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Photochemical Hydrolysis of Barbitals[*1]

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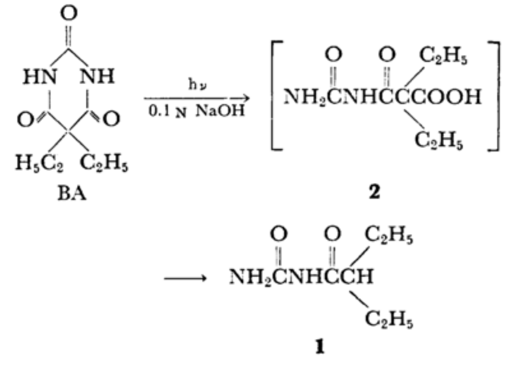
The irradiation of barbital (BA) and *N,N'*-dimethylbarbital (DMBA) in aqueous alkaline media gave diethylacetylurea and *N,N'*-dimethyldiethylmalonamide respectively. On the basis of the results of kinetic studies, the above photochemical hydrolyses of BA and DMBA were shown to be an attack of the hydroxide ion on the singlet excited states of BA monoanion and DMBA respectively. Such nucleophilic reagents as amines, mercaptide, and cyanide ions retarded the photochemical hydrolyses by quenching the excited state of the substrates.

A few examples of photochemical solvolysis reactions have hitherto been reported in the literature. Zimmerman and his co-workers1) have observed that certain benzyl acetates and trityl ethers are readily solvolyzed upon irradiation in aqueous media. Havinga and his co-workers2) have reported that the hydrolysis of certain aromatic phosphate and sulfate esters is accelerated by light. Recently, Barltrop and Schofield3) have found that the substituted aromatic carbamate esters of glycine are hydrolyzed upon the irradiation of the aqueous solutions. The driving force of these photochemical solvolysis reactions has been supposed to be a decrease in electron density around the reaction center through the $\pi \rightarrow \pi^*$ excitation process of aromatic compounds.4)

During the course of our studies of the chemistry of barbitals, we found that barbital is readily hydrolyzed to diethylacetylurea upon the irradiation of its aqueous sodium hydroxide solution with ultraviolet light. This photochemical reaction constitutes a very rare example of a photochemical solvolysis in which an aromatic ring is not involved as an entity of the excitation. This paper will describe our investigation of the photochemical reactions of barbital and its derivatives in aqueous media.

Results and Discussion

Photoproducts. When a solution of barbital (BA) in a 0.1 N aqueous sodium hydroxide was irradiated with a low-pressure mercury arc at room temperature, crystals gradually appeared on the wall of the reaction vessel. After several hour's irradiation, the collection of the deposited crystals and their recrystallization gave diethylacetylurea (**1**) in a 95% yield. The structure of the compound **1** was confirmed by a comparison of its physicochemical properties with those of an authentic sample and by elemental analysis. However, even when the solution was heated at 80°C in the dark for two periods of time the same as the light reaction period, the starting material was recovered in an almost quantitative yield. These facts clearly demonstrate that the hydrolysis of barbital is accelerated by irradiation with ultraviolet light. The urea, **1**, is supposed to be formed by the attack of the hydroxide ion on the carbonyl carbon atom at the 4 position of BA. The first intermediate produced by this reaction would be the keto acid (**2**). This keto acid **2** might be unstable under the reaction conditions and might be decomposed spontaneously to the isolable product **1.**



BA

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[*1] This paper constitutes Part I of a series of papers entitled "Photochemistry of Heterocyclic Compounds."

1) H. E. Zimmerman and S. Somasekhara, *J. Am. Chem. Soc.*, **85**, 922 (1963); H. E. Zimmerman and V. E. Sandel, *ibid.*, **85**, 915 (1963).

2) E. O. Havinga, R. O. de Jongh and W. Dorst, *Rec. Trav. Chim.*, **75**, 378 (1956); E. O. Havinga, *Chimia*, **16**, 145 (1962); D. A. de Bie and E. O. Havinga, *Tetrahedron*, **21**, 2359 (1965).

3) J. A. Barltrop and P. Schofield, *J. Chem. Soc.*, **1965**, 4758.

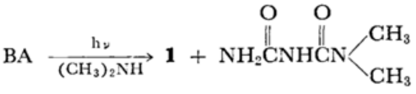
4) For a list and the mechanism of such reactions, see D. C. Nechers, "Mechanistic Organic Photochemistry," Reinhold Publishing Co., New York, N. Y. (1967), pp. 253—260.

TABLE 1. THE PHOTOREACTION PRODUCTS OF BA IN THE PRESENCE OF VARIOUS NUCLEOPHILIC REAGENTS

Irradiated compound	Nucleophile	Product	Yield %	Irradiation time, hr
BA	0.1 N NaOH	Diethylacetylurea	95	14
	$(CH_3)_2NH$	Diethylacetylurea	35	66
		N,N-Dimethylbiuret	35	
	$C_2H_5NH_2$	Diethylacetylurea	30	66
	KCN	Diethylacetylurea	75	110
	C_2H_5SNa	Diethylacetylurea	—	90
DMBA	0.1 N NaOH	*N,N'*-Dimethyldiethylmalonamide	67	68

Since we suspected that this photochemical hydrolysis would have the nature of a nucleophilic solvolysis of BA, the photoreactions of BA were undertaken in the presence of various nucleophilic reagents. The results are summarized in Table 1.

No photochemical reaction was observed upon the irradiation of BA in water or in an aqueous hydrochloric acid, BA being recovered in both cases. The irradiation of an aqueous solution of BA in the presence of ethylamine, potassium cyanide, and sodium ethylmercaptide produced the same product, diethylacetylurea, as that obtained in the photoreaction of BA and sodium hydroxide. However, when an aqueous solution of BA in the presence of dimethylamine was irradiated, a 1 : 1 mixture of the urea **1** and *N,N*-dimethylbiuret (**3**) was obtained in a 70% yield.



$$BA \xrightarrow[(CH_3)_2NH]{h\nu} \mathbf{1} + NH_2\overset{O}{\overset{\|}{C}}NH\overset{O}{\overset{\|}{C}}N\begin{matrix}CH_3\\CH_3\end{matrix}$$

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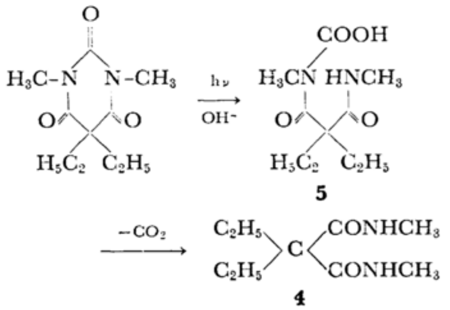
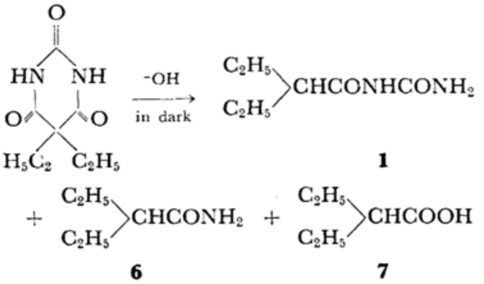
Unfortunately, the mechanism of the formation of the biuret, **3**, could not be elucidated in this investigation; therefore, it will not be discussed further here.

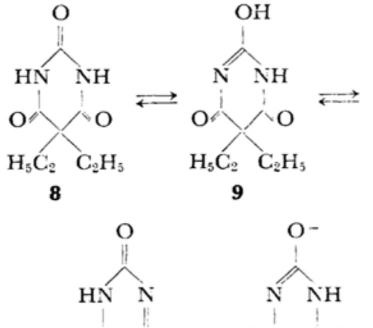
The photoreaction of *N,N'*-dimethyl barbital (DMBA) was also investigated. The irradiation of a suspension of DMBA in a 0.1 N aqueous sodium hydroxide with stirring afforded *N,N'*-dimethyl diethyl malonamide (**4**) in a 67% yield. This compound is supposed to be formed by the attack of the hydroxide ion on the carbonyl carbon at the 2 position of DMBA.



The hydrolysis of BA has been known to proceed with some difficulty in the dark to give **1** along with diethylacetamide (**6**) and diethylacetic acid (**7**), the relative yields of these compounds depending on the reaction conditions.[5] For this reason, the photochemical reactions reported in this paper will provide a convenient method for the preparation of the compounds of the **1**, **6**, and **7** types.



Light-absorbing Species during the Photochemical Hydrolysis of BA and DMBA. There exist tautomeric equilibria for BA in an aqueous solution; the plausible tautomeric forms include **8**, **9** and **10**, among others:



Sato[6] has concluded, on the basis of his molecular orbital calculations, that **9** is the most likely form in

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[5] a) H. Ruhkopf, *Ber.*, **73**, 938 (1940); b) E. H. Volwiler and D. L. Tabern, *J. Am. Chem. Soc.*, **58**, 1352 (1936); c) M. Freifelder, A. O. Geiszler and G. E. Stone, *J. Org. Chem.*, **26**, 203 (1961).

[6] Y. Sato, *Nippon Kagaku Zassi (J. Chem. Soc. Japan, Pure Chem. Sect.)*, **78**, 924 (1957).

an aqueous solution. Furthermore, since $pK_1=7.85$ and $pK_2=12.7$ for BA,[7] BA would exist exclusively in the form of a monoanion of **9**, *i. e.*, **11** in a 0.1 N sodium hydroxide solution (pH ~11.3), in which most of the present experiments were carried out.

The spectral properties of BA were also studied in some detail. Figure 1 shows the ultraviolet spectra of $\sim 1\times 10^{-4}$ M of BA in buffered aqueous solutions of various pH values. The absorbance at an absorption maximum of 240 mμ, As_{240}, decreased with a decrease in the pH values of the solutions. When As_{240} values were plotted against the concentrations of the monoanion of BA (BA^-) present in the solutions (the concentrations of BA^- were calculated from the pK_a of BA), a straight line passing through the origin was obtained, as is shown in Fig. 2. These results indicate that the only species which shows the absorption at 240 mμ is BA^-. From the data in Fig. 2, the molar extinction coefficient of BA^- was calculated to be 1.03×10^4.

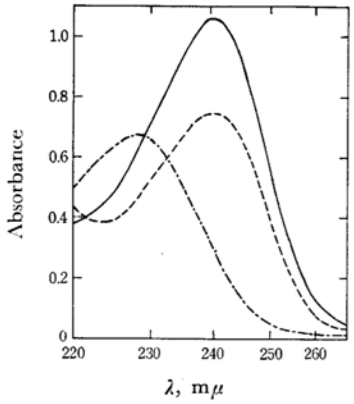

Fig. 1. Absorption spectra of BA and DMBA.
—— BA in 2×10^{-4} M NaOH
·—· DMBA in 2×10^{-4} M NaOH
---- BA in buffer solution at pH 8.27

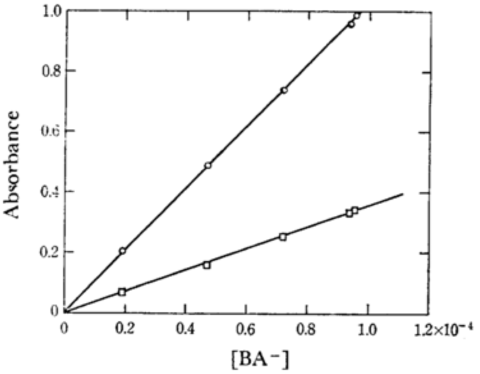

Fig. 2. Plots of absorbance *vs.* concentration of BA^-.
-○- at λ 240 mμ -□- at λ 254 mμ

The hydrolysis products of BA have no appreciable absorption at ≧240 mμ under the present reaction conditions, and the illuminating light used in our experiments was practically that of the wavelength at 254 mμ. Therefore, the above results also indicate that the only light-absorbing species during the photochemical hydrolysis of BA in an aqueous solution (pH>7.0) is BA^-.

The light-absorbing species of DMBA during the photochemical hydrolysis is apparently DMBA itself, since DMBA does not exhibit the tautomeric equilibria and its absorption maximum lies at 229 mμ ($\varepsilon_{229}=6.74\times 10^3$); also, the hydrolysis products of DMBA has no absorption at ≧229 mμ under the present reaction conditions.

Kinetic Studies. In order to get some clue to the mechanism of the photochemical hydrolysis, kinetic studies of the hydrolysis of BA in the aqueous solutions were made under a variety of conditions.

If the rate of hydrolysis of BA is assumed to be proportional to the light intensity absorbed by BA^- (the only light-absorbing species present in the reaction system), then the rate of the reaction (and, hence, the rate of the disappearance of BA^-) is given by Eq. (1):

$$-d[BA^-]/dt = \Phi K I_{abs} \tag{1}$$

where Φ is the quantum yield for the reaction, and where K is a unit conversion factor which transforms the number of photons absorbed per second into moles per liter per photons absorbed. I_{abs} is expressed in terms of Lambert and Beer's law:

$$I_{abs} = I_0(1 - e^{-\varepsilon[BA^-]d}) \equiv I_0 A \tag{2}$$

where I_0 is the incident light intensity, ε is the molar extinction coefficient of BA^- at the wavelength band incoming from the illuminating light source, and d is the thickness of the reaction vessel through which the incident light passes. The combination of Eqs. (1) and (2), and the integration of the resulting equation, lead to:

$$[BA^-]_t + (\ln A)_t/\varepsilon d = -\Phi K I_0 t + C \tag{3}$$

where C is the integration constant.

If our assumption is correct, the plot of the values on the left side of Eq. (3) against the time should give a straight line. Thus, the relative quantum yield, Φ', defined by Eq. (4) can be calculated from the slope of the straight line:

$$\Phi' = \Phi K I_0 \tag{4}$$

In our experiments the values of $[BA^-]_t$, the concentrations of BA^- at a given time, t, were determined from the readings of As_{240} (see the previous section):

$$[BA^-]_t = (As_{240})_t/\varepsilon_{240} \tag{5}$$

The term of $(\ln A)_t/\varepsilon d$ was calculated by the use of Eq. (6):

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[7] Y. Sato, *ibid.*, **78**, 382 (1957).

$$(\ln A)_t/\varepsilon d = 2.303 \log (1 - e^{-\varepsilon [BA^-]_t d})/\varepsilon d \qquad (6)$$

$\varepsilon = 3.55 \times 10^3$ was obtained from the data represented in Fig. 1 as the molar extinction coefficient of BA^- at 254 mμ (see the previous section and also the Experimental section). The d was measured as 3.5 cm.

The rate measurements for the hydrolysis of BA were carried out in buffered aqueous solutions of various pH values and in a 0.1 N sodium hydroxide solution. The plot of the $[BA^-]_t + (\ln A)_t/\varepsilon d$ function against the time furnished a straight line in every case. Typical data are shown in Fig. 3. The relative quantum yields, Φ', calculated from the slopes of the straight lines are summarized in Table 2. When a reciprocal of Φ' was plotted against a reciprocal of the hydroxide ion concentration, a straight line was obtained, as is shown in Fig. 4. This result demonstrates that the hydroxide ion may be involved in the rate-determining step of the reaction.

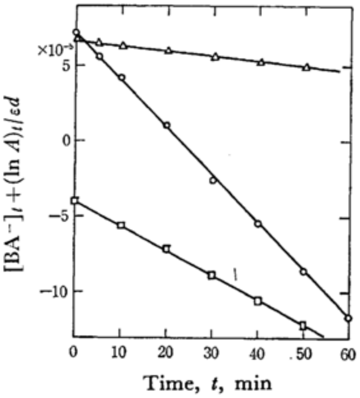


Fig. 3. Plots of Eq. (3) for BA^-.
-○- Reaction in 0.1 N NaOH
-△- Reaction in an aqueous solution containing dimethylamine
-□- Reaction in buffered solution at pH 7.70

Table 2. Relative quantum yield, Φ'

I) Φ' for BA in aqueous solutions at various pH values

pH	$1/[OH^-]$	Φ'	$1/\Phi'$
7.70	200×10^4	1.47×10^{-6}	6.80×10^5
8.03	58.1×10^4	2.29×10^{-6}	4.38×10^5
8.46	34.7×10^4	2.59×10^{-6}	3.87×10^5
8.87	13.5×10^4	2.83×10^{-6}	3.53×10^5
9.50	3.16×10^4	3.01×10^{-6}	3.32×10^5

II) Φ' for the reactions of BA and DMBA with various nucleophiles

Irradiated compound	Nucleophile	Concn. mol/l	Φ'
BA	NaOH	2×10^{-4}	3.18×10^{-6}
	NaOH	2×10^{-4}	3.13×10^{-6}*
	C_2H_5SNa	3×10^{-3}	3.01×10^{-6}
	KCN	1×10^{-2}	2.79×10^{-6}
	KCN NaOH	1×10^{-2} 2×10^{-4}	2.85×10^{-6}
	$C_2H_5NH_2$	1×10^{-2}	0.552×10^{-6}
	$C_2H_5NH_2$ NaOH	1×10^{-2} 2×10^{-4}	0.552×10^{-6}
	$(CH_3)_2NH$	1×10^{-2}	0.333×10^{-6}
	$(CH_3)_2NH$ NaOH	1×10^{-2} 2×10^{-4}	0.333×10^{-6}
DMBA	NaOH	2×10^{-4}	0.367×10^{-6}

* This value was obtained under bubbling nitrogen.

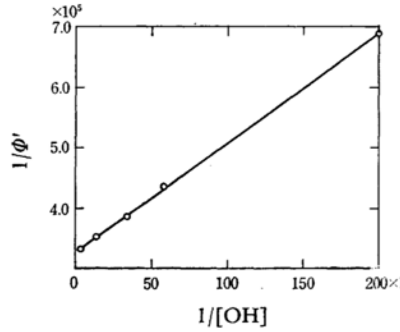


Fig. 4. Plot of $1/\Phi'$ *vs.* $1/[^-OH]$ in the photochemical hydrolysis of BA^-.

The rates of the photochemical reactions of BA with various nucleophiles were also measured. The shapes of the spectra of BA in the presence of nucleophiles were similar to those in the buffered solutions represented in Fig. 1. Thus, the rates of the disappearance of BA^- were followed by measuring the As_{240} of BA^-, and the relative quantum yields were obtained as has been described for the reactions in the buffered solutions. A typical datum is shown in Fig. 3, while the results are summarized in Table 2. The Φ' decreased in the order of hydroxide ion $\geq$ sodium mercaptide $\geq$ potassium cyanide $>$ ethylamine $>$ dimethylamine. However, when the reactions of BA with various nucleophiles were carried out in the presence of sodium hydroxide, the relative quantum yields of the reactions remained at the same values as those in the absence of sodium hydroxide, as is shown in Table 2. This observation can be explained by noting that the excited state of BA^- may be partially quenched in a characteristic manner determined by the nature of the nucleophiles, and that the only attacking reagent in these photochemical reactions is actually the hydroxide ion, which does not practically quench the excited state of BA^- and which would have its strongest affinity for the excited state of BA^-.

A further important observation was that when the photochemical hydrolysis of BA in 0.1 N sodium hydroxide was carried out in a nitrogen stream, no change in the relative quantum yields was observed (Table 2). This finding suggests that the photochemical hydrolysis of BA starts directly from its singlet excited state.

A kinetic study of the photochemical hydrolysis of DMBA was also made in a 0.1 N sodium hydroxide solution. The rate was measured by following the decrease in the As_{229} of DMBA. The relative quantum yield was obtained by the use of Eqs. (3) and (4). In this case ε was estimated to be 2.02×10^2 from the spectral data (ε was taken to be equal to the molar extinction coefficient of DMBA at 254 mμ under the present reaction conditions). The approximate ratio of the relative quantum yield of BA^- to DMBA was 1 : 0.1 (see Table 2).

Mechanistic Pathways. The results and discussion presented earlier suggest that the pathways outlined in Chart 1 are involved in the photochemical hydrolysis reactions of BA in aqueous solutions. The symbols used in Chart 1 have the usual meanings, while Q represents any quencher participating in the reactions. The reactions probably start from the singlet excited state of BA^- (BA^{-*}). The BA^{-*} reacts with hydroxide ion to give a 1 : 1 complex of the type X. The complex may be formed by the addition of the hydroxide ion to the carbonyl carbon atom at the 4 position rather than the 2 position of BA^-, since the accumulation of a negative charge around the carbonyl group at the 2 position prevents the addition of the hydroxide ion to that group. The complex thus formed collapses spontaneously to the hydrolyzed product, **1**, through the keto acid, **2**. The nucleophilic reagents other than hydroxide ion act as quenchers for BA^{-*} and partially prevent the formation of the complex.

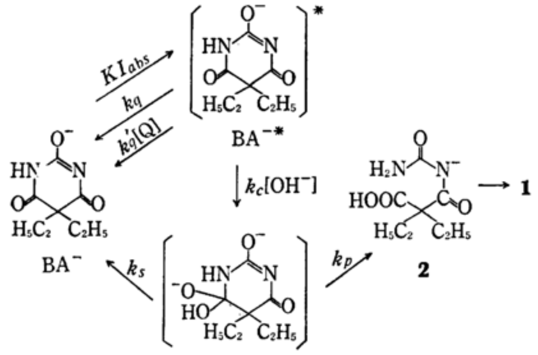


Chart 1

Making the usual steady-state assumption for BA^{-*} and the complex X, the rate equation (7) can be obtained from the above reaction scheme:

$$-\frac{d[BA^-]}{dt} = \frac{d(\mathbf{2})}{dt} = \frac{k_c k_p[^-OH]KI_{abs}}{(k_s+k_p)[k_q+k'_q[Q]+k_c[^-OH]]} \qquad (7)$$

The quantum yield and the relative quantum yield defined in this investigation for the disappearance of BA^- become, then, Eqs. (8) and (9) respectively:

$$\Phi = \frac{k_c k_p[^-OH]}{(k_s+k_p)[k_q+k'_q[Q]+k_c[^-OH]]} \qquad (8)$$

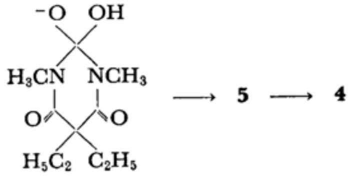
$$\Phi' = \frac{k_c k_p[^-OH]}{(k_s+k_p)[k_q+k'_q[Q]+k_c[^-OH]]} \times KI_0 \qquad (9)$$

When $[Q] \simeq 0$, *i.e.*, when the photochemical hydrolysis is carried out in buffered solutions, the relation of Eq. (10) is obtained:

$$\frac{1}{\Phi'} = \frac{1}{KI_0}\frac{k_s+k_p}{k_p} + \frac{k_q(k_s k_p)}{k_c k_p[^-OH]} \qquad (10)$$

Our observations are consistent with this theoretical relationship (see Fig. 4). Since at present we do not have much information about the quenching ability of the nucleophiles, no detailed discussion is given in this paper. However, amines are often known to act as effective quenchers of excited-state molecules.

In the case of DMBA, the reaction proceeds similarly except that a complex of the type of (**12**) may be formed between the carbonyl carbon atom at the 2 position and the hydroxide ion. There is no reason for preventing the addition of the hydroxide ion to that position, because no tautomeric equilibrium exists in this compound and, hence, no accumulation of negative charge around the carbonyl group at the 2 position can be expected. The complex thus produced collapses to the expected product.



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Experimental

The melting points are uncorrected. The infrared spectra were recorded with a Hitachi EPI-S2 infrared spectrometer. The ultraviolet spectra were obtained with a Hitachi recording spectrophotometer. The microanalysis were performed with a Yanagimoto MT-1 CHN Corder.

Materials. Barbital (BA) was of a Nakarai reagent grade and was purified by recrystallization from ethanol before use. *N,N'*-Dimethylbarbital (DMBA) was prepared by the method of Dox.[8] The other reagents were purchased from various companies and were purified by recrystallization or distillation.

Photochemical Hydrolysis of Barbital (BA). A solution of 500 mg of BA in 100 m*l* of 0.1 N aqueous sodium hydroxide in a quartz vessel was irradiated for 14 hr with a 15-W low-pressure mercury arc placed at

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[8] W. Dox, *J. Am. Chem. Soc.*, **58**, 1633 (1936).

a distance of 10 cm. During irradiation, the product deposited out on the surface of the vessel as crystals. After irradiation, the crystals thus produced were collected by filtration and recrystallized from ethanol, mp 205—206°C. The product, 400 mg (95%), was identified as diethylacetylurea by the elemental analysis and by comparison with an authentic sample prepared by the method of Volwiler and Tabern,[9] which was found to be identical in every respect.

Found: C, 53.29; H, 9.17; N, 17.81%. Calcd for $C_7H_{14}N_2O_2$: C, 53.14; H, 8.92; N, 17.71%.

An aqueous solution of BA containing ethylamine, potassium cyanide, or sodium ethylmercaptide was irradiated similarly. The product isolated was diethylacetylurea in all of the above cases.

A solution containing 1 g of BA, 5 m*l* of 40% dimethylamine, and 100 m*l* of water was also irradiated in a similar manner. After 66 hrs' irradiation, the crystals which had deposited on the surface of the vessel were collected by filtration and identified as diethylacetylurea. The filtrate was evaporated to dryness under reduced pressure; the recrystallization of the residue gave 250 mg (35%) of *N,N*-dimethylbuiret, mp 170—171°C. The structure of this compound was confirmed by the elemental analysis and by comparison with an authentic sample prepared by the method of Davis and Blanchard,[10] which was found to be identical in every respect.

Found: C, 36.89; H, 7.14; N, 32.02%. Calcd for $C_4H_9N_3O_2$: C, 36.63; H, 6.92; N, 32.05%.

Hydrolysis of Barbital in the Dark. A solution of 500 mg of BA in 30 m*l* of 0.1 N aqueous sodium hydroxide was allowed to stand at 80°C for 17 hr. The mixture was then acidified with a dilute hydrochloric acid under cooling. The precipitated crystals were collected by filtration and found to be barbital. The evaporation of the filtrate also gave barbital. The total amount of barbital recovered was 350 mg (70%).

Photochemical Hydrolysis of *N,N'*-Dimethylbarbital (DMBA). Since the solubility of DMBA in water was too small to make a homogeneous aqueous solution with a relatively high concentration, the experiment was carried out as follows. A mixture of 1.2 g of DMBA in 100 m*l* of 0.1 N aqueous sodium hydroxide in a quartz vessel, where a small amount of DMBA remained insoluble as an oil, was irradiated in a manner similar to that described above, while being stirred with a magnetic stirrer. The oil, DMBA, went into solution with irradiation. After 68 hr's irradiation, although a very small amount of the oil still remained insoluble, the reaction mixture was neutralized with a dilute hydrochloric acid, and extracted with ether and then with chloroform. Both extracts were dried over sodium sulfate. The evaporation of the ether extract gave 100 mg (8%) of the starting materials, DMBA. The evaporation of the chloroform extract under reduced pressure afforded, after recrystallization from benzene, 0.7 g (67%) of *N,N'*-dimethylmalonamide; mp 149—150°C, IR 3300, 1650, 1530 cm^{-1} (KBr).

Found: C, 58.07; H, 9.91; N, 14.80%. Calcd for $C_9H_{18}N_2O_2$: C, 58.03; H, 9.74; N, 15.04%.

A mixture of 1.1 g of DMBA in 100 m*l* of water was irradiated for 63 hr in a manner similar to that described above. When the mixture was then worked up similarly, the starting material, DMBA, was recovered in almost a quantitative yield.

Kinetic Measurements. An aqueous solution (100 m*l*, 10^{-4} M) of BA or DMBA was placed in a quartz tube of 3.5 cm in diameter and 10 cm long. The solutions were irradiated at room temperature with a 15 W low-pressure mercury arc placed 30 cm from the samples. Four-m*l* portions of the solutions were pipetted into a spectrophotometric cell at intervals. The hydrolysis rates for the samples were followed by measuring the decreases in the absorbance at 240 mμ in the case of the BA's, and at 229 mμ in the case of the DMBA's with a Hitachi Perkin-Elmer 139 UV-Vis spectrophotometer. Special care was taken to fix a relative position between the reaction vessel and the light source so that the irradiation was carried out by the light beam of a constant intensity throughout a whole series of samples for which the kinetic studies were made. For this reason, the kinetic data obtained in this investigation were always reproducible.

Since an unfiltered light beam was used for irradiation, no attempt was made to calculate the exact quantum yields for the reactions. However, it was found from the spectral examination that the light source used radiates mostly the light beam at 2537Å in the region where the absorption spectra of the samples were detected.

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[9] E. H. Volwiler and D. L. Tabern, *J. Am. Chem. Soc.*, **58**, 1352 (1936).

[10] T. L. Davis and K. C. Blanchard, *ibid.*, **51**, 1804 (1929).