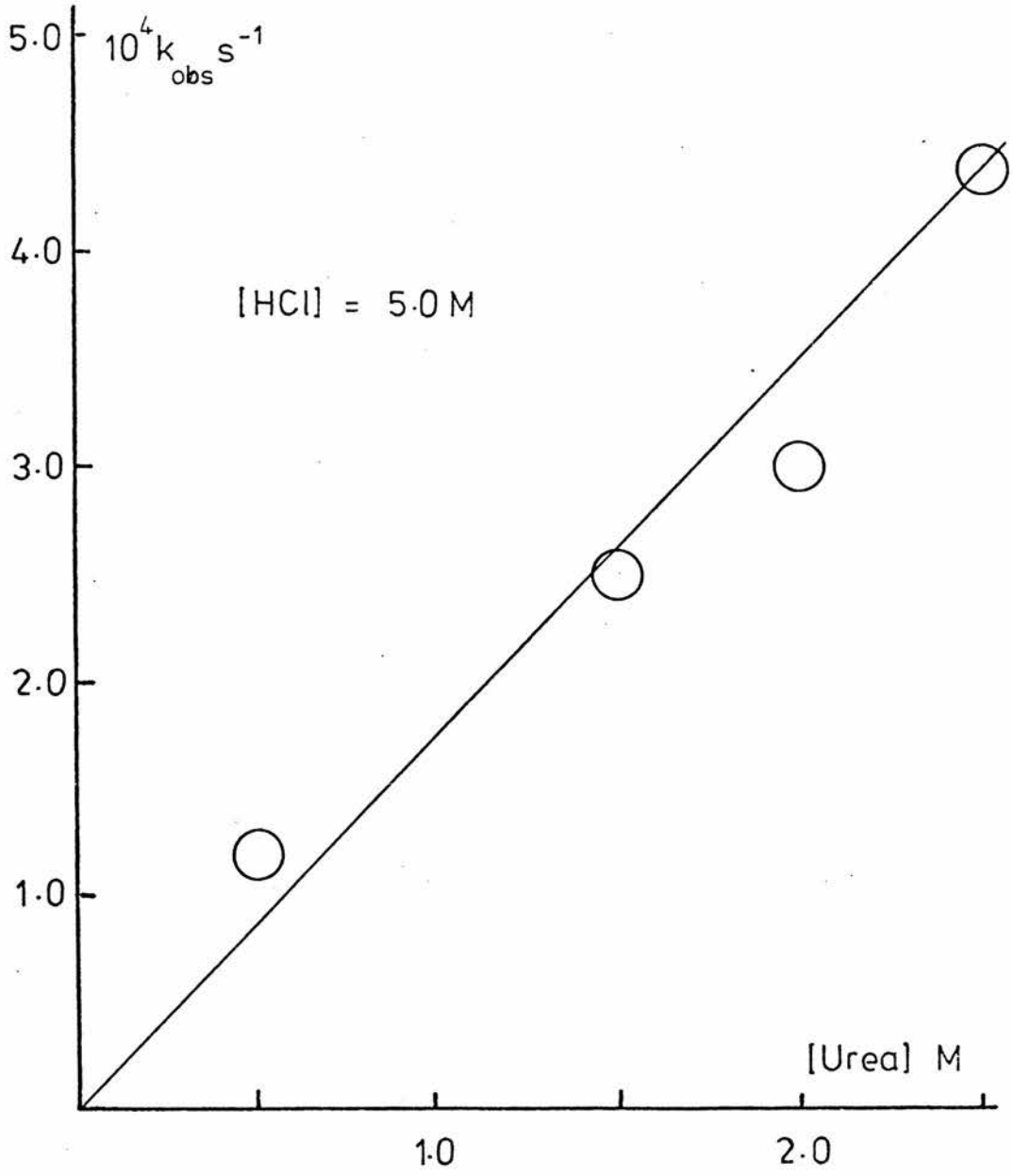


Figure 8. Variation of k_{obs} with stoicheiometric urea concentration in reaction with 1,1,1-trifluoropentane-2,4-dione at 40°

EXPERIMENTAL

Preparation of 4, 6-dimethylpyrimidin-2(1H)-ones[51].

Urea (60.1g) in boiling absolute ethanol (500 ml) was treated with pentane-2, 4-dione (100g) and concentrated HCl (135 ml) added with stirring. Reaction became exothermic after some 5 minutes and required moderation by cooling. The mixture was kept for 24 hours after which 4, 6-dimethyl-pyrimidin-2(1H)-one hydrochloride was isolated by filtration. The same method was used to prepared the corresponding pyrimidinones with N-methylurea and N, N'-dimethylurea. The physical data for these compounds are summarised in Table 5.

Preparation of diurea compound of pentane-2, 4-dione.

Pentane-2, 4-dione (2g) was added to a solution of urea (2.4g) in water (20 ml) containing hydrochloric acid (5 ml) and the mixture was allowed to stand at room temperature until a precipitate had formed. The white crystals were filtered off and recrystallised from boiling water, m.p. 300°.

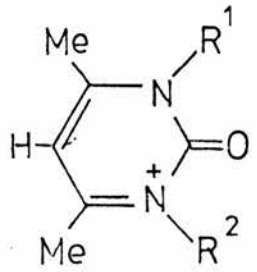
$C_7H_{12}N_4O_2$	Molecular ion peak at 184		
Required	45.6% C	6.6% H	30.4% N
Found	45.0% C	6.7% H	30.2% N

Kinetic method.

The rate constants were determinated by monitoring the change in absorbance due to the product of the reaction with time. 0.1 ml of

Table 5.

Physical data for 4,6-dimethylpyrimidin-2(1H)-ones.



X	$R^1 = R^2 = H$
XII	$R^1 = Me$, $R^2 = H$
XII	$R^1 = R^2 = Me$

Analysis and mass spectra

	m.p. (°C)	Formula	Required (%) C	H	N	Found (%) C	H	N	Molecular ion peak
X	300°	$C_6H_9N_2O_1Cl_1$	44.9	5.7	17.4	44.3	5.5	17.4	124
XI	260°	$C_7H_{11}N_2O_1Cl_1$	48.1	6.3	16.0	48.1	6.4	16.2	-
XII	206°	$C_8H_{13}N_2O_1Cl_1$	50.9	7.0	14.9	47.8	7.0	14.2*	152

* weight gain during weighing

Proton n.m.r. data (in D_2O)

X Singlets at 2.60 (2 x CH_3-C), 7.80 (=CH-)

XI Singlets at 2.57 and 2.68 δ (2 x CH_3-C), 3.66 δ (CH_3-N), 6.84 δ (=CH-)

XII Singlets at 2.67 δ (2 x CH_3-C), 3.71 δ (2 x CH_3-N), 6.92 δ (=CH-)

0.02% solution of pentane-2,4-dione in water was added to a solution of the urea in HCl contained in a cuvette in a thermostatted (40^{o}) holder of a Unicam SP700 spectrophotometer. The wavelengths used were 303 and 306 nm for urea and N-methylurea respectively. Rate constants were determined by the method of Swinbourne[81].

With N,N'-dimethylurea and with the substituted pentane-2,4-diones the rate constants were determined from spectra recorded in a Unicam SP800 spectrophotometer with a thermostatted block. A technique similar to above was used with solutions of 3-methylpentane-2,4-dione (0.1%), 3,3-dimethylpentane-2,4-dione (2%) and 1,1,1-trifluoropentane-2,4-dione (0.115%). The wavelengths used in the determinations were taken from the maxima of the peaks corresponding to the final products.

Preparation of 3-methylpentane-2,4-dione[77].

Pentane-2,4-dione (66.8 ml), methyl iodide (50 ml), anhydrous potassium carbonate (84g) and dry acetone (74 ml) were heated under reflux in a water bath for 24 hours. The product was cooled, the solid separated and the residue distilled. B.p. $170-172^{o}$/760 mm Hg. (lit. $170-172^{o}$/760 mm Hg).

Preparation of 3,3-dimethylpentane-2,4-dione[79].

To a stirred mixture of 3-methyl-2-butanone (0.1 mol) and acetic anhydride (0.2 mol) cooled in a water bath at room temperature was added

rapidly boron trifluoride-diacetic acid complex (BTDA) (0.2 mol). After stirring at room temperature overnight, the reddish brown reaction mixture was poured into a solution of sodium acetate (0.4 mol) in water (300 ml) and the resulting mixture refluxed for 1-3 hours. The product was extracted three times with ether and the extracts combined. The ethereal solution was washed free of acid with saturated sodium bicarbonate solution and dried with Drierite. The solvent was removed and the residue distilled under vacuum. B.p. 93^{o}/40 mm Hg. (lit. 172-174^{o}/760 mm Hg).

Note : The BTDA was obtained from Harshaw Chemical Company.

Products for 3-methylpentane-2,4-dione.

The products of the reaction of urea and N-methylurea with 3-methylpentane-2,4-dione were prepared as for pentane-2,4-dione by the method of Kosalapoff and Roy[59].

Urea product XXV or XXVI : m.p. $>300^{o}$, poor mass spectrum

$C_8H_{14}N_4O_2$			
Required	48.5% C	7.1% H	28.3% N
Found	48.6% C	6.4% H	28.1% N

Methylurea product (XXVII), HCl salt : m.p. 245^{o} dec., molecular ion peak 152

$C_8H_{13}N_2OCl$			
Required	50.9% C	6.9% H	14.9% N
Found	51.1% C	6.8% H	14.1% N

Work with fluorinated pentane-2,4-diones.

Small samples of 1,1,1-trifluoro- and 1,1,1,5,5,5-hexafluoropentane-2,4-dione were obtained from Koch-Light Laboratories Ltd.

The product (XXVII or XXIX) of the reaction between urea and 1,1,1-trifluoropentane-2,4-dione was prepared by the method of Kosalapoff and Roy[59].

M.p. 225° dec., molecular ion peak 178

$C_6H_6N_2OCl\,F_3$ (HCl salt)

Required	33.6% C	2.8% H	13.1% N
Found	37.0% C	3.0% H	15.6% N

The analysis result is not very good but only a small sample of an impure product was obtained and there was not enough for recrystallisation.

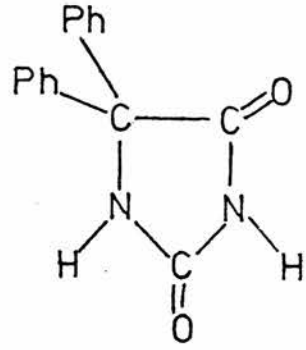
CHAPTER III

REACTION WITH BENZIL UNDER ALKALINE CONDITIONS

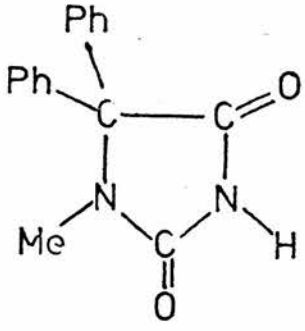
INTRODUCTION

Urea, N-methylurea and N,N'-dimethylurea readily undergo reaction with benzil and substituted benzils in the presence of alkali. The products of this reaction with benzil were reported in 1908 by Biltz[82]. Urea and N-methylurea yield the appropriate 5,5-diphenylhydantoins, while a diol product results with N,N'dimethylurea.

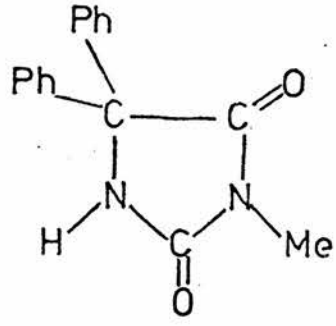
A study was carried out to investigate the mechanism of the reaction and to account for the formation of a different product with N,N'-dimethylurea. The evidence presented here shows that the first, rate-determining, step is attack on benzil by the urea anion followed by rapid cyclisation. With urea and N-methylurea the resulting intermediate then undergoes a slow benzilic acid type rearrangement to yield the hydantoin. The N,N'-dimethylurea compound is unable to undergo this rearrangement and therefore does not undergo further reaction.



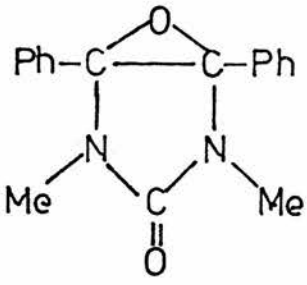
XXX



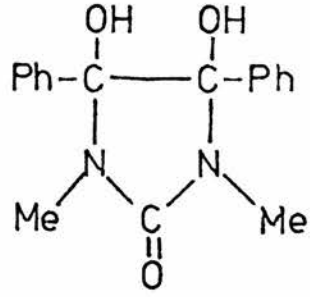
XXXI



XXXII



XXXIII



XXXIV

RESULTS AND DISCUSSION

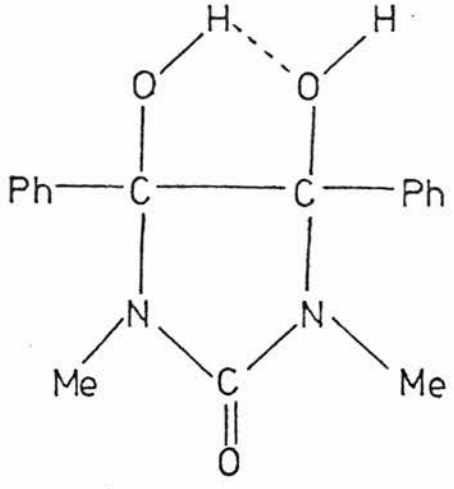
Preparation and identification of the products.

The products were prepared by refluxing the appropriate urea with benzil in ethanol containing potassium hydroxide. The product obtained from urea was found to be identical to an authentic sample of commercially prepared 5,5-diphenylhydantoin (XXX). Two different hydantoin structures are possible with N-methylurea. Therefore samples of 1-methyl- and 3-methyl-5,5-diphenylhydantoins (XXXI and XXXII) were prepared and the latter was found to be identical with the methylurea product.

The product of the reaction with N,N'-dimethylurea was not 1,3-dimethyl-5,5-diphenylhydantoin as comparison with an authentic sample showed. Biltz[82] suggested that the product had the structure (XXXIII) with an epoxide ring present. Spectral evidence appeared to be in agreement with this structure. The mass spectrum had an apparent molecular ion peak corresponding to this, and the proton n.m.r. indicated only one type of a methyl group (as opposed to two peaks expected for a hydrantoin structure). The I.R. spectrum also shows only one peak due to carbonyl absorption in the region 1600-1800 cm^{-1}. However, two peaks in the region 3000-3500 cm^{-1} were unexplained and elemental analysis was not in agreement with this structure.

A diol structure, 4,5-dihydroxy-1,3-dimethyl-4,5-diphenyl-2-imidazolidone (XXXIV), is therefore proposed instead. The mass spectrum peak at

Figure 9. Intramolecular hydrogen bonding



m/e = 280 can be explained as (M - H_2O) and the proton n.m.r. and I.R. data are consistent with this structure. The two peaks in the I.R. region 3000-3500 cm^{-1} can be attributed to the two hydroxy groups which may not absorb at the same frequency because of intramolecular hydrogen bonding (Figure 9). Moreover the elemental analysis is in agreement with this structure.

Spectral changes observed during the reaction.

Benzil is not very soluble in water but, by dissolving it in ethanol and adding a drop of the ethanolic solution to a cuvette of water, enough of it dissolves to give an absorbance in the ultra-violet region. The absorbance peak of benzil is at 265 nm in water and at 257 nm in aqueous alkali.

Benzil itself undergoes rearrangement to benzilic acid under alkaline conditions[83]. At 25° one thus observes a slow decrease in the absorbance due to the carbonyl groups of benzil. This reaction is, however, much slower than the reaction with urea and need not be taken into consideration.

In the presence of excesses of urea and hydroxide ion, the absorbance due to benzil decreases within minutes to about a third of its initial value, where it remains virtually unchanged. Similar spectral changes are observed with N-methylurea, whereas with N,N'-dimethylurea the absorbance decreases right down to zero.

Isotopic dilution experiment.

The observed spectral changes do not necessarily represent the

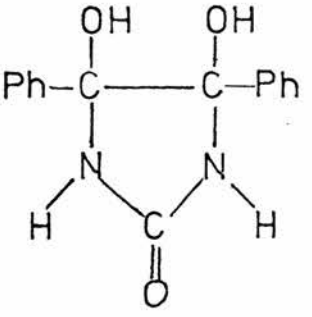
complete reaction leading to the formation of the hydantoin in the cases of urea and N-methylurea. This is particularly so in view of the complex nature of the reaction and of the conditions under which the spectral changes were observed being different from the conditions under which the products were prepared. It was therefore decided to carry out an isotopic dilution experiment.

Using ^{14}C-labelled urea, it was found that hardly any 5,5-diphenylhydantoin had been formed by the end of the spectral changes. However, in a second experiment when the reaction was allowed to proceed overnight after the completion of the initial spectral changes, some 5,5-diphenylhydantoin was found to have been formed.

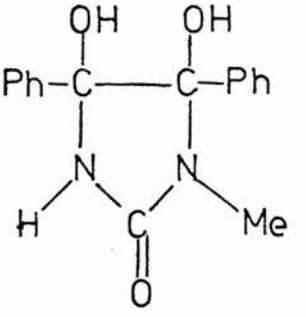
These results show that the initial spectral changes do not involve the formation of the hydantoin. Instead it indicates that rearrangement of the intermediate product to the hydantoin must be a slow step.

Discussion of the spectral changes.

We have thus eliminated the possibility that the observed spectral changes include the rearrangement to the hydantoin. From observation of the spectral changes in the case of N,N'-dimethylurea, it appears that one must be looking at a reaction involving the loss of both carbonyl groups of benzil since the benzil absorbance falls to zero. The reaction must involve the attack of benzil by N,N'-dimethylurea followed by rapid cyclisation since the spectral changes do not agree with fast attack followed by slow cyclisation.

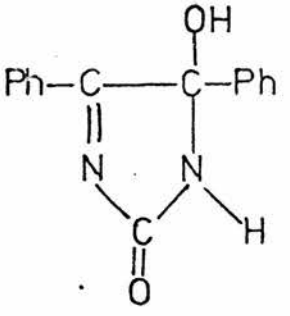


(a)

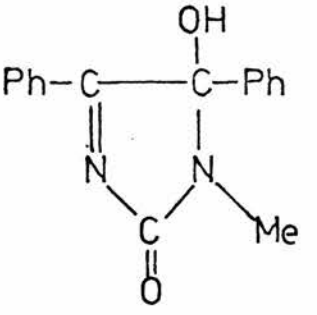


(b)

XXXV



(a)



(b)

XXXVI

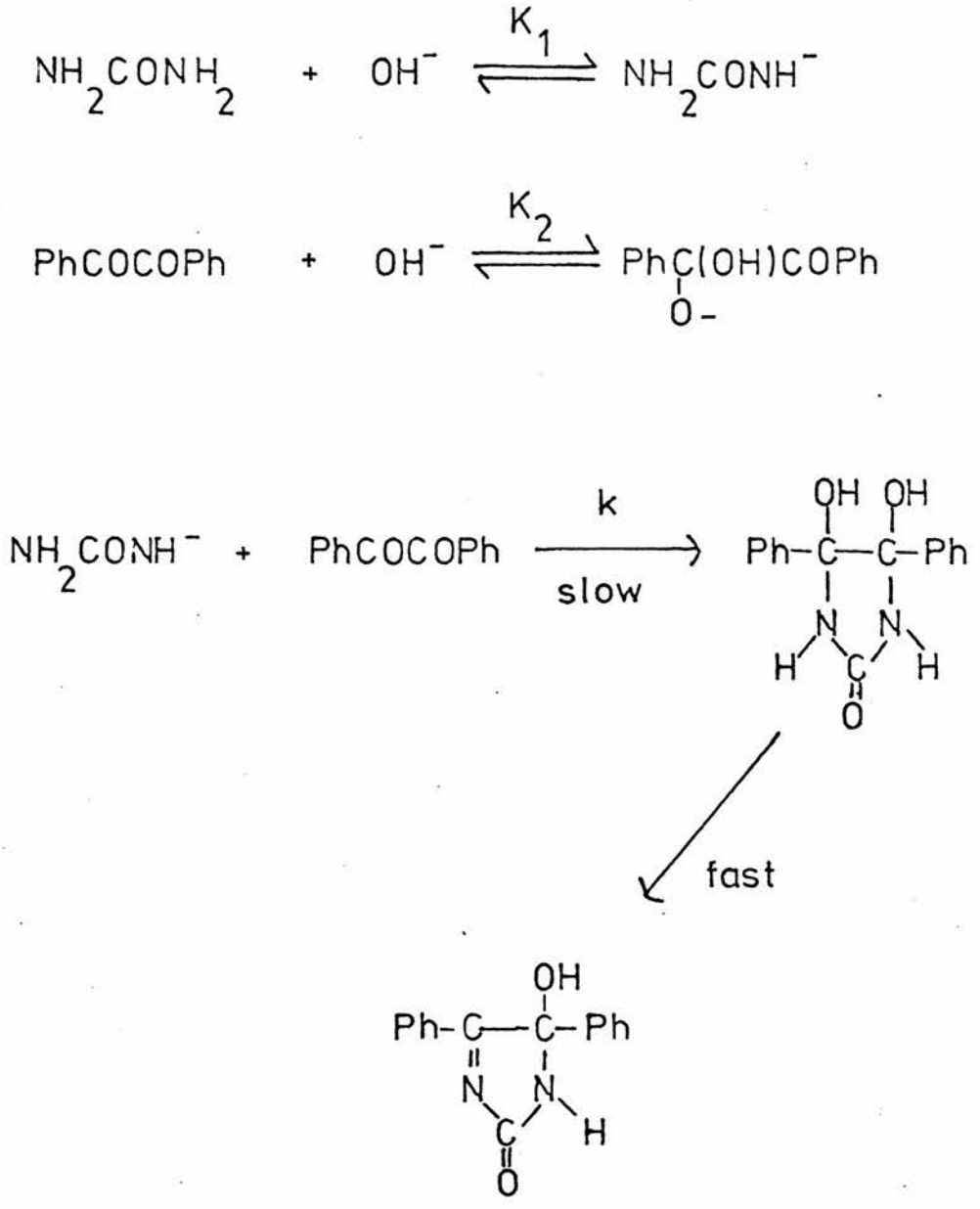
The kinetic results (see later) obtained with urea, N-methylurea and N,N'-dimethylurea all follow the same pattern and it is not unreasonable to assume that the three ureas all react with benzil with the same rate-determing step. With urea and N-methylurea, cyclisation to form the diol (XXXV) is accompanied by elimination of water to yield (XXXVI) which contains a C=N bond. This helps to explain why the benzil absorbance does not fall down to zero for urea and N-methylurea, as a C=N bond would be expected to have an absorbance in the same region as the benzil carbonyl groups. Due to the presence of two methyl groups, the N,N'-dimethylurea diol (XXXIV) is unable to eliminate water to form a C=N bond and hence absorbance falls right down to zero.

Support for the interpretion of these spectral changes comes from the work of Jencks[34] with furfural. The addition of hydroxylamine, O-methylhydroxylamine or semicarbazide to a solution of furfural at neutral pH results in a rapid drop in the absorption due to furfural as a carbinolamine intermediate is formed. As dehydration of the intermediate to form a C=N bond occurs, a new absorbance slowly forms at almost the same wavelength. Similar results were observed by Reinman and Jencks[41] in the reaction of hydroxylamine with p-chlorobenzaldehyde.

Kinetic investigation.

The kinetics of the disappearance of benzil, which is a first-order reaction, were examined for each of urea, N-methylurea and N,N'-dimethylurea.

Scheme 8. Reaction of urea with benzil



In each of the three cases, the effect of varying the urea and the hydroxide ion concentrations on the rate constant was investigated. The results thus obtained are tabulated (Tables 6, 7, 8). Plots of the observed rate constant, k_{obs}, against the urea and the hydroxide concentration are also shown in Figures 10 and 11. As seen from the plots, there is a linear relationship between k_{obs} and the urea concentration $[NH_2CONH_2]$. With the hydroxide ion concentration, k_{obs} is found to increase initially as $[OH^-]$ is increased, then to level off at a maximum at higher $[OH^-]$.

Comparison of the rate constants also show that N, N'-dimethylurea, N-methylurea and urea are in order of increasing reactivity.

Proposed scheme.

On the basis of the results obtained above, Scheme 8 is proposed. The scheme shows that the slow step is attack of benzil by the urea anion on one carbonyl group, followed by rapid cyclisation and elimination of water to give XXXVIa via the diol.

The catalytic effect of the hydroxide ion on the reaction suggests that the attack is by the urea anion. The existence of the urea anion as an attacking species has been suggested by previous workers, notably in the reactions of urea with formaldehyde[84], with glyoxal[85] under basic conditions and also in the alkaline hydrolysis of ureas[86]. The existence of amide salts such as $CH_3CONH^-K^+$ gives further support to the plausibility of an urea anion.

With the substituted ureas, the presence of the methyl groups

Table 6.

Kinetics of the reaction of urea and benzil at 25°

(a) [NaOH] = 0.50 M

[Urea] M	0.020	0.040	0.060	0.080	0.01
$10^2 k_{obs}$ s^{-1}	0.51	1.07	1.51	2.09	2.89

(b) [Urea] = 0.10 M

[NaOH] M	0.020	0.060	0.080	0.10	0.20	0.25
$10^2 k_{obs}$ s^{-1}	0.50	1.08	1.31	1.42	1.85	1.87

(c) [Urea] = 0.050 M

[NaOH] M	0.050	0.10	0.15	0.20	0.25
$10^2 k_{obs}$ s^{-1}	0.47	0.67	0.87	0.93	0.91

$[benzil]_o$ = ca. 10^{-5} M

Table 7.

Kinetics of the reaction of N-methylurea and benzil at 25°

(a) [NaOH] = 0.50 M

[Methylurea] M	0.020	0.040	0.060	0.080	0.10
$10^2 k_{obs}$ s^{-1}	0.23	0.50	0.73	0.88	1.16

(b) [Methylurea] = 0.10 M

[NaOH] M	0.020	0.040	0.060	0.080	0.10
$10^2 k_{obs}$ s^{-1}	0.25	0.41	0.54	0.59	0.66

$[Benzil]_o$ = ca. 10^{-5} M

Table 8.

Kinetics of the reaction of N, N'-dimethylurea and benzil at 25°

(a) [NaOH] = 0.50 M

[Dimethylurea] M	0.10	0.20	0.30	0.40	0.50
$10^2 k_{obs}$ s^{-1}	0.27	0.51	0.70	0.95	1.33

(b) [Dimethylurea] = 0.50 M

[NaOH] M	0.020	0.060	0.10	0.20	0.30	0.50
$10^2 k_{obs}$ s^{-1}	0.20	0.44	0.52	0.73	0.89	1.13

$[\text{Benzil}]_o$ = ca. 10^{-5} M

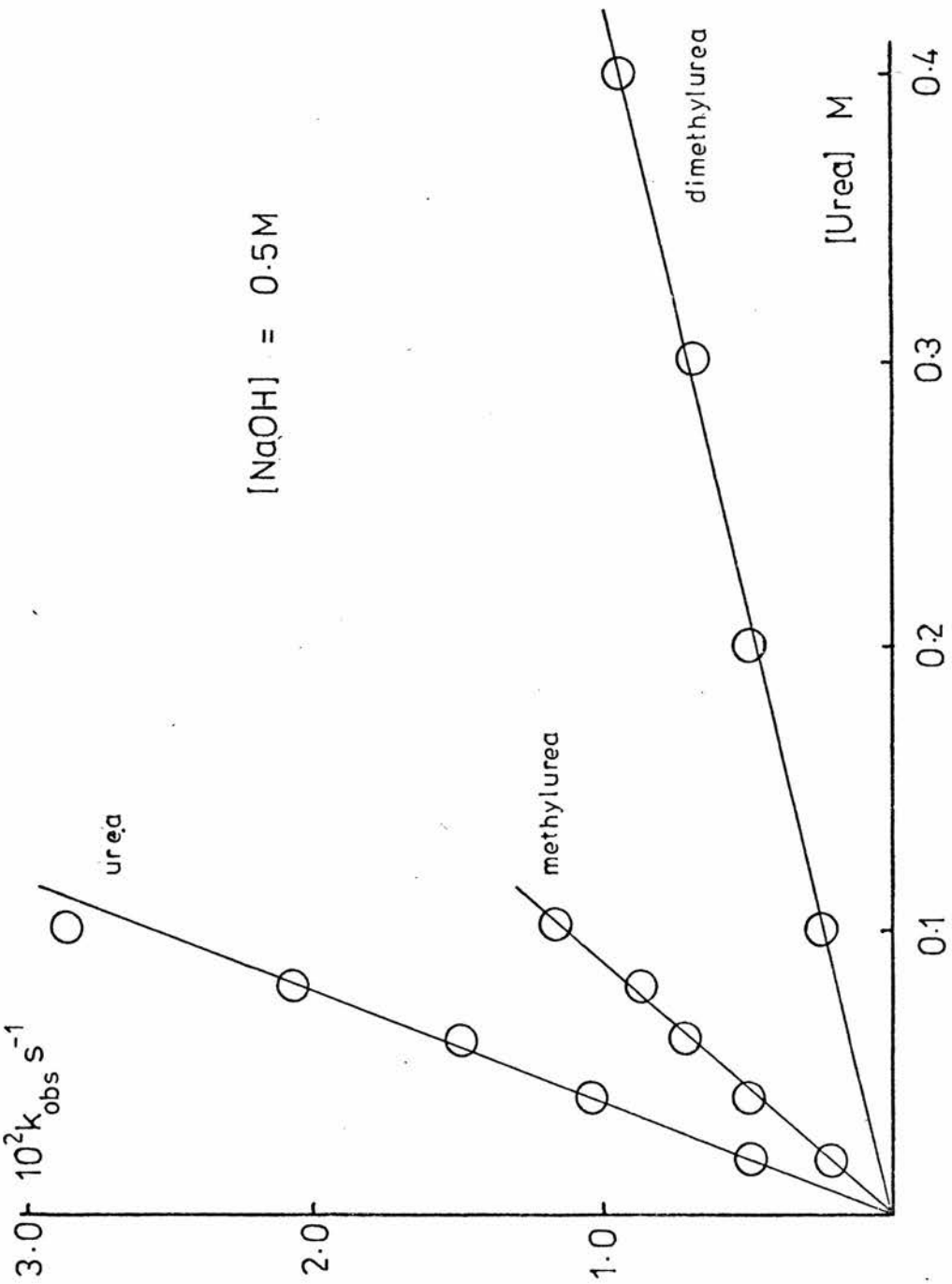


Figure 10. Variation of k_{obs} with stoicheiometric urea concentration in reactions of urea, N-methylurea and N,N'-dimethylurea with benzil at 25°

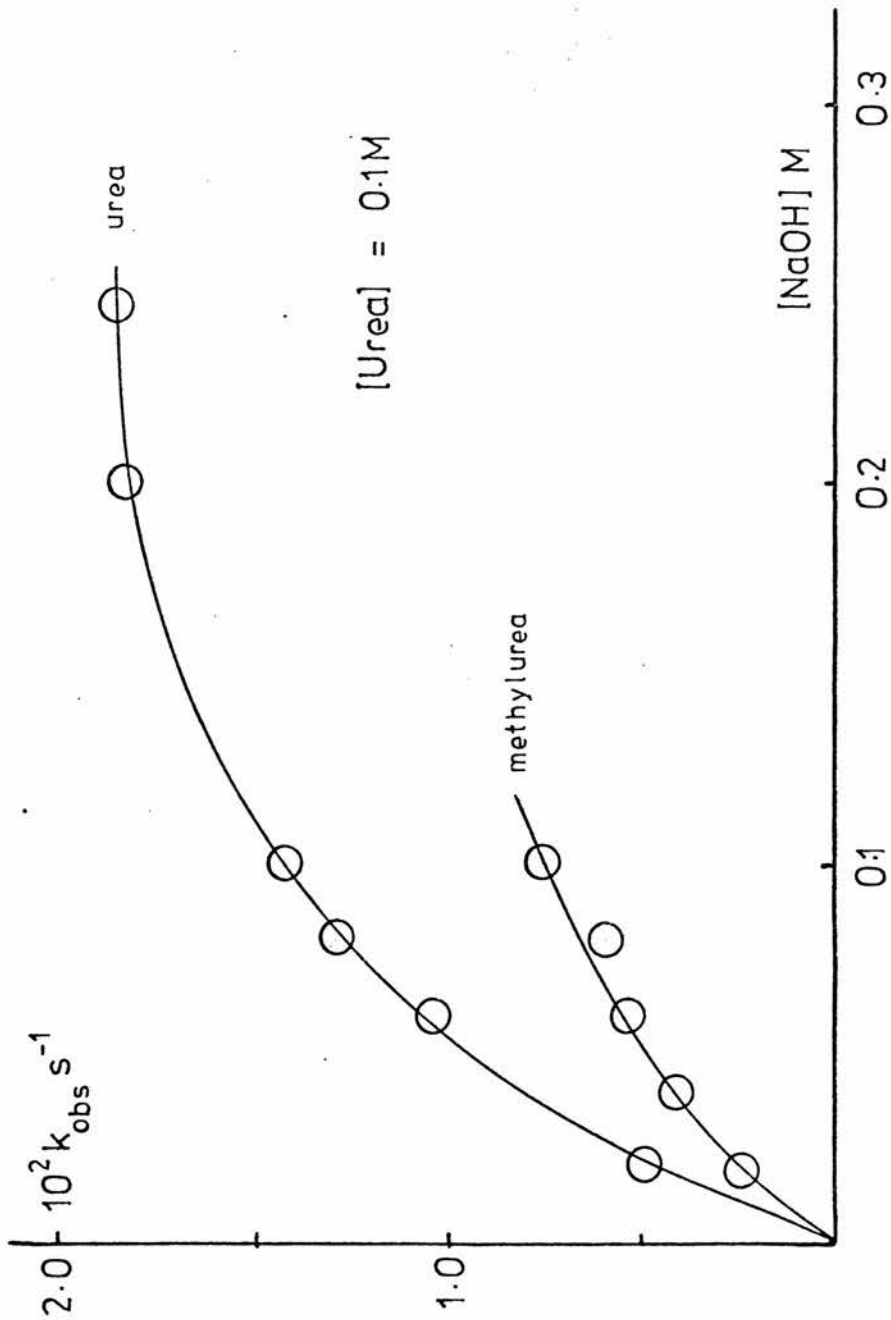


Figure 11. Variation of k_{obs} with stoicheiometric hydroxide ion concentration during reactions of urea and methylurea with benzil at 25°

makes the nitrogen atom more nucleophilic and anion formation would become more difficult. Slower attack of benzil would thus be expected from N-methylurea and N, N'-dimethylurea and this is found to be so.

Let us then take the rate equation:

$$\text{rate} = k[NH_2CONH^-][PhCOCOPh] \qquad (1)$$

Assuming that K_1 is very small and that K_2 is much larger, we can substitute $K_1[OH^-][NH_2CONH_2]$ for $[NH_2CONH^-]$, and $[PhCOCOPh]_{st}/(1 + K_2[OH^-])$ for $[PhCOCOPh]$ where $[PhCOCOPh]_{st}$ is the stoicheiometric concentration of benzil to give:

$$\text{rate} = \frac{k K_1[OH^-][NH_2CONH_2][PhCOCOPh]_{st}}{1 + K_2[OH^-]} \qquad (2)$$

The experimentally observed equation for the disappearance of benzil:

$$\text{rate} = k_{obs}[PhCOCOPh]_{st} \qquad (3)$$

is then combined with (2) to give an expression for k_{obs} for the reaction scheme:

$$k_{obs} = \frac{k K_1[OH^-][NH_2CONH_2]}{1 + K_2[OH^-]} \qquad (4)$$

This expression for k_{obs} shows a linear relationship between k_{obs} and the urea concentration and this is in agreement with the experimentally observed results.

The observed variation of k_{obs} with the hydroxide ion concentration can also be explained as follows. At low $[OH^-]$, $K_2[OH^-] \ll 1$ and the rate

expression (4) becomes:

$$k_{obs} = k K_1 [OH^-][NH_2CONH_2] \quad (5)$$

which is a linear relationship. At high $[OH^-]$, $K_2 [OH^-] \gg 1$ and the rate expression (4) becomes:

$$k_{obs} = \frac{k K_1 [NH_2CONH_2]}{K_2} \quad (6)$$

so that k_{obs} becomes independent of $[OH^-]$.

Rearrangement of (4) gives:

$$\frac{[NH_2CONH_2]}{k_{obs}} = \frac{1}{k K_1 [OH^-]} + \frac{K_2}{k K_1} \quad (7)$$

Thus a plot of $[NH_2CONH_2]/k_{obs}$ against $1/[OH^-]$ should yield a straight line. Such plots for urea, N-methylurea and N, N'-dimethylurea are shown in Figures 12 and 13. The straight lines thus obtained are a confirmation of the proposed scheme.

The y-intercept, K_2/kK_1, when divided by the slope $1/kK_1$ gives K_2 which should be independent of the urea used. The values of K_2 were thus calculated for urea, N-methylurea and N, N'-dimethylurea and were found to be in close agreement as shown in Table 9.

Kinetics in heavy water.

A similar kinetic investigation was carried out on the reaction between urea and benzil in heavy water in the presence of sodium deuteroxide.

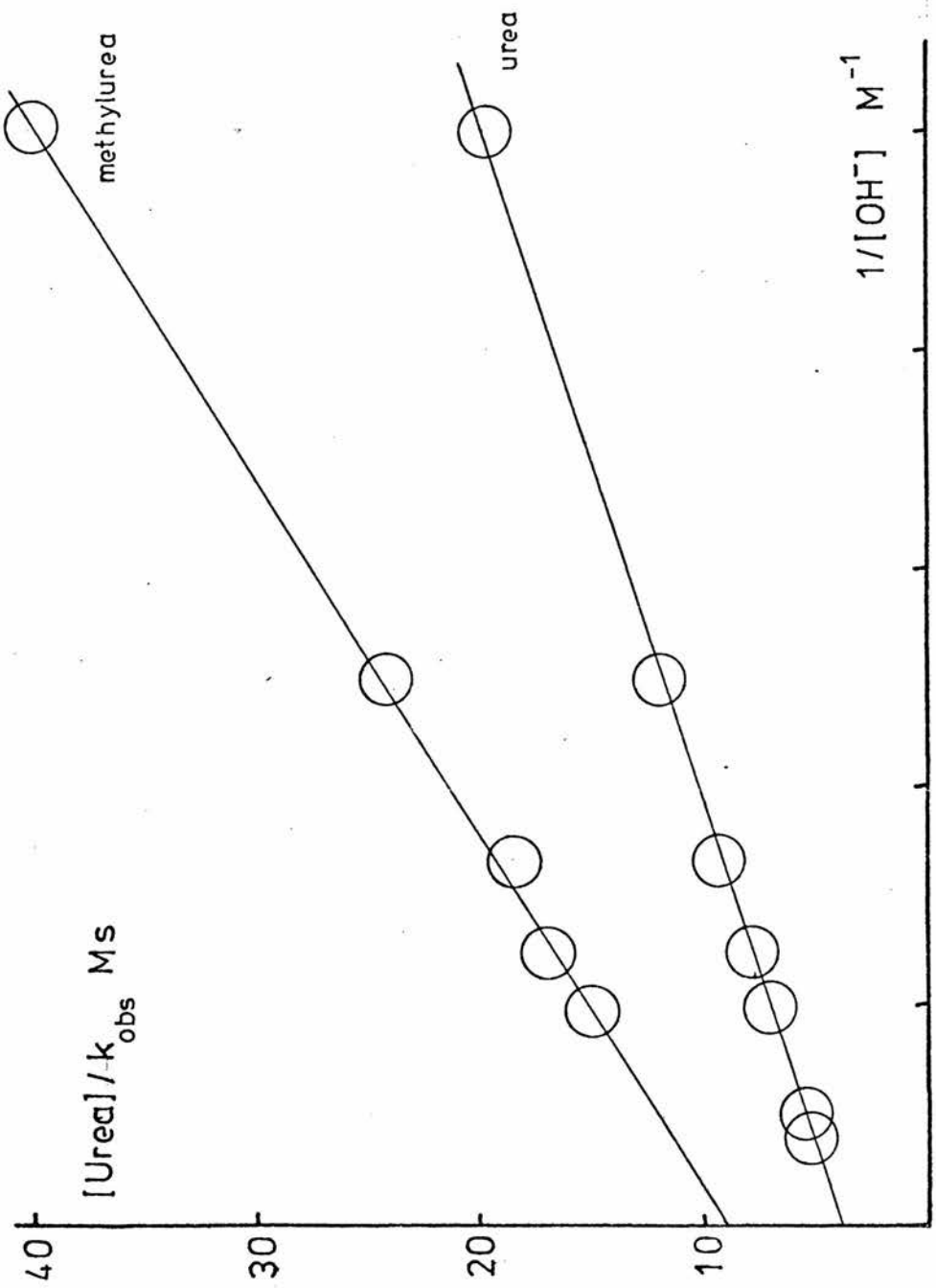


Figure 12. Plot of [Urea]/k_{obs} against 1/[OH^-] for reaction of urea and methylurea with benzil at 25°

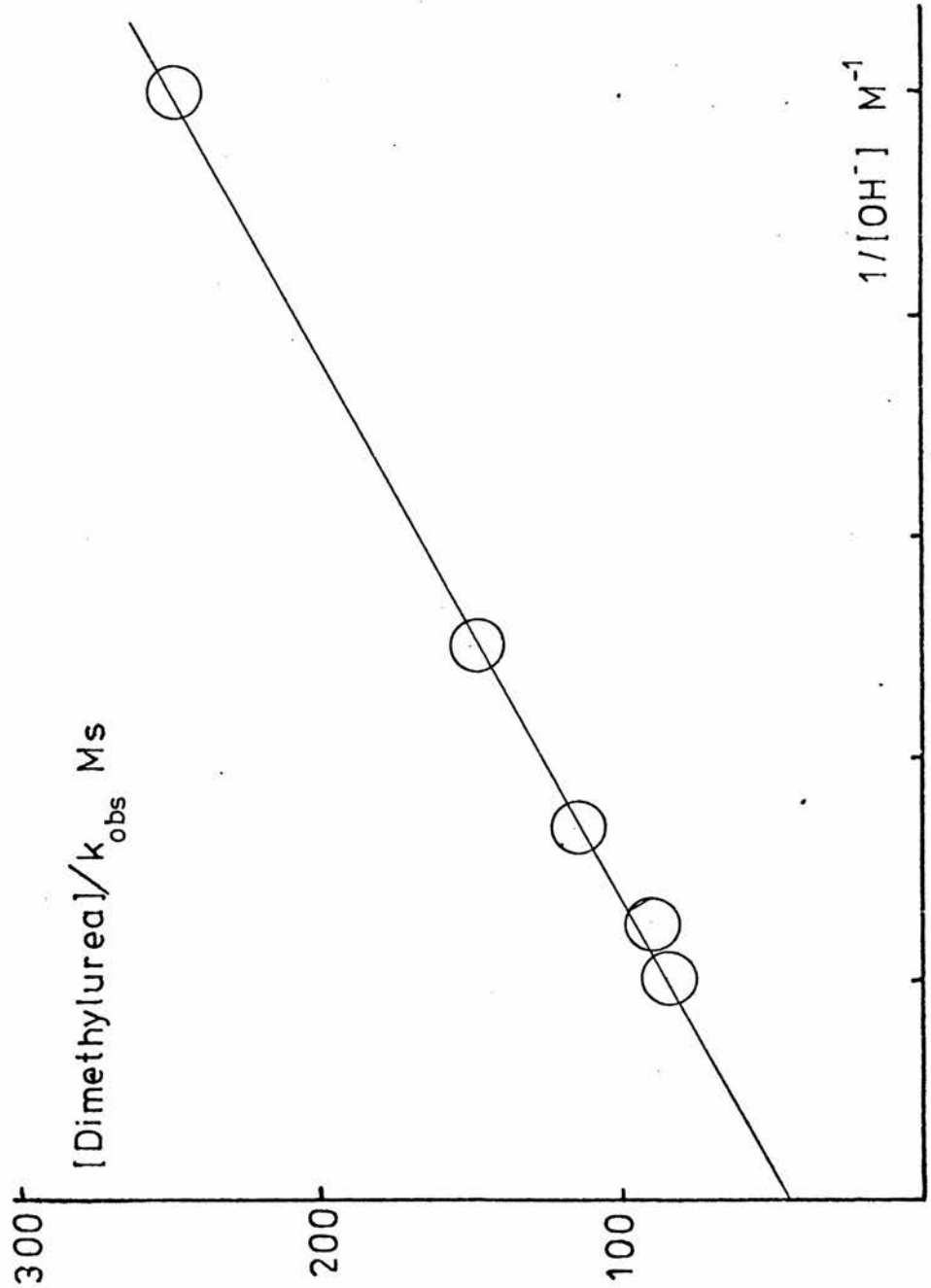


Figure 13. Plot of [Dimethylurea]/k_{obs} against 1/[OH^-] for reaction of N, N'-dimethylurea with benzil at 25°

Table 9.

Effect of substituents in benzil on its reactions with urea, N-methylurea, and N,N'-dimethylurea

		Urea	Methylurea	Dimethylurea
(a)	Benzil			
	K_2 M^{-1}	12	12	11
(b)	4,4'-Dimethylbenzil			
	K_2 M^{-1}	5	1.8	1.5
	k^{Me}/k	0.42	0.33	0.23
(c)	4,4'-Dimethoxybenzil			
	K_2 M^{-1}	0.30	0.64	0.48
	k^{OMe}/k	0.07	0.09	0.06

Rate constants were obtained for different sodium deuteroxide concentrations and are shown in Table 10. A plot of $k_{obs}^{D_2O}$ against deuteroxide ion concentration, $[OD^-]$, was obtained and is shown superimposed on the one of $k_{obs}^{H_2O}$ against $[OH^-]$ in Figure 14.

In heavy water the reaction is shown to vary in the same manner with deuteroxide ion concentration as it does in normal water. However, reaction is found to be faster in heavy water than in normal water. This result is consistent with the proposed mechanism since OD^- is a stronger base than OH^-. This would result in the formation of more urea anion in heavy water and hence in a faster reaction.

The kinetic isotope effects $k_{obs}^{H_2O} / k_{obs}^{D_2O}$ were calculated for different $[OD^-]$ and are shown in Table 10. Taking the rate expression (4), the kinetic isotope effect is given by

$$\frac{k_{obs}^{H_2O}}{k_{obs}^{D_2O}} = \frac{k^H K_1^H (1 + K_2^D [OD^-])}{k^D K_1^D (1 + K_2^H [OH^-])} \qquad (8)$$

This expression shows that the kinetic isotope effect varies with alkali concentration.

Rearrangement to the hydantoin and evidence for the intermediate.

A reaction similar to that of urea with benzil, to form diol compounds (4,5-dihydroxy-2-imidazolidones) has been reported by Vail and coworkers[85]. These compounds arise from the reaction of urea and

Table 10.

Kinetics of the reaction of urea and benzil

in heavy water at 25°

[Urea] = 0.1 M

[NaOD] M	0.0585	0.117	0.234
$10^2 k_{obs}^{D_2O}$ s^{-1}	1.65	2.15	2.50
$k_{obs}^{H_2O} / k_{obs}^{D_2O}$	0.64	0.71	0.75

$[\text{Benzil}]_o$ = ca. 10^{-5} M

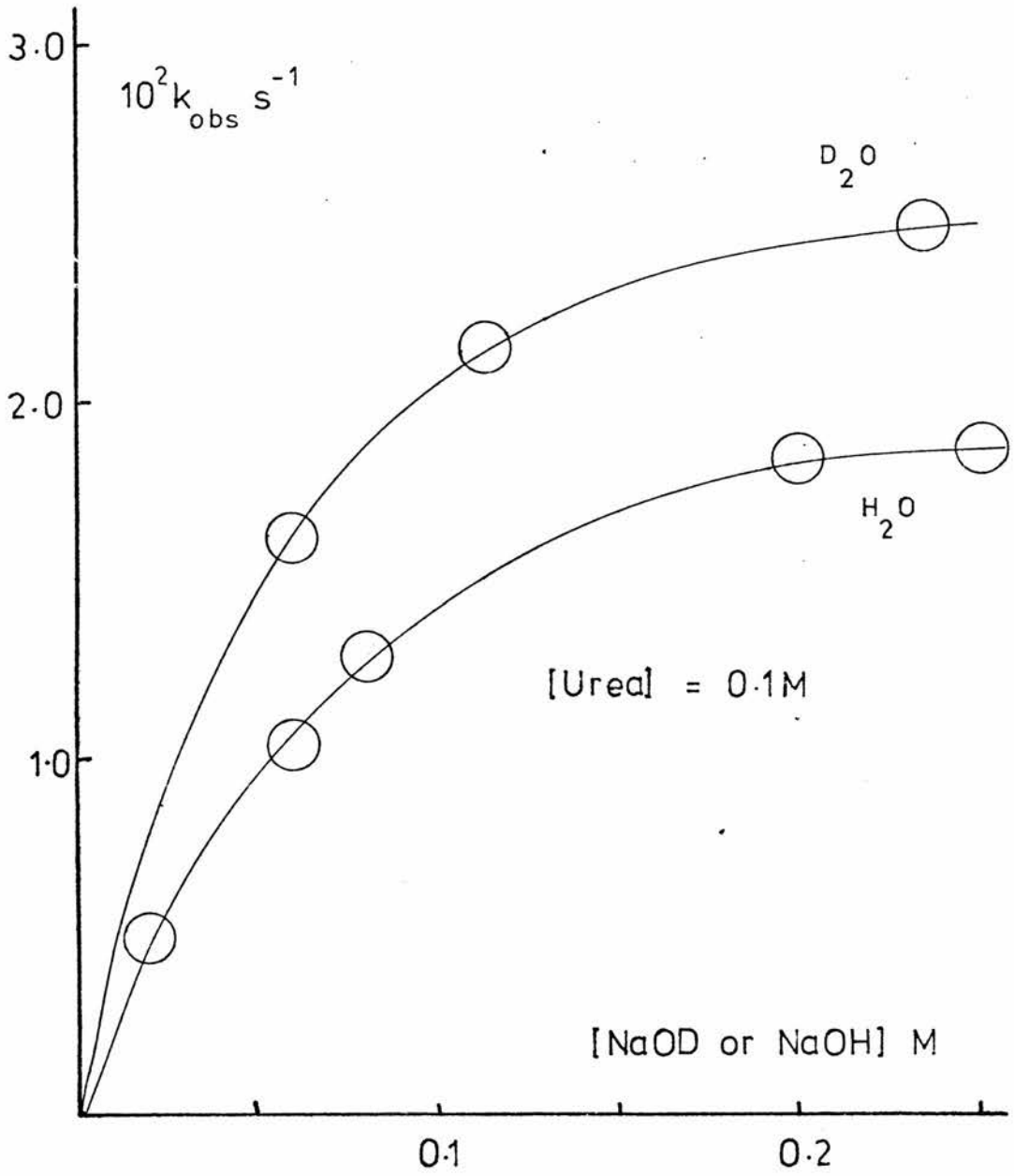
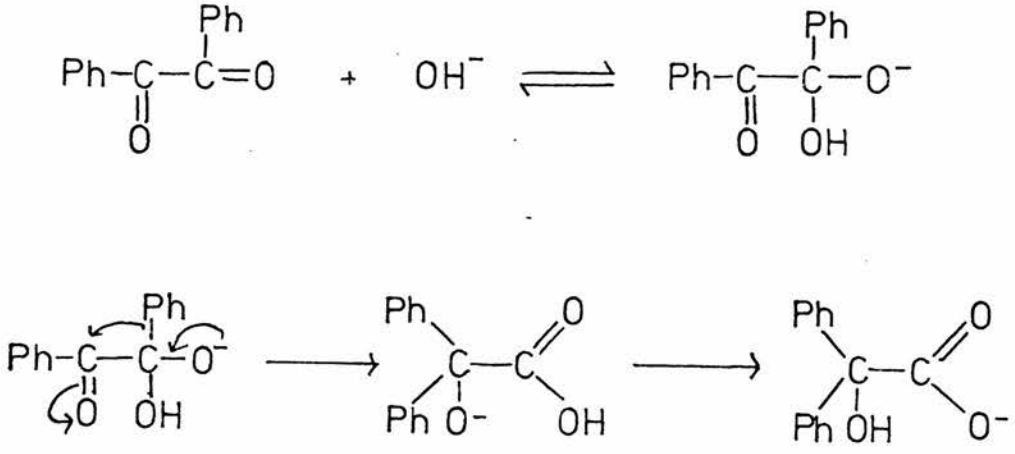
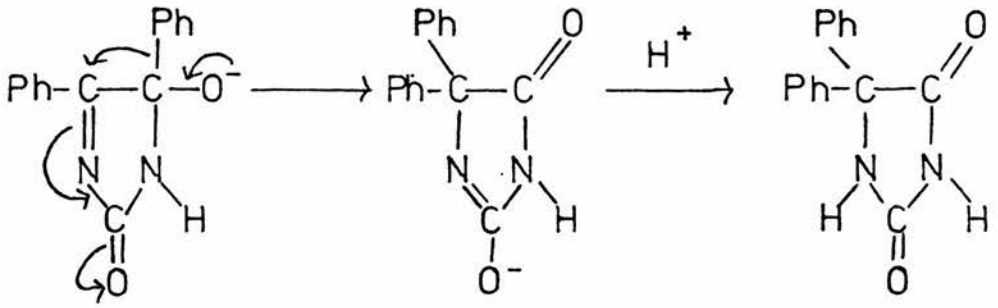


Figure 14. Variation of k_{obs} with deuteroxide or hydroxide ion concentration for reaction of urea with benzil in heavy water and in normal water

Scheme 9. Benzilic acid rearrangement[87]



Scheme 10. Rearrangement to hydantoin



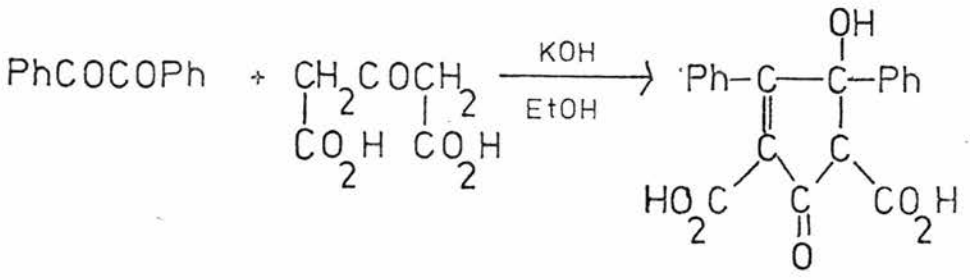
N,N'-dimethylurea with glyoxal under basic conditions. Glyoxal has a similar structure to benzil except for the fact hydrogen atoms replace the two phenyl groups of benzil. Rearrangement of 4,5-dihydroxy-2-imidazolidone to give the appropriate hydantoin apparently does not occur, possibly because the hydrogen atom is not such a good migrating species as the phenyl group.

With benzil, efforts to isolate either the diol (XXXV) or the C=N (XXXVI) intermediates have been without success. But the spectral changes already discussed give support for the proposed C=N intermediate. In addition, the fact that the diol product obtained with N,N'-dimethylurea is unable to undergo further reaction provides another piece of evidence.

Further support for this intermediate can be obtained by considering the possible mechanism of the rearrangement of the urea and N-methyl intermediates to the corresponding hydantoins. Rearrangement must involve the migration of a phenyl group and this is what occurs in the benzilic acid rearrangement. The generally accepted mechanism for the benzilic acid rearrangement is shown in Scheme 9[87]. If a proton is abstracted from XXXVI, this intermediate can then undergo a parallel rearrangement to the hydantoin as shown in Scheme 10. The driving force of the rearrangement is the formation of a stable carbonyl group in the 4-position.

It is also helpful to consider the rearrangement of the N-methylurea intermediate (XXXVIb). The presence of the methyl group means that rearrangement via the mechanism proposed in Scheme 10 cannot possibly result in the

Scheme 11. Reaction of β-ketoglutaric acid with benzil



formation of 1-methyl-5,5-diphenylhydantoin. Instead 3-methyl-5,5-diphenylhydantoin must result and this is, indeed, the product that was isolated with N-methylurea.

One may wonder why the urea diol does not eliminate two molecules of water to form two C=N bonds. The probable explanation is that there would be too much strain in the resulting 5-membered heterocyclic ring with two C=N bonds. It is of interest to note that when β-ketoglutaric acid reacts with benzil in ethanol containing potassium hydroxide, a product[88] remarkably similar in structure to that of XXXVIa is formed (Scheme 11). Rather than two molecules of water being eliminated to form two C=N bonds, only one molecule of water is eliminated to form a single double bond.

Reaction with substituted benzils.

The reactions of the three ureas with 4,4'-dimethyl- and 4,4'-dimethoxy-benzils were also investigated. The products were prepared by the method used for benzil. The expected hydantoins resulted with urea and N-methylurea, while N,N'-dimethylurea yielded the appropriate diols.

A similar kinetic investigation was also carried out for the two substituted benzils and the results are given in Tables 11 and 12. Both benzils follow the same kinetic pattern observed for benzil. Plots of $[NH_2CONH_2]/k_{obs}$ against $1/[OH^-]$ also gave straight lines similar to those obtained with benzil. These results show that the mechanism of the reaction remains unchanged. As noted before, values of K_2 should be independent of the urea for

Table 11.

Kinetics of the reaction of urea, N-methylurea, and N,N'-dimethylurea with 4,4'-dimethylbenzil at 25°

(1) Urea

(a) [NaOH] = 0.50 M

[Urea] M	0.020	0.040	0.060	0.080	0.10
$10^2 k_{obs}$ s^{-1}	0.30	0.68	1.02	1.36	1.93

(b) [Urea] = 0.10 M

[NaOH] M	0.10	0.20	0.30	0.40	0.50
$10^2 k_{obs}$ s^{-1}	0.89	1.27	1.56	1.80	1.89

(2) N-Methylurea

(a) [NaOH] = 0.50 M

[Methylurea] M	0.10	0.20	0.30	0.40	0.50
$10^2 k_{obs}$ s^{-1}	0.85	2.03	3.38	5.12	6.45

(b) [Methylurea] = 0.50 M

[NaOH] M	0.10	0.20	0.30	0.40	0.50
$10^2 k_{obs}$ s^{-1}	2.06	3.60	4.76	5.58	6.45

(3) N,N'-Dimethylurea

(a) [NaOH] = 0.50 M

[Dimethylurea] M	0.10	0.20	0.30	0.40	0.50
$10^3 k_{obs}$ s^{-1}	1.92	3.48	5.15	6.27	8.12

(b) [Dimethylurea] = 0.50 M

[NaOH] M	0.10	0.20	0.30	0.40	0.50
$10^3 k_{obs}$ s^{-1}	2.45	4.30	5.42	6.48	8.12

$[4,4'\text{-Dimethylbenzil}]_o$ ca. 10^{-5} M

Table 12.

Kinetics of the reaction of urea, N-methylurea, and N,N'-dimethylurea with 4,4'-dimethoxybenzil at 25°

(1) Urea

(a) [NaOH] = 0.50 M

[Urea] M	0.050	0.10	0.15	0.20	0.25
$10^2 k_{obs}$ s^{-1}	0.46	0.85	1.32	1.87	2.24

(b) [Urea] = 0.25 M

[NaOH] M	0.050	0.10	0.15	0.20	0.25
$10^2 k_{obs}$ s^{-1}	0.25	0.44	0.75	1.10	1.16

(2) N-Methylurea

(a) [NaOH] = 0.50 M

[Methylurea] M	0.10	0.20	0.30	0.40	0.50
$10^2 k_{obs}$ s^{-1}	0.46	1.03	1.96	2.48	3.89

(b) [Methylurea] = 0.50 M

[NaOH] M	0.10	0.20	0.30	0.40	0.50
$10^2 k_{obs}$ s^{-1}	0.76	1.36	2.05	2.69	3.89

(3) N,N'-Dimethylurea

(a) [NaOH] = 0.50 M

[Dimethylurea] M	0.30	0.40	0.50	0.60	0.80	1.00
$10^3 k_{obs}$ s^{-1}	2.13	2.81	3.43	3.92	4.72	4.99

(b) [Dimethylurea] = 1.00 M

[NaOH] M	0.10	0.20	0.30	0.40	0.50
$10^3 k_{obs}$ s^{-1}	1.24	2.30	3.31	4.20	4.99

$[4,4'\text{-Dimethoxybenzil}]_o$ ca. 10^{-5} M

each benzil. These values are shown in Table 9 and, apart from a poor value for urea with 4,4'-dimethylbenzil, are found to be in good agreement. The presence of electron-repelling or electron-donating substituents on the phenyl groups would make the benzil less susceptible to attack by a nucleophile and this is reflected in the K_2 values obtained for benzil and the two substituted benzils.

It is possible to calculate the effect of the substituent on the value of k. This calculation is made from the slope, $1/k\,K_1$, of the plot of $[\,NH_2CONH_2\,]/\,k_{obs}$ against $1/[\,OH^-\,]$. By keeping to the same urea for the three different benzils (i.e. K_1 constant) the ratios k^{Me}/k and k^{OMe}/k are calculated for the substituted benzils relative to benzil itself. These ratios are shown in Table 9 and substitutent effects are seen to be consistent with the proposed reaction scheme.

EXPERIMENTAL

Preparation of products from benzil.

A solution of urea (6g) in ethanol (50 ml) was added to benzil (21g). After addition of aqueous KOH (10 M, 5 ml) the mixture was refluxed for 2 h. On addition of water to the solution the product precipitated and was filtered off and recrystallised from ethanol.

The N-methylurea and N,N'-dimethylurea products were prepared similarly. The N,N'-dimethylurea product precipitated only after standing for some time and was recrystallised, with difficulty, from DMSO. The same procedure was also used with the substituted benzils. Elemental analyses and mass spectra were obtained for these compounds and were found to be in agreement with the expected hydantoin or diol structures. The physical data for these compounds are summarised in Tables 13, 14 and 15.

Preparation of 5,5-diphenyl-1-methylhydantoin.

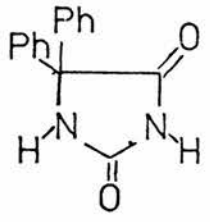
5,5-diphenyl-1-methyl hydantoin was prepared from 5,5-diphenyl-thiohydantoin by the method of Cattelain and Chabrier[89] which starts with 5,5-diphenylthiohydantoin and involves three stages:

1) Preparation of 2-methyl-5,5-diphenylthiohydantoin:

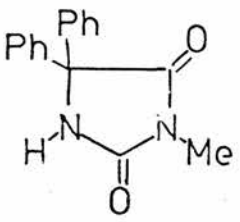
To a solution of 5,5-diphenylthiohydantoin (7g) in ethanol (50 ml), was added successively sodium hydroxide (3M, 10 ml) and methyl iodide (2 ml). The solution was refluxed on a steam bath for 4 h. The precipitate, which

Table 13.

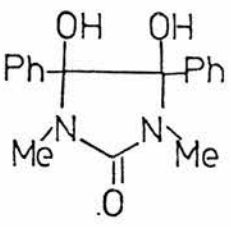
Physical data for the benzil products :



(i)



(ii)



(iii)

(i) M.p. 286°, molecular ion peak 252

Analysis : $C_{15}H_{12}N_2O_2$

Required :	71.4% C	4.8% H	11.1% N
Found :	71.4% C	4.7% H	11.2% N

(ii) M.p. 204°, molecular ion peak 266

Analysis : $C_{16}H_{14}N_2O_2$

Required :	72.2% C	5.3% H	10.5% N
Found :	72.1% C	5.1% H	10.1% N

(iii) M.p. 190°, molecular ion peak 280 (M-18)

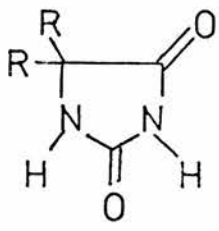
Analysis : $C_{17}H_{18}N_2O_3$

Required:	68.4% C	6.1% H	9.4% N
Found :	68.2% C	6.2% H	9.6% N

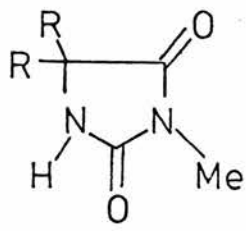
Table 14.

Physical data for the 4,4'-dimethylbenzil products :

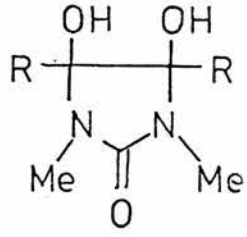
R = *p*-Me-C_6H_4



(i)



(ii)



(iii)

(i) M.p. 230°, molecular ion peak 280

Analysis : $C_{17}H_{16}N_2O_2$

Required :	72.8% C	5.8% H	10.1% N
Found :	72.6% C	5.8% H	10.1% N

(ii) M.p. 189°, molecular ion peak 294

Analysis : $C_{18}H_{18}N_2O_2$

Required :	73.5% C	6.2% H	9.5% N
Found :	72.5% C	6.2% H	9.3% N

(iii) M.p. 169°, molecular ion peak 308 (M-18)

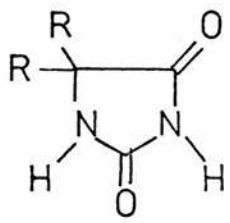
Analysis : $C_{19}H_{22}N_2O_3$

Required :	69.9% C	6.8% H	8.6% N
Found :	69.0% C	6.8%H	8.3% N

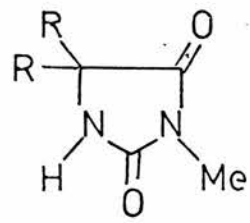
Table 15.

Physical data for the 4,4'-dimethoxybenzil products :

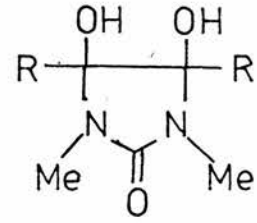
R = *p*-MeO-C_6H_4



(i)



(ii)



(iii)

(i) M.p. 225°, molecular ion peak 312

Analysis : $C_{17}H_{16}N_2O_4$

Required :	65.4% C	5.2%H	9.0% N
Found :	64.6% C	5.1% H	8.8% N

(ii) M.p. 151°, molecular ion peak 326

Analysis : $C_{18}H_{18}N_2O_4$

Required :	66.3% C	5.6%H	8.6% N
Found :	65.2% C	5.4% H	8.4% N

(iii) M.p. 159°, molecular ion peak 340 (M-18)

Analysis : $C_{19}H_{22}N_2O_5$

Required :	63.7% C	6.2% H	7.8% N
Found :	63.1% C	6.1% H	7.1% N

formed on cooling, was filtered, washed with alcohol at 60° and dried.

2) Preparation of 1,2-dimethyl-5,5-diphenylthiohydantoin:

To a solution of 2-methyl-5,5-diphenylthiohydantoin (4g) in ethanol (25 ml) at 95°, was added successively sodium hydroxide (3M, 5 ml) and methyl iodide (2 ml). The solution was refluxed for 4 h on a steam bath. The product, which precipitated on cooling, was filtered, washed with alcohol at 60° and dried.

3) Preparation of 1-methyl-5,5-diphenylhydantoin:

The 1,2-dimethyl-5,5-diphenylthiohydantoin (2g) was dissolved in ethanol (30 ml) at 95°. Concentrated hydrochloric acid (1 ml) was added and the solution boiled for 2 min. On cooling, the crystals came out and were filtered, washed in alcohol and dried. M.p. 212° (lit. 215-216°).

The methyl peak in the proton n.m.r. spectrum was a singlet at δ 2.92 (DMSO).

Preparation of 5,5-diphenyl-3-methylhydantoin[90].

A mixture of diphenylglycine (2.5g), methyl isocyanate (0.81g) and NaOH (0.38g) in water (12.5 ml) was shaken for 2 h. After filtration the filtrate was acidified. The resulting precipitate was filtered off and boiled with 20% HCl for 2 h. The product was filtered off, washed, dried and recrystallised from ethanol, m.p. 207°

Analysis :	$C_{16}H_{14}N_2O_2$		
Required :	C = 72.2%	H = 5.3%	N = 10.5%
Found :	C = 72.1%	H = 5.3%	N = 10.4%

The methyl peak in the proton n.m.r. spectrum was a singlet at δ 3.06 ($CDCl_3$).

The product from the reaction of methylurea with benzil melted at 208° and the proton n.m.r. spectrum was the same as that of 5,5-diphenyl-3-methylhydantoin. Identity was confirmed by a mixed m.p.

Preparation of 1,3-dimethyl-5,5-diphenylhydantoin.

1,3-Dimethyl-5,5-diphenylhydantoin was prepared by N-methylation of 5,5-diphenylhydantoin (based on a N-methylation method used by Olsen[91]).

5,5-Diphenylhydantoin (2.5g), methyl iodide (8.5g) and silver oxide (10g) were dissolved in anhydrous dimethylformamide (100 ml). The solution was stirred magnetically at room temperature all day. The mixture was then filtered and the solid washed with a small amount of dimethylformamide. To the filtrate was added 4x its volume of chloroform. The chloroform phase was washed several times with water and dried ($MgSO_4$). The drying agent was removed by filtration and the solvent evaporated off to yield the product, which was recrystallised from toluene, m.p. 190°.

Analysis :	$C_{17}H_{16}N_2O_2$		
Required :	C = 72.8%	H = 5.8%	N = 10.0%
Found :	C = 73.0%	H = 5.7%	N = 10.2%

The two methyl groups resulted in two singlets in the proton n.m.r. spectrum at δ 2.50 and 2.76.

The product of the reaction of benzil and N,N'-dimethylurea melted

at 190° and had a single peak in the proton n.m.r. due to the methyl groups, at δ 2.59. Mixed m.p. confirmed that this product was not 1,3-dimethyl-5,5-diphenylhydantoin.

Isotopic dilution experiments.

Benzil (0.5 ml of 0.2% solution in ethanol) was added to a solution of ^{14}C-urea (250$\mu C_i\ g^{-1}$, 0.3g) in NaOH (0.1 M, 50 ml) and allowed to react for 0.5 h. at room temperature. After neutralisation by addition of HCl (5 M, 1 ml) to stop reaction, 5,5-diphenylhydantoin (0.2g) was added to equilibrate with any radioactive 5,5-diphenylhydantoin present in solution. The mixture was stirred for 1 h. and the hydantoin was filtered off, thoroughly washed to remove traces of urea, and recrystallised from ethanol. Recrystallisation was repeated until the level of radioactivity remained constant. In a second experiment the reaction was allowed to continue overnight before neutralisation.

For counting, the 5,5-diphenylhydantoin (0.01g) was dissolved in dioxan solution (10 ml) containing scintillators naphthalene and PPO. (Dioxan solution : naphthalene (10g), PPO (0.5g) made up to 100 ml with dioxan). The samples were counted on a Beckman LS100 liquid scintillation counter. The samples were counted with not more than 5% error.

To determine the amount of quenching (and hence the counting efficiency), a sample of hexadecane of known activity was dissolved in dioxan in the presence of unradioactive 5,5-diphenylhydantoin and counted. Quenching

was found to be approximately 50% and entirely due to the dioxan solution and not the hydantoin itself.

On the basis of the known activity of the urea calculations were made to determine the expected activity of the 5, 5-diphenylhydantoin assuming that 100% reaction had occured.

$1\ \mu C_i = 3.7 \times 10^4$ disintegrations s^{-1}

Activity of urea = $250\ \mu C_i\ g^{-1}$

$= 250 \times 3.7 \times 10^4\ d\ s^{-1}\ g^{-1}$

$= 9.25 \times 10^6\ d\ s^{-1}\ g^{-1}$

$= 60 \times 9.25 \times 10^6\ d\ s^{-1}\ mol^{-1}$

$= 5.55 \times 10^8\ d\ s^{-1}\ mol^{-1}$

Molarity of benzil in reaction mixture = 0.0001 M

$\therefore$ 50 ml of solution contains 5×10^{-6} moles

in 100% reaction 5×10^{-6} moles of 5, 5-diphenylhydantoin will be formed.

After reaction, 0.2g of unradioactive 5, 5-diphenylhydantoin was added to the radioactive material

$\frac{0.2}{252} = 7.94 \times 10^{-4}$ moles of hydantoin added

Activity of hydantoin $= 5.55 \times 10^8 \times \frac{5 \times 10^{-6}}{7.94 \times 10^{-4}}$ counts $s^{-1}\ mol^{-1}$

$= 3.49 \times 10^6$ counts $s^{-1}\ mol^{-1}$

This value is for 100% counting efficiency so that at 50% counting efficiency the activity becomes :

$$\text{Expected activity of hydantoin} = \frac{1.75 \times 10^{6} \text{ counts } s^{-1} \text{ mol}^{-1}}{}$$

The actual values (corrected for the background count) obtained for the two experiments are given below:

Activity after 0.5 h $= 2.00 \times 10^{3}$ counts s^{-1} mol^{-1}

Activity after overnight reaction $= 8.09 \times 10^{4}$ counts s^{-1} mol^{-1}

These results show that the amount of hydantoin formed overnight has increased by about 40 times and that about 5% reaction has occured. Thus the observed disappearance of benzil does not correspond to the production of the hydantoin. A stable intermediate must be formed and this must undergo slow reaction to yield the hydantoin.

Kinetic method.

The rates were determined by monitoring the decrease in absorbance due to benzil. One drop of a 0.2% solution of benzil in ethanol was added to a solution of urea in aqueous NaOH contained in a cuvette in a thermostatted (at 25^{o}) holder of a Unicam SP700 spectrophometer. The wavelength used was 257 nm. The rate constants were calculated by the method of Swinbourne[81]. The same technique was used with the substituted benzils at wavelengths of 278 and 305 nm for 4,4'-dimethyl and 4,4'-dimethoxy benzils respectively.

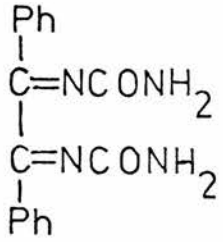
Kinetics in heavy water.

The same technique as outlined above was used. Solutions of sodium

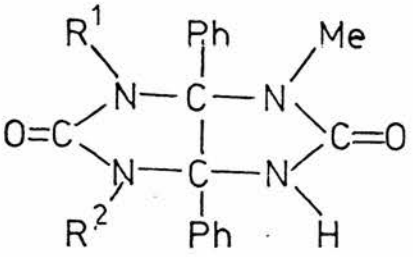
deuteroxide in heavy water were prepared as follows. Pieces of sodium were removed from paraffin and added to toluene. The pieces were then removed from the toluene, cut to leave exposed faces, and added to a fresh beaker of toluene of known weight. The pieces of sodium of known weight were again removed from the toluene, dried and added in small quantities to a flask containing a suitable amount of D_2O. The resulting NaOD solution was standardised against acid.

CHAPTER IV

REACTION WITH BENZIL UNDER ACIDIC CONDITIONS

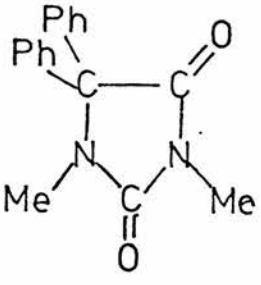


XXXVII

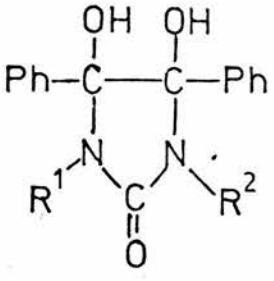


(a) R^1 = H, R^2 = Me
(b) R^1 = Me, R^2 = H

XXXVIII



XXXIX



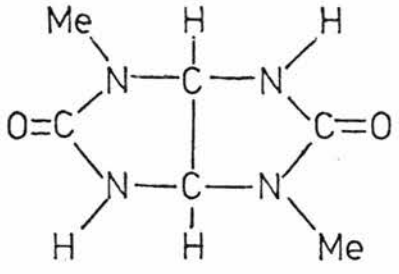
(a) R^1 = R^2 = H
(b) R^1 = H, R^2 = Me
(c) R^1 = R^2 = Me

XL

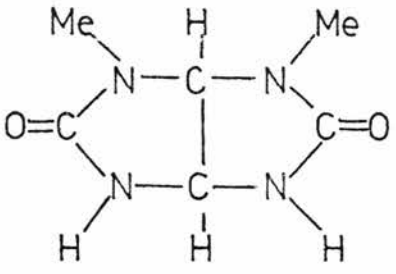
INTRODUCTION

Benzil reacts with urea, N-methylurea and N,N'-dimethylurea in the presence of acid to yield three different products. Urea forms a diureide (XXXVII), N-methylurea results in a bicyclic product (XXXVIII) and N,N'-dimethylurea forms a hydantoin (XXXIX). An investigation was undertaken into the mechanism of the reactions in an effort to explain the reasons for the formation of three different products.

The results show that the rate-determining step must be the same in all three reactions and that the resulting intermediates must subsequently undergo further reaction to give the different products. The rate-determining step is believed to be the slow attack of a protonated carbonyl group of benzil by unprotonated urea, followed by rapid cyclisation to give a diol intermediate (XL). The urea and N-methylurea diols undergo further attack by the urea, while the N,N'-dimethylurea intermediate undergoes a pinacol-pinacolone type rearrangement to give the hydantoin.



(a)



(b)

XLI

RESULTS AND DISCUSSION

Preparation and identification of the products.

The products were prepared by refluxing benzil with urea, N-methylurea & N,N'-dimethylurea in benzene in the presence of trifluoroacetic acid. The Dean and Stark apparatus was used to remove water. The urea product was found to be benzil diureide (XXXVII) and the N-methylurea product was a bicyclic compound (XXXVIII). The two different structures were assigned primarily on the basis of mass spectral evidence. The urea product shows a major peak at $M^+/2$ corresponding to the splitting of the molecule into two equal halves. A mass spectrum of benzil also shows a corresponding strong peak at $M^+/2$. With N-methylurea, the absence of such a peak is significant although there is a peak for M^+ itself. The structure proposed for N-methylurea cannot be split into two equal halves without breaking at least three bonds.

Two isomeric structures (XXXVIII (a) and (b)) are possible for the bicyclic system depending on the relative position of the two N-methyl groups. It was difficult to find a satisfactory solvent for a proton n.m.r. of the product in order to determine which isomer is the major one. However, Nematollahi and Ketcham[92] prepared an analogous product (XLI) from N-methylurea and glyoxal. On the basis of proton n.m.r. evidence they showed that the two isomers exist in a ratio of 4:7 for diagonally opposite (a)/ directly opposite (b) methyl groups. Only by extensive fractional recrystallisation, was it possible to separate the two isomers with different melting

points. They also reported that dipole measurements on the bicyclic systems showed the two rings to be in a cis configuration.

N,N'-Dimethylurea yielded 1,3-dimethyl-5,5-diphenylhydantoin (XXXIX) which was found to be identical with an authentic sample prepared by N-methylation[91] of 5,5-diphenylhydantoin.

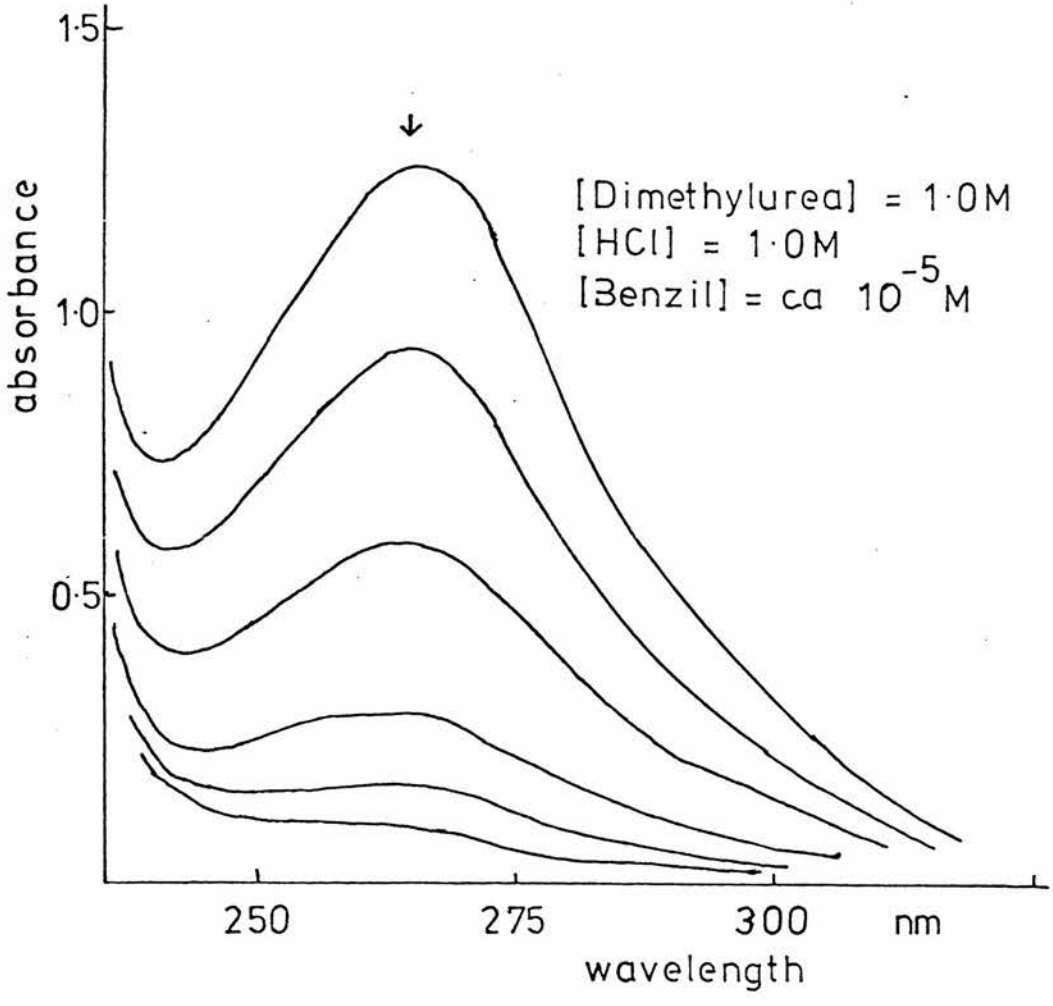
An attempt was made to carry out the reaction with asymmetrical N,N-dimethylurea but only starting materials were isolated. It is also possible to prepare the same products by refluxing the appropriate ureas with benzil in ethanol in the presence of hydrochloric acid.

Azeotropic distillation.

While the products were being prepared, azeotropic distillations, using the Dean and Stark apparatus, were carried out at the same time. Based on the azeotropic properties of a benzene/water vapour mixture, this is a useful technqiue for measuring the amount of water produced during a reaction. Results showed that, with urea and N-methylurea, two moles of water were formed for every mole of benzil reacted. Only one mole of water per mole of reacted benzil was obtained with N,N'-dimethylurea. These results are consistent with the products isolated. The urea and N-methylurea products require the elimination of two molecules of water while the hydantoin from N,N'-dimethylurea need eliminate only one molecule of water.

With N,N-dimethylurea no water was formed and this is a further indication that no reaction occured in its reaction with benzil.

Figure 15. Spectral changes of reaction between N, N'-dimethylurea and benzil at ca. 0, 2, 5, 10 and 30 min (40^{o})



Spectral changes during reaction.

On dissolving benzil in ethanol and adding a drop of the ethanolic solution to a cuvette of moderately concentrated hydrochloric acid, an absorbance was observed at 265 nm due to benzil. This absorbance remained virtually unchanged over a period of several hours at a temperature of 50^{o}. In the presence of urea, the absorbance falls slowly to zero over a period of several hours. Similar spectral changes were observed with N-methylurea and N,N'-dimethylurea. Typical spectral changes are illustrated in Figure 15.

Kinetics of the reaction.

The kinetics of the reaction were examined by monitoring the disappearance of absorbance at 265 nm due to benzil during reaction with each of the three ureas, and the effect of varying the urea and acid concentrations was investigated. The rate constants thus obtained are shown in Tables 16, 17 and 18 and these were plotted against the stoicheiometric urea and the acid concentrations. Figures 16 and 17 show typical plots.

The plots all follow the same pattern for urea, N-methylurea and N,N'-dimethylurea. The rate constant k_{obs} is seen to increase with urea concentration but the curve begins to level off at higher urea concentrations. As a function of acid concentration, k_{obs} increases initially to a maximum, then decreases linearly with increased $[H^{+}]$. With urea, the initial increase of k_{obs} with $[H^{+}]$ is not observed, probably because rate constants were not obtained at low enough acid concentrations.

Table 16.

Kinetics of the reaction of urea and benzil at 50^{o}

(a) [HCl] = 5.0 M

[Urea] M	1.0	1.3	1.7	2.0
$10^{4}k_{obs}s^{-1}$	1.23	1.86	2.18	2.39

(b) [Urea] = 1.0 M

[HCl] M	0.50	1.5	2.5	5.0	7.5
$10^{4}k_{obs}s^{-1}$	3.75	3.23	2.90	1.23	0.64

$[Benzil]_{o}$ = ca. 10^{-5} M

Table 17.

Kinetics of the reaction of N-methylurea and benzil at 50°

(a) [HCl] = 1.0 M

[Methylurea] M	0.20	0.50	1.0	2.0	2.5
$10^3 k_{obs}\ s^{-1}$	0.57	1.31	2.01	3.30	3.30

(b) [Methylurea] = 1.0 M

[HCl] M	0.20	0.50	1.0	2.0	3.0	4.0	5.0
$10^3 k_{obs}\ s^{-1}$	0.81	1.57	2.01	2.36	1.89	1.41	1.10

$[\text{Benzil}]_o$ = ca. 10^{-5} M

Table 18.

Kinetics of the reaction of N,N'-dimethylurea and benzil at 50°

(a) [HCl] = 1.0 M

[Dimethylurea] M	0.25	0.50	1.0	1.5	2.5
$10^3 k_{obs}\ s^{-1}$	2.87	5.15	6.91	8.12	8.15

(b) [Dimethylurea] = 1.0 M

[HCl] M	0.25	0.50	1.0	2.0	4.0	5.0
$10^3 k_{obs}\ s^{-1}$	2.84	4.86	6.91	8.80	5.41	3.10

$[\text{Benzil}]_o$ = ca. 10^{-5} M

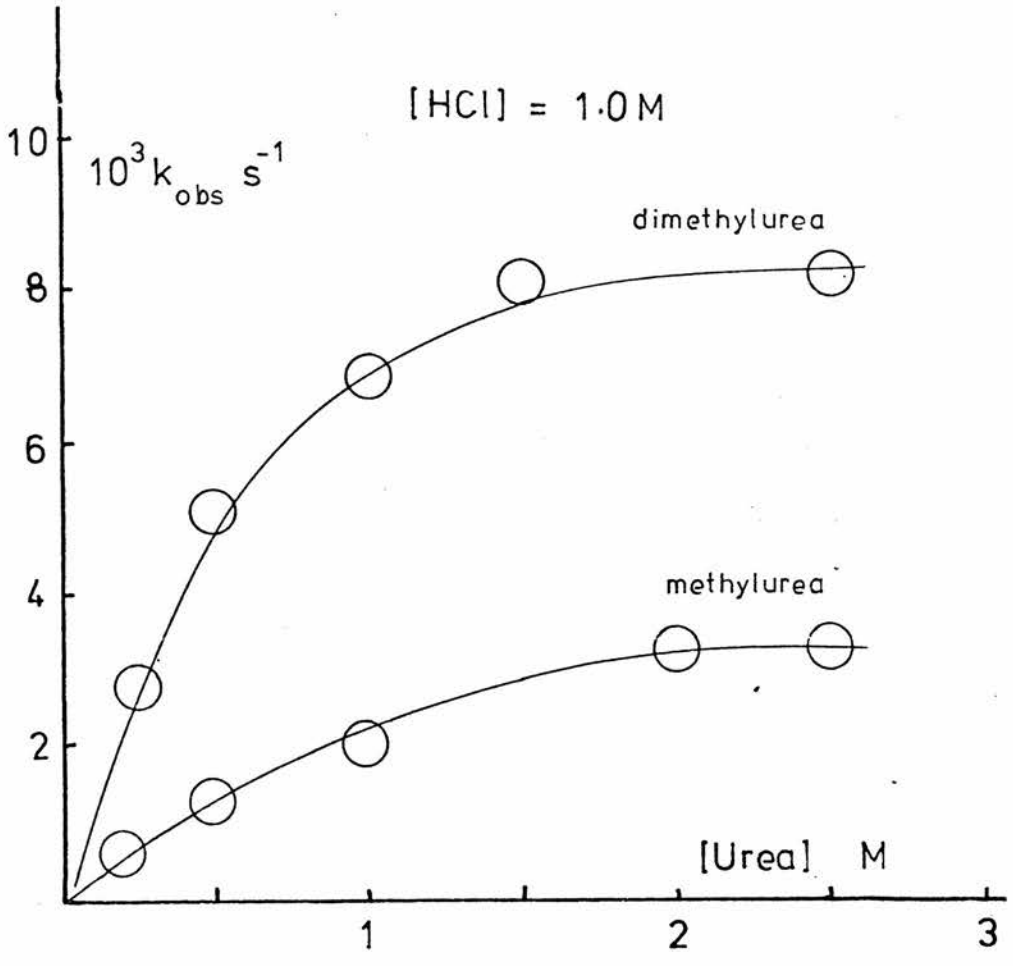


Figure 16. Variation of k_{obs} with stoicheiometric urea concentration for reaction of N-methylurea and N, N'-dimethylurea with benzil at 50°

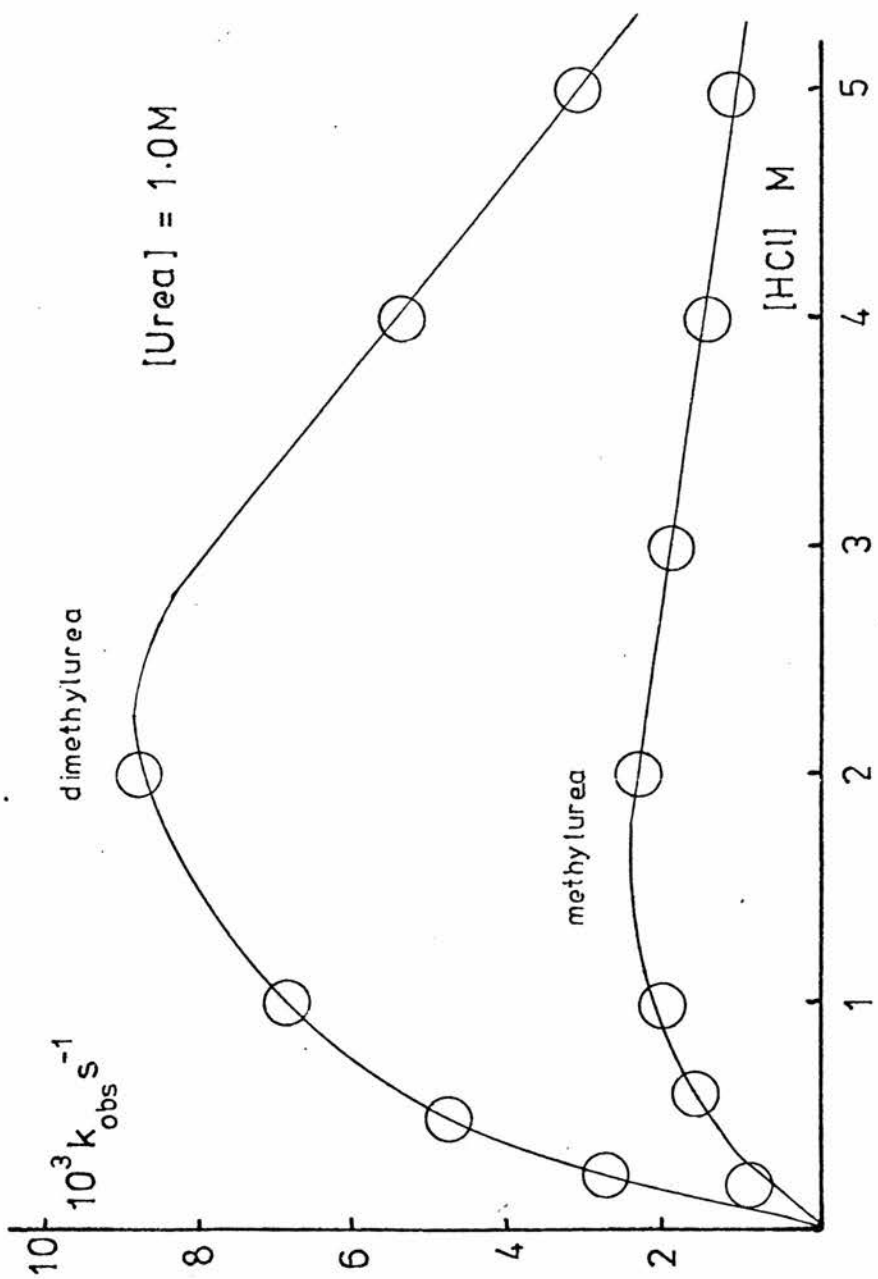
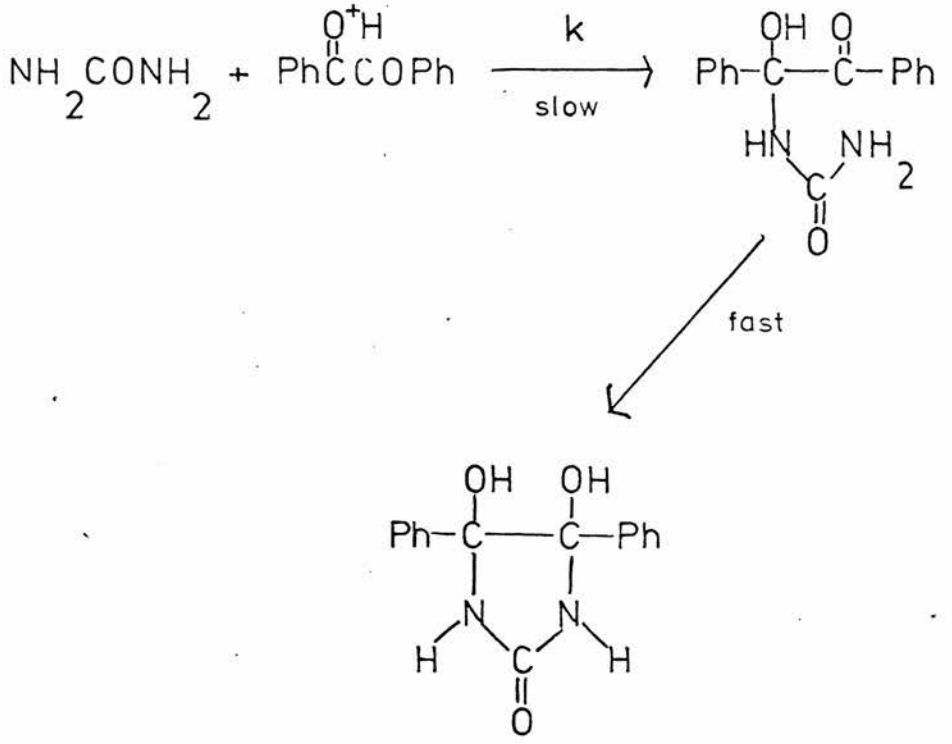


Figure 17. Variation of k_{obs} with hydrochloric acid concentration in reaction of N-methylurea and N,N'-dimethylurea with benzil at 50°

Scheme 12. Reaction of urea with benzil



Increased reactivity occurs with increased N-methylation of the urea. The maxima of the plots of k_{obs} against $[H^+]$ also occur at higher $[H^+]$ the more N-methylated the urea is.

Proposed scheme.

The spectral changes and the kinetics of the reaction with benzil are similar for urea, N-methylurea and N,N'-dimethylurea. The observed step must therefore be the same for each of these ureas. The decrease of the benzil absorbance to zero also indicates that the reaction must involve the loss of both carbonyl groups. This suggests that the reaction must be the slow attack of benzil by the urea followed by rapid cyclisation (Scheme 12). Bruice and Benkovic[63] have observed that when a reaction changes from inter molecular to intra molecular, the intra molecular process is much favoured by the decrease in the magnitude of the entropy change.

As the kinetics show that the rate of reaction is dependent on the acid concentration, it seems likely that reaction must be occuring between a protonated and an unprotonated species. The most probable situation is that of unprotonated urea attacking the protonated carbonyl group of benzil. Urea is known to be protonated on the oxygen atom[10,13] and it is difficult to visualise the O-protonated urea attacking the polarised carbonyl group especially as reaction must involve the amino group of the urea. Nevertheless, N-protonation[14] probably also occurs to a very small extent and the possibility of N-protonated urea attacking the unprotonated benzil cannot be ruled out altogether. However,

Vail et al.[85], in their study of the reaction of urea with glyoxal under acidic conditions, also proposed attack by the unprotonated urea on the protonated glyoxal.

Consider the following equilibria :

$$NH_2CONH_2 + H^+ \underset{}{\overset{K_1}{\rightleftharpoons}} NH_2COH^+NH_2$$

$$PhCOCOPh + H^+ \underset{}{\overset{K_2}{\rightleftharpoons}} PhCOH^+COPh$$

Let U and B stand for urea and benzil respectively. Then :

$$[U] = \frac{[U]_{st}}{1 + K_1[H^+]} \qquad (1)$$

and

$$[B^+] = K_2[B]_{st}[H^+] \qquad (2)$$

where $[U]_{st}$ and $[B]_{st}$ are the stoicheiometric concentrations of urea and benzil respectively. Assuming that reaction is between unprotonated urea and protonated benzil, we have :

$$\text{rate} = k[BH^+][U] \qquad (3)$$

substituting (1) and (2) into (3) :

$$\text{rate} = \frac{k K_2[B]_{st}[H^+][U]_{st}}{1 + K_1[H^+]} \qquad (4)$$

$$= k_{obs}[B]_{st} \qquad (5)$$

An expression for the observed rate constant is thus obtained from (4) and (5) :

$$k_{obs} = \frac{k K_2[H^+][U]_{st}}{1 + K_1[H^+]} \qquad (6)$$

The observed rate constant can be seen to increase linearly with the stoicheiometric urea concentration. At low $[H^+]$, $K_1[H^+] \ll 1$ and (6) becomes :

$$k_{obs} = k K_2 [H^+][U]_{st} \qquad (7)$$

so that k_{obs} increases linearly with $[H^+]$. At high $[H^+]$, $K_1[H^+] \gg 1$ and (6) becomes :

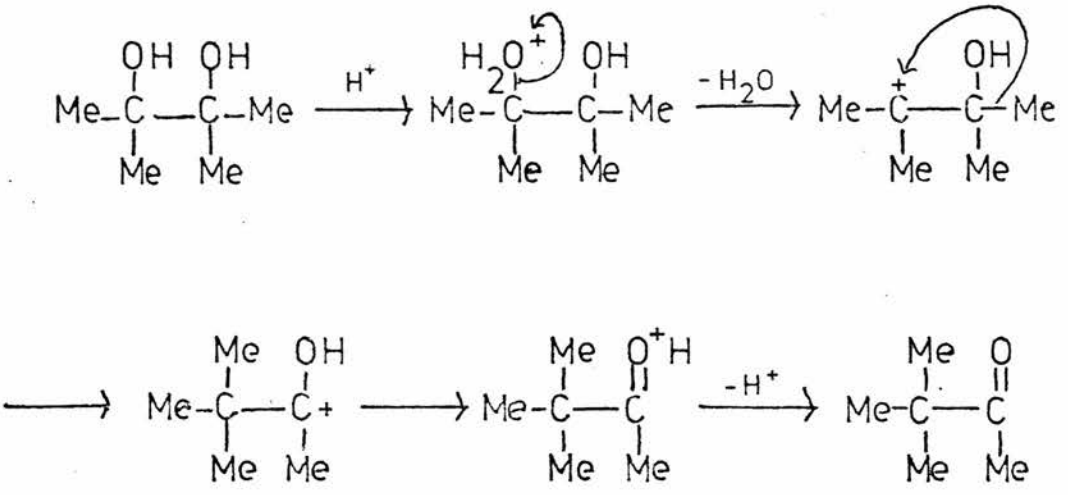
$$k_{obs} = \frac{k K_2 [U]_{st}}{K_1} \qquad (8)$$

where k_{obs} is independent of $[H^+]$.

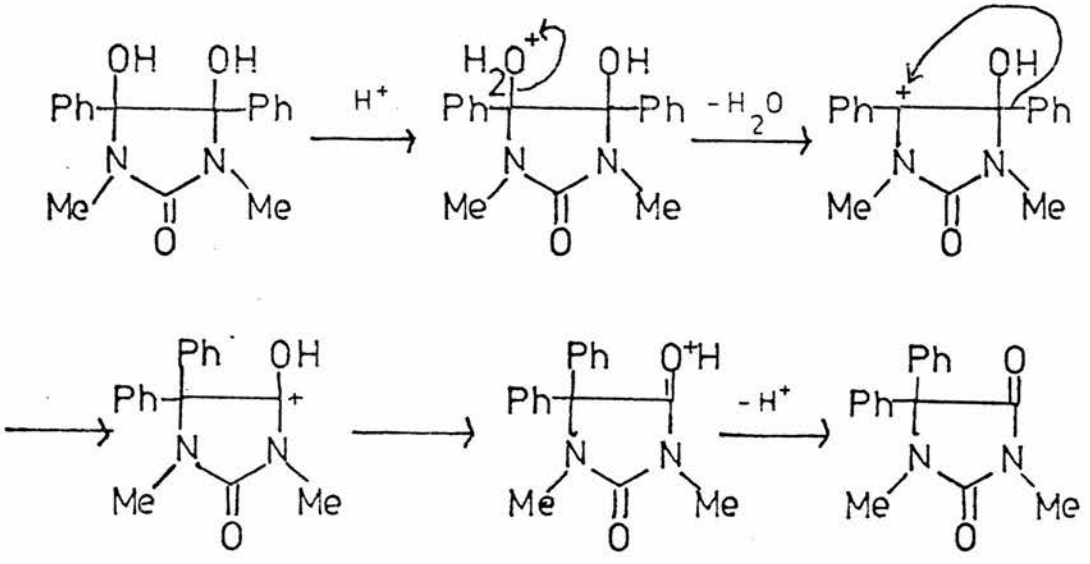
These equations show that there is general agreement between the proposed scheme and the observed kinetics. Slight deviations occur because complications enter into the mathematical treatment of the reaction. The high urea and acid concentrations, used in the kinetic determinations, must be taken into account in a more accurate mathematical treatment. This would involve the use of acidity functions relevant to the protonation of urea and benzil which are not fully known.

For example, in the acid range (0.5 M to 7.5 M) over which the kinetics were investigated with urea, the acidity increases by a factor of about 500 to 1000 (depending upon whether the H_A or the H_O scale is used). When seen in this perspective, the change in k_{obs} is seen to be very small compared with the change in acidity and can be considered to be virtually independent of the acidity. The apparent change in k_{obs} with $[H^+]$ more likely reflects the decrease in the amount of unprotonated urea as the acidity increases.

Scheme 13. Pinacol-pinacolone rearrangement[94]



Scheme 14. Rearrangement to 1,3-dimethyl-5,5-diphenylhydantoin



Thus as the acid concentration is increased, more urea is protonated and less unprotonated urea is available for reaction with benzil. At the same time more benzil is protonated and becomes available for reaction. The rate of the reaction thus becomes dependent upon the balance of these two opposing factors and this effect is demonstrated in the plots of k_{obs} against $[H^+]$ in the cases of N-methylurea and N,N'-dimethylurea.

The deviation of the plot of k_{obs} against the stoicheiometric urea concentration is also easily explained. When the urea concentration is increased (at a fixed acid concentration), more urea is protonated and the amount of free acid available to protonate the benzil decreases.

Thus when one considers the overall picture, the kinetics do indicate the proposed scheme even though there are deviations from the equations.

Rearrangement of the N,N'-dimethylurea intermediate.

The pinacol-pinacolone rearrangement is well known and there are many examples[93] of dihydroxy compounds undergoing this type of rearrangement. The generally accepted mechanism[94] is shown in Scheme 13. The three main steps are :

(a) protonation of the hydroxy group

(b) loss of water to form carbonium ion

(c) methyl migration with rearrangement

The driving force of the rearrangement is the tendency of the electron-deficient

carbonium ion intermediate to form a more stable oxonium ion.

Hydroxybenzoin (PhCH(OH)CH(OH)Ph) undergoes a similar rearrangement to give diphenylacetaldehyde (Ph_2CHCHO)[95]. Thus the N,N'-dimethylurea diol (XLc) can undergo an exactly parallel rearrangement as shown in Scheme 14 to give 1,3-dimethyl-5,5-diphenyl hydantoin.

Evidence for the intermediate.

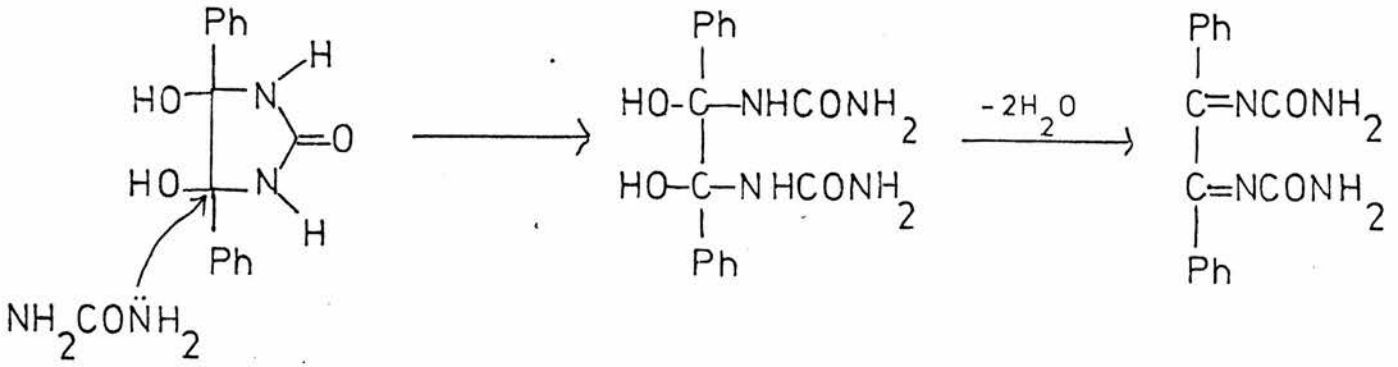
Attempts were made to isolate the diol intermediate from urea and N-methylurea, but without success. The N,N'-dimethylurea diol had already been prepared by the reaction of benzil with N,N'-dimethylurea in the presence of alkali as described in the previous chapter.

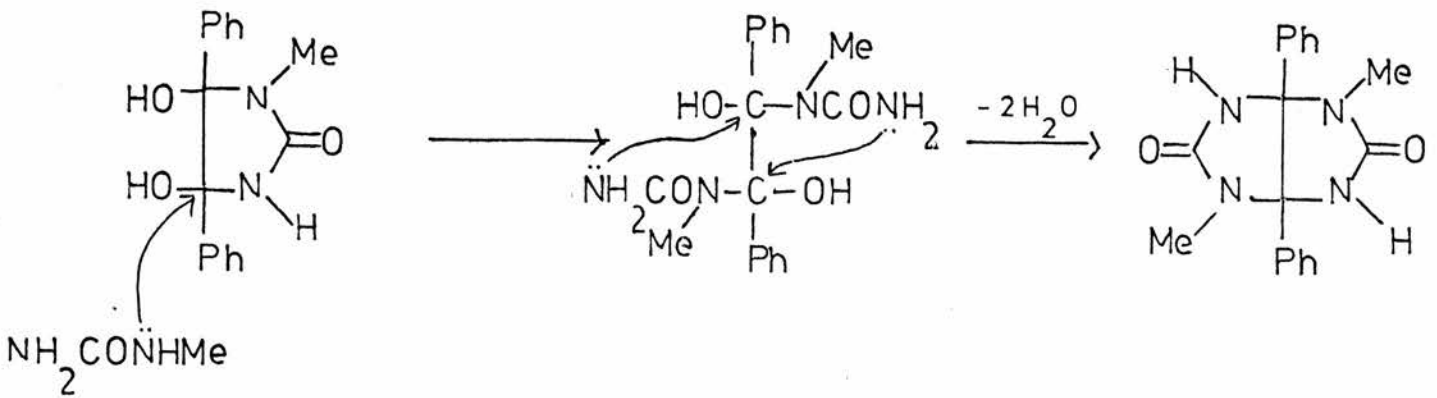
In an experiment, this diol was refluxed in ethanol in the presence of hydrochloric acid to see if the pinacol-pinacolone rearrangement occurs. Instead of the expected hydantoin, benzil was isolated. The diol had obviously been hydrolysed by acid to give the original starting materials. A probable explanation for this is that rearrangement is a slow reaction and that the rate of hydrolysis is faster than the rate of rearrangement. When the reaction is carried out with starting materials, an excess of N,N'-dimethylurea is always present so that the reaction is being driven towards the formation of the diol and eventually to the hydantoin.

Support for the diol intermediate therefore rests on the following points :

(a) reaction involves the loss of both benzil carbonyl groups.

Scheme 15. Further reaction of urea and N-methylurea diol intermediates





(b) the kinetic pattern is the same for urea, N-methylurea and N,N'-dimethylurea in spite of three different products being isolated. This suggests a common intermediate.

(c) entropy changes favour intramolecular cyclisation rather than an intermolecular attack by a second urea molecule.

(d) the N,N'-dimethylurea diol is the obvious intermediate for a pinacol-pinacolone type rearrangement to the hydantoin.

The question as to why three different products result from the diol intermediate now arises. One may wonder why all three ureas do not form hydantoins via the pinacol-pinacolone rearrangement or bicyclic structures like the one obtained with N-methylurea. It appears that, with urea and N-methylurea, the diols must be attacked by a second urea molecule. With urea, the ring opens again and the second urea molecule attaches itself to the benzil skeleton. Elimination of water then occurs to give XXXVII as shown in Scheme 15. With N-methylurea, attack could occur with or without ring opening. The methyl end of the molecule is more nucleophilic and is more likely to attack than the other end. If ring-opening similar to that shown for urea occurs, the resulting structure cannot eliminate water across the C-N bond because of the methyl groups. Instead the free $-NH_2$ ends attack the hydroxy groups as shown in Scheme 15 to give the bicyclic structure (XXXVIII).

Another possible explanation is that the diurea products (XXXVII

and XXXVIII) are of low solubility so that they precipitate out readily. This may result in the reaction being driven towards the formation of these products rather than rearrangement to give the corresponding hydantoins.

The presence of electron-repelling groups in the N, N'-dimethylurea diol (XLc) may make the benzil carbon atoms more resistant to attack by a second molecule of N, N'-dimethylurea. The diol may then undergo slow rearrangement to give the hydantoin instead of forming a bicyclic structure analagous to that of N-methylurea.

EXPERIMENTAL

Preparation of the products from benzil.

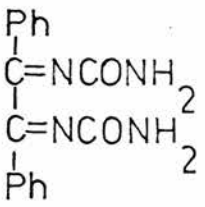
A solution of urea (6g), benzil (10.5g) and trifluoroacetic acid (10 ml) in benzene (200 ml) was refluxed for about 1 h. after which the product started to precipitate and cause "bumping". The white solid was filtered off and washed with water and acetone. A suitable solvent for recrystallisation was not found. N-Methylurea (7.4g) and N,N'-dimethylurea (8.8g) were used in a similar manner to prepare their respective products. The solutions were refluxed for 6 h. and the white solids obtained on evaporation of the benzene. The N-methylurea and N,N'-dimethylurea products were recrystallised from ethanol and toluene respectively. When the same method was used for asymmetrical N,N -dimethylurea, only starting materials were isolated. The physical data for these compounds are shown in Table 19.

Preparation of 1,3-dimethyl-5,5-diphenylhydantoin.

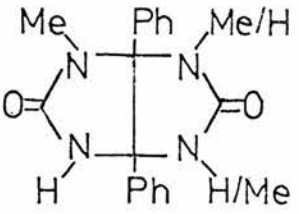
This preparation is based on the N-methylation method used by Olsen[91]. 5,5-Diphenylhydantoin (2.5g), methyl iodide (8.5g) and silver oxide (10g) were dissolved in anhydrous dimethylformamide (100 ml). The solution was stirred magnetically at room temperature all day. The mixture was then filtered and the solid washed with a small volume of dimethylformamide. To the filtrate was added 4 x its volume of chloroform. The chloroform phase was washed several times with water and dried ($MgSO_4$). The drying agent

Table 19.

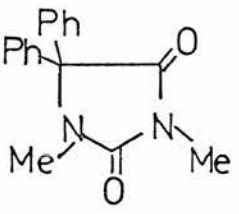
Physical data for the benzil products.



(i)



(ii)



(iii)

(i) M.p. 300° Molecular ion peak 294, M/2 peak 147

Analysis :	$C_{16}H_{14}N_4O_2$		
Required :	65.3% C	4.8%H	19.0% N
Found :	65.3% C	4.7%H	18.8% N

(ii) M.p. 300° Molecular ion peak 322, no M/2 peak

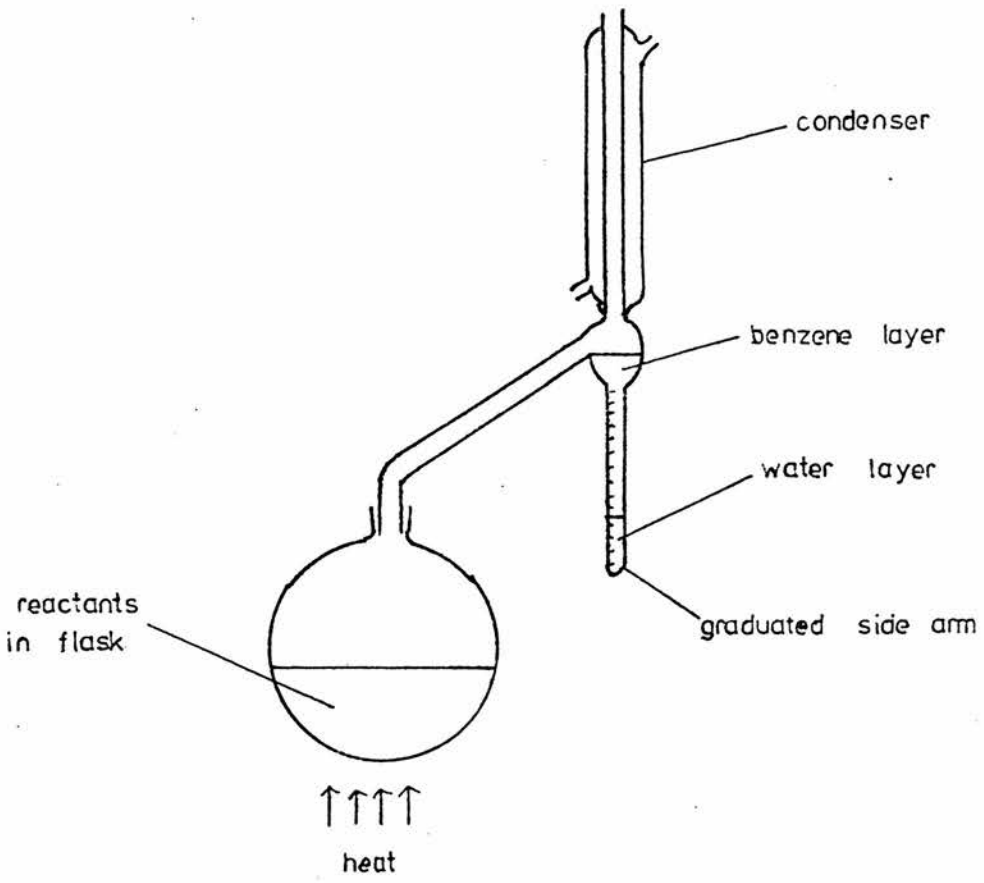
Analysis :	$C_{18}H_{18}N_4O_2$		
Required :	67.1% C	5.6%H	17.4% N
Found :	66.8% C	5.7%H	17.6% N

(iii) M.p. 190° Molecular ion peak 280

Analysis :	$C_{17}H_{16}N_2O_2$		
Required :	72.8% C	5.8%H	10.0% N
Found :	72.8% C	5.8%H	10.2% N

Proton n.m.r. : two singlets at δ 2.50 and δ 2.76 corresponding to two methyl groups (toluene)

Figure 18. Dean and Stark apparatus



was removed by filtration and the solvent evaporated off to yield the product, which was recrystallised from toluene, m.p. 190°. 1,3-Dimethyl-5,5-diphenylhydantoin had a molecular ion peak of 280, and two methyl singlets at δ 2.50 and δ 2.76 (toluene) in the proton n.m.r..

Analysis	$C_{17}H_{16}N_2O_2$		
Required	72.8% C	5.8% H	10.0% N
Found	73.0% C	5.7% H	10.2% N

A mixed m.p. with the product of the reaction of N,N-dimethylurea and benzil showed that the two products were identical.

Azeotropic distillation.

Azeotropic distillations using the Dean and Stark apparatus were carried out during the preparation of the benzil products. A diagram of the apparatus is shown in Figure 18. As the reactants were refluxed, benzene and water distilled off as an azeotrope. When the vapour condensed, the liquid collected in the graduated side arm where the benzene and water form two immiscible layers. As the side arm filled up, the surplus benzene from the top layer gradually flowed back into the flask, leaving the water layer intact. The amount of water formed during the reaction can thus be measured in the side arm.

In the distillations carried out, trifluoroacetic acid present in the benzene also distilled over and dissolved into the water layer. This resulted in the volume of water being exaggerated. To eliminate this serious error,

small samples of water were withdrawn from the layer after completion of the distillation and titrated against standard aqueous NaOH. Calculations of the amount of trifluoroacetic acid present then gave the corrected volumes of water. Allowances were also made for traces of water already present in the starting materials.

For every 0.05 mole of benzil and 0.1 mole of the urea used the following amounts of water were produced :

urea	0.067 mole
N-methylurea	0.094 mole
N,N'-dimethylurea	0.053 mole

With urea, reaction only proceeded for 1 h. before being stopped because of "bumping". However, water was still being produced freely, and it is not unreasonable to suggest that true amount of water for complete reaction is probably nearer 0.1 mole.

The results show that, with urea and N-methylurea, two molecules of water form for every molecule of benzil and every two molecules of one urea reacted. Only one molecule of water is produced per molecule of benzil in the case of N,N'-dimethylurea.

Kinetic method.

The rates were determined by following the decrease in the U.V. absorbance due to benzil. A drop of a 0.2% solution of benzil in ethanol was added to a solution of the urea in aqueous hydrochloric acid contained in a

cuvette in a thermostatted (50^{o}) holder of a Unicam SP700 spectrophotometer. The wavelength used was 265 nm. The rate constants were calculated by the method of Swinbourne[81].

Experiment with the N,N'-dimethylurea diol (XLc).

The diol (4,5-dihydroxy-1,3-dimethyl-2-imidazolidone XLc) was prepared during the work done with benzil under alkaline conditions as described in Chapter III. The diol (1g) was refluxed in ethanol (50 ml) containing concentrated hydrochloric acid (10 ml) for two hours. The solution was added to a large volume of water and the resulting precipitate filtered off. Instead of the expected 1,3-dimethyl-5,5-diphenylhydantoin, the precipitate was found to be benzil.

CHAPTER V

REACTION WITH BUTANE-2, 3-DIONE

INTRODUCTION

The reaction of butane-2,3-dione, often known as diacetyl, with urea is well known in the field of clinical chemistry as a method for the determination of urea in blood and urine. In 1939 Fearon[96] found that the reaction of butane-2,3-dione, followed by oxidation, gave colours with urea and certain other compounds containing the group -NHCONH-. In 1942, Ormsby[97] applied this reaction to the determination of urea and since then, this method has been widely used and is often prefered to the urease method.

The urease method[98,99,100] is an indirect method involving the measurement of ammonia liberated as a result of the action of the enzyme urease on urea. Disadvantages in the urease method arise from the fact that other ammonia may already be present in the sample and this needs to be measured, from urease inhibition or inactivation and from reagent instability. Also the determination of ammonia is dubious.

The butane-2,3-dione method[98,99,100], by contrast, does not measure ammonia, uses stable reagents and is quite sensitive and specific. Its main disadvantages are that the colour is photosensitive, unstable and requires development in boiling water and that the time for colour development is dependent on the urea concentration. The odour of butane-2,3-dione is also unpleasant to some.

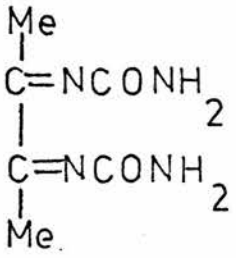
The method used with butane-2,3-dione is given in most analytical clinical chemistry textbooks[98,99]. Generally, either butane-2,3-dione or its

monoxime is used. If the monoxime is used, the presence of an oxidising agent, such as potassium persulphate, is required to destroy any hydroxylamine formed. Thiosemicarbazide is often added to intensify the colour and to minimise photosensitivity while the presence of certain cations such as ferric ions helps to stabilise the colour. The action of these reagents is not understood.

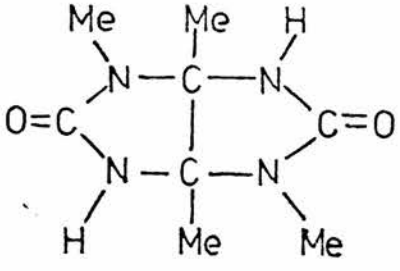
Lugosi et. al.[101] showed that the product of the reaction of butane-2,3-dione with urea is the same whether butane-2,3-dione or its monoxime is used as the reagent. The monoxime, in the presence of acid, breaks down to butane-2,3-dione and hydroxylamine so that it is the butane-2,3-dione itself that reacts with urea.

This work looks into the reaction of butane-2,3-dione with urea to try to elucidate the mechanism of the reaction and to try and identify the substance that is responsible for the formation of the colour that forms such an important reaction for the estimation of urea. Although white crystalline solids, similar to those obtained from the reaction of benzil, were isolated from the reaction of butane-2,3-dione with urea and N-methylurea, these products continue to react in the presence of acid to produce highly coloured solutions. The reaction of butane-2,3-dione with urea is obviously much more complex than that of benzil. Much time and effort was spent trying to isolate pure samples of the coloured products and to identify them. Unfortunately the nature and identity of these coloured substances still remains a mystery. For this reason, little can be said about the mechanism of the reaction as one

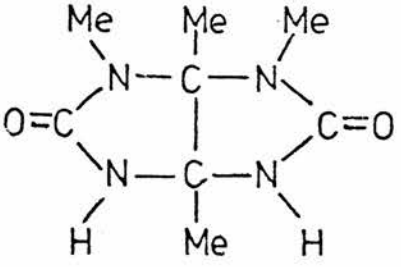
cannot begin to speculate on the reaction pathway when the final product is still unknown. The reaction between urea and butane-2,3-dione is further complicated by the self-condensation reaction of butane-2,3-dione under acidic conditions.



XLII



(a)



(b)

XLIII

RESULTS AND DISCUSSION

Test tube experiments.

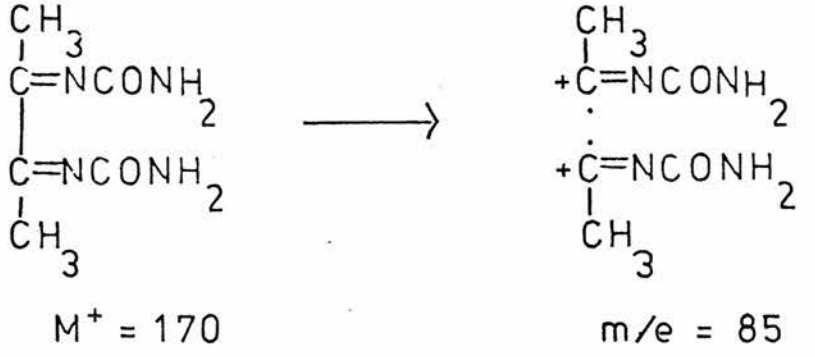
When a little butane-2,3-dione was added to a test tube containing a solution of urea in aqueons hydrochloric acid, a yellow colour was formed and a white solid precipitated within minutes. The same procedure was repeated with N-methylurea, N,N'-dimethylurea and N,N-dimethylurea. N-Methylurea resulted in an orange-red solution and a precipitate only formed after standing for a long time. With N,N'-dimethylurea, a deep purple colour resulted, but no precipitate was formed even after standing for a long time. N,N-Dimethylurea forms a golden yellow colour which will change very slowly to a slightly orangey colour.

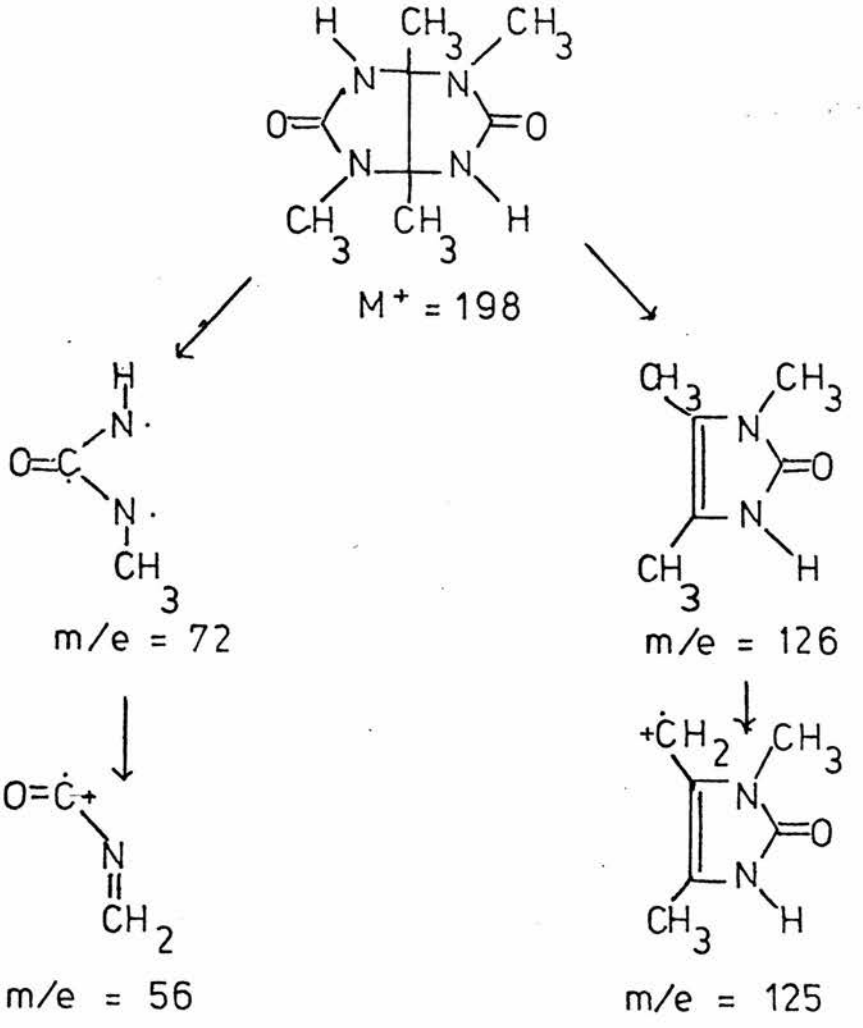
Isolation and identification of the white products.

The above test tube reactions were repeated on a larger scale to prepare the products of the reaction using the method of Lugosi et. al.[101]. A white precipitate was easily obtained with urea, while N-methylurea also produced a white precipitate after the solution was allowed to stand for some time. It was not possible to isolate the corresponding products from either of the dimethylureas even when the solutions were either allowed to stand for a long time or evaporated down. N,N'Dimethylurea resulted in a viscous purple liquid and N,N-dimethylurea only yielded crystals of N,N-dimethylurea itself.

The two products thus isolated were submitted for analysis and mass

Scheme 16. Fragmentation in mass spectra





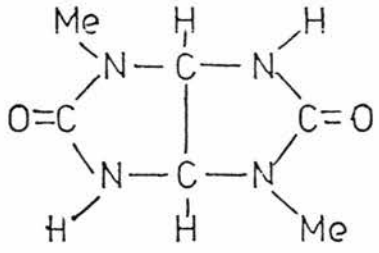
spectroscopy. The urea product was found to have a straight chain structure (XLII) while the N-methylurea product had a bicyclic structure (XLIII), often known as a glycoluril. In previous work with urea and butane-2,3-dione, some workers have assigned a glycoluril structure to the product of the reaction between urea and butane-2,3-dione. The glycoluril structure is isomeric with the straight chain butane-2,3-dione diureide structure (XLII). However Lugosi et. al.[101] favoured the butane-2,3-dione diureide structure on the basis of two experimental observations. They found that the urea compound liberated nitrogen gas in the nitrous acid test which is characteristic for primary amides (and amines).

$$RCONH_2 + HNO_2 \longrightarrow RCOOH + N_2 + H_2O$$

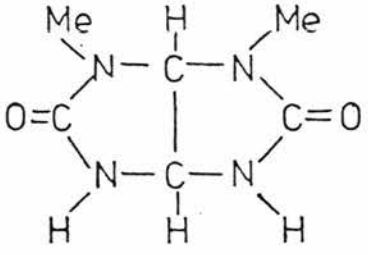
Only the diureide structure (and not the glycoluril structure) could react as a primary amide. Lugosi et. al.[101] also found that the I.R. spectrum of the compound contained bands characteristic of a primary amide and of a conjugated C=N double bond.

In this study, the two structures for urea and N-methylurea products were assigned primarily on the basis of mass spectral evidence. The urea compound (XLII) has a small molecular ion peak at m/e = 170 and a large peak at m/e = 85 which must correspond to the fragmentation of the molecule into two equal halves as illustrated in Scheme 16.

The N-methylurea compound (XLIII) had a large molecular ion peak at m/e = 198, but only a small peak at m/e = 99. This suggests that the



(a)



(b)

XLIV

methylurea product has a fragmentation pattern different from that observed with urea. The most abundant fragments in the mass spectrum were at m/e = 56, 125 and 126 and these fragments can be readily explained if the structure (XLIII) undergoes the fragmentation shown in Scheme 16. A peak at m/e = 72 was also recorded.

The glycoluril structure for N-methylurea has two possible isomers (XLIIIa) and (XLIIIb). Both isomers can undergo the above fragmentation pattern in the mass spectrum. A proton n.m.r. study would distinguish between them structure (XLIIIa) would result in two methyl singlets corresponding to the two sets of equivalent methyl groups. With structure (XLIIIb), there would be three methyl singlets as the two butane-2,3-dione methyl groups would be non-equivalent. However it was not possible to find a suitable solvent for a proton n.m.r. spectrum of the compound to be recorded. Dipole measurements should also distinguish between the two isomers, but the facilities for taking dipole measurements were not available.

It is quite possible that both isomers of XLIII may exist together. Nematollahi and Ketcham[92] prepared a similar compound (XLIV) with N-methylurea and glyoxal. They found that both isomers exist together and that XLIVb) apparently predominates. They were able to separate the two isomers after extensive fractional crystallisation.

Spectral changes of the reaction.

The spectral changes of the reaction between urea and butane-2,3-dione

Figure 19. Spectral changes of reaction between urea and butane-2,3-dione at ca. 0, 3, 5 and 9 min (60°C). (Continued on next page)

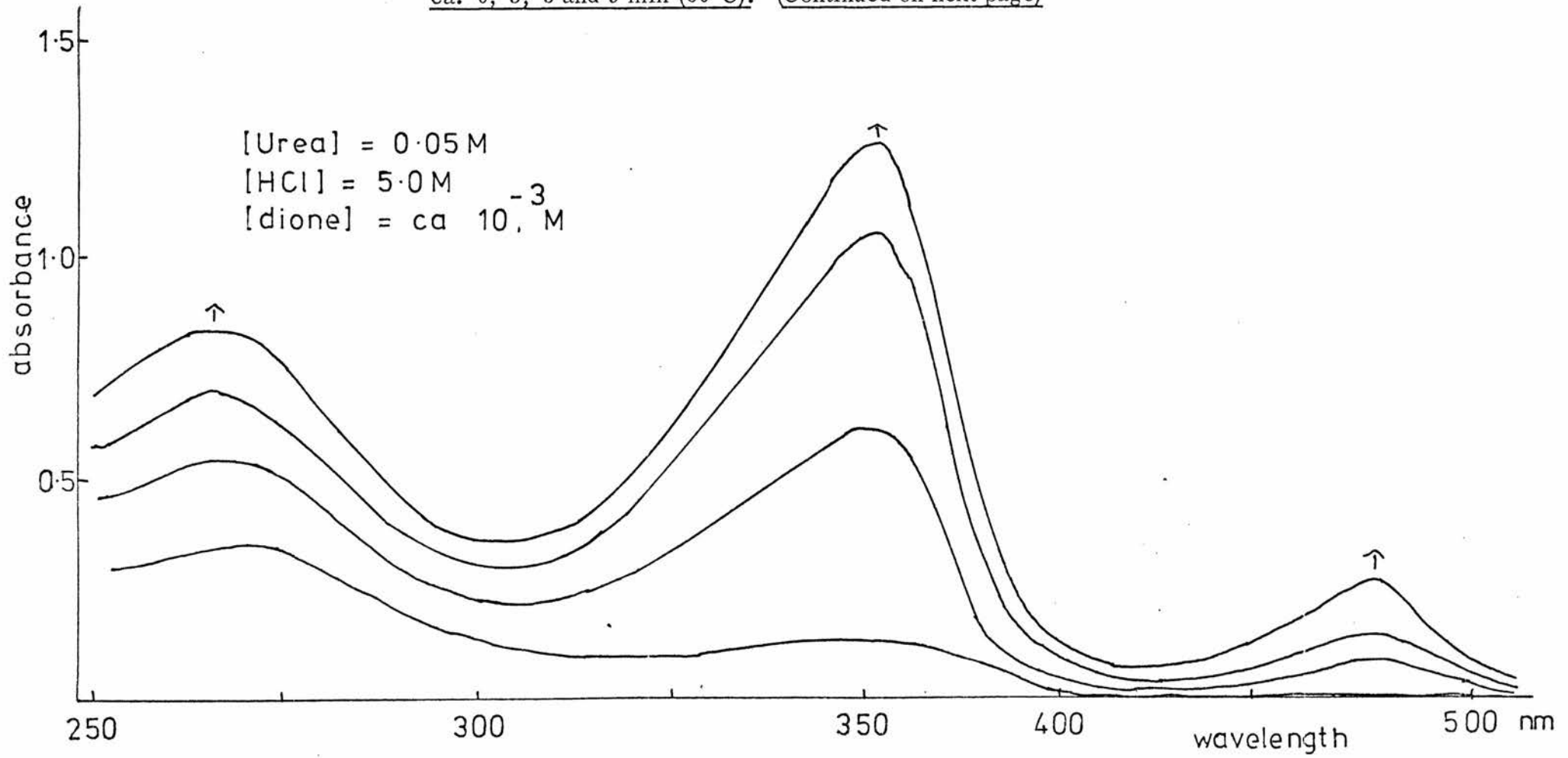
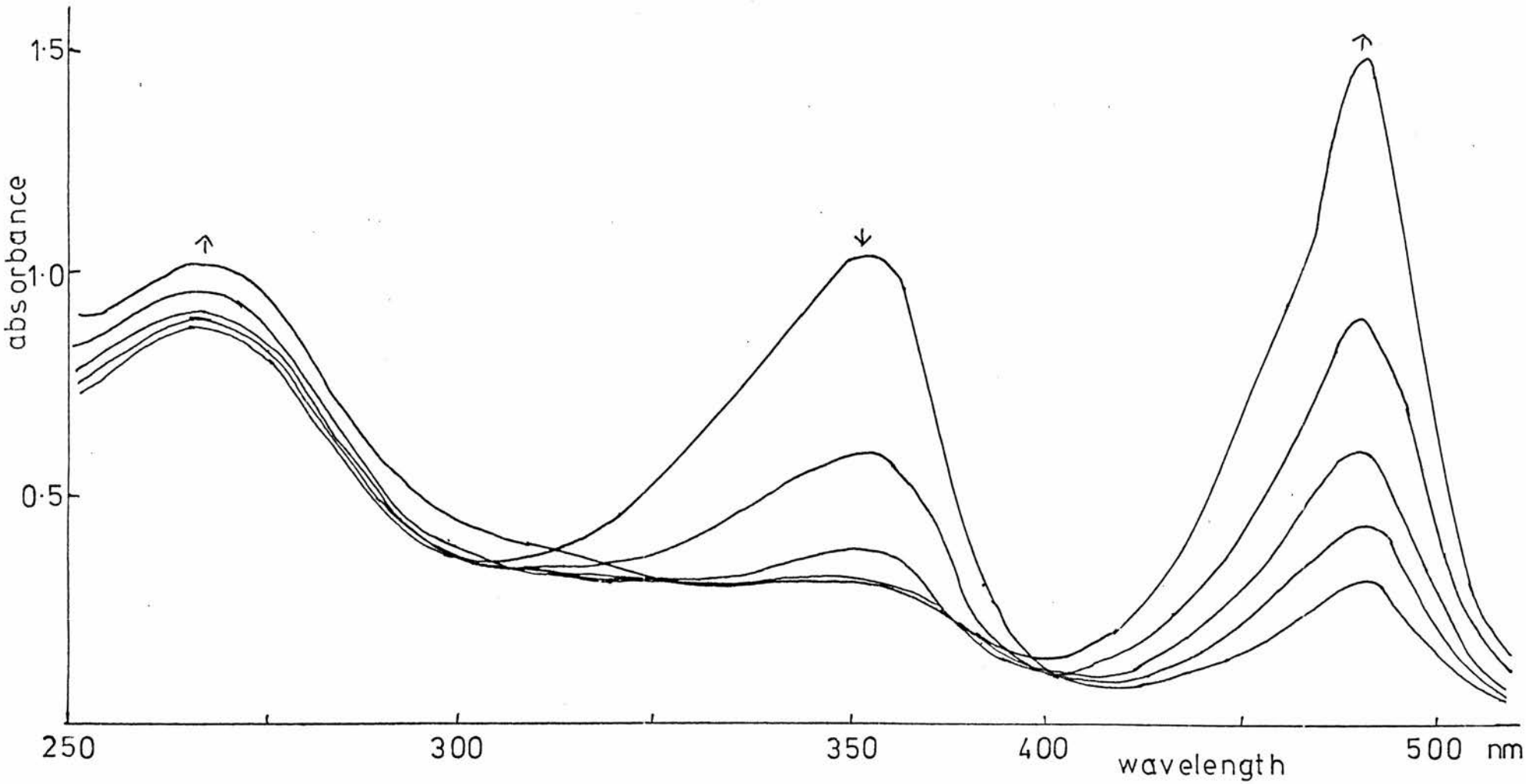


Figure 19. Spectral changes (continued) at ca. 12, 20, 30, 50 and 90 min



are fairly complex. For best results, it was found that a high acid concentration (abour 5 M) and a relatively low urea concentration (about 0.05 M) were the most suitable conditions. If the urea and acid conditions were about the same (e.g. around 1 M), then the spectral changes were very confusing. Typical spectral changes of the reaction are shown in Figure 19.

Basically, the spectral changes for urea involve the formation of a peak at 354 nm, and this absorbance subsequently falls back to zero as another peak is formed at 480 nm. The absorbance at 480 nm is responsible for the characteristic colour formed during the reaction. As well as the formation of these two prominent peaks, there is an increase in absorbance over the region 225 to 300 nm with a broad peak being formed at ca. 265 nm. When the reaction is carried out at room temperature, the first peak at 354 nm is formed in about half an hour, while the second peak at 480 nm develops over a period of several hours. At higher temperatures (60^{o}) the spectral changes are faster.

With N-methylurea, the spectral changes are very similar to, but faster than,those observed with urea. An absorbance is formed at 366 nm within about 10 minutes and this also subsequently decreases with the formation of a second peak at 486 nm. There is a similar broad absorbance formed in the far U.V. region with the formation of a broad peak at 265 nm. At higher temperatures (e.g. 60^{o}), the formation of the peak at 366 nm is apparently by-passed and the spectral changes proceed directly to the formation of the peak

at 486 nm. This by-pass would seem to suggest that the relative rates of the two reactions leading to the formation of the two prominent peaks are altered so that the second reaction is fast enough to prevent the accumulation of a substantial amount of the intermediate product responsible for the absorbance at 366 nm.

With N,N'-dimethylurea, it at first appears that no intermediate peak is formed and that the reaction proceeds directly towards the formation of an absorbance at 498 nm (which is responsible for the colour). However if the spectral changes of the reaction are observed closely under varying conditions (different concentrations and/or temperature), it is sometimes just possible to detect slight absorbance changes at ca. 330 nm which probably correspond to the intermediate peak analogous to those observed with urea and N-methylurea. Like the above two ureas, a broad peak is also formed at 265 nm.

The broad peak formed at 265 nm is of interest. When the spectral changes of butane-2,3-dione in aqueous acid were examined, there was a definite increase in the absorbance at 265 nm leading to the formation of a peak at that wavelength over a period of time. This change in absorbance can probably be attributed to the self-condensation reaction of butane-2,3-dione (more will be said about this later) under acid conditions. What is not clear is whether the broad peak at 265 nm observed in the reactions of urea, N-methylurea and N,N'-dimethylurea should be attributed to the self-condensation of

butane-2,3-dione or whether the peak is part of the reaction of the urea with the diketone. The concentration of the butane-2,3-dione in the reaction observed on the U.V. spectrophotometer is very low and, with an excess of urea present, one might expect all the butane-2,3-dione to react with the urea. However, if the butane-2,3-dione underwent self-condensation at a rate competitive with the rate of the reaction with the urea, this would account for the formation of a peak at 265 nm. It is worth noting that the increase in absorbance at 265 nm is not as great in the reactions of butane-2,3-dione with the ureas as it is in the reaction of butane-2,3-dione alone. This observation could be due to the fact that not all of the butane-2,3-dione present undergoes self-condensation as some of it has reacted with the urea.

The spectral changes of the reaction of butane-2,3-dione with N,N-dimethylurea and N,N,N',N'-tetramethylurea were also examined briefly. With N,N-dimethylurea the spectral changes very much resemble those of butane-2,3-dione itself, but there is also an additional broad absorbance increase at about 300 nm, and a peak eventually forms just beyond 450 nm if the reaction is allowed to proceed for long enough. It is evident that N,N-dimethylurea does undergo some reaction, but that the reaction is much slower than with the other three ureas already considered. N,N,N',N'-Tetramethylurea merely exhibited the spectral changes of butane-2,3-dione itself although the diketone absorbance was partly masked by the strong absorbance of tetramethylurea itself. There were no additional spectral changes and it appears fairly certain

that tetramethylurea does not react with butane-2,3-dione at all.

Kinetics of the reaction.

In the early days of this present work it was decided to examine the kinetics of the reaction of urea with butane-2,3-dione in the presence of acid by monitoring the increase in the absorbance at 238 nm at 25°. However, the extent of the reaction and of the spectral changes were not fully appreciated at that time. The fact that butane-2,3-dione apparently undergoes self-condensation was not realised either. In retrospect, it is now seen that the choice of the wavelength at which the kinetics would be examined was a poor one, and that the results thus obtained have little meaning. For this reason, the results are not given here. No further attempt was made to examine the kinetics by, for example, monitoring the formation of the peaks at either 354 or 480 nm. Work was concentrated on trying to isolate and identify the coloured products of the reactions of urea, N-methylurea and N,N'-dimethylurea with butane-2,3-dione. It was felt that there was little point in looking into the kinetics of a reaction where the final product was still unknown. As it will be seen shortly, the spectral changes observed during the reaction are not associated with the formation of the diurea products.

The reaction of the diurea products in the presence of acid.

The spectra of the two white products obtained with urea and N-methylurea were examined. Both solids are almost insoluble in water and

in hydrochloric acid, but it is possible to dissolve them a little with heating. Both products show no absorbance at all over the region 225-500 nm. The final spectra of the reactions with butane-2,3-dione, therefore, do not correspond with the spectra of these two solids.

If the acid solutions (5 M HCl) of the two solids are allowed to stand for several hours, spectral changes similar to those recorded for the reaction of the urea with butane-2,3-dione are observed. The urea product (XLII), for instance, forms a peak at 354 nm and this decreases as a new peak at 480 nm is formed. There is also an increase in the absorbance over the range 225 to 300 nm but there is no pronounced peak at 265 nm. With the N-methylurea product, the spectral changes were observed at 40^{o}. The formation of the peak at 366 nm was by-passed, but the peak at 486 nm was formed. The absorbance increase over the range 225-300 nm was less marked than for the urea product.

These spectral changes suggest several possible situations. One possibility is that XLII and XLIII are the intermediate products of the reaction and that their formation is not really observed in the spectral changes. In the presence of acid, XLII and XLIII continue to react to form the coloured products and it is this reaction that is being observed in the spectra. Another possibility is that XLII and XLIII break down in acid to give butane-2,3-dione and the urea which subsequently recombine again. If this did occur, one might expect to see a more pronounced peak at 265 nm if some of the liberated butane-2,3-dione

underwent self-condensation. The very low concentration of the urea thus liberated would also not be very favourable towards recombination.

It should also be borne in mind that XLII and XLIII do not necessarily play a real role in the course of the reaction. As it has been observed during the work with pentane-2,4-dione and with benzil, the formation of a cyclic product from one molecule of diketone and one molecule of urea is favoured because of the entropy changes involved. The diurea product seems to form only because the cyclic product reacts with a further molecule of urea or because the diurea product is formed in small quantities and tends to precipitate out because of its high insolubility.

The coloured products.

Many attempts were made to isolate and characterise the coloured products of the reaction between the ureas and butane-2,3-dione but without success. Water had already been used as a solvent to prepare the white products XLII and XLIII, so a variety of other solvents were tried instead. Hydrochloric gas dissolved in methanol was used to avoid the presence of an appreciable amount of water. The method of Kosalapoff and Roy[59], which uses boiling ethanol and concentrated hydrochloric acid, was adapted from the work with pentane-2,4-dione. Reaction proceeded very readily in these two solvents and urea formed a brown precipitate. With N-methylurea and N,N'-dimethylurea intense orange and purple/blue colours were formed respectively, and the solutions were evaporated to remove the solvent to leave behind viscous and

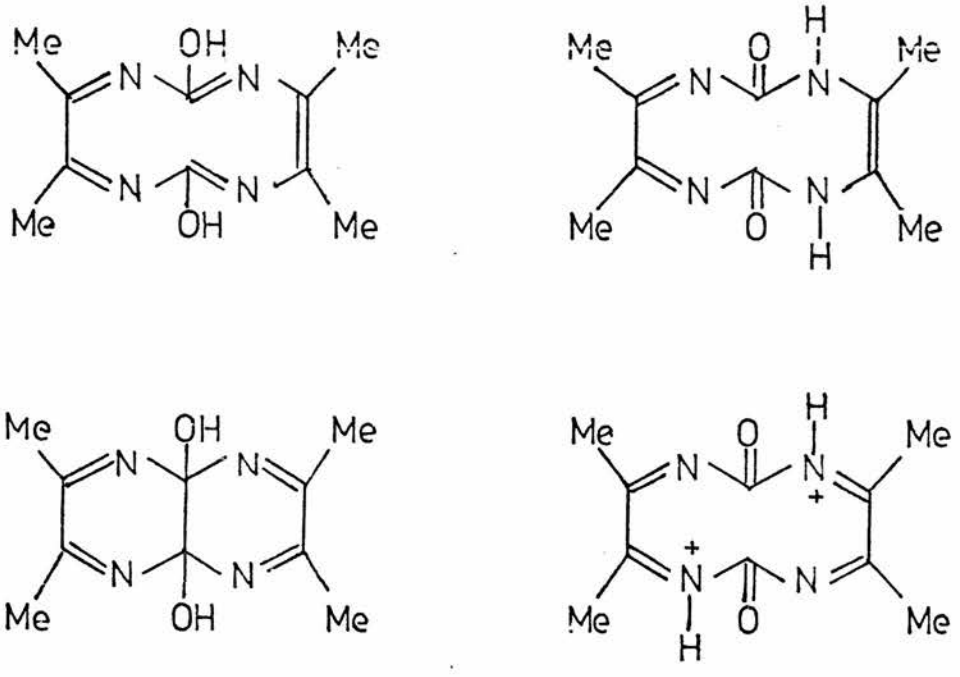
tarry liquids. Sometimes, if the liquids were allowed to dry out completely, hard glass-like materials were obtained.

Solvents that did not contain hydroxy groups were also tried. It was felt that the presence of hydroxy groups might result in hydrogen-bonding which might interfere with the satisfactory isolation of the products. Toluene and methylene chloride were both tried out together with trifluoroacetic acid (which dissolves readily in these solvents). Reaction proceeded readily in both solvents with the formation of a brown slurry with urea and highly coloured viscous liquids with N-methylurea and N,N'-dimethylurea. Toluene was not a very satisfactory solvent as two immisible layers of liquid tended to form as water was produced during the reaction and it was also more difficult to remove by evaporation. Methylene chloride, by virtue of its low boiling point, was much easier to remove.

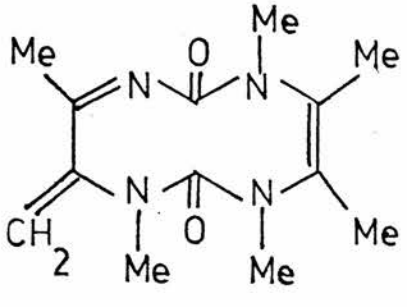
Various attempts were made to recrystallise and purify these products by using different solvents and solvent mixtures. However, it was not possible to obtain satisfactory pure and crystalline samples. The samples obtained from the above methods were submitted for mass spectroscopy. Unfortunately nearly all the samples submitted proved to be either involatile or resulted in such poor mass spectra that gave virtually no information on the identity of the products.

Occasionally a few high mass peaks did appear in the mass spectrum. However it was not possible to say definitely whether any particular peak was

Figure 20.



Some structures proposed for m/e = 222 for the urea product



A structure proposed for m/e = 264 for the N, N'dimethylurea product

the molecular ion peak. Other peaks were so small that it was impossible to say whether they could be assigned to the product or to impurities. The formulation of a structure became a matter of speculation. For example, a peak was recorded at m/e = 222 in the mass spectrum of the urea product obtained in methylene chloride/trifluoroacetic acid. High peaks were also recorded at m/e = 111 and 112. Some of the structures proposed are shown in Figure 20. The peak at m/e = 111 could arise from the splitting of the molecule into two equal halves, while the one at m/e = 112 must have an extra proton. The structures shown are quite reasonable from the reaction point of view, and the highly conjugated nature of the molecules would help to account for the characteristic colour of the reaction.

With the N-methylurea product obtained in ethanol, a mass peak was recorded at m/e = 260. If N-methylurea formed a structure analogous to those proposed for urea, one would expect two extra methyl groups and a molecular ion peak of m/e = 250 or 252 depending upon whether the hydrogen atoms on the nitrogens were replaced by the methyl groups or not. It is therefore somewhat difficult to suggest any analogous structure for N-methylurea which would explain the peak at m/e = 260.

The ethanolic N, N'-dimethylurea product had a peak at m/e = 264 which, upon high-resolution measurement, was found to correspond to $C_{13}H_{20}N_4O_2$. The structure in Figure 20 was therefore proposed. However a methyl group appears to be missing and this is difficult to explain unless it was lost during the fragmentation of the molecule in the mass spectrophotometer.

It was not possible to obtain any further evidence to give support to any of these structures, so they remain highly speculative. All the samples were too impure for elemental analysis to be carried out. Proton n.m.r. studies were of no use because of the impurity of the substances and because of the problems of finding a suitable solvent. It was also thought that, even if n.m.r. spectra were obtained, the spectra would be of little value as the products would merely give rise to a series of single peaks corresponding to the methyl groups, and there would be no splitting patterns.

The nature of the products obtained and the poor mass spectra obtained from them suggested the possibility that the products might be of a polymeric nature. It was not possible to ascertain whether the products were indeed polymeric or not.

Column chromatography was also tried to separate the components of the products so that purer samples would be obtained. Alumina packed in petroleum was used, and ethanol, methanol and chloroform were all tried out as eluting solvents. The N-methylurea and N,N'-dimethylurea viscous liquids were diluted with a little solvent and eluted down the column. It was possible to observe two bands in the column. There was an initial yellow band followed by a coloured band. Fractions were collected off the column, evaporated to yield viscous liquids and sent for mass spectroscopy but the mass spectra were all poor. All that was learned from the chromatography experiment was that there were definitely two components present in the product samples.

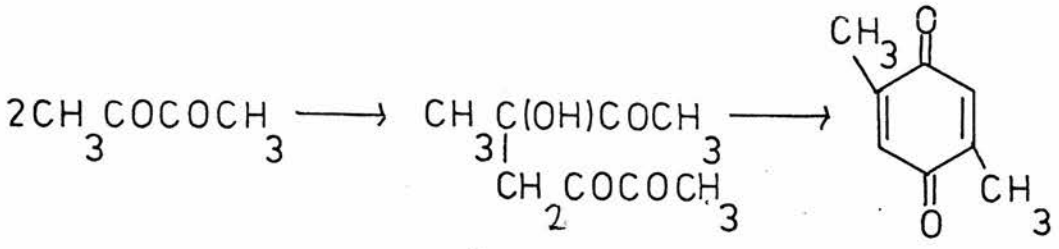
An attempt was made to isolate the coloured product using the white

diurea solid (XLII) as a starting point. XLII was refluxed in ethanol/HCl and in methylene chloride/trifluoroacetic acid for several hours. In both cases some of the starting material XLII was filtered off after refluxing was stopped, and the coloured part was extracted and submitted for a mass spectrum but without any useful result.

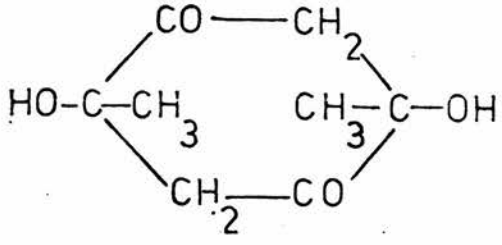
Spectra of many of these coloured substances were obtained to see how they compared with the final spectra of the reactions. Nearly all the spectra showed the presence of the peaks due to the colour and some also showed the intermediate peaks. What was noteworthy about most of these spectra was the presence of very strong absorbance in the region 200-300 nm which was often greater than the absorbances due to the colour. When the reactions are carried out on a synthetic scale, the concentration of the butane-2,3-dione is much greater than when the reactions are examined in the spectrophotometer. If the butane-2,3-dione underwent a considerable amount of self-condensation during the synthetic reactions, this would account for the very large absorbance in the spectra of the coloured substances.

The effect of adding aqueous alkali to solutions of the colour was also examined. When aqueous sodium hydroxide was added to a solution of the purple N,N'-dimethylurea product dissolved in water, the solution turned yellow. The purple colour was restored by the addition of hydrochloric acid. The same effect was seen with theN-methylurea product, but the colour change was less pronounced. With the urea product, no significant colour change was

Scheme 17. Self-condensation of butane-2,3-dione



aldol quinone



XLV

observed. It seems that protonation is involved in colour formation, particularly with N-methylurea and N, N'dimethylurea.

Self-condensation of butane-2,4-dione.

Butane-2,3-dione undergoes self-condensation in the presence of both alkali and acid. Under alkaline conditions, an aldol is first formed and this undergoes further reaction to form a quinone[102] (see Scheme 17). On treatment with cold hydrochloric acid, butane-2,3-dione forms a trimer $(CH_2COCOCH_3)_3$[103] but the structure of the product is not known. Butane-2,3-dione also forms a dimer, which is said to have the structure (XLV)[104], in the presence of acid.

The fact that butane-2,3-dione undergoes self-condensation was confirmed when the diketone was refluxed in benzene in the presence of trifluoroacetic acid. A dark brown sticky mass was obtained, but the structure of the condensation product was not established, although peaks higher than m/e = 270 were recorded in the mass spectrum. A similar brown mass is obtained if butane-2,3-dione is left to stand in cold concentrated hydrochloric acid.

The extent of the self-condensation reaction of butane-2,3-dione was not fully appreciated when most of this work was undertaken. It is now evident that this reaction plays an important part during the reaction of butane-2,3-dione with urea. The spectral changes must show two main reactions : one of butane-2,3-dione with itself and the other with urea. The formation of a

polymeric product with butane-2,3-dione has obviously interfered with the isolation of a pure sample of the coloured product and this probably explains why one was not able to characterise successfully the coloured substances. It would be of interest to know whether the urea reacts with the butane-2,3-dione self-condensation product or whether reaction is via a simple butane-2,3-dione/urea adduct.

One may wonder why such a complex reaction is used as a method of determination of urea. Presumably the peak formed at 480 nm is a measure of the amount of urea reacted and this absorbance is not interfered with by the self-condensation reaction which shows absorbance changes at 265 nm.

The role of the methyl groups of butane-2,3-dione.

It has already been observed that benzil, with its two phenyl groups, does not give rise to any of the intense colours seen during the reaction of butane-2,3-dione with urea. A brief look was taken into the reactions of other α-diketones with urea, N-methylurea and N,N'-dimethylurea. Test tube experiments with pyruvic aldehyde (propane-1,2-dione) showed that in the presence of acid the same intense colours are formed with the ureas. A brief examination of the spectral changes of the reactions with pyruvic aldehyde showed the same pattern of reactions as that observed with butane-2,3-dione. Pyruvic aldehyde apparently also undergoes self-condensation as evident from absorbance changes analogous to those of butane-2,3-dione at 265 nm. Acetylbenzoyl (1-phenylpropane-1,2-dione) also forms intense colours during

reaction with urea and this diketone will be discussed more fully in the next chapter.

By contrast, glyoxal showed none of these characteristic colours, and the spectral changes of its reaction with urea were quite different. From these observations it is evident that the presence of at least one methyl group adjacent to a carbonyl group is a prerequisite for the formation of these intense colours. One possible explanation is that the presence of methyl groups allow the formation of a keto-enol tautomer and this tautomer may be the reactive species. It has already been seen that pentane-2,4-dione reacts in the keto-enol form. Alicyclic α-diketones tend to be 100% keto-keto as this form is stabilised by the carbonyl groups being on opposite sides of the molecule and this is responsible for the characteristic yellow colour of alicyclic α-diketones. In cyclic α-diketones, this stabilisation is not possible and extensive enolisation occurs and most keto-enol α-diketones are colourless. When enolisation is not possible, the yellow diketo form will occur in cyclic compounds[105]. Schwarzenbach and Wittwer[106] have shown that neat butane-2,3-dione does have a very small proportion of the keto-enol form (0.0056%). If, like pentane-2,4-dione, the proportion decreases in the presence of water the proportion of the keto-enol form may be even smaller in the reaction solutions. This does not, however, exclude the possibility that the keto-enol form is still the reactive species. For instance, Lapworth[107] has shown that the bromination of acetone in the presence of aqueous acid must occur via the enol form of

acetone, and neat acetone has been found to be only 0.00025% enol[106]. The presence of acid apparently accelerates the attainment of equilibrium between the two tautomeric forms.

Colour formation may not be due to keto-enol tautomerism , but simply due to the fact that further reaction somehow involves the methyl groups. It can be seen that the self-condensation reactions of butane-2,3-dione themselves involve reaction of the methyl groups. Reaction could occur between the methyl groups and either the carbonyl group or a free amino group of the urea. However, it is not possible to say, at this stage, what the reaction may be especially when the nature of the coloured produects is still unknown.

It is of interest to note that the reaction of cyclohexane-1,2-dione and of its dioxime with urea also results in the formation of strong colours ranging from emerald green to blue and to violet[108]. This reaction has actually been reported as a method of determination of urea in urine[108]. Cyclohexane-1,2-dione can also undergo keto-enol tautomerism and the neat liquid is 100% enol[109] although the proportion decreases in water. Cyclohexane-1,2-dione does not possess any methyl groups but it does have methylene groups adjacent to the two carbonyl groups. So it seems likely that the presence of a methylene group is necessary for colour formation.

EXPERIMENTAL

Preparation of the product[101].

To urea (5g) and butane-2,3-dione (2.5g) in water (12.5 ml) was added concentrated HCl (5 ml) dropwise with constant stirring. The solution was allowed to stand for 2 h. and the product was filtered off. The product was recrystallised from boiling water after treatment with Norit A (activated charcoal).

The N-methylurea product was prepared similarly using N-methylurea (6.2g) and allowing the solution to stand overnight. Attempts to prepare the corresponding N,N'- and N,N-dimethylurea products in a similar manner were without success.

Physical data.

Urea product (XLII) : molecular ion peak 170, m.p. $> 300^{o}$

Analysis :	$C_6H_{10}N_4O_2$		
Required :	42.3% C	5.9%H	32.9% N
Found :	42.4 % C	6.0% H	32.7% N

Methylurea product (XLIII) : molecular ion peak 198, m.p. 305^{o}

Analysis :	$C_8H_{14}N_4O_2$		
Required :	48.5% C	7.1% H	28.3% N
Found :	48.5% C	7.3% H	28.2% N

Spectra.

Spectra of the products were recorded on a Unicam SP 800 spectrophotometer. Spectral changes were also followed by recording spectra of the reaction mixture at selected time intervals using, where appropriate, a thermostatted heating block. To follow the reaction, 0.1 ml of a solution of butane-2,3-dione (0.5 - 2.0% in water) was added to a cuvette containing the urea (0.05 or 0.01 M) in hydrochloric acid (5 M).

Other experimental work.

There is no need to describe here the full details of the experiments carried out to try to isolate and characterise the coloured substances as the work produced no definite and reproducible results. The general methods used have already been described adequately in the section 'Results and discussion'.

CHAPTER VI

REACTION WITH 1-PHENYLPROPANE-1,2-DIONE

INTRODUCTION

The lack of success in the identification of the coloured products in the reactions of butane-2,3-dione prompted an investigation into the reaction of another α-diketone, 1-phenylpropane-1,2-dione (acetylbenzoyl),with urea. 1-Phenylpropane-1,2-dione has been proposed as a reagent for the determination of urea[110] but it seems that it has never been widely used in hospital laboratories.

It was thought that 1-phenylpropane-1,2-dione, with its single methyl group, might simplify the reaction with urea to some extent and make it easier to identify the products and to propose a mechanism for the reaction. Benzil, as it has been seen, does not form deep colours during reaction with urea so 1-phenylpropane-1,2-dione seemed to be the logical choice of a α-diketone to study. Unfortunately work with this diketone did not result in any more success than the previous work with butane-2,3-dione. Results did, however, show that 1-phenylpropane-1,2-dione reacts with urea in a manner similar to that observed with butane-2,3-dione, and a similar diurea product was isolated.

RESULTS AND DISCUSSION

1-Phenylpropane-1,2-dione was prepared in two steps. The first step involved the preparation of its monoxime from 1-phenylpropane-2-one using a method used to prepare the monoxime of butane-2,3-dione[111]. The monoxime was then converted into the diketone in the second step[112]. The 1-phenylpropane-1,2-dione was used in the following experiments.

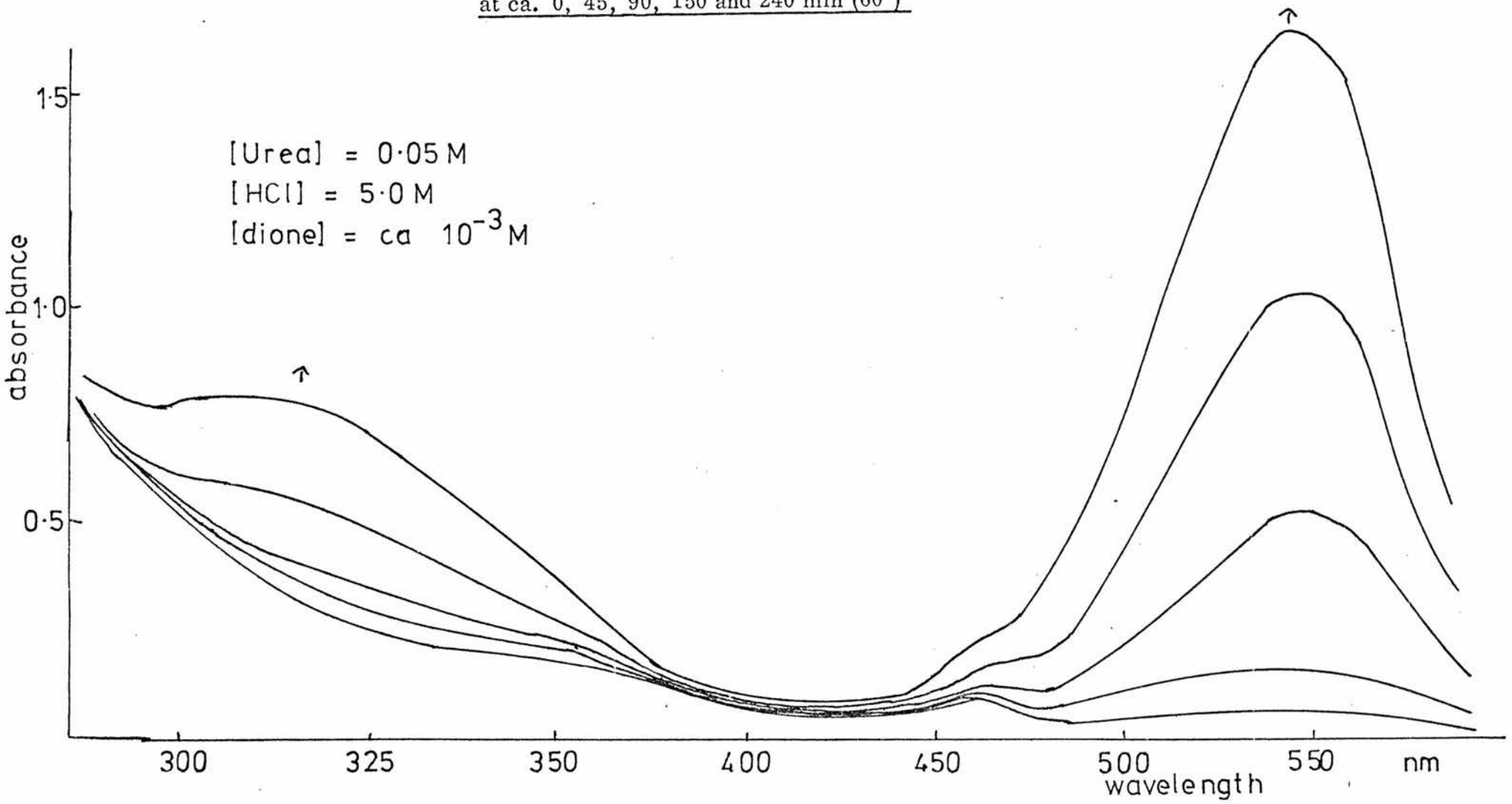
Test tube experiments.

When a little 1-phenylpropane-1,2-dione was added to test tubes containing urea, N-methylurea and N,N'-dimethylurea dissolved in aqueous hydrochloric acid, strong pink colours were formed. N,N'-Dimethylurea also eventually formed a blue-violet colour. N,N-Dimethylurea did not result in any colour formation.

Spectral changes during reaction.

The spectral changes of the reaction of 1-phenylpropane-1,2-dione with urea, N-methylurea and N,N'-dimethylurea in the presence of acid were examined at 60°. With urea, a strong absorbance, attributed to the colour formation, was formed over several hours at 546 nm as the reaction proceeded. Another absorbance also formed simultaneously at 315 nm. Spectral changes in the region 200-300 nm were not observed as they were masked by the strong absorbance of the diketone. Reaction with N-methylurea exhibited similar spectral changes with a peak due to the pink colour formed at 526 nm while

Figure 21. Spectral changes of reaction between urea and 1-phenylpropane-1,2-dione at ca. 0, 45, 90, 150 and 240 min (60^{o})



another peak formed at approximately 318 nm (this was partly obscured by the diketone absorbance). Typical spectral changes are illustrated in Figure 21.

The initial spectral changes of the reaction with N, N'-dimethylurea were similar to those observed with urea and N-methylurea. Like the other two ureas, the N, N'-dimethylurea reaction results in the formation of an absorbance at 507 nm giving rise to the pink colour but after one hour this absorbance fell back to almost zero over a period of about six hours as a new absorbance is very slowly formed at 578 nm. This new absorbance corresponds to the intense blue-violet colour observed in the test tube experiment. Like urea and N-methylurea an absorbance is also formed at about 320 nm.

The 1-phenylpropane-1, 2-dione spectral changes are seen to differ in some respects from those observed with butane-2, 3-dione. For instance, the reactions proceed directly towards colour formation and no intermediate peak analogous to the ones observed in the 360 nm region with butane-2, 3-dione. It should be kept in mind that the formation of the intermediate peak was by-passed in some of the spectral changes of the butane-2, 3-dione reactions. The spectral changes of N, N'-dimethylurea are unusual in that two different absorbances corresponding to two different colours are formed. It is not possible to say here what is the significance of this observation or why N, N'dimethylurea should react somewhat differently from urea and N-methylurea.

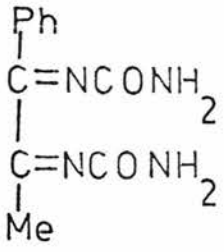
The absorbance formation observed in the 320 nm region with all three ureas was initially thought to be due to the self-condensation of the diketone

(analogous to the peak formed at 265 nm for the self-condensation of butane-2,3-dione). However, when the spectral changes of 1-phenylpropane-1,2-dione alone in acid were observed it was found that the changes were not in the 320 nm region but further over in the ultra-violet region. The diketone has an absorbance at 262 nm which falls with time as a new peak is formed at 234 nm and the spectral changes were very slow. So the spectral changes in the 320 nm region must be part of the reaction of the diketone with the ureas. As the strong absorbance of 1-phenylpropane-1,2-dione obscured the 200-300 nm region, it was not possible to see whether the diketone undergoes self-condensation during the reactions with the three ureas.

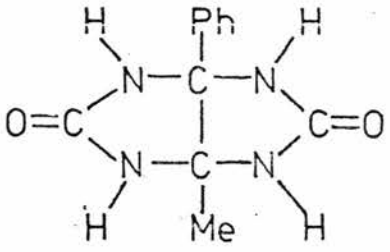
Azeotropic distillation.

Azeotropic distillations using benzene and trifluoroacetic acid were carried out during the reactions of 1-phenylpropane-2,3-dione with urea, N-methylurea and N,N'-dimethylurea. This technique has been described previously, in the work with benzil in the presence of acid, as a method of measuring the amount of water formed during reaction. It was thought that this experiment would indicate whether, after the loss of two moles of water due to the possible initial formation of a 1:2 diketone/urea adduct, any more water had subsequently been lost during further reaction to yield the coloured product.

Results showed that, with urea, N-methylurea and N,N'-dimethylurea, approximately two moles of water were formed for every mole of diketone and



XLV



XLVI

every two moles of the urea reacted together. The formation of two moles of water would be expected for the formation of a diurea product analogous to those isolated with butane-2,3-dione. However, the results also tend to suggest that any further reaction leading to colour formation does not involve the loss of any more water.

Isolation and identification of the products.

(a) Urea

The reaction of urea with 1-phenylpropane-1,2-dione in benzene/trifluoroacetic acid during the azeotropic distillation experiment yielded a purple sticky mass from which a pale lilac coloured solid was obtained. The mass spectrum provided very little information with only small peaks recorded at m/e = 160 and 147 and other larger peaks at lower masses. The product was submitted for elemental analysis but it was not possible to interpret the result.

When the lilac compound was recrystallised from water an orange/pink solid was obtained. The mass spectrum and the analysis result for this recrystallised product was similar to that of the lilac solid.

The filtrate from recrystallisation, when subsequently evaporated down, gave a cream coloured solid. The mass spectrum of this compound was rather poor but the analysis result corresponded reasonably well to that required for a diurea compound (XLV or XLVI).

Other solvents were tried out to prepare the products. Water

(previously used to prepare the butane-2,3-dione products) was unsuitable since 1-phenylpropane-1,2-dione was virtually immiscible with water. However, ethanol was found to be a good choice and a white diurea product (XLV or XLVI) was successfully isolated. Care had to be taken to keep the acid concentration low so that the reaction did not proceed rapidly towards colour formation. The mass spectrum recorded a peak at m/e = 232 which corresponded to the molecular ion peak. The linear diurea structure (XLV) was favoured rather than a bicyclic structure (XLVI) because of the presence of strong peaks at m/e = 147 and 85 which would correspond to the fragmentation of the molecule across the bond between the 1- and 2- carbon atoms.

The unrecrystallised lilac solid was refluxed in trifluoroacetic acid for several hours and eventually a dark purple solid was isolated from the reaction. The mass spectrum showed a few small peaks above m/e = 200 and an elemental analysis result was obtained but it was not possible to come to any valid conclusions on the identity of the coloured compound.

A similar attempt to isolate the coloured substance was made by refluxing the diurea compound (XLV) in ethanol and hydrochloric acid for several hours. A purple solid was obtained but its mass spectrum did not give any useful information.

(b) N-Methylurea and N,N'-Dimethylurea.

After the azeotropic distillation experiments with N-methylurea and N,N'-dimethylureas, the benzene and the trifluoroacetic acid were removed

by evaporation leaving syrupy liquids. The N-methylurea product was a dark red syrup and the N,N'-dimethylurea product had an intense dark blue colour. Because of the viscous nature of the liquids, neither of the products were suitable for mass spectrophotometry or elemental analysis. Proton n.m.r. spectra were obtained of both compounds but it was not possible to deduce much information about the structures. As it will be seen later both products were impure and were mixtures of two or more compounds so that the n.m.r. results were of little meaning.

Both viscous liquids were investigated by thin layer chromatography. It was found that plates coated with cellulose gave the best results. The spots were applied using solutions of the compounds dissolved in acetone. Different solvents and solvent mixtures were tried[113] and it was found that for the N-methylurea compound,a n-butane/glacial acetic acid/water mixture gave the best separation of the components. The N-methylurea product separated into two easily distinguished components, an orange yellow band followed by a purple pink band. With N,N'-dimethylurea, a benzene/acetone mixture gave the best results. Three component could be detected; a greyish component which did not travel up the plate at all; a pink component which moved up the plate a little and finally, a yellow component which travelled almost as far as the solvent front.

Small samples of the coloured components were obtained by running several plates of the compounds and then scrapping off the cellulose containing the separated components. The components were then extracted from the

cellulose[114].

The two N-methylurea components and the two coloured components from the three N,N'-dimethylurea components were submitted for mass spectroscopy. It was thought that the purer components might result in better spectra but unfortunately the results were poor and provided no worthwhile information, although peaks corresponding to N-methylurea and N,N'-dimethylurea themselves were recorded.

Attempts were also made to prepare the white products corresponding to the diurea compound obtained with urea by using ethanol as a solvent but, even with a low concentration of acid present, reaction tended to go directly towards colour formation and the white products remained elusive.

From the foregoing it can be seen that attempts to characterise the coloured products were, as in the case of butane-2,3-dione, without success and little can be said about the mechanism of the reactions of the ureas with 1-phenylpropane-1,2-dione until the identities of the final products are known.

Miscellaneous observations.

A number of miscellaneous observations were made.

1) The lilac solid obtained with urea was found to be photosensitive as when it was left exposed to the light, the exposed surfaces darkened gradually to a dark purple colour.

2) The lilac and orange/pink solids obtained from urea are probably mixtures which contain traces of colour. Even the purple solid obtained by

refluxing the lilac solid in trifluoroacetic acid is not pure. When this purple solid was added to methanol, the methanol had a purple/pink colour and a pale lilac solid was left at the bottom of the vessel. When the methanol solution was acidified the colour intensified, indicating that the reaction leading to colour formation was still incomplete.

3) When the diurea compound (XLV) was dissolved in aqueous hydrochloric acid, the characteristic colour developed gradually. Reaction of the diurea compound in the presence of acid is therefore more than simple protonation which would be instanteous. The rate of formation of the colour was monitored approximately by following the reaction on the U. V. spectrophotometer. If urea was present in the acid solution, the rate of colour formation appeared to be slower than when no urea was present. If a little 1-phenylpropane-1,2-dione was present, colour formation appears to be accelerated but when the solution was left overnight, all traces of the characteristic colour had disappeared completely. The presence of another α-diketone (such as benzil or butane-2,3-dione) also results in a similar disappearance of the characteristic colour. This observation is difficult to explain. Presumably the diketone must react in such a way as to destroy the coloured compound.

4) The effect of adding alkali to the characteristic colours was examined. When a solution of the colour in acid was neutralised by the addition of aqueous sodium hydroxide the colour virtually disappeared (leaving a very pale pink solution). Upon reacidification, the colour was gradually restored (not instantly

as one might expect from a simple deprotonation/protonation reaction).

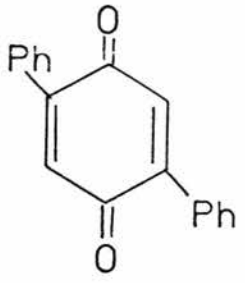
With N-methylurea, when the syrup was dissolved in acid, an intense red solution resulted. The colour disappeared when neutralised. But when the solution was reacidified a deep pink colour gradually appeared. This colour was different from the original red colour and was more like the pink colour seen with urea. It should be kept in mind, however, that the red syrup was a mixture of at least two components and the different behaviour of the two components in a neutralisation/reacidification may result in a different colour (see 5 below).

5) Thin layer chromatography of the N-methylurea product resulted in the isolation of two components : a purple one and an orange-yellow one. The orange-yellow component was dissolved in methanol and when the orange solution was acidified a deep pink colour formed instantly. This indicates that the orange/yellow component must be the unprotonated counterpart of the purple component.

The orange/pink solid isolated from urea may also contain small amounts of the corresponding unprotonated component. Recrystallisation of the lilac solid may have resulted in removal of all traces of acid and in deprotonation so that an orange/pink solid was obtained.

Self-condensation of 1-phenylpropane-1, 2-dione.

As it has already been observed from the spectral changes of 1-phenylpropane-1, 2-dione in acid, the diketone undergoes some form of reaction in the presence of acid. This reaction is probably a self-condensation



XLVII

reaction. In the presence of alkali, 1-phenylpropane-1,2-dione forms a quinone type product (XLVII)[115] similar to that obtained with butane-2,3-dione[102]. Although no mention of the self-condensation of 1-phenylpropane-1,2-dione in the presence of acid was found in the literature surveyed it is not unreasonable to suggest that it is quite probable that the diketone does undergo some form of self-condensation similar to that reported for butane-2,3-dione[103,104]. Since the absorbance of 1-phenylpropane-1,2-dione obscured the region 200-300 nm it was not possible to determine whether the diketone undergoes self-condensation during the reactions with the three ureas. The rate of self-condensation of 1-phenylpropane-1,2-dione may be slower than that of butane-2,3-dione so that the self-condensation reaction may not interfere with the reaction with urea as much as it does in the case of butane-2,3-dione.

EXPERIMENTAL

Preparation of 1-phenylpropane-1, 2-dione.

1-Phenylpropane-1, 2-dione was prepared in two main steps :

a) preparation of its monoxime from 1-phenylpropane-2-one using a method based on that for the preparation of the monoxime of butane-2, 3-dione.

b) conversion of the monoxime into the diketone.

a) Preparation of the monoxime of 1-phenylpropane-1, 2-dione[111].

(i) $EtOH + HNO_2 \xrightarrow[H_2SO_4]{NaNO_2} EtONO + H_2O$

(ii) $EtONO + PhCH_2COCH_3 \longrightarrow PhC(NOH)COCH_3 + EtOH$

(i) Preparation of ethyl nitrite : two solutions were made up

Solution A : Sodium nitrite (620g), ethanol (285 ml) were dissolved in water to make a total volume of 2.5 l.

Solution B : Concentrated sulphuric acid (255 ml, sp.g. 1.84) and ethanol (285 ml) were diluted with water to a volume of 2.5 l.

Ethyl nitrite was generated continously in the gaseous form by allowing solution B to flow into solution A.

(ii) Preparation of the monoxime : In a 2-litre 3-necked flask (with condenser, thermometer and inlet tube for the ethyl nitrite) arranged for external cooling was placed 1-phenylpropan-2-one (1154g) which had been dried and filtered from anhydrous copper sulphate (75g).

Hydrochloric acid (40 ml, sp.g. 1.19) was added and the temperature raised to 40°C. Ethyl nitrite from the previous preparation was bubbled in, the temperature being kept between 40-55°. After all ethyl nitrite had passed in (about $1\frac{1}{2}$ h.) the crude product was filtered off from the ethanol and used in the next preparation.

b) Preparation of 1-phenylpropane-1,2-dione from the monoxime[112].

$$PhC(NOH)COCH_3 + H_2O \xrightarrow{H_2SO_4} PhCOCOCH_3 + NH_2OH$$

In a 1-litre flask arranged for steam distillation (with a spray trap between the flask and the condenser) the monoxime (50g) and 10% sulphuric acid (500g) were mixed. The mixture was steam distilled until about 2 l. of distillate was collected. During distillation, the flask was heated so that the volume of the reaction mixture was kept roughly constant. Distillation required about 6 h. and at the end of this time the liquid in the flask was clear. The lower yellow layer of diketone in the distillate was separated. The water layer was then saturated with salt and more diketone was extracted with ether (1 x 80 ml and 2 x 25 ml per litre of aqueous solution). The ether extracts were combined with the diketone layer and dried over sodium sulphate. The ether was removed and the residual material distilled from a Claisen flask under reduced pressure. 1-Phenylpropane-1,2-dione collected at 114-116°/20 mm. B.p. (lit.) 216-218°.

Spectra.

Spectra were recorded on a Unicam SP800 spectrophotometer. Spectral changes of the reaction were monitored by recording spectra, at selected time intervals, of the reaction mixture. The reaction solution was made up by adding 0.1 ml of 0.2 or 2% aqueous solution of 1-phenylpropane-1,2-dione to a cuvette containing the urea (0.05 M) dissolved in hydrochloric acid (5 M). The cuvette was placed in a thermostatted block (60^{o}).

Azeotropic distillations.

The azeotropic distillation experiments were carried out using the Dean and Stark apparatus. The general method used and a diagram of the apparatus have already been given in Chapter 4 (page 95). The measured water volumes were all corrected by titration to estimate the amount of dissolved trifluoroacetic acid.

The urea (0.1 mole) was refluxed with 1-phenylpropane-1,2-dione (0.05 mole) in benzene (100 ml) and trifluoroacetic acid (10 ml) for about 6 h. The following corrected amounts of water were obtained :

urea	0.1 mole
N-methylurea	0.083 mole
N,N'-dimethylurea	0.089 mole

By making allowance for incomplete reaction it will be seen that approximately two moles of water results from the reaction of every two moles of the urea with one mole of the diketone.

Isolation and identification of the products.

a) Urea products

1) lilac solid : the product form the azeotropic distillation was filtered off, washed with ether and then with water.

Mass spectrum : no useful information

M.p. 215°

Analysis : Required ?

Found 60.9% C 4.6% H 15.1% N

2) orange/pink solid : the lilac solid was recrystallised from a large volume of boiling water.

Mass spectrum : no useful information

M.p. 230° dec.

Analysis : Required ?

Found 61.6% C 4.7% H 16.9% N

3) cream solid : water was evaporated from the filtrate of the orange/pink solid recrystallisation and a cream solid was obtained

Mass spectrum : no useful information

M.p. > 300°

Analysis : $C_{11}H_{12}N_4O_2$ (diurea compound, XLV)

Required 56.9% C 5.2% H 24.1% N

Found 56.3% C 4.9% H 23.0% N

4) diurea compound : to the 1-phenylpropane-1,2-dione (0.75g) in ethanol (10 ml) was added concentrated hydrochloric acid (1 ml) and excess urea (1.5g). The solution was heated briefly and gently on a steam bath until a precipitate was formed. The addition of more water to the ethanol resulted in a better precipitation. The precipitate was filtered and washed with acetone to remove traces of the diketone.

Mass spectrum : molecular ion peak at m/e = 232

M.p. $> 300^{o}$

Analysis : $C_{11}H_{12}N_4O_2$ (diurea compound, XLV)

Required	56.9% C	5.2% H	24.1% N
Found	57.0% C	5.2% H	24.0% N

5) purple solid : the lilac compound was refluxed in trifluoroacetic acid for a few hours. The acid was removed by evaporation, the product dissolved in methanol and the residue filtered off. The methanol was evaporated off and the resulting solid dried in a dessicator.

Mass spectrum : poor

M.p. $142\text{-}143^{o}$

Analysis :	Required		?	
	Found	51.1% C	4.1% H	15.8% N

6) purple solid : the diurea compound was refluxed in ethanol and hydrochloric acid for several hours. The ethanol was removed by evaporation and the residue dried in a des cator.

Mass spectrum : poor

b) N-Methylurea and N,N'-Dimethylurea products.

The products were obtained by removing the benzene and trifluoroacetic acid by evaporation from the solutions used in the azeotropic distillation experiments. It was not possible to obtain crystalline solids from the syrupy liquids.

Both products were examined by thin layer chromatography. Avicel coated plates (supplied by Anachem) were used. The products were dissolved in acetone and spotted on to the plates. Suitable solvents were chosen by using a technique where rows of spots were placed on one plate and then a different solvent or solvent mixture was applied to the centre of each spot using a thin drawn out capillary tube. The solvent moves radially out of the centre of the spot for a distance of about one centimetre. By using this TLC technique[113] on a . ature scale it is possible to try out a wide range of solvents to find the most suitable ones.

For the N-methylurea product the best eluting solvent was a mixture of butane, glacial acetic acid and water (60:15:25 by volume). The best solvent mixture for the N,N'-dimethylurea product was a benzene/acetone mixture (10:5 by volume). The separation of the components on the plates is illustrated

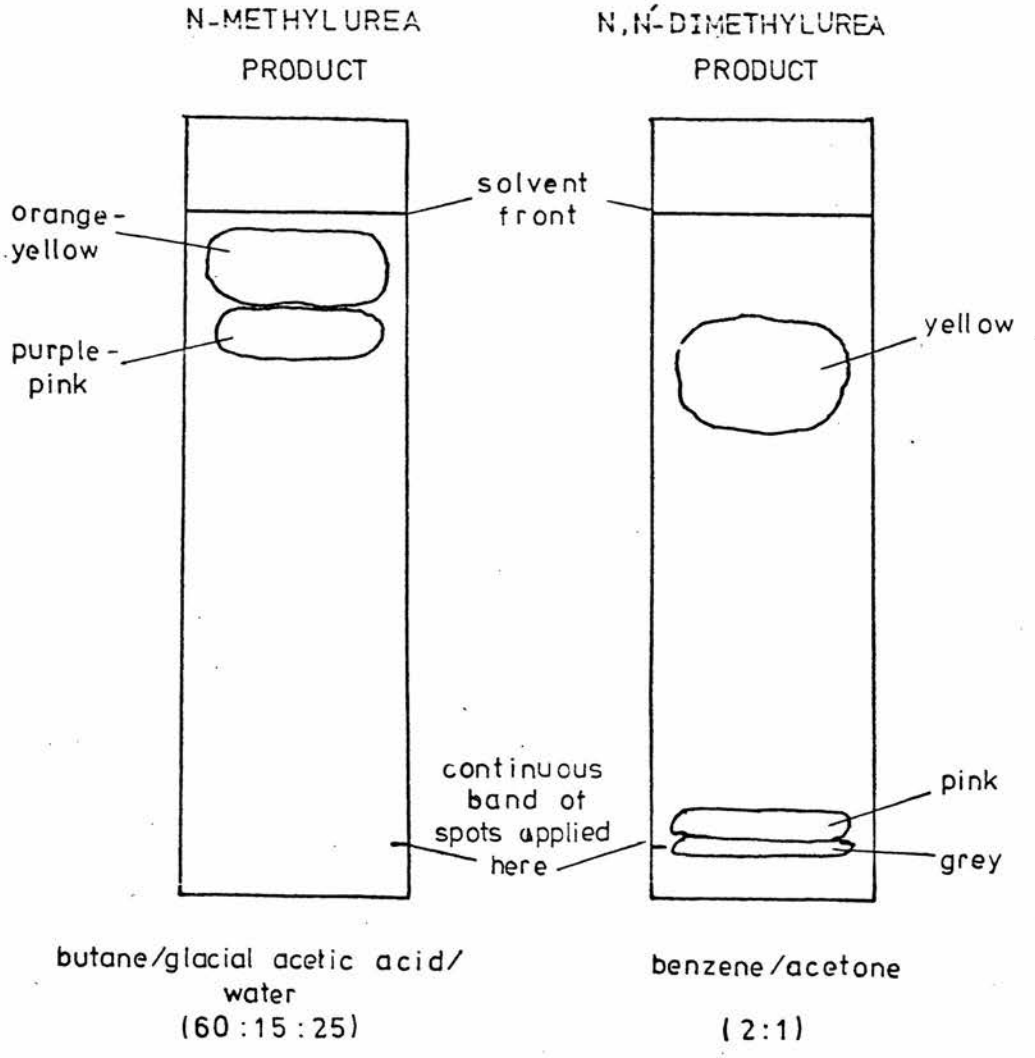


Figure 22. Thin layer chromatography plates of the N-methylurea and N, N'-dimethylurea products

in Figure 22.

The purple pink and orange/yellow components were scraped off the N-methylurea plates and the colours extracted by washing the cellulose with pure ethanol and filtering off the cellulose. The filtrates were then evaporated off to remove the ethanol[114]. The same procedure was carried out with the pink and yellow components of the N,N'-dimethylurea product. All extracted samples were submitted for mass spectra but no useful information was obtained from the spectra although the spectra did record prominent peaks corresponding to N-methylurea and N,N'-dimethylurea respectively. The amounts of the samples thus isolated were too tiny for much further work to be carried out on them.

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