

Photochemistry of Bioactive Compounds. Solution-Phase

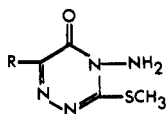
Photochemistry of Asymmetric Triazin-5(4H)-ones

Brian E. Pape and Matthew J. Zabik*

The photolysis of 4-amino-6-R-3-(methylthio)-*as*-triazin-5(4H)-ones (R = cyclohexyl, *tert*-butyl, isopropyl) in carbon tetrachloride, benzene, methanol, water, or in the crystalline state yields the

respective 5-hydroxy-6-R-3-(methylthio)-1,2,4-triazine as the major product. Minor reactions proceed by routes which include desulfurization and oxidation. Reaction mechanisms are considered.

A number of 4-amino-6-alkyl substituted 3-(methylthio)-*as*-triazin-5(4H)-ones were previously tested for herbicidal activity by Vero Beach Laboratories, Inc., and are currently being developed by Chemagro Corp., Kansas City, Mo., under license. Representatives of this class of compounds included in this investigation of photochemical reactivity include: BAY 94337 [4-amino-6-*tert*-butyl-3-(methylthio)-*as*-triazin-5(4H)-one] (I), BAY 88410 [4-amino-6-isopropyl-3-(methylthio)-*as*-triazin-5(4H)-one] (II), and BAY 86791 [4-amino-6-cyclohexyl-3-(methylthio)-*as*-triazin-5(4H)-one] (III).



Asymmetric heterocyclic nitrogen compounds have been the subject of extensive investigation (Paquette, 1968; Smolin and Rapoport, 1959). Even a superficial review of the literature indicated several plausible reaction pathways that might be operative in the photodecomposition of I-III: expulsion of molecular nitrogen with the formation of the intermediate biradical; desulfurization of the carbon-three methylthio group; oxidation of a hetero atom; reduction of or addition to the carbonyl function; dimerization; and addition to the unsaturated ring (Calvert and Pitts, 1966; Crosby, 1969; Mustafa, 1964; Neckers, 1967; Pape and Zabik, 1970; Plimmer *et al.*, 1969).

EXPERIMENTAL

Materials and Methods. HERBICIDES. Compounds I-III were obtained from Chemagro as technical material and were recrystallized from benzene to greater than 99% purity. Alternatively, they may be recrystallized from 1,2-dichloroethane. Final purification may be accomplished by tlc using silica gel and benzene-ethyl ether (1:1) or chloroform-acetone (9:1). Chemical authenticity was supported by ir, mass, and nmr spectra.

SOLVENTS. All solvents were of analytical grade. Water was distilled, degassed, deionized, and had a pH of approximately 6.8.

PHOTOCHEMICAL EQUIPMENT. All photolyses were done in a Rayonet Photochemical Reactor (The Southern N. E.

Ultraviolet Co.) fitted with lamps having a peak energy output at 300 and 350 nm (Catalog No. N.P.R.-3000, -3500, respectively). All irradiations were done through borosilicate glass. Solutions were magnetically stirred, with solution temperatures maintained at approximately 25°C.

ANALYTICAL EQUIPMENT. Thin-layer chromatography (tlc) was done on precoated silica gel (HF-254) plates, with chloroform-acetone (9:1) or benzene-ethyl ether (1:1). Column chromatography was done on silicic acid AR 100 mesh (Mallinckrodt), using chloroform-acetone (9:1). Gas-liquid partition chromatography (glpc) analyses were accomplished using a 3% OV-1 or 1% SE-30 liquid phase on Gas Chrom Q (Applied Science Laboratories), with an isothermal temperature range of 160-200°C.

All melting points were uncorrected. Infrared (ir) and ultraviolet (uv) spectra were determined with a Perkin-Elmer 337 and Beckman DB-G grating spectrophotometer, respectively. Nuclear magnetic resonance (nmr) spectra were recorded using a Varian A-60 high resolution instrument. Samples were dissolved in deuterated chloroform-*d*₁ or acetonitrile-*d*₃, with tetramethylsilane as an internal standard. Mass spectra were obtained with an LKB 9000 gas chromatograph-mass spectrometer. Spectra obtained by direct or indirect (1% SE-30 liquid phase on 60/80 mesh Gas Chrom Q; 6 ft × 1/8 in. i.d.; isothermal temperature, 150-200°C; ionization voltage, 70 eV) introduction were essentially identical.

Elemental analyses were performed by Spang Micro-analytical Laboratory, Ann Arbor, Mich.

Photochemical Procedures. PHOTOLYSIS OF 4-AMINO-6-ALKYL SUBSTITUTED 3-(METHYLTHIO)-AS-TRIAZIN-5(4H)-ONES (I, II, III) IN CARBON TETRACHLORIDE, BENZENE, METHANOL, AND WATER. Photolysis of saturated solutions of I-III in carbon tetrachloride (~0.25 g/100 ml of solvent) at >290 nm resulted in reaction and precipitation of the respective major photoproduct (IV-VI). With short irradiation time, *i.e.* 4 hr or ~10% conversion of I-III, product yield was greater than 90%. Prolonged photolysis (>72 hr) resulted in multiple products (with total conversion of I-III, yield of IV-VI exceeded 60%).

Reactions were stopped with the total disappearance of I-III; solvent was removed under partial vacuum; and the amorphous residue was dissolved in chloroform-acetone (9:1). This solution was chromatographed on a silicic acid column [chloroform-acetone (9:1)]. Fractions were analyzed by glpc and tlc; pure product fractions were reduced under vacuum; and final drying was done in a drying pestle.

Comparative analysis of aliquots of starting material, pho-

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

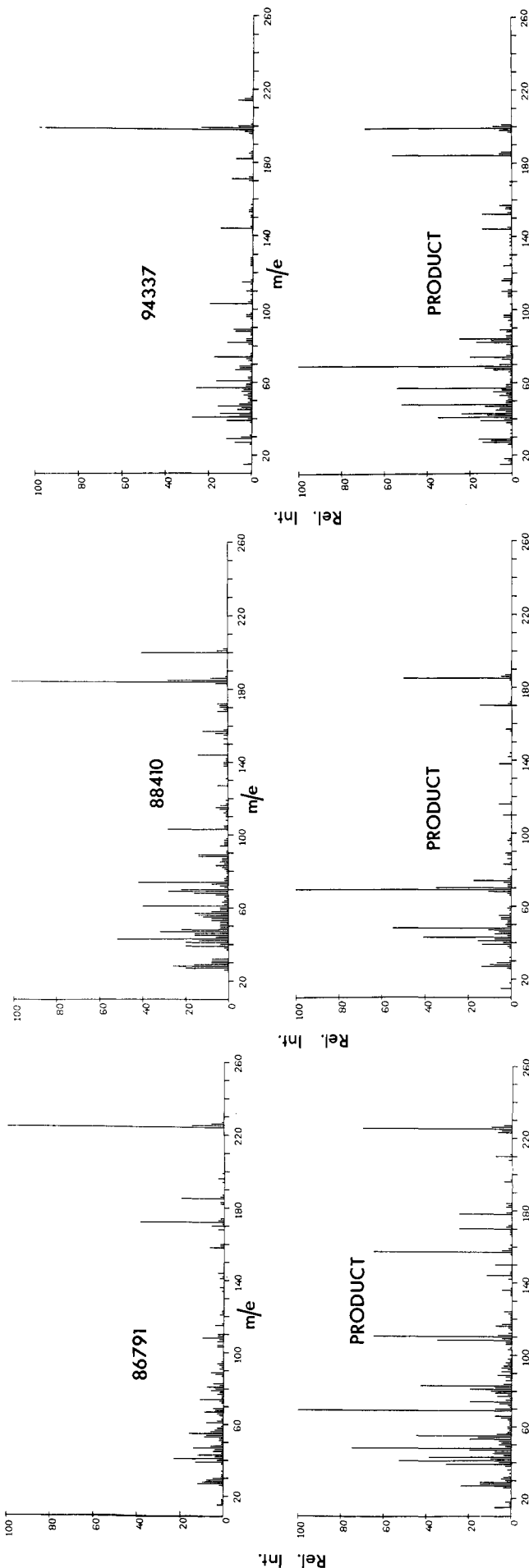


Figure 1. Mass spectra of *as*-triazin-5(4*H*)-ones and respective photoproducts

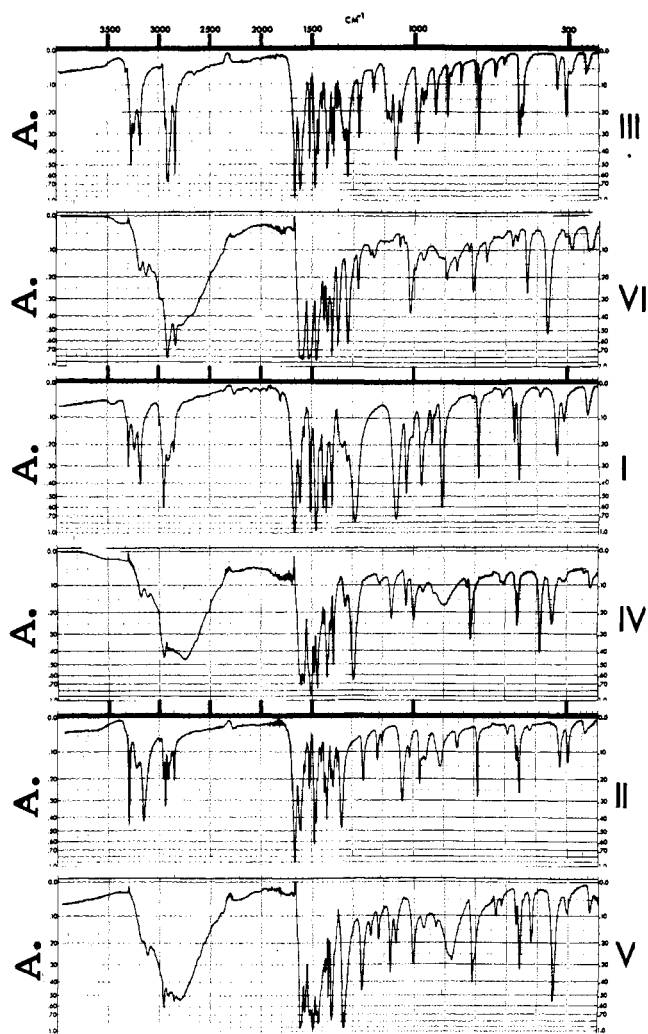


Figure 2. Infrared spectra of *as*-triazin-5(4*H*)-ones I-III and respective photoproducts IV-VI

tolysis solutions, and isolated photoproducts by glpc and tlc showed the product to be stable under these chromatographic procedures. Solutions of I-III held in the dark were determined to be stable over time.

PHOTOLYSIS OF I-III IN OTHER SOLVENTS. Photolysis of I-III in benzene, methanol, and water yielded essentially identical results: conversion of I-III to appropriate major product identical to that formed in carbon tetrachloride. Photolysis in water required the extraction of product with ethyl ether or chloroform.

PHOTOLYSIS OF I-III IN THE CRYSTALLINE STATE. Compounds I-III were dissolved in ethyl ether and distributed over the inside surface of a borosilicate flask (using rotation and air stream). Irradiation through glass resulted in a photo-reaction, with formation of a major product identical to those isolated from solution-phase reactions.

RESULTS AND DISCUSSION

Elemental Analyses and Melting Points. Elemental analyses showed that the major photoproducts of I-III had lost the equivalent of NH (Table I).

Thin-Layer Chromatography and Gas-Liquid Partition Chromatography. Tlc and glpc behavior of starting materials and photolysis products (Table II) suggested that the major

Table I. Elemental Analyses and Melting Points of Photoproducts

Photoproduct analysis	Carbon		Hydrogen		Nitrogen		Sulfur		°C Determined
	Calcd	Found	Calcd	Found	Calcd	Found	Calcd	Found	
C ₈ H ₁₃ N ₃ OS (IV)	48.21	48.16	6.59	6.57	21.01	21.00	16.01	16.10	194 ^a
C ₇ H ₁₁ N ₃ OS (V)	45.38	45.26	6.00	5.95	22.69	22.80	17.30	17.24	142 ^b
C ₁₀ H ₁₅ N ₃ OS (VI)	53.24	53.20	6.72	6.65	18.63	18.60	14.21	14.18	193 ^a

^a Decomposition prior to melting. ^b Slight decomposition with melting.

Table II. Thin-Layer Chromatographic and Gas-Liquid Partition Chromatographic Data for Asymmetric Triazin-5(4H)-ones and Photoproducts

Compound	Tlc data		Glpc data	
	Solvent system ^a	Relative R _f (1 = 1.00)	Column ^b	Retention time, min
I	A	1.00	A	3.3
	B	1.00	B	3.7
II	A	0.81	A	2.7
	B	0.76	B	3.0
III	A	0.92	A	11.8
	B	0.87	B	
IV	A	0.66	A	3.5
	B	0.54	B	4.2
V	A	0.56	A	3.6
	B	0.35	B	4.4
VI	A	0.71	A	
	B	0.41	B	

^a Solvent system: (A) = chloroform/acetone (9:1 v/v). (B) = benzene/ethyl ether (1:1 v/v). ^b Column: (A) = 3% OV-1 liquid phase on 80/100 Mesh Gas Chrom Q; 6 ft stainless steel column, 1/8 in. i.d.; carrier gas flow 25 ml/min helium; flame ionization detection. (B) = 1% SE-30 liquid phase on 60/80 mesh Gas Chrom Q; 6 ft borosilicate glass column, 1/8 in. i.d.; carrier gas flow 40 ml/min helium; electron ionization detection.

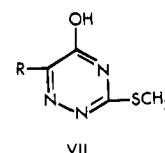
isolated products (IV–VI) were more polar than their respective precursors [refer to Pape and Zabik (1970) for behavior correlations noted for series of carbon-two substituted *s*-triazine analogs].

Mass Spectroscopy. The mass spectra of these photoproducts are characterized by a molecular ion *m/e* 15 units below their respective starting material: the even mass number and isotopic abundance supported the loss of NH. Although, in each case, the base peak appeared at *m/e* 69 and suggested a common molecular genesis, the fragmentation pattern was insufficient to determine whether rearrangement of the heterocyclic ring had occurred (Figure 1).

Infrared Spectroscopy. The ir spectra of I–III and their respective products exhibited striking dissimilarities: loss of primary amine stretching vibrations in the 3300 cm⁻¹ region; increased absorption and complexity in the 1600–1700 cm⁻¹ region of the ir—suggestive of an intramolecularly bonded

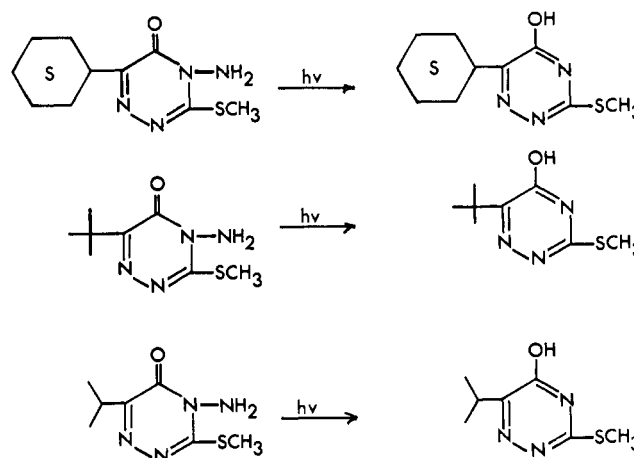
carbonyl or enol function; and appearance of an intense absorption between 2500–3000 cm⁻¹, strikingly similar to the observed enol–keto tautomerism occurring in the ir spectra of 2-hydroxy-*s*-triazines (Padgett and Hamner, 1958; Pape and Zabik, 1970) (Figure 2).

These data suggested the 1,2,4-triazine ring system (VII) as the photoproduct.



Nuclear Magnetic Resonance Spectra. The nmr spectra of I–III and products (Table III) supported the proposed structural system by the absence of a primary amine (2H) signal and the relatively unaltered chemical shifts of the SCH₃ and alkyl functions in product spectra. The absence of a one hydrogen signal for the enol–keto tautomer is attributed to exchange.

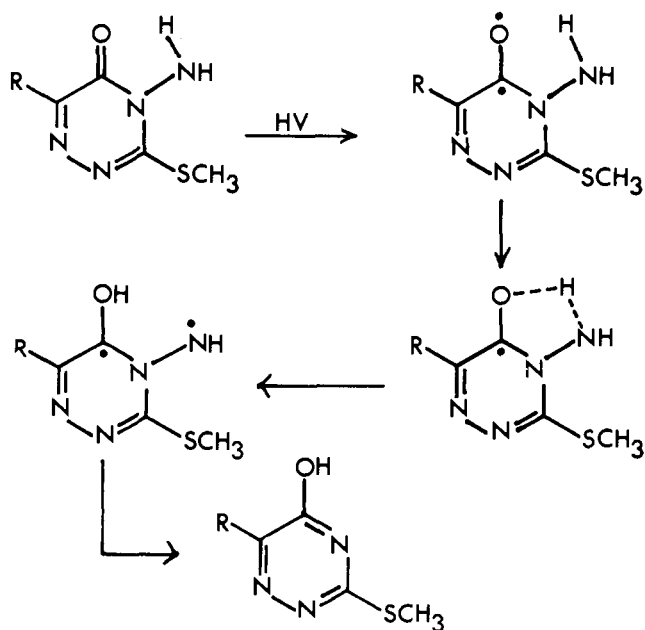
These data allowed the assignment of structures to the respective photoproducts of I–III as 5-hydroxy-6-*tert*-butyl-3-(methylthio)-1,2,4-triazine (IV), 5-hydroxy-6-isopropyl-3-(methylthio)-1,2,4-triazine (V), and 5-hydroxy-6-cyclohexyl-3-(methylthio)-1,2,4-triazine (VI).

Table III. Nuclear Magnetic Resonance (nmr) Data of Asymmetric Triazin-5(4H)-one Photoproducts^a

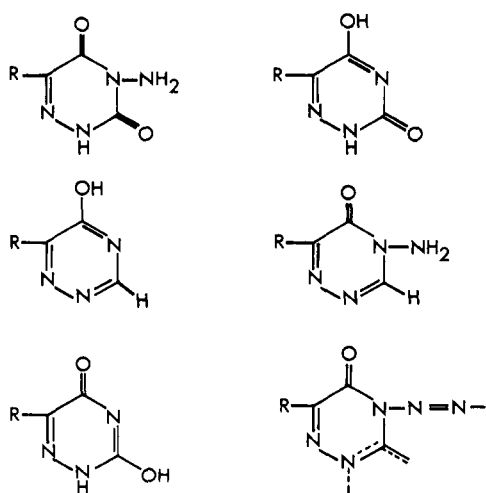
Compound	Nmr solvent	-SCH ₃	-NH ₂	-Alkyl
I	CDCl ₃	7.25 (3 H) (s)	4.85 (2 H) (s)	8.40 (9 H) (s)
II	CDCl ₃	7.35 (3 H) (s)	4.85 (2 H) (s)	8.60 (6 H) (d) 6.55 (1 H) (M)
III	CDCl ₃	7.38 (3 H) (s)	4.95 (2 H) (s)	8.30 (11 H) (m)
IV	CD ₃ CN	7.78 (3 H) (s)		9.0 (9 H) (s)
V	CD ₃ CN	7.80 (3 H) (s)		9.17 (6 H) (d) 7.15 (1 H) (m)
VI	CD ₃ CN	7.70 (3 H) (s)		(8.85) (11 H) (m)

^a Nmr chemical shifts expressed in tau (τ) values, relative to tms. (s) = singlet, (d) = doublet, (m) = multiplet.

Reaction Mechanism. One attractive reaction pathway for the conversion of I-III \rightarrow IV-VI involves an intramolecular hydrogen abstraction, mechanistically analogous to the γ -hydrogen abstraction of aliphatic ketones (Calvert and Pitts, 1966). This would involve excitation of the carbonyl, *via* some unelucidated excited state, to yield a "biradical." This radical would then abstract an amine hydrogen *via* an intramolecular five-membered cyclic transition state, followed by electron shift, with elimination of NH to yield product.



Minor Photoproducts. Chromatographic and mass spectral data suggest that the minor photoproducts formed after prolonged irradiation of I-III or IV-VI in solution or as a solid consist of compounds whose formation is explicable in terms of hetero atom oxidations, intramolecular rearrangements, and desulfurization. Although not definitely identified, reaction mechanisms leading to such product multiplicity are based on reported literature and structural/photocatalytic analogies.



Formation of the "dicarbonyl" analogs of I-III may proceed *via* a sulfone or sulfoxide intermediate formed by photooxidation of the methylthio group [Plimmer *et al.* (1969) postulated that the unstable sulfone or sulfoxides of 2-methylthio-*s*-triazines would yield their 2-hydroxy analogs]. The cyclic hydroxylated ketones might then be formed by the competitive elimination of NH from the "dicarbonyl," analogous to I-III \rightarrow IV-VI. Hydroxy or keto desulfurization products may be formed *via* an elimination mechanism similar to that reported for *s*-triazines (Plimmer *et al.*, 1969; Pape and Zabik, 1970). Other pathways may include dimerization *via* amine hydrogen abstraction to yield azo compounds (Rosen *et al.*, 1970) and head-head or head-tail dimerization products (Neckers, 1967). At present, there is no analytical evidence to support the occurrence of these latter products.

CONCLUSIONS

The photolysis of I-III under a wide range of reaction conditions and at wavelengths greater than 290 nm indicates the potential environmental significance of such nonbiological degradations. Determination of photoproduct formation and residual level in the field would dictate toxicological evaluations and analytical procedures necessary to studies of its occurrence and ecological "burden." These particular triazinone photoproducts ("deaminated" compounds) are considerably less effective biologically than their corresponding parent compounds (Waggoner, 1971).

ACKNOWLEDGMENT

The authors are grateful for the cooperation and assistance of T. B. Waggoner, Biochemical Section, Chemagro Corp. Mass spectra were determined in the laboratory of C. C. Sweeley by J. E. Harten.

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Received for review April 26, 1971. Accepted July 2, 1971. Presented at the Joint Conference, CIC-ACS 159th Mtg., Division of Pesticide Chemistry (Probationary), Toronto, Canada, May 1970. Research supported in part by grants from the National Institute of Health, Food and Drug Administration, and Environmental Protection Agency (Grant No. CC-00246-03 and 5R01 FD-00223-05, and 8R01EP-00801-06) and the Michigan Agricultural Experiment Station. Michigan Agricultural Experiment Station Journal Article No. 5571.