

Mechanistic Studies in the Chemistry of Urea. Part 4.¹ Reactions of Urea, 1-Methylurea, and 1,3-Dimethylurea with Benzil in Acid Solution

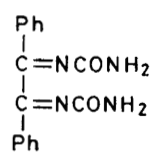
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In acid solution benzil reacts with urea and with 1-methylurea to give the bicyclic products (2) and (3b) and with 1,3-dimethylurea to give 1,3-dimethyl-5,5-diphenylhydantoin (5). The initial step in the reaction is attack by urea on protonated benzil to give the diol (6). Further reaction of (6) is governed by its tendency to eliminate water.

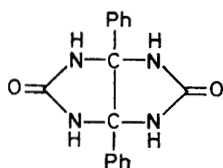
REACTIONS of urea, 1-methylurea, and 1,3-dimethylurea with benzil under alkaline conditions to give hydantoin with the first two and a diol with the third were described in Part 2.² There is also reaction under acidic conditions, and again the product depends upon the *N*-substitution of the urea. Studies of the products and mechanisms of these reactions are described in this report.

RESULTS AND DISCUSSION

(a) *Urea*.—Reaction of urea with benzil in ethanol containing HCl gave a crystalline product with empirical formula $C_8H_7N_2O$. If the reaction was carried out in benzene with trifluoroacetic acid (TFA) it was possible to remove the water formed during the reaction as an azeotrope and to measure the amount formed. Two moles of water were eliminated for each mole of benzil present. This did not change in the presence of a large excess of urea. The product obtained by using the azeotropic method was the same as that by using ethanolic HCl. The obvious possible products, consistent with the above results, are (1) and (2). The mass spectrum had no



(1)

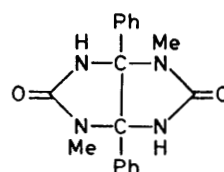


(2)

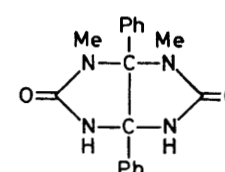
molecular ion peak corresponding to (1) and (2), but a strong one at $M^+/2$. This result favours (1) as, for the production of this fragment, fission of only one bond is required. However, the ^{13}C n.m.r. spectrum strongly favours (2). For this it was necessary to use TFA as a solvent, but it was found possible to recover the material unchanged and so no destructive reaction occurs in the solution. Apart from those corresponding to the carbon atoms of the phenyl group, there were chemical shifts at δ 165.73 and 87.02 p.p.m. The former is that of the amide carbonyl group, but the latter is not typical for carbon in a C=N group. However, the shift is right for the central carbon atom of (2). Thus, we believe that 3a,7a-diphenyltetrahydroimidazo[4,5-*d*]imidazole-2,5-dione (2) is the product of reaction. The $M^+/2$ peak in the mass spectrum may be due to a doubly charged species.

(b) *1-Methylurea*.—A similar product was obtained by

the reaction of 1-methylurea with benzil, with the concomitant formation of two moles of water. The mass spectrum showed a strong molecular ion peak and so there is no evidence to suggest a structure analogous to (1). If the product has a bicyclic structure there are two possibilities, (3a and b). We may distinguish

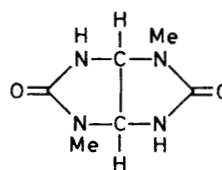


(3a)

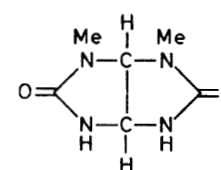


(3b)

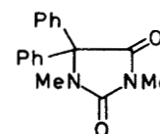
between them by the use of ^{13}C n.m.r. spectroscopy. In (3a) the two phenyl groups are equivalent, while in (3b) they are not. The spectrum of the product had eight peaks in the region associated with aromatic carbon atoms (δ 135.78—128.17 p.p.m.) and so the structure must be (3b). Also, there are shifts at δ 93.74 and 84.06 p.p.m. corresponding to the two non-identical, bridging carbon atoms. In (3a) these two carbon atoms are identical. Thus the product of reaction is 1,6-dimethyl-3a,7a-diphenyltetrahydroimidazo[4,5-*d*]imidazole-2,5-dione (3b). Nematollahi and Ketcham³ prepared an analogous product from 1-methylurea and



(4a)



(4b)



(5)

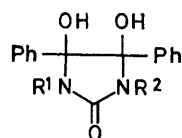
glyoxal. However, they found that both isomers, (4a and b), were formed, in the ratio 4 : 7.

(c) *1,3-Dimethylurea*.—Here only one mole of water was released for each mole of 1,3-dimethylurea present, and this suggested a different product from those

obtained with the other ureas. A possibility is 1,3-dimethyl-5,5-diphenylhydantoin (5) and this was proved by comparison with an authentic sample. The i.r. spectra and m.p. of the two were identical.

(d) 1,1-Dimethylurea.—No water was eliminated on refluxing 1,1-dimethylurea and benzil in benzene containing TFA. When ethanolic hydrogen chloride was used the starting material were recovered unchanged. No product analogous to (2) can form from 1,1-dimethylurea and, although other reactions are possible, they do not appear to occur under the conditions used.

In order to investigate the mechanisms of the reactions described above we studied the kinetics of reaction, with water as the solvent. Benzil is only very slightly soluble in water but there is sufficient to give a reasonable absorbance in the far u.v. In aqueous hydrogen chloride benzil is completely stable over many hours. However, on addition of urea, 1-methylurea, or 1,3-dimethylurea the absorbance at 265 nm falls to zero during the course of several hours. The solubility of benzil is too low to permit isolation of the product formed at this stage of the reaction, but the spectral changes are consistent with reaction at both carbonyl groups to give a species without multiple bonds in this part of the molecule. The carbonyl group of the amide function has only a very weak absorbance. The reaction appears to be the same for all three ureas, although the final products, as we have shown, are not all of the same type. We suggest that the reaction being studied in the spectrophotometer is the formation of (6). This is eminently reasonable for



- (6) a; R¹ = R² = H
 b; R¹ = Me, R² = H
 c; R¹ = R² = Me

1,3-dimethylurea as (6c) can undergo a pinacol rearrangement⁴ to give (5). Also diols of this type are known compounds.⁵ Internal cyclisation of the initially formed carbinolamine (7) to give (6) is likely to be faster than attack by a second molecule of urea, although obviously this reaction must occur eventually in order for (2) and (3b) to form. If we are right in assuming that the initial step is formation of (6), then we can use the observed kinetics to obtain the mechanism of this reaction. The disappearance of benzil in the presence of large excesses of urea and acid was found to be a first-order reaction (rate constant k_{obs}). The variation of k_{obs} with urea and acid concentration was examined and the results are given in the Table.

The very high concentrations of both urea and acid used, necessary to make the reaction have a reasonable rate, make it difficult to give a quantitative analysis of the kinetics. However, qualitatively the results are in agreement with the mechanism shown in Scheme 1.

Kinetics of the reaction of urea, 1-methylurea, and 1,3-dimethylurea with benzil in acid at 50°

(1) Urea

(a) [HCl] = 5.0M

[Urea]/M	1.0, 1.3, 1.7, 2.0
$10^4 k_{\text{obs}}/s^{-1}$	1.2, 1.9, 2.2, 2.4

(b) [Urea] = 1.0M

[HCl]/M	0.50, 1.5, 2.5, 5.0, 7.5
$10^4 k_{\text{obs}}/s^{-1}$	3.6, 3.2, 2.9, 1.2, 0.64

(2) 1-Methylurea

(a) [HCl] = 1.0M

[Methylurea]/M	0.20, 0.50, 1.0, 2.0, 2.5
$10^3 k_{\text{obs}}/s^{-1}$	0.51, 1.3, 2.0, 3.3, 3.3

(b) [Methylurea] = 1.0M

[HCl]/M	0.20, 0.50, 1.0, 2.0, 3.0, 4.0, 5.0
$10^3 k_{\text{obs}}/s^{-1}$	0.81, 1.6, 2.0, 2.4, 1.9, 1.4, 1.1

(3) 1,3-Dimethylurea

(a) [HCl] = 1.0M

[Dimethylurea]/M	0.25, 0.50, 1.0, 1.5, 2.5
$10^3 k_{\text{obs}}/s^{-1}$	2.9, 5.2, 6.9, 8.1, 8.2

(b) [Dimethylurea] = 1.0M

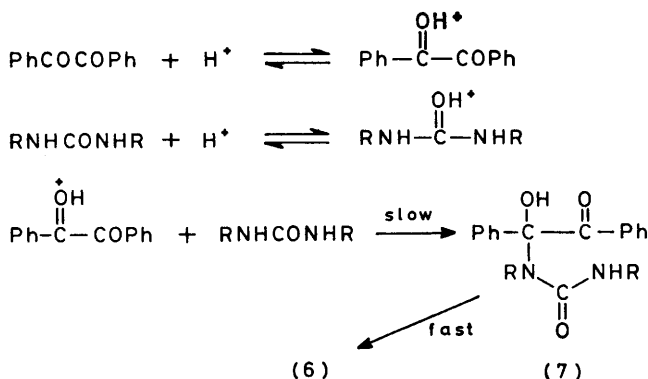
[HCl]/M	0.25, 0.50, 1.0, 2.0, 4.0, 5.0
$10^3 k_{\text{obs}}/s^{-1}$	2.8, 4.9, 6.9, 8.8, 5.4, 3.1

[Benzil]₀ = ca. 10⁻⁵M

The significant part is that reaction occurs between the neutral urea molecule and protonated benzil.

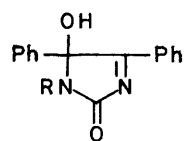
Let us first consider the effect of increasing the urea concentration at constant acid concentration. In all cases k_{obs} at first increases but then remains constant. Addition of urea will increase the amount of free urea but decrease the acid available to protonate the benzil. Therefore, k_{obs} should remain constant. However, at low urea concentration there is sufficient acid to protonate the urea almost completely and so k_{obs} declines.

The effect of changing the acid concentration is more complex. For 1-methylurea and 1,3-dimethylurea the value of k_{obs} goes through a maximum. With urea k_{obs} decreases as the acid is made more concentrated. In all cases the effect is not very great. These effects are understandable if protonation of urea, which removes a reactive species, and protonation of benzil, which produces a reactive species, follow different acidity scales. Further speculation concerning the relevant acidity scales is engaging but unrewarding; there are no data.



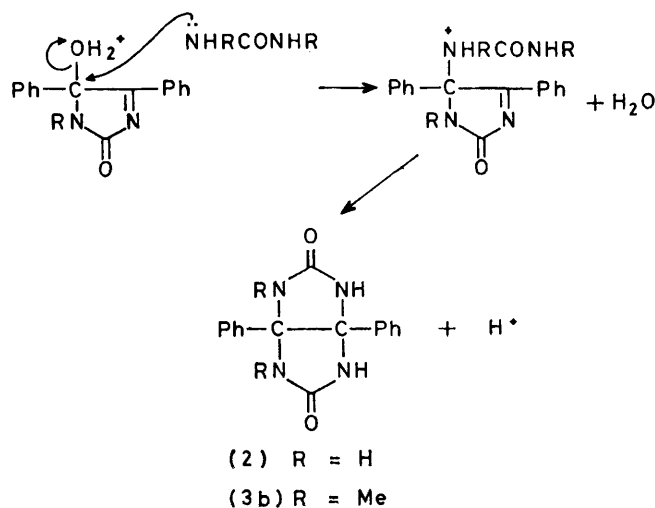
SCHEME 1

We must now consider the further reactions of (6). With (6c) there are no problems. The driving forces behind the conversion to (5) are the same as that in the pinacol rearrangement: elimination of water and creation of a carbonyl group. The same reaction could occur with (6a and b) but does not. Attempts were made to prepare and isolate (6a and b) but were unsuccessful, and so we could not investigate the reactions



(8) a; R = H
b; R = Me

directly. They differ from (6c) in that water can be eliminated to give (8a or b) and this process may prevent occurrence of a pinacol rearrangement. However, the spectral evidence is that (8a and b) have only a transient existence. In the alkaline reaction considered previously² such intermediates were postulated and required for the proposed mechanism. The spectral evidence supporting their formation is the observation that, in alkaline solution, the absorbance in the far u.v.



SCHEME 2

does not fall to zero. In acid solution we suggest that they react rapidly with more urea, or 1-methylurea, to give (2) or (3b), with elimination of more water. A suggested mechanism is shown in Scheme 2. In acid solution (8) is protonated and thus a good leaving group

(water) is formed which facilitates attack by urea. The alkylated nitrogen of urea is the more nucleophilic site and thus formation of (3b), rather than (3a), is rationalised. Reaction is completed by cyclisation, possibly by *N*-protonation and creation of a cationic centre on carbon. The driving force behind most the reactions described has been the elimination of water.

In the following paper we describe some reactions of 1-phenylpropane-1,2-dione with urea. The presence of the methyl group provides the molecule with a new reaction centre.

EXPERIMENTAL

Materials.—Urea, 1-methylurea, and 1,3-dimethylurea were recrystallised from ethanol before use.

Synthetic Method.—That for urea is typical of the procedure used. Urea (0.1 mol), benzil (0.05 mol), TFA (10 ml), and benzene (200 ml) were refluxed in a Dean and Stark apparatus until water production ceased (6 h). The product was filtered off as crystals and washed with ethanol. No suitable solvent for recrystallisation was found. 3a,7a-Diphenyltetrahydroimidazo[4,5-d]imidazole-2,5-dione (2) had m.p. 300°, $M^+ / 2$ 147, δ_C 87.02, 128.00, 130.36, 131.78, 135.26, and 165.73 p.p.m. (Found: C, 65.3; H, 4.7; N, 18.8. $C_{18}H_{14}N_4O_2$ requires C, 65.3; H, 4.8; N, 19.0%); 1,6-dimethyl-3a,7a-diphenyltetrahydroimidazo[4,5-d]imidazole-2,5-dione (3b) was recrystallised from ethanol, m.p. 306°, $M^+ / 2$ 322, δ_C 30.01, 84.06, 93.74, 128.17, 129.24, 130.05, 130.33, 130.69, 130.98, 131.37, 131.72, 135.78, and 164.63 p.p.m. (Found: C, 66.8; H, 5.7; N, 17.6. $C_{18}H_{18}N_4O_2$ requires C, 67.1; H, 5.6; N, 17.4%).

1,3-Dimethyl-5,5-diphenylhydantoin was obtained by the methylation of 5,5-diphenylhydantoin by the method of Olsen,⁶ m.p. 190°, $M^+ / 2$ 280, δ (toluene) 2.50 and 2.76. This material was identical with that obtained from the reaction of 1,3-dimethylurea and benzil.

Kinetic Method.—A small amount of an ethanolic solution of benzil was added to a solution of urea and HCl contained in a flask in a constant-temperature water bath. At timed intervals samples were removed and the absorbance at 265 nm measured on a Unicam SP 500 spectrophotometer. The values of k_{obs} were calculated by the method of Swinbourne.⁷

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