Photochemical Reactions of Azido-1,3,5-triazines with Hydrocarbons and Ketones

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2-Azido-4,6-dimethoxy-1,3,5-triazine (**1**) produced 2-cyclohexylamino-4,6-dimethoxy-1,3,5-triazine as the sole major product upon irradiation at 254 nm in cyclohexane by the intermolecular insertion of the triazinyl nitrene into cyclohexane, while in the reaction with cyclohexene a derivative of the aziridine type was produced by the addition of triazinyl nitrene to the double bond of cyclohexene. In the photochemical reaction of **1** with ketones, 3,3-dialkyl derivatives of 5,7-dimethoxy-3*H*-[1,2,4]oxadiazolo[4.3-*a*]-*s*-triazine were obtained. The reaction is assumed to proceed *via* the electrophilic attack of the singlet nitrene on the carbonyl oxygen of the ketones followed by cyclization to give the final products. However, in the thermal reaction of **1** with ketones only 2-amino-4,6-dimethoxy-1,3,5-triazine was obtained.

In a previous paper,[1] the authors reported that the thermal reactions of azido-1,3,5-triazines with non-olefinic hydrocarbons proceed *via* a nitrene intermediate producing insertion and hydrogen abstraction products and that the reactions with olefinic hydrocarbons take place *via* a bimolecular mechanism involving the formation of an intermediate of the triazoline type to give alkenylamino- and amino-1,3,5-triazines as the final products.

Photolyses of a number of organic azides involving the formation of nitrene intermediates have been extensively investigated.[2] Although little is known about the photochemical reactions of azido nitrogenheteroaromatics, the reactions are considered to proceed *via* a nitrene intermediate producing amines,[3] azo-compounds,[3,4] insertion,[5] and ring contraction products,[6] *etc.* Recently, the formation of a nitrene intermediate was observed in the photolysis of azido-1,3,5-triazine;[7] amino-1,3,5-triazines were obtained upon irradiation of azido-1,3,5-triazines in methanol.[8] However, the details of the photochemical reactions of azido-1,3,5-triazines have not yet been determined. On the other hand, the photolysis of azido-1,3,5-triazines is of interest from the view point of the effect of the presence of three ring nitrogen atoms—the effect of an electron-attracting aryl nucleus on the photochemical reaction of arylazide. In addition, the photolysis of azido-1,3,5-triazines may provide useful and convenient methods for the preparation of a number of 1,3,5-triazine derivatives which would otherwise be difficult to prepare. This paper reports the photochemical reactions of azide-1,3,5-triazines with some hydrocarbons and ketones.

Results and Discussion

Photochemical Reactions of Azido-1,3,5-triazines with Hydrocarbons. When azido-1,3,5-triazines were irradiated in cyclohexane at 254 nm, a regular spectral change with isosbestic points was observed in every case, regardless of constituents of the 1,3,5-triazine nucleus, as is shown in Fig. 1.

In the photochemical reaction of 2-azido-4,6-dimethoxy-1,3,5-triazine (**1**) in cyclohexane, 2-cyclohexylamino-4,6-dimethoxy-1,3,5-triazine (**2**) was obtained as the sole major photoproduct; in the reaction mixture, no amount of the corresponding amino-1,3,5-triazine (**3**) was observed.

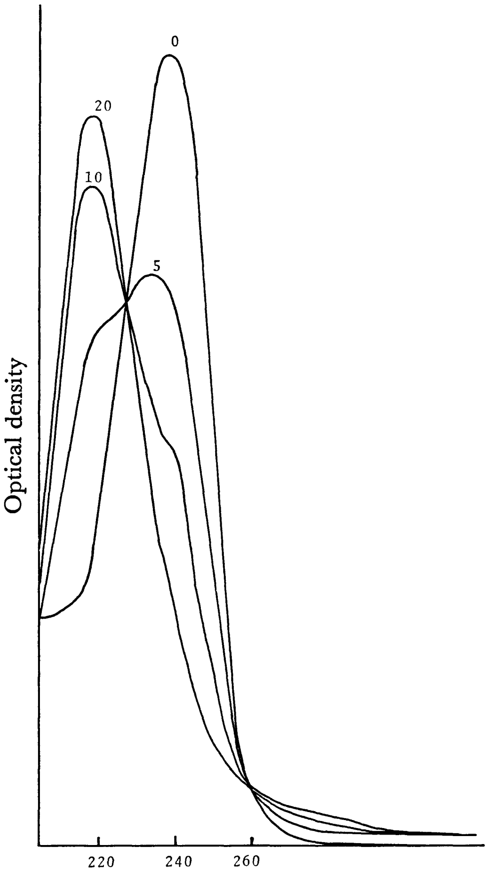
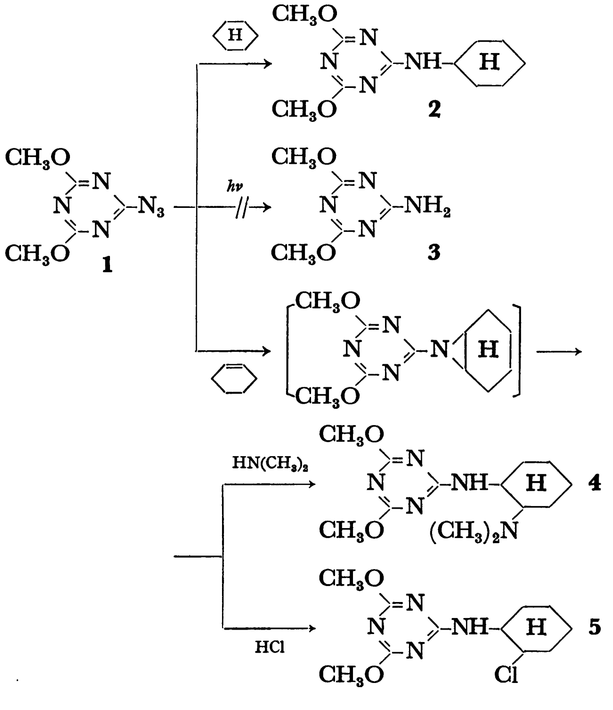


Fig. 1. Spectral change of cyclohexane solution of 2-azido-4,6-dimethoxy-1,3,5-triazine with lapse of time at 254 nm. Numbers refer to time at measurement in min.

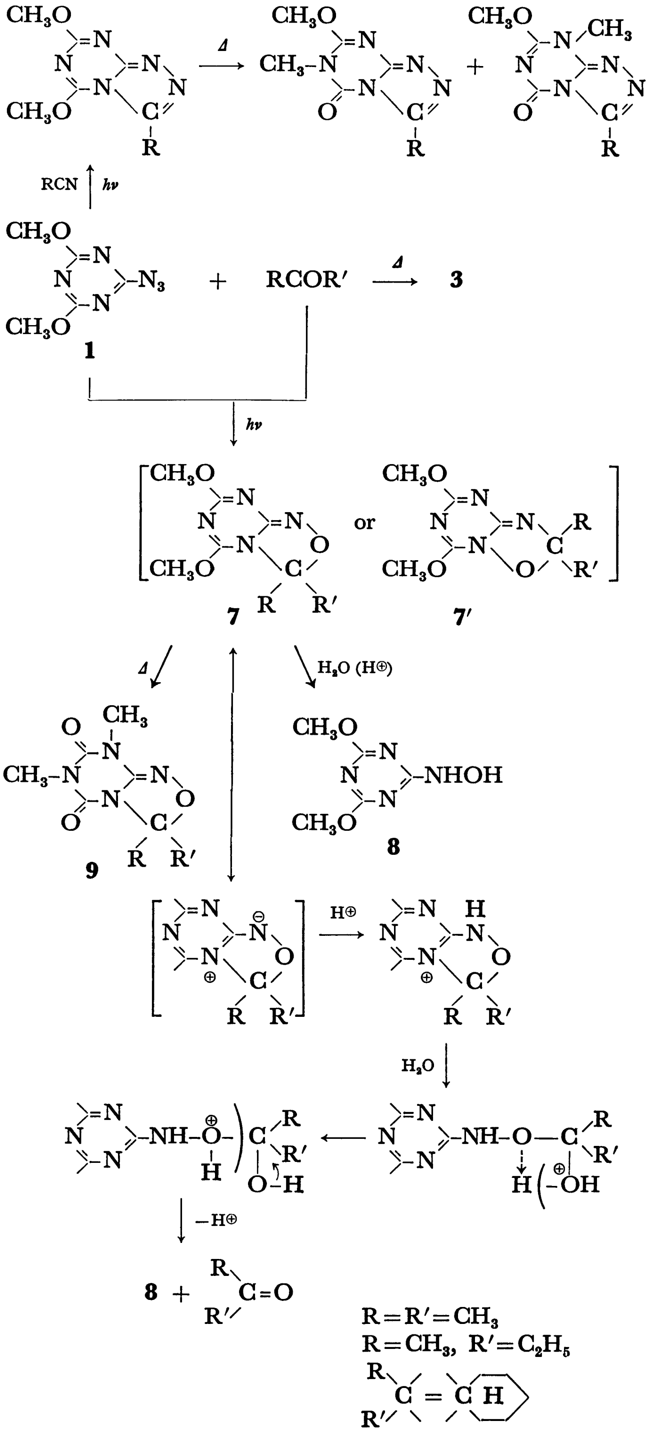
On the other hand, when azido-1,3,5-triazines were irradiated at 254 nm in EPA at 77 K, a new spectrum involving vibrational structure assignable to the corresponding triplet nitrene appeared in the long-wavelength region[9] in all cases. These triplet nitrenes should result from an intersystem crossing of the singlet nitrenes produced by the photodecomposition of the azido-1,3,5-triazines. Ordinary monoazido-1,3,5-triazines are thermally very stable,[1] thus without irradiation they did not react with cyclohexane at room temperature. The photochemical reaction of azido-1,3,5-triazine with cyclohexane can be said to proceed *via* a singlet nitrene intermediate, judging from the formation of cyclohexylamino-1,3,5-triazine and the absence of the hydrogen abstraction product (amino-1,3,5-triazine) in the reaction mixture.

It has been pointed out that in the photochemical reactions of ordinary arylazides with hydrocarbons,[10,11] intermolecular nitrene insertion products are not obtained as the major product. However, in the case of azido-1,3,5-triazine, the reaction proceeded in a similar manner to those of acyl and sulfonyl azides to give the intermolecular insertion products. Thus, even though the 1,3,5-triazine nucleus is an aromatic group, the 1,3,5-triazinyl nitrene behaves as if it were acyl or sulfonyl nitrene rather than ordinary aryl nitrene; the peculiar situation of 1,3,5-triazinyl nitrenes correlates with the strong electron-withdrawing power of this heteroaromatic nucleus.

On the other hand, the photochemical reaction of compound **1** in cyclohexene yielded many kinds of byproducts along with one major product. Since isolation and purification of the major product were found to be difficult, the reaction mixture was treated with dimethylamine and hydrochloric acid. The former treatment gave 2-(2-dimethylaminocyclohexylamino)-4,6-dimethoxy-1,3,5-triazine (**4**) while the latter gave 2-(2-chlorocyclohexylamino)-4,6-dimethoxy-1,3,5-triazine (**5**), suggesting that the major photoproduct of **1** with cyclohexene is a derivative of the aziridine type (**6**) resulting from the addition of 1,3,5-triazinyl nitrene to the double bond of cyclohexene. If 2-(cyclohexenylamino)-4,6-dimethoxy-1,3,5-triazine were produced during the photolysis as in the thermal reaction,[1] the final products **4** and **5** would not be produced by these treatments.



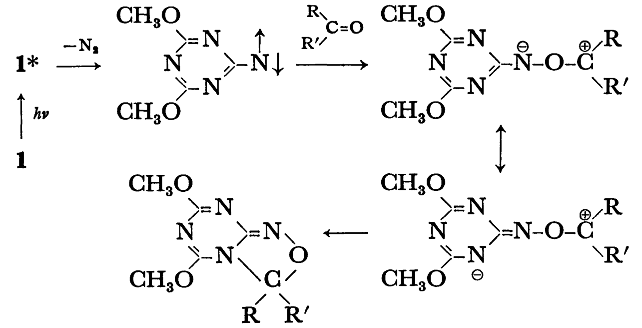
Photochemical Reactions of Azido-1,3,5-triazines with Ketones. Although there are many studies on the photochemical reactions of organic azides, little is known about the photochemical reactions of azides with ketones; only recently, it was reported that ethyl azidoformate reacts with acetone photochemically to give 2-ethoxy carbonyl-3,3-dimethoxyloxazirane, acetonyl carbamate, *etc.*[12] On the other hand, the present authors have recently reported that azido-1,3,5-triazine reacts photochemically with some nitriles to give the derivatives of *s*-triazolo[4.2-*a*]-1,3,5-triazine by the cycloaddition of triazinyl nitrene to nitriles.[9] When 2-azido-4,6-dimethoxy-1,3,5-triazine was irradiated at 254 nm



in acetone, an adduct consisting of the corresponding nitrene and acetone in a molar ratio of 1: 1 was obtained. The compound has two kinds of methoxyl groups and the lack of the characteristic IR band of the saturated aliphatic carbonyl group indicates that the compound has a bicyclic structure resulting from the cycloaddition of the nitrene to acetone, as is shown by **7** or **7′**. Similar photoproducts were obtained when **1** was irradiated at 254 nm in methylethyl ketone and cyclohexanone. On the other hand, it is known that the attempted intermolecular reaction of sulfonyl nitrene with cyclohexanone failed to give any products arising from the nitrene addition.[13] Therefore, even though 1,3,5-triazinyl nitrene behaves similarly to acyl and sulfonyl nitrenes, 1,3,5-triazinyl nitrene is not a mere adherent of acyl or sulfonyl nitrene. From the spectral data, it is difficult to distinguish between the two possible isomers **7** and **7′**. However, these photoproducts were readily hydrolyzed by dilute acid to give hydroxyamino-1,3,5-triazine (**8**) in a good yield indicating that **8** was derived from 7 (3,3-dialkyl derivatives of 5,7-dimethoxy-3*H*-[1,2,4]oxadiazolo[4.3-*a*]-*s*-triazine), because hydroxyamino-1,3,5-triazines do not result from **7′** by hydrolysis in the presence of an acid. The acidic hydrolysis of the photoproducts to give hydroxyamino-1,3,5-triazine (**8**) can be accounted for by the preceding scheme.

From these results, the photoproducts of **1** with ketones and nitriles are found to be very closely related to each other in chemical composition. In the photochemical reaction of **1** with nitriles, the cycloaddition of 1,3,5-triazinyl nitrene is known to proceed *via* a singlet nitrene. On the other hand, the photocycloadditions of carbethoxynitrene to acetone and nitriles[14,15] yielding 2-ethoxycarbonyl-3,3-dimethyloxazirane[12] and 2-alkyl-5-ethoxy-1,3,4-oxadiazoles also are known to proceed *via* a singlet nitrene.

In this case also, the photocycloaddition of triazinyl nitrene to ketones is assumed to proceed *via* a singlet nitrene; the singlet mechanism may be supported by the following data. The starting material (**1**) in aliphatic ketones absorbs more than 95% of the 254 nm incident light, although the solvent has a weak absorption band (n→π*) at 254 nm ($\varepsilon<4$),[16] and the singlet nitrene should be formed by the decomposition of the excited singlet azido-1,3,5-triazine, whose quantum yield is close to unity.[9] The solvents of ketones, themselves, are triplet quenchers of the starting material, and no effect of the quenchers or dissolved oxygen on the photocycloaddition would oppose the triplet pathway. It is known that the singlet nitrenes are electrophilic. Therefore, it seems likely that the initial step in the present reaction is the electrophilic attack of the singlet nitrene on the carbonyl oxygen in the ketones followed by cyclization producing the final products, where **1*** is an excited singlet state of **1**. On the other hand, in the thermal reactions of azido-1,3,5-triazines with ketones no product arising from the nitrene addition was produced, for example, when **1** was heated at 180 °C in acetone, 2-amino-4,6-dimethoxy-1,3,5-triazine (**3**) was obtained as the sole major product in a 67% yield. The formation of **3** in this case can be understood in terms of the hydrogen abstraction reaction of the triplet 1,3,5-triazinyl nitrene. In the thermal reaction, there is another possibility that compound **7**, even if produced, decomposes owing to its thermal instability to give compound **3**. However, when compound **7** was heated at 180—190 °C in acetone, the main product obtained was found to be compound **9** resulting from the O→N migration of the methyl groups with a small amount (7%) of compound **3**. Thus, the formation of **7** as an intermediate in the thermal reaction can be neglected; it is apparent that the photochemical and thermal reactions of azido-1,3,5-triazine with ketones proceeded *via* different routes.



Experimental

All the melting points are uncorrected.

2-Azido-4,6-dimethoxy-1,3,5-triazone (**1**) was prepared by the condensation of 2-chloro-4,6-dimethoxy-1,3,5-triazine with sodium azide.[1] Irradiated solutions were concentrated and crystallized products were separated and purified by column chromatography and recrystallization. The assignments of the photoproducts were performed by means of NMR, IR, UV, and mass spectra, elemental analyses and by a mixed-melting-point test with an authentic sample. A low pressure mercury lamp was used as the 254 nm radiation source with a Vycor glass filter.

Photochemical Reaction of Compound 1 with Cyclohexane. A solution of 2.0 g of compound **1** in 300 ml of cyclohexane was irradiated for 10 days. From the irradiated solution 850 mg of the starting material was recovered. Crude 2-cyclohexylamino-4,6-dimethoxy-1,3,5-triazine obtained by purification using column chromatography (silica gel; benzene–acetone= 10: 1 by volume) was recrystallized from methanol to give 720 mg (yield 48%) of the pure product. Mp 125—127 °C (lit,[1] 127—128 °C).

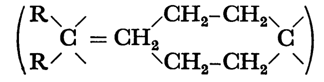
Photochemical Reaction of Compound 1 with Cyclohexene. In this case the primary photoproduct formed in the beginning was found to decompose gradually upon further irradiation. Therefore, the irradiation was stopped at the point of 25% conversion of the starting material. After the solvent hat been evaporated *in vacuo*, the residue was dissolved in 30 ml of acetone and the solution was treated with 10 g of a 40% dimethylamine solution. After standing for 2 hr at room temperature, the solution was treated with an excess of a 2M hydrochloric acid solution to make the mixture acidic, and then, the solution was extreacted with benzene. The aqueous layer was neutralized with sodium carbonate and was extracted with ether to give 800 mg of a pasty substance from which 200 mg (yield 13%) of 2-(2-dimethylaminocyclohexylamino)-4,6-dimethoxy-1,3,5-triazine was obtained by recrystallization from methanol–water. Mp 119.5—120.5 °C. (Found: C, 55.25; H, 8.03; N, 25.11%. Calcd for $C_{13}H_{23}N_5O_2$: C, 55.48; H, 8.24; N, 25.28%) NMR ($CDCl_3$), δ 1.50 (m, 8H), 2.21 (s, 6H), 2.44 (m, 1H), 3.60 (m, 1H), 4.00 (s, 6H), 6.17 (broad, 1H). The benzene layer was evaporated and the residue was dissolved in a small amount of ethanol. From the ethanolic solution the crystalline precipitate of 2-(2-chlorocyclohexylamino-4,6-dimethoxy-1,3,5-triazine was obtained by the addition of a small amount of water. Mp 170—171 °C (benzene–ligroin). Yield: 580 mg (39%). (Found: C, 48.71; H, 6.43; N, 20.78%. Calcd for $C_{11}H_{17}ClN_4O_2$: C, 48.44; H, 6.28; N, 20.54%) Mass: $m/e=272$. NMR ($CDCl_3$), δ 1.60 (m, 9H), 4.00 (s, 7H), 6.20 (broad, 1H). Thus, in the photochemical reaction of compound **1** with cyclohexene, the yield of the derivative of the aziridine type should exceed 50% of the decomposed azide.

Photochemical Reaction of Compound 1 with Ketones. A typical run is the case of the reaction of compound **1** with acetone. A solution of 1.0 g of compound **1** in 20 ml of acetone was irradiated for 24 hr. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (alumina: benzene–acetone=10:5 by volume) to give 300 mg of the starting material and 3,3-dimethyl-5,7-dimethoxy-3*H*-[1,2,4]oxadiazolo[4.3-*a*]-*s*-triazine in a 30% yield. Mp 144—145 °C (benzene–ligroin). (Found: C, 45.05; H, 5.43; N, 26.22%. Calcd for $C_8H_{12}N_4O_3$: C, 45.28; H, 5.70; N, 26.40%) Mass: $m/e=212$. NMR ($CDCl_3$), δ 1.70 (s, 6H), 3.92 (s, 3H), 4.07 (s, 3H). IR (KBr, cm^{-1}) (C=N), 1665.

Hydrolysis of Compound 7 in the Presence of Hydrochloric Acid. A mixture of 800 mg of compound **7** and 7 ml of a dilute hydrochloric acid solution (the pH of the solution was about 3.0) was warmed in a water bath for 3 min. After cooling, the solution was neutralized with sodium carbonate to give 550 mg (yield 85%) of hydroxyamino-4,6-dimethoxy-1,3,5-triazine as a crystalline precipitate. Mp 174—175 °C (under decomposition) (Methanol). (Found: C, 35.10; H, 4.82; N, 32.35 %. Calcd for $C_5H_8N_4O_3$: C, 34.88; H, 4.68; N, 32.55%). The compound was identified by a mixed-melting-point test with an authentic sample prepared by the condensation of 2-chloro-4,6-dimethoxy-1,3,5-triazine with hydroxylamine in the presence of sodium carbonate.

Similarly, in the reaction of compoun **1** with methyl ethyl ketone, compound **7** ($R=CH_3$, $R'=C_2H_5$) was obtained in a 52% yield. Mp 110—111 °C (benzene–ligroin). (Found: C, 47.83; H, 6.42; N, 24.92%. Calcd for $C_9H_{14}N_4O_3$: C, 47.78; H, 6.23; N, 24.76%). NMR ($CDCl_3$), δ 0.98 (t, 3H), 1.67 (s, 3H), 2.00 (m, 2H), 3.94 (s, 3H), 4.10 (s, 3H).

In the reaction of compound **1** with cyclohexanone, compound **7** was obtained in a 46% yield. Mp 137—138 °C (benzene–ligroin). (Found: C, 52.51; H, 6.44; N, 21.98%. Calcd for $C_{11}H_{16}N_4O_3$: C, 52.37; H, 6.39; N, 22.21%) NMR ($CDCl_3$), δ 1.80 (m, 10H), 3.94 (s, 3H), 4.08 (s, 3H).



$$\left(\begin{array}{c}R\\R\end{array}C=CH_2\begin{array}{c}CH_2{-}CH_2\\CH_2{-}CH_2\end{array}C\right)$$

7

Rearrangement of Compound 7 in Acetone. When a solution of 600 mg of compound **7** ($R=R'=CH_3$) in 50 ml of acetone was heated at 180—190 °C in an autoclave, 30 mg (7% yield) of crude 2-amino-4,6-dimethoxy-1,3,5-triazine [mp 210—214 °C (dioxane) (lit.,[17] 219 °C)] and 150 mg (yield 25%) of a product of mp 87—88 °C (methanol) were obtained. The latter compound was assigned to compound **9**, on the basis of the follwoing data. (Found: C, 45.45; H, 5.85; N, 26.31%. Calcd for $C_8H_{12}N_4O_3$: C, 45.28; H, 5.70; N, 26.40%). Mass: $m/e=212$. IR (KBr, cm^{-1}) (C=O), 1700, 1750: (C=N), 1650. NMR (CCl_4), δ 1.70 (s, 6H), 3.19 (s, 3H), 3.23 (s, 3H).

Thermal Reaction of Compound 1 with Acetone. When a solution of 3.0 g of compound **1** in 50 ml of acetone was heated at 180 °C for 12 hr in an autoclave, 2-amino-4,6-dimethoxy-1,3,5-triazine [mp 211—214 °C (dioxane)] was obtained in a 67% yield.

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