Photochemistry of Bioactive Compounds. Solution-Phase Photochemistry of Symmetrical Triazines

Brian E. Pape and Matthew J. Zabik*

Photolysis of 2-fluoro and 2-bromo-4,6-bis(ethylamino)-s-triazine in methanol and water at 253.7 and 300 nm yielded the 2-methoxy and 2-hydroxy analogs as the major products. Photolysis of the 2-iodo-s-triazine analogs of atrazine, propazine, and simazine in methanol, ethanol, and 1-butanol at 300–360 nm yielded the respective 2-alkoxy and 2-hydroxy compounds as the major product(s). Reaction mechanisms are considered. Consideration of thermal, photochemical, and spectroscopic data is suggestive of the participation of a Chugaev-type cyclic transition state in the photochemical dealkylation of s-triazines. Photolysis of 2-azido-4-ethylamino-6-methylthio-s-triazine in methanol at 253.7 and 300 nm yielded 2-amino-4-ethylamino-6-methylthio-s-triazine, 2-amino-4-ethylamino-s-triazine, and 2-azido-4-ethylamino-s-triazine. The observation of a "sensitized" photodecomposition of 4,6-bis(isopropylamino)-s-triazine is reported.

The photochemistry of s-triazines (Table I) has only recently been investigated in detail. Earlier investigations have demonstrated that photodecomposition occurs in natural sunlight. In addition, changes in the uv spectra of photolyzed solutions and decreases in the phytotoxicity of the unidentified product mixtures have been reported (Comes and Timmons, 1965; Jordan et al., 1963, 1965). Jordan et al. (1970) summarized the literature on s-triazine photodecomposition to that date.

Recently, Plimmer and coworkers studied the photolysis of III and IX at 220 nm in methanol solution by combined glpc–mass spectrometry. Simazine (III) yielded IX, XV, and XVIII, and other methylated products, possibly involving methylation of a ring nitrogen. Photolysis of IX yielded XVIII and methylated products (Plimmer, 1969). Plimmer et al. (1969) also reported the conversion of XXII to XV as the result of irradiation of the solid material.

Recent investigations in this laboratory (Pape and Zabik, 1970) have demonstrated the generality of the photochemical solvolysis of 2-chloro-s-triazines in alcohols and water between 253.7 and 300 nm. Photolysis of I, II, and III in methanol and in water yielded VII, VIII, IX, and IV, V, VI, respectively. These and other product studies were initially suggestive of a carbonium ion mechanism. The irradiation of 2-methylthio-s-triazines XX, XXI, and XXII in hydrocarbon, alcoholic, or aqueous solution resulted in the formation of the 4,6-di(alkylamino)-s-triazines XIII, XIV, and XV, respectively. Solvent participation reactions indicated an intramolecular elimination with hydrogen transfer. Our studies of changes in uv spectra of 2-chloro-s-triazines under laboratory conditions at 280 nm are identical to those reported by Comes and Timmons (1965) and Jordan et al. (1963, 1965) in sunlight and support the conversion of these triazines to their 2-hydroxy analogs under field conditions. The purpose of the present investigation was to extend the knowledge of the photochemistry of substituted triazines.

Objectives of these photochemical studies included: (1) the study of 2-fluoro-4,6-bis(ethylamino)-s-triazine, 2-bromo-4,6-bis(ethylamino)-s-triazine, and 2-iodo-s-triazines in methyl alcohol and in water; (2) the photolysis of 2-azido-4,6-methylthio-s-triazine; and (3) preliminary investigation of the significance of photochemical "sensitization" on the fate of the s-triazine system. The more detailed investigation of the solution-phase photolysis of 2-iodo-s-triazines X, XI, and XII was extended as part of a study of mechanistic photochemistry to determine the kinetic and product specificity influences of the carbon-2 substituents (2-F, Cl, Br, 1 and 2-OCH_3, OH, H) of symmetrical triazines. The directions and implications of considerations of the mechanism of s-triazine N-dealkylation have been influenced by collaborations with Z. D. Tadic and S. K. Ries, who have recently completed work on the thermal reactions of s-triazines (Tadic and Ries, 1971).

EXPERIMENTAL MATERIALS AND METHODS

s-Triazines. Authentic s-triazines I–III, IV–VI, VII–IX, XX–XXII, XVI, and XVII were supplied by Geigy Agricultural Chemicals, Ardsley, N. Y. s-Triazines XIII–XV were prepared photochemically (Pape and Zabik, 1970). The 2-iodo-s-triazines X–XVII were supplied by Tadic and Ries, and were purified to greater than 99.5% purity by column chromatography on 100 mesh silicic acid [chloroform–acetone (9:1)]. Compound XXIII was provided by CIBA Agrochemical Company, and was recrystallized from methanol until greater than 99% purity was obtained. Identity was confirmed by ir and mass spectra.

Solvents. Solvents were of analytical grade. Water used in photolysis reactions was distilled and had a pH of approximately 6.5.

Chromatography. Column and thin-layer chromatographic (tlc) separations of products were accomplished on silicic acid (AR, 100 mesh) and silica gel, respectively. The chromatographic solvent system was chloroform–acetone (9:1). Gas–liquid partition chromatography (glpc) was achieved on a 6-ft stainless steel column, packed with 5% Carbowax 20M on 60/80 mesh Gas Chrom Q (Applied Science Laboratories, Inc., State College, Pa.). Column temperatures ranged from 150–220°C (isothermal conditions) and the carrier gas flow was 40 ml per min (prepurified helium).

Instrumentation. Infrared (ir) spectra were determined with a Perkin-Elmer 337 grating spectrophotometer. Ultraviolet (uv) spectra were obtained with a Beckman model DB-G instrument. The nmr spectra were obtained on a Varian A-60 high resolution spectrometer, using deuterated chloroform, with tms as an internal standard. Analysis by glpc–mass spectrometry was conducted on a LKB 9000 gas

Department of Entomology, Pesticide Research Center, Michigan State University, East Lansing, Michigan 48823.

chromatograph–mass spectrometer. A 6-ft borosilicate glass column of 3% SE-30 liquid phase on 100 mesh Gas Chrom Q was used for indirect introduction of samples. Column flow was 40 ml per min, and operating temperature ranged from 150–220°C (isothermal).

RESULTS AND DISCUSSION

2-Azido-4-isopropylamino-6-methylthio-s-triazine. Irradiation of XXIII in methanol at 253.7 or 300 nm yielded 2-amino-isopropylamino-6-methylthio-s-triazine (XXIV), 2-amino-4-isopropylamino-s-triazine (XXV), 2-azido-isopropylamino-s-triazine (XXVI), and unidentified volatile sulfur compounds. The evolution of molecular nitrogen was noted during these reactions. The identity of photoproducts XXIV, XXV, and XXVI was based on ir and mass spectra [for functional group ascriptions and spectral correlations, refer to Pape and Zabik (1970), Plimmer et al. (1969), and Padgett and Hammer (1958)]. Prolonged photolysis resulted essentially in the total conversion of XXIII to XXV, indicating that XXIV and XXVI are intermediates in the formation of XXV. The photolysis of XXIII to XXIV, and of XXVI to XXV, appears to be quite facile, understandable due to the strong driving force afforded by the loss of molecular nitrogen (Calvert and Pitts, 1966).

The photolysis of XXIII in carbon tetrachloride yielded only XXVI. There was no elimination of N_2, with the formation of XXIV or XXV. This is consistent with the inavailability of a source of reducing hydrogen, and also suggests that the elimination of the equivalent of CH_2S with the formation of XXVI is an intramolecular photoprocess. Such an intramolecular process is also consistent with the data of Plimmer et al. (1969), which showed that the irradiation of prometryne (XXI) deposits yielded 4,6-bis(isopropylamino)-s-triazine (with the elimination of the equivalent of CH_2S).
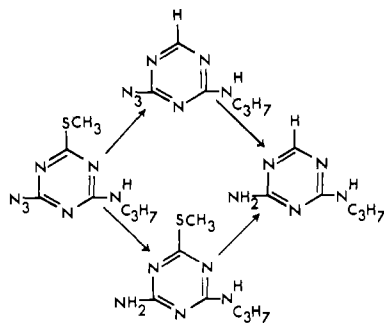
"Sensitized" Reactions. The irradiation of 4,6-bis(isopropylamino)-s-triazine (XIV) in acetone, a triplet sensitizing solvent which also may participate via hydrogen abstraction, at 300 nm resulted in a photoreaction. The identification of products and the generality of such "photosensitized" conversion of s-triazines at wavelengths greater than 290 nm are being investigated.

2-Fluoro and 2-Bromo-s-triazines. The photolysis of XVI and XVII in a mixture of methanol and water (1:1) at 253.7 or 300 nm yielded the 2-methoxy and 2-hydroxy analog (simetone and hydroxysimazine) as the major products. The 2-hydroxy analog precipitated from solution upon concentration of the final reaction mixture, while the 2-methoxy analog was isolated by column chromatography. Their ir spectra were identical to authentic standards.

2-Iodo-s-triazines. Photolysis of solutions of 2-iodo-s-triazines X, XI, and XII (~1 mg/ml) in dry methanol,

Table I. Authentic s-Triazines and Photoproducts

		Substituents		
s-Triazine	Designation	R_1	R_2	R_3
Atrazine	(I)	Cl	C_2H_5	C_3H_7
Propazine	(II)	Cl	C_3H_7	C_3H_7
Simazine	(III)	Cl	C_2H_5	C_2H_5
Hydroxyatrazine	(IV)	OH	C_2H_5	C_3H_7
Hydroxypropazine	(V)	OH	C_3H_7	C_3H_7
Hydroxysimazine	(VI)	OH	C_2H_5	C_2H_5
Atratone	(VII)	OCH_3	C_2H_5	C_3H_7
Prometone	(VIII)	OCH_3	C_3H_7	C_3H_7
Simetone	(IX)	OCH_3	C_2H_5	C_2H_5
Iodoatrazine	(X)	I	C_2H_5	C_3H_7
Iodopropazine	(XI)	I	C_3H_7	C_3H_7
Iodosimazine	(XII)	I	C_2H_5	C_2H_5
	(XIII)	H	C_2H_5	C_3H_7
	(XIV)	H	C_3H_7	C_3H_7
	(XV)	H	C_2H_5	C_2H_5
Fluorosimazine	(XVI)	F	C_2H_5	C_2H_5
Bromosimazine	(XVII)	Br	C_2H_5	C_2H_5
	(XVIII)	OCH_3	H	C_2H_5
Ametryne	(XX)	SCH_3	C_2H_5	C_3H_7
Prometryne	(XXI)	SCH_3	C_3H_7	C_3H_7
Simetryne	(XXII)	SCH_3	C_2H_5	C_2H_5

	R_1	R_2	R_3
(XXIII)	C_3H_7	SCH_3	N_3
(XXIV)	C_3H_7	SCH_3	NH_2
(XXV)	C_3H_7	H	NH_2
(XXVI)	C_3H_7	H	N_3

ethanol, and 1-butanol at 300–360 nm resulted in a progressive discoloration of solution to a deep brown and the precipitation of a crystalline product, purified by filtration and solvent washing. These precipitated photoproducts of X–XII were determined to be their respective 2-OH analogs IV, V, and VI (based on comparison of their ir spectra with authentic samples). The formation of I_2 was suggested by uv spectroscopy, and confirmed by titration with sodium thiosulfate. The presence of the respective 2-OCH_3 analogs (VII, VIII, and IX in methanol reactions) and the 2-ethoxy and 2-n-butoxy analogs formed in their respective alcohols was confirmed by glpc–mass spectrometry. Analysis of alkyl halides (RI) was not attempted.

These initial studies suggested the possibility of a primary photochemical process resulting in the formation of the appropriate 2-alkoxy compound, with its subsequent hydrolysis by HI to yield the 2-OH products. The participation of a solvent-cage/radical-pairing phenomenon in these processes was suggested by the absence of any detectable 2-H compounds in the methanol reactions of X–XII. Data suggest that the cleavage of the primary products, the aromatic ethers (2-OR), was not an important photochemical process.

The photochemistry of HI, CH_3I, and n-C_4H_9I is well documented (Calvert and Pitts, 1966). Excitation of HI involves promotion of a nonbonding halogen electron to a higher dissociative state ($\Phi \cong 1.0$ at 253.7 nm). The solution-phase photolysis of alkyl iodides is also characterized by dissociation (RI + $h\nu \rightarrow$ R$\ddagger$ I), where R$\ddagger$ is translationally and/or vibrationally excited ("hot"), i.e., that for the light and heavy dissociative fragments formed photochemically, most of the kinetic energy must be carried by the light fragment. It might be speculated that the formation of IV–VI from X–XII could occur as the result of two photochemical processes: formation of the appropriate 2-alkoxy product, and its subsequent attack by a "hot" H$\ddagger$ radical formed upon the photodissociation of HI. Other experimental evidence does not support such a mechanism.

In another experiment, a solution of XI (~ 0.001 mg/ml) in glass distilled cyclohexane was photolyzed at 300–360 nm to yield V (25%), XIV (70%), and bicyclohexane (determined by glpc–mass spectrometry). These data are not consistent with the exclusive participation of a carbonium ion mechanism; formation of V is explainable in terms of a simple solvolysis reaction with a trace of water, but XIV would not be expected if a true carbonium ion mechanism were operative. In such dilute solution it is quite unlikely that chemical reduction of XI by HI would be significant. The operation of a competitive mechanism is suggested by these data. That the solvolysis reaction in alcoholic solution is preferred to proton abstraction in a hydrocarbon medium has recently become evident in rate studies (Pape and Zabik, 1971). Indeed, in a binary solvent system (cyclohexane saturated with methanol), XI yields only V and VIII on photolysis.

Photolysis of XI was also carried out under different conditions during this investigation. Photolysis in CCl_4 solution yielded unidentified products which were separated on tlc; quite likely some of these included 2-H (XIV) and 2-X dimerization products. Again, these data support a competitive, free radical mechanism. Irradiation of crystalline XI proceeded with discoloration. No products were identified.

The nature of the leaving group appears to be critical to the rate-determining step. Iodine is an excellent leaving group, and the photolysis of X–XII proceeds much more rapidly and at longer wavelengths than I–III.
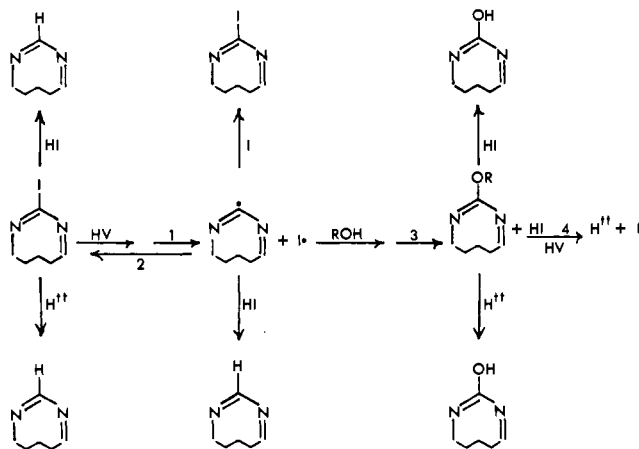
decay, as well as chemical hydrolysis and radical trapping. An exclusive free radical photochemical process of the decay of X–XII would involve the homolytic cleavage of the triazine carbon–iodine bond to yield the respective radicals (proceeding via some unelucidated excited state). These two radicals would then have three alternatives: (1) recoupling to yield X–XII; (2) diffusion out of the solvent-cage to escape recoupling, necessarily followed by requisite attack on solvent or solute, most probably via hydrogen abstraction; or (3) hydrogen abstraction and radical coupling within the solvent-cage.

The fact that no XIV was detected in the photolyzate of XI in methanol suggests the participation of a "secondary" radical-coupling/solvent-cage mechanism, where I· would abstract the hydroxyl hydrogen from methanol to yield HI + ·OCH_3, with ·OCH_3 and the carbon radical of the triazine ring then coupling to yield VII–IX. It is, of course, possible that ·OCH_3 could attack X–XII to yield VII–IX (analogous to the base-catalyzed solvolysis of 2-halo-s-triazines in alcohols). Formation of V during the photolysis of XI is then explicable in terms of the chemical or photochemical (H$\ddagger$) hydrolysis of VIII. Although it is intuitively more attractive to consider the hydrolysis to be chemical under these reaction conditions, kinetic experiments are underway to remove this ambiguity. The homolytic, free radical decay of X–XII, and participation in competitive pathways is required in the CCl_4 solution photolysis of XI. The formation of XIII–XV is explicable in terms of the chemical reduction of X–XII by HI, or trapping of the triazinyl radical by HI (Calvert and Pitts, 1966). The radical may also be trapped by iodine (an even more efficient trapping agent than HI), iodine formation arising from the photodissociation of HI and alkyl halides. Under condensed phase conditions, H$\ddagger$ may participate in the reduction of X–XII or in the cleavage of VII–IX to yield products.

The photolysis of X–XII to yield IV–VI and VII–IX in methanol might be expected to proceed via a mechanism analogous to that of the 2-chloro-s-triazines, i.e., those data having been suggestive of a heterolytic cleavage of the carbon–chlorine bond to yield the carbonium ion. However, the multiplicity of these X–XII reactions in longer chain alcohols, in CCl_4, and in the crystalline state necessitates a free radical pathway.

2-Chloro-s-triazines. Irradiation of solutions of I–III in 1-butanol, 1-octanol, and 1-decanol at greater than 290 nm (borosilicate glass) and analysis of the photolyzate by com-
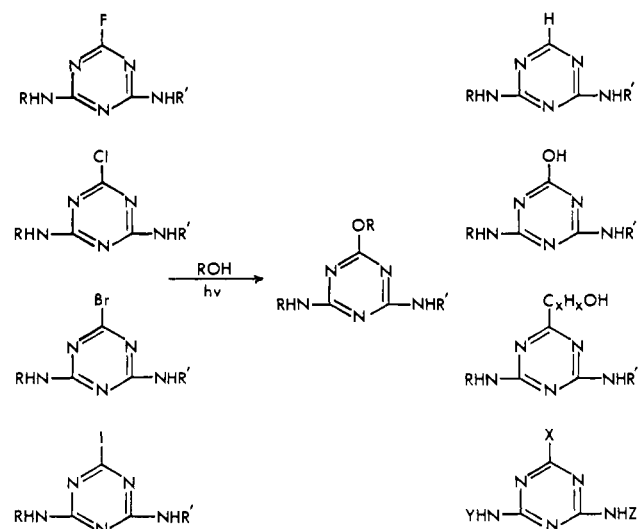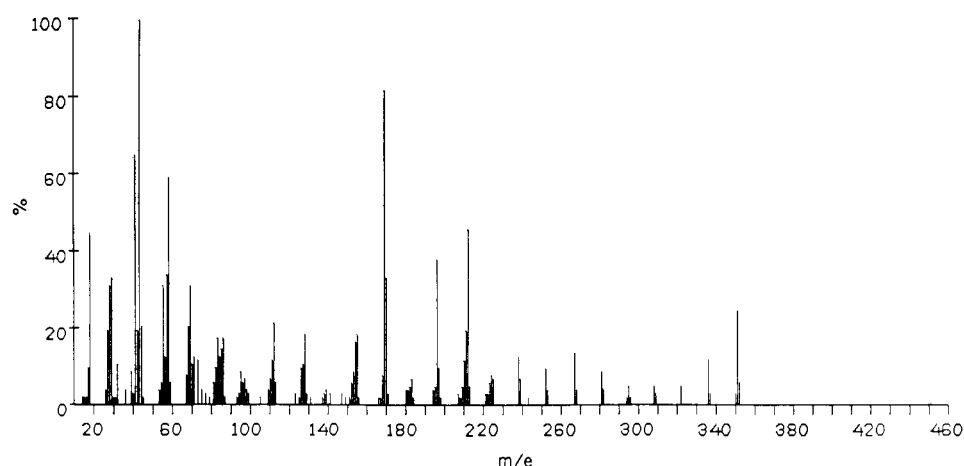

Based on the multiplicity of product formation and the well documented photochemistry of HI and alkyl halides, the product-formation reaction of the 2-iodo-s-triazines is viewed as a free radical/competitive-pathway mechanism which may involve radical coupling, hydrogen abstraction, and photochemical participation in the initial (intermediate) product

Figure 1. Graphical representation of mass spectrum of 2-*n*-decoxy-4,6-bis(isopropylamino)-*s*-triazine (70 eV)

bined glpc–mass spectrometry demonstrated the formation of multiple triazine photoproducts. Such product multiplicity requires a free radical mechanism. The glpc data indicated that the complexity of the product mixture increased with the length of the carbon chain of the alcoholic solvent used in the reaction. The dechlorinated and carbon-2 *n*-alkoxy products of I–III have been definitively identified in these reactions. The classical mass spectral fragmentation patterns exhibited by these long-chain *n*-alkoxy-*s*-triazines is striking (Figure 1). Other products have glpc characteristics and mass spectra suggestive of hydroxylated alkyl and ring-substituted addition products. The photolysis of XVI–XVII under similar conditions yielded essentially identical results.
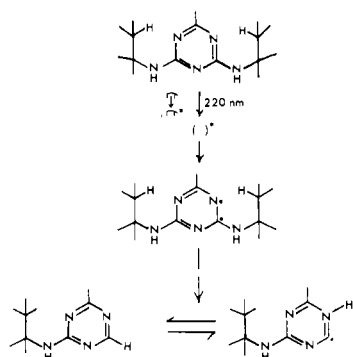
The original interpretation of the photolytic data of I–III in methanol, no evolution of HCl and VII–IX as the major mechanistic product, which suggested the ionic mechanism, must be reinterpreted in terms of these new data. These original data are explicable in terms of (1) solubilities of HCl in alcohol solution; (2) formation of the hydrochloride salt of the 4,6-di(alkylamino)groups of I–III or VII–IX; and (3) a selective radical-coupling/solvent-cage preference for the formation of the carbon-2 methoxy product, analogous to that noted in the reactions of X–XII.

Photochemical Dealkylation. An interesting correlation has been noted between the uv spectroscopy and photochemistry of *s*-triazines and recently noted thermal dealkylation reactions (Tadic and Ries, 1971). Tadic and Ries propose a cyclic transition state (Chugaev reaction) in these monomolecular dealkylations of 2-F, Cl, Br, I, OCH₃-4, 6-di(alkylamino)-*s*-triazines. The results of Plimmer (1969), which demonstrated the occurrence of *N*-dealkylation reactions at

220 nm, are consistent with the participation of an analogous cyclic transition state. *s*-Triazines have λ_{max} in the 220 nm region of the uv, ascribed to a $\pi \rightarrow \pi^*$ transition of C==N of the ring (Pape and Zabik, 1970). A six-membered cyclic transition state would favor such a reaction.

CONCLUSIONS

Consideration of the uv spectroscopic data of our earlier study and comparison with data of the *s*-triazine photoconversions reported by others in natural sunlight suggests that the hydroxylation of 2-chloro-*s*-triazines to yield the 2-hydroxy analogs occurs in sunlight. The present investigation indicates that the products of *s*-triazines formed upon photolysis depend not only on the nature of the carbon-2 substituent, but also upon subsequent photochemical/chemical reactions. The conversion of X–XII to IV–VI, apparently proceeding *via* an alkoxy intermediate (VII–IX), indicates the generality of these photolytic solvolyses of 2-halo-*s*-triazines in alcoholic solvents. Further studies are indicated to elucidate the role of solvent participation and competitive mechanisms. The participation of a Chugaev-type cyclic transition state in the photochemical *N*-dealkylation reactions of a variety of *s*-triazines is suggested by uv, photochemical, and thermal data. The kinetics and excited states of these *N*-dealkylations are being investigated. The facile photodecomposition of XXIII is expected to occur under field conditions to yield XXIV, XXV, XXVI, N₂, and volatile sulfur compounds. The hydrogen substitution at carbon-6 appears to be intramolecular. The photochemical "sensitization" of the *s*-triazine ring is indicated as a possible avenue for the further degradation of metabolic and photolytic products (2-hydroxy and 2-H analogs).

ACKNOWLEDGMENT

LITERATURE CITED

Calvert, J. G., Pitts, J. N., Jr., "Photochemistry," Wiley, New York,
  N.Y., 1966, p 474.
Comes, R. D., Timmons, F. L., *Weeds* 13(2), 81 (1965).
Jordan, L. S., Day, B. E., Clevx, W. A., *Res. Progr. Rept. Western
  Control Conf.* 78 (1963).
Jordan, L. S., Farmer, W. J., Goodin, J. R., Day, B. E., "Residue
  Reviews, Vol. 32, The Triazine Herbicides," Springer-Verlag,
  New York, N.Y., 1970, p 267.
Jordan, L. S., Mann, J. D., Day, B. E., *Weeds* 13, 43 (1965).
Padgett, W. M., II, Hamner, W. F., *J. Org. Chem.* 80, 803 (1958).
Pape, B. E., Zabik, M. J., J. AGR. FOOD CHEM. 18, 202 (1970).
Pape, B. E., Zabik, M. J., unpublished data, 1971.

Plimmer, J. R., Kearney, P. C., Klingebiel, U. I., *Tetrahedron Lett.*
  No. 44, 3891 (1969).
Plimmer, J. R., U.S.D.A., Beltsville, Md., personal communication
  (July, 1969).
Tadic, Z. D., Ries, S. K., J. AGR. FOOD CHEM. 19, 46 (1971).

Photochemistry of Bioactive Compounds. Photolysis of Arylamidine Derivatives in Water

George C. C. Su and Matthew J. Zabik*

N'-(4-Chloro-*o*-tolyl)-N,N-dimethylformamidine (I)
and its hydrochloride salt (II) were irradiated
($\lambda >286$ nm) in water at pH 7.1 and 3.1, respectively.
Spectral and tlc analyses indicated reaction for I,
but no reaction for II. The photoproducts for I
were N-(4-chloro-*o*-tolyl)formamide (IV) ($\sim95\%$)
and   bis-4-(N,N-dimethyl-N'-*o*-tolylformamidine)
ether (VI) ($\sim5\%$). Infrared and mass spectral
data for VI are presented. Formal mechanisms
for reactions giving rise to these products have been
proposed.

The new pesticide N'-(4-chloro-*o*-tolyl)-N,N-dimethyl-
formamidine (I) and its hydrochloride salt (II) both
have effective action against mites (Dittrich, 1966,
1967) and insects (Jenny, 1971).   Experiments on the
metabolism of I by apple seedlings (Sen Gupta and Knowles,
1969) revealed conversion of I to N-methyl-N'-(4-chloro-*o*-
tolyl)formamidine (III), N-(4-chloro-*o*-tolyl)formamide (IV),
4-chloro-*o*-touluidine (V), and possibly the glucoside N-(4-
chloro-*o*-tolyl)-D-glucosylamine. Photolyses (254 nm, 364
nm, and sunlight) of I on silica gel chromatoplates and in
ethanol solution (Knowles and Sen Gupta, 1969) were re-
ported to yield I, III, IV, V (IV being the major product),
plus several unidentified compounds. The authors also
observed the hydrolysis of I on silica gel chromatoplate in
the dark to yield IV. These investigators employed the
solvent system diethylamine–benzene (5:95 v/v) for developing
thin-layer chromatoplates. In our study the control "dark
reaction" of I and II showed no detectable reaction in water.
The tlc solvent system in this case was the less basic ethanol–
benzene–chloroform (20:20:60 v/v).

We now report the photolyses ($\lambda >286$ nm) of I and II in
distilled water at pH 7.1 and 3.1, respectively, and in "natural
water" (pH 7.9) obtained from the Red Cedar River at the
intersection of Farm Lane on the campus of Michigan State
University, East Lansing, Mich. A previously unreported
photoproduct of I has been isolated and characterized by
detailed analysis of the ms and ir spectra.

Department of Entomology, Pesticide Research Center,
Michigan State University, East Lansing, Michigan 48823.
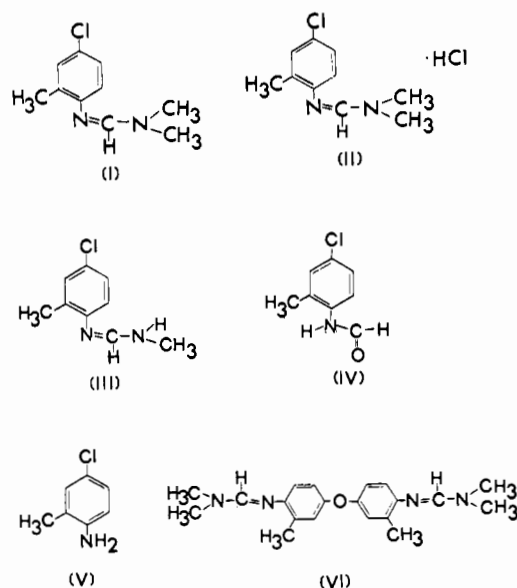
MATERIALS AND METHODS

N'-**(4-Chloro-*o*-tolyl)-N,N-dimethylformamidine (I).** Com-
pounds I (98.7% purity, Batch 0267/5444) and II (99.6%
purity, Batch 2033-3) were obtained from NOR-AM Agri-
cultural Products, Inc., Woodstock, Ill. Purification of I
was achieved by sublimation at room temperature (~25°C)
and 0.1 Torr. The sublimed material was shown to be pure
by tlc and glpc. The hydrochloride salt II was pure as
determined by tlc, and was used without further purification.