Mechanistic Studies in the Chemistry of Urea. Part 2.[1] Reaction with Benzil, 4,4′-Dimethylbenzil, and 4,4′-Dimethoxybenzil

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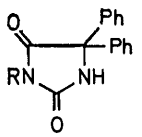
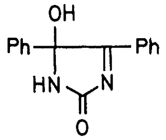
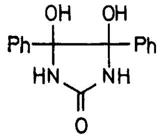
Urea and *N*-methylurea react with benzil and substituted benzils in alkaline conditions to form 5,5-diphenylhydantoins, or the appropriately substituted compounds. The mechanism of reaction is rate-determining attack by the urea anion on benzil, rapid cyclisation, and slow rearrangement. The mechanism was deduced from a kinetic study. With *NN*′-dimethylurea the product is a diol.

Although urea is generally considered an unreactive compound, it reacts readily with diketones. With pentane-2,4-dione the product is a pyrimidone and the mechanism of this reaction has been discussed in Part 1.[1] The reactions of α-diketones with ureas are more complex but one α-diketone which does give easily identifiable products is benzil. In this paper we report the mechanism of the reaction of urea, *N*-methylurea, and *NN*′-dimethylurea with benzil, 4,4′-dimethylbenzil, and 4,4′-dimethoxybenzil in alkaline conditions.

Biltz[2] reported that refluxing urea or *N*-methylurea with benzil in ethanol containing sodium hydroxide resulted in formation of 5,5-diphenylhydantoin (Ia) or 3-methyl-5,5-diphenylhydantoin (Ib). For the former reaction we confirmed that (Ia) was the product by comparison with a commercial sample. We prepared authentic samples of 1-methyl- and 3-methyl-5,5-diphenylhydantoin and found that the latter is identical with the product of reaction.


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


(II)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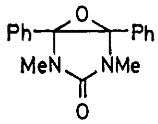
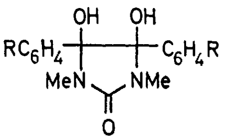
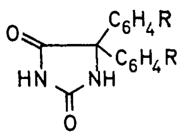
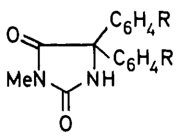

(IV)


(V) R = H
(VIII) R = *p*—Me
(XI) R = *p*—OMe


(VI) R = *p*—Me
(IX) R = *p*—OMe


(VII) R = *p*—Me
(X) R = *p*—OMe

Benzil is only slightly soluble in water in the absence of ethanol, but sufficient dissolves to give an absorbance at 257 nm suitable for a kinetic study. On addition of alkali there is, at 25°, a very slow decrease in this absorbance due to the benzilic acid rearrangement but it is incomplete after 5 h.[3] However, on addition of urea the absorbance decreases to *ca.* 1/3 of its initial value, where it remains essentially unchanged, within minutes. We thought it unlikely that this simple spectral change represents as complex a reaction as the formation of diphenylhydantoin from urea and benzil. Starting with ^{14}C-labelled urea, and by the use of an isotopic dilution technique, we found that no diphenylhydantoin had formed when the initial spectral change was complete. Benzil has such a low solubility in water that it was not possible to demonstrate this by isolation of the product. We believe, for reasons which will be described at various points in this paper, that the initial reaction is formation of (II), probably *via* the diol (III). Formation of the C=N bond in (II) explains why the absorbance at 257 nm does not fall to zero, which would be the case if reaction ceased on formation of the diol. Over a much longer time (many hours) this absorbance does decrease and formation of diphenylhydantoin was detected by an isotopic dilution experiment.

The kinetics of the initial reaction of urea and *N*-methylurea with benzil were examined in detail. In the presence of excesses of urea (or *N*-methylurea) and hydroxide ion the disappearance of benzil is a first-order reaction. The effects of changing the concentrations of urea and of hydroxide ion are shown in Tables 1 and 2. There is a linear relationship between k_{obs} and the concentration of urea; however, as [$^-$OH] is increased k_{obs} increases

Table 1

Kinetics of the reaction of urea and benzil at 25°

(a) [NaOH] = 0.50M						
[Urea]/M	0.020	0.040	0.060	0.080	0.01	
$10^2k_{obs}/s^{-1}$	0.51	1.07	1.51	2.09	2.89	
(b) [Urea] = 0.10M						
[NaOH]/M	0.020	0.060	0.080	0.10	0.20	0.25
$10^2k_{obs}/s^{-1}$	0.50	1.08	1.31	1.42	1.85	1.87
(c) [Urea] = 0.050M						
[NaOH]/M	0.050	0.10	0.15	0.20	0.25	
$10^2k_{obs}/s^{-1}$	0.47	0.67	0.87	0.93	0.91	
$[\text{Benzil}]_0$ = *ca.* 10^{-5}M						

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[1] Part 1, A. R. Butler and E. Leitch, *J.C.S. Perkin II*, 1976, 832.

[2] H. Biltz, *Ber.*, 1908, **41**, 1379.

[3] F. Westheimer, *J. Amer. Chem. Soc.*, 1936, **58**, 2209.

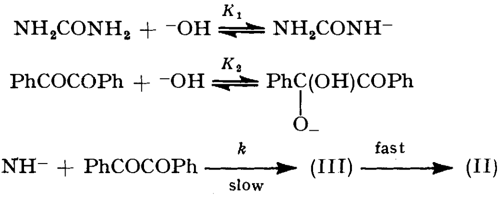
initially but reaches a maximum. Catalysis by hydroxide ion suggests attack by the anion of urea, while the effect of hydroxide ion at high concentration indicates removal of one reactant. We propose, therefore, the mechanism shown in Scheme 1, where the slow step is attack by urea anion on one carbonyl group of benzil. We know that cyclisation must be faster than attack from a study of the kinetics of reaction of *NN'*-dimethylurea (see later). If we make the very reasonable assumptions that K_1 is very small, but K_2 is much larger, then we can convert the rate equation (1) into (2), where $[\mathrm{PhCOCOPh}]_{\mathrm{st}}$ is the stoicheiometric concentration of benzil.

TABLE 2

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

(a) [NaOH] = 0.50M					
[Methylurea]/M	0.020	0.040	0.060	0.080	0.10
$10^2k_{\mathrm{obs}}/\mathrm{s}^{-1}$	0.23	0.50	0.73	0.88	1.16
(b) [Methylurea] = 0.10M					
[NaOH]/M	0.020	0.040	0.060	0.080	0.10
$10^2k_{\mathrm{obs}}/\mathrm{s}^{-1}$	0.25	0.41	0.54	0.59	0.66

$[\mathrm{Benzil}]_0 = ca.\ 10^{-5}\mathrm{M}$



$$\mathrm{NH_2CONH_2} + {}^{-}\mathrm{OH} \overset{K_1}{\rightleftharpoons} \mathrm{NH_2CONH^-}$$

$$\mathrm{PhCOCOPh} + {}^{-}\mathrm{OH} \overset{K_2}{\rightleftharpoons} \mathrm{PhC(OH)COPh}\ (\mathrm{O^-}\text{ on C})$$

$$\mathrm{NH_2CONH^-} + \mathrm{PhCOCOPh} \xrightarrow[\text{slow}]{k} (\mathrm{III}) \xrightarrow{\text{fast}} (\mathrm{II})$$

SCHEME 1

$$\begin{aligned}\text{rate} &= k(\mathrm{NH_2CONH^-})(\mathrm{PhCOCOPh}) \qquad (1)\\ &= kK_1[{}^{-}\mathrm{OH}][\mathrm{NH_2CONH_2}][\mathrm{PhCOCOPh}]_{\mathrm{st}}/(1 + K_2[{}^{-}\mathrm{OH}]) \qquad (2)\end{aligned}$$

The experimentally observed rate equation under the condition described above is (3), and combination of (2)

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

and (3) gives expression (4) for k_{obs} in terms of the

$$k_{\mathrm{obs}} = kK_1[{}^{-}\mathrm{OH}][\mathrm{NH_2CONH_2}]/(1 + K_2[{}^{-}\mathrm{OH}]) \qquad (4)$$

reaction scheme. This expression is in agreement with the experimental results. From (4) there should be a linear relationship between k_{obs} and the urea concentration. The effect of hydroxide ion on k_{obs} is more complex. At low $[{}^{-}\mathrm{OH}]$, where $K_2[{}^{-}\mathrm{OH}] \ll 1$, k_{obs} will be a linear function of $[{}^{-}\mathrm{OH}]$ but at high $[{}^{-}\mathrm{OH}]$, where $K_2[{}^{-}\mathrm{OH}] \gg 1$, k_{obs} becomes independent of $[{}^{-}\mathrm{OH}]$. This is what was observed. Rearrangement of (4) gives (5) and plots of $[\mathrm{urea}]/k_{\mathrm{obs}}$ against $1/[{}^{-}\mathrm{OH}]$, for both urea and *N*-methylurea, are linear (Figure 1).

$$[\mathrm{NH_2CONH_2}]/k_{\mathrm{obs}} = 1/kK_1[{}^{-}\mathrm{OH}] + K_2/kK_1 \qquad (5)$$

This linearity is confirmation of the proposed mechanism. The product intercept/slope is K_2, which should be independent of the urea used. The values obtained were 11.9 and 12.3 l mol^{-1} for urea and *N*-methylurea respectively.

The reaction is faster in heavy than in isotopically normal water, but the size of the kinetic isotope effect depends upon the concentration of the alkali. With $[{}^{-}\mathrm{OH}]$ and $[{}^{-}\mathrm{OD}]$ both equal to 0.234, 0.117, and 0.0585M the kinetic isotope effects were 0.75, 0.71, and 0.64. These results are consistent with the proposed mechanism. From (4) the kinetic isotope effect (k.i.e.) is given by (6), and so, clearly, the k.i.e. should vary with

$$\text{k.i.e.} = \frac{k_{\mathrm{obs}}^{\mathrm{H_2O}}}{k_{\mathrm{obs}}^{\mathrm{D_2O}}} = \frac{k^{\mathrm{H}}K_1^{\mathrm{H}}(1 + K_2^{\mathrm{D}}[{}^{-}\mathrm{OD}])}{k^{\mathrm{D}}K_1^{\mathrm{D}}(1 + K_2^{\mathrm{H}}[{}^{-}\mathrm{OH}])} \qquad (6)$$

the alkali concentration. The manner in which it does so depends upon the values of K_2^{D} and K_2^{H}, which are unknown.

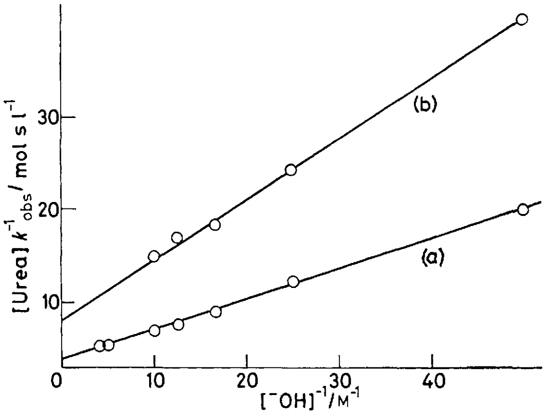


FIGURE 1 Plot of $[\mathrm{urea}]/k_{\mathrm{obs}}$ against $1/[{}^{-}\mathrm{OH}]$ for the reaction of (a) urea and (b) *N*-methylurea with benzil

So far we have not produced strong evidence that (II) is the significant intermediate in the formation of 5,5-diphenylhydantoin. The spectrum of the initial product of reaction has an absorbance at the same wavelength as the carbonyl group of benzil, but it is less intense. This suggests the presence of a PhC=O or PhC=N group and is consistent with the formation of (II). Efforts to isolate (II) were unsuccessful. We must now discuss the possible rearrangement of (II) to the hydantoin. Migration of a phenyl group in alkaline solution is reminiscent of the benzilic acid rearrangement. The generally accepted mechanism for this reaction is shown in Scheme 2.[4] If a proton is removed from (II) it may rearrange to the hydantoin by an exactly similar mechanism (Scheme 3). The driving force behind this rearrangement is undoubtedly formation of a carbonyl group at the 1-position. A methyl group at the 3-position does not impede the reaction, but formation of 1-methyl-5,5-diphenylhydantoin is impossible. This is consistent with the product formed from *N*-methylurea. If an intermediate other than (II) is proposed it is difficult to find a reasonable mechanism

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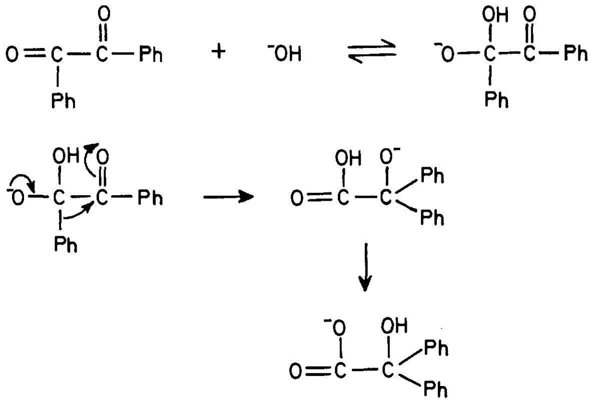
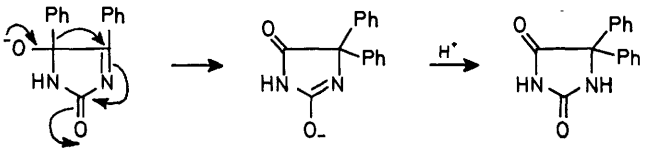
[4] I. Roberts and H. C. Urey, *J. Amer. Chem. Soc.*, 1938, **60**, 880.

for its rearrangement to the hydantoin. Such negative evidence is not compelling, but it has some force.

An examination of the reaction between benzil and *NN'*-dimethylurea is instructive. The product of reaction is not 1,3-dimethyl-5,5-diphenylhydantoin. This fact was established by comparison with an authentic sample of that compound. Biltz [2] suggested that the product is (IV) and the molecular ion peak in the mass spectrum is in agreement with this. Also, there is evidence in the ^{1}H n.m.r. spectrum for only one type of methyl group (there would be two in the corresponding hydantoin) and only one peak in the region 1 600—1 800 cm^{-1} of the i.r. spectrum, indicating only one carbonyl group in the compound. However, the elemental analysis for the product is not consistent with (IV); it corresponds to the diol (V) (see Table 7). This does not affect the evidence for ^{1}H n.m.r. and i.r. spectra and the peak in the mass spectrum could be (M — H_2O). So we believe that the product of reaction is the diol (V). The fact that (V) does not rearrange to the hydantoin is easy to understand on the basis of the mechanism in Scheme 3, as (V) cannot eliminate water to give a compound analogous to (II). This is support for the intermediacy of (II).



SCHEME 2



SCHEME 3

Spectral changes accompanying the reaction of *NN'*-dimethylurea are different from those for urea and *N*-methylurea. The absorbance in the far u.v. disappears completely as no PhC=N group is generated. However, the kinetics of the consumption of benzil show the same pattern as the reactions involving urea or *N*-methylurea (Table 3). A plot of [dimethylurea]/k_{obs} against 1/[$^-$OH] is linear (Figure 2) and it is reasonable to deduce that urea, *N*-methylurea, and *NN'*-dimethylurea react with benzil with the same rate-determining step. If this is considered along with the spectral changes involved, the only possibility is slow attack by the urea anion followed by rapid cyclisation. For urea and *N*-methylurea cyclisation is accompanied by elimination of water. Cyclisation cannot be the slow step as this would necessitate a rapid decrease in absorbance in the far u.v. (due to reaction at one carbonyl group)

TABLE 3

Kinetics of the reaction of *NN'*-dimethylurea and benzil at 25°

(a) [NaOH] = 0.50M

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

(b) [Dimethylurea] = 0.50M

[NaOH]/M	0.020	0.060	0.10	0.20	0.30	0.50
10^2k_{obs}/s^{-1}	0.20	0.44	0.55	0.73	0.89	1.13

[Benzil]$_0$ = *ca.* 10^{-5}M.

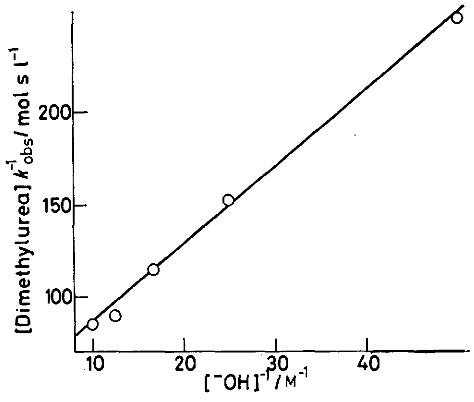


FIGURE 2 Plot of [dimethylurea]/k_{obs} against 1/[$^-$OH] for the reaction of *NN'*-dimethylurea with benzil

TABLE 4

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

(1) Urea

(a) [NaOH] = 0.50M

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

(b) [Urea] = 0.25M

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

(2) *N*-Methylurea

(a) [NaOH] = 0.50M

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

(b) [Methylurea] = 0.50M

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

(3) *NN'*-Dimethylurea

(a) [NaOH] = 0.50M

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

(b) [Dimethylurea] = 1.00M

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

followed by a slower spectral change corresponding to cyclisation. This does not occur.

We examined the reactions of urea, N-methylurea, and NN'-dimethylurea with 4,4′-dimethyl- and 4,4′-dimethoxy-benzil. The products of reaction were the expected hydantoins or, in the case of NN'-dimethylurea, the diols. Details of the kinetics of reactions are given in Tables 4 and 5. The kinetic pattern is the same as that for benzil and in all cases plots of [urea]/k_{obs} against 1/[$^-$OH] were linear. This indicates that the mechanism of reaction is unchanged.

TABLE 5

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

(1) Urea					
(a) [NaOH] = 0.50M					
[Urea]/M	0.020	0.040	0.060	0.080	0.10
$10^2k_{obs}/s^{-1}$	0.30	0.68	1.02	1.36	1.93
(b) [Urea] = 0.10M					
[NaOH]/M	0.10	0.20	0.30	0.40	0.50
$10^2k_{obs}/s^{-1}$	0.89	1.27	1.56	1.80	1.89
(2) N-Methylurea					
(a) [NaOH] = 0.50M					
[Methylurea]/M	0.10	0.20	0.30	0.40	0.50
$10^2k_{obs}/s^{-1}$	0.85	2.03	3.38	5.12	6.45
(b) [Methylurea] = 0.50M					
[NaOH]/M	0.10	0.20	0.30	0.40	0.50
$10^2k_{obs}/s^{-1}$	2.06	3.60	4.76	5.58	6.45
(3) NN'-Dimethylurea					
(a) [NaOH] = 0.50M					
[Dimethylurea]/M	0.10	0.20	0.30	0.40	0.50
$10^3k_{obs}/s^{-1}$	1.92	3.48	5.15	6.27	8.12
(b) [Dimethylurea] = 0.50M					
[NaOH]/M	0.10	0.20	0.30	0.40	0.50
$10^3k_{obs}/s^{-1}$	2.45	4.30	5.42	6.48	8.12

As described previously, values of K_2 can be calculated from the kinetic data and, for each benzil, should be independent of the urea. The values obtained are shown in Table 6 and are consistent with this prediction. The effect of substituents on K_2 is that expected for electron-donating substituents in a reaction involving attack by an anion. We cannot explain the value obtained for 4,4′-dimethylbenzil from its reaction with urea. The slope of a plot of [urea]/k_{obs} against 1/[$^-$OH] is $1/kK_1$ and thus, using the same urea (K_1 constant), it is possible to calculate the effect of a substituent on the value of k. The ratios $k^{Me}:k^{H}$ and $k^{OMe}:k^{H}$ calculated from the data are given in Table 6. They are internally consistent and consistent with attack by an anion as the rate-determining step. Thus, substituent effects are in complete agreement with the proposed reaction scheme.

TABLE 6

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

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

EXPERIMENTAL

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

A similar procedure was used with N-methyl- and NN'-dimethyl-urea and with the substituted benzils. With NN'-dimethylurea the products precipitated only after standing for some time and were recrystallised, with difficulty, from dimethyl sulphoxide. All the compounds obtained gave elemental analyses and mass spectra corresponding to the expected hydantoin or diol. Physical data for all these compounds are collected in Table 7.

TABLE 7

Physical data for new compounds

Compound	M.p. (°C)	Found (%) C	H	N	Formula	Required (%) C	H	N	Molecular ion peak
(Ia)	286	71.4	4.7	11.2	$C_{15}H_{12}N_2O_2$	71.4	4.8	11.1	252
(Ib)	204	72.1	5.1	10.1	$C_{16}H_{14}N_2O_2$	72.2	5.3	10.5	266
(V)	190	68.2	6.2	9.6	$C_{17}H_{18}N_2O_3$	68.4	6.1	9.4	298 (M − 18)
(VI)	230	72.6	5.8	10.1	$C_{17}H_{16}N_2O_2$	72.8	5.8	10.1	280
(VII)	189	72.5	6.2	9.3	$C_{18}H_{18}N_2O_2$	73.5	6.2	9.5	294
(VIII)	169	69.0	6.8	8.3	$C_{19}H_{22}N_2O_3$	69.9	6.8	8.6	308 (M − 18)
(IX)	225	64.6	5.1	8.8	$C_{17}H_{16}N_2O_4$	65.4	5.2	9.0	312
(X)	151	65.2	5.4	8.4	$C_{18}H_{18}N_2O_4$	66.3	5.6	8.6	326
(XI)	159	63.1	6.1	7.1	$C_{19}H_{22}N_2O_5$	63.7	6.2	7.8	340 (M − 18)

1-Methyl-5,5-diphenylhydantoin was prepared from 5,5-bisphenylthiohydantoin by the method of Cattelain and Chabrier,[5] m.p. 212°. The methyl peak in the ^{1}H n.m.r. spectrum was a singlet at δ 2.92 (Me$_2$SO).

3-*Methyl*-5,5-*diphenylhydantoin*.[6]—A mixture of diphenylglycine (2.5 g), methyl isocyanate (0.81 g), and NaOH (0.38 g) was stirred for 2 h. After filtration the filtrate was

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[5] E. Cattelain and P. Chabrier, *Bull. Soc. chim. France*, 1947, **14**, 639.

[6] C. J. West, *J. Biol. Chem.*, 1918, **34**, 187.

acidified. The 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° (Found: C, 72.1; H, 5.3; N, 10.4. $C_{16}H_{14}N_2O_2$ requires C, 72.2; H, 5.3; N, 10.5%). The methyl peak in the ^1H n.m.r. spectrum was a singlet at δ 3.06 ($CDCl_3$).

The product from the reaction of methylurea and benzil melted at 208° and the ^1H n.m.r. spectrum was the same as that of 3-methyl-5,5-diphenylhydrantoin. Identity was confirmed by a mixed m.p.

1,3-*Dimethyl*-5,5-*diphenylhydantoin* was prepared by the reaction of methyl iodide with 5,5-diphenylhydantoin.[7] The product was recrystallised from ethanol, m.p. 190° (Found: C, 73.0; H, 5.7; N, 10.2. $C_{17}H_{16}N_2O_2$ requires C, 72.8; H, 5.8; N, 10.0%). The methyl groups produced two singlets in the ^1H n.m.r. spectrum, δ 2.50 and 2.76.

The product of reaction of benzil and dimethylurea melted at 190° and had a single peak in the ^1H n.m.r. due to the methyl groups, δ 2.59. Mixed m.p. confirmed that the 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 μCi g^{-1}; 0.3 g) in 0.1M-NaOH (50 ml) and allowed to react for 0.5 h at room temperature. After addition of HCl (5M; 1 ml) to stop the reaction 5,5-diphenylhydantoin (0.2 g) was added and the mixture stirred for 1 h. The hydantoin was filtered off, washed thoroughly, and recrystallised from ethanol to a constant activity. For radioactive counting the material was dissolved in dioxan and the scintillators were naphthalene and PPO with a counting efficiency of 50%. The sample of diphenylhydantoin obtained had an activity of 86.1 count s^{-1} mol^{-1}.

Assuming that all the benzil had been converted into 5,5-diphenylhydantoin during this part of the reaction, the activity would have been 1.75×10^6 count s^{-1} mol^{-1}. In a second experiment the mixture was allowed to stand overnight before neutralisation and the hydantoin isolated had an activity of 4.04×10^4 count s^{-1} mol^{-1}, indicating that conversion to the hydantoin occurs in a much slower process. The quenching, and hence the counting efficiency, was determined by counting a sample of hexadecane of known activity in the same solution in the presence of 5,5-diphenylhydantoin. The counter used was a Beckman LS100. These experiments show clearly that disappearance of the benzil does not correspond to production of hydantoin and indicates formation of a stable intermediate.

Kinetic Method.—The rates were determined by monitoring the decrease in absorbance due to benzil. One drop of 0.2% solution of benzil (or substituted benzil) in ethanol was added to solution of urea in aqueous NaOH contained in a cuvette in a thermostatted holder of a Unicam SP 700 spectrophotometer. The wavelengths used were as follows: benzil (257 nm), 4,4′-dimethylbenzil (278 nm), and 4,4′-dimethoxybenzil (304 nm). The rate constants were calculated by the method of Swinbourne.[8]

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