Photochemistry of Bioactive Compounds

Photodecomposition of 2-(1,3-Dioxolane-2-yl)-Phenyl-N-Methyl Carbamate

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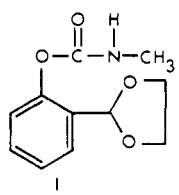
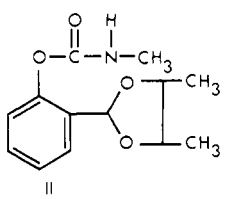
Photodecomposition of 2-(1,3-dioxolane-2-yl)-phenyl-N-methyl carbamate (Ciba's C-8353) in methyl alcohol at 253.7 and 300 nm resulted in the formation of 3-methyl-2H-1,3-benzoxazine-2,4-(3H)-dione, in yields greater than 85%. Photolysis in water at 300 and 360 nm yielded 2-(1,3-dioxolane-2-yl)-phenol and 2-N-methylcarbamyl-benzaldehyde as the only isolable products. The mass spectrometry of these systems is considered in some detail.

Ciba's C-8353 [2-(1,3-dioxolane-2-yl)-phenyl-N-methyl carbamate] I is representative of a new class of substituted phenylcarbamate insecticides presently under development. Some information has been reported previously on the photodegradation of otherinsecticidal carbamates. Unidentified cholinesterase inhibitors have been separated by thin-layer chromatography after the irradiation of materials with laboratory ultraviolet light and in natural sunlight (Crosby *et al.*, 1965). Zectran (4-dimethylamino-3,5-xylyl methylcarbamate) and metacil (4-dimethylamino-3-cresyl methylcarbamate) undergo a photooxidation of the dimethylamino moiety. Degradation products include the toxic 4-methylamino and 4-amino analogs, and the less toxic 4-methylformamido and 4-formamido analogs. No report was made of the photochemical hydrolysis of the carbamate's ester linkage (Abdel-Wahab and Casida, 1967). Investigations of the photolysis of the insecticide sevin (1-naphthyl N-methylcarbamate) have shown that hydrolysis does occur in aqueous solution, but not in hydrocarbon solutions (Aly, 1969).

The present investigation was undertaken to gain information on the photochemistry of this new class of ring-substituted phenyl-carbamate insecticides.



I



II

MATERIALS AND METHODS

Insecticidal Carbamates. The C-8353 I and C-10015 [2-(4,5-dimethyl-1,3-dioxolane-2-yl)-phenyl-N-methyl carbamate] II were obtained from CIBA Agrochemical Company, Division of CIBA Corp., Vero Beach, Fla. They were received as a technical grade (95% purity) and were recrystallized from benzene or benzene-*n*-heptane (1 to 1) until gas-liquid partition chromatography (glpc) and thin-layer chromatography (tlc) showed no impurities. Chemical authenticity was supported by observed melting point (mp), infrared (ir) spectrum, and nuclear magnetic resonance (nmr) spectrum.

Solvents. Methyl alcohol used in photochemical reactions was glass-distilled (Burdick and Jackson Laboratories, Inc., Muskegon, Mich.). At all other times, analytical grade solvents were used. All water used as a solvent in photolysis reactions was distilled and deionized, and had a pH of approximately 7.

Photochemical Equipment. Solution-phase reactions were held in quartz vessels and irradiated in a Rayonet photochemical reactor (The Southern N. E. Ultraviolet Co., Middletown, Conn.). Lamps having a primary ultraviolet emission at 253.7, 300, and 360 nm were used in this investigation (Cat. No. N.P.R.-2537, -3000, -3600, respectively). Photolysis was carried out at approximately 25° C in a magnetically stirred system.

Analytical Equipment. Melting points were determined with a hot-block apparatus, using glass coverslips. All determinations are reported as uncorrected values.

Infrared spectra were determined as potassium bromide discs with a Perkin-Elmer 337 grating spectrophotometer (Perkin-Elmer Corp., Norwalk, Conn.).

Ultraviolet (uv) spectra were obtained in spectrophotometric grade solvents (Mallinckrodt Chemical Works, St. Louis, Mo.), and were recorded with a Beckman DB-G grating spectrophotometer (Beckman Instruments, Inc., Fullerton, Calif.).

Nuclear magnetic resonance spectra were recorded using a Varian A-60 high-resolution instrument (Varian Associates, Palo Alto, Calif.). Samples were dissolved in deuterated acetone-d_6, methanol-d_4, or methylene chloride-d_2 (Mallinckrodt). Tetramethylsilane was used as an internal standard.

Gas-liquid chromatographic analyses were accomplished with a Beckman GC-4 instrument, equipped with a rotary fraction collector and flame ionization detector. The column was a 5% (by weight) Carbowax 20-M liquid phase on 60/80 mesh Gas-Chrom Q (Applied Science Laboratories, Inc., State College, Pa.). Operating parameters were generally as follows: stainless steel column of $^1/_8$-in. outside diameter, 6 ft in length; column flow of 40 ml prepurified helium (99.997% purity) per min; column temperature of 150–180° C; detector temperature of 250° C.

Thin-layer chromatography was accomplished on precoated analytical plates of silica gel HF-254 with fluorescent indicator (Brinkmann Instruments, Inc., Westbury, N.Y.) using solvent systems consisting of methylene chloride-acetonitrile (1 to 1), ethyl ether-*n*-hexane (3 to 1), and ethyl ether.

A combination of glpc and tlc was used to determine if these materials or their photoproducts underwent a thermal or catalytic decomposition and/or rearrangement under chromatographic conditions. C-8353 did undergo a thermal decomposition when subjected to glpc, forming the phenolic

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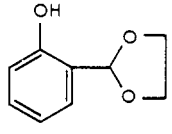
derivative (III) as the only detectable product. Conversion to phenols under similar conditions has been reported for several other carbamates.

Column chromatography was accomplished with a 2 by 800 cm column of 100 mesh silicic acid (Mallinckrodt), 2 to 1 ethyl ether-hexane developer, and an automated fraction collector.

Mass spectra were obtained using an LKB-9000 gas chromatograph-mass spectrometer (LKB Instruments, Inc., Rockville, Md.). Spectra were determined using the direct inlet system at an ionizing potential of 70 or 13 electron volts (eV).

Elemental analyses for carbon, hydrogen, and nitrogen were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.



III

EXPERIMENTAL

Photolysis of C-8353 in Methyl Alcohol. Solutions of C-8353 ranging in concentration from 0.1 to 5.0 g in 400 ml of methanol were photolyzed with uv lamps having primary emissions at 253.7 and 300 nm. The course of the photochemical reaction was followed by glpc and tlc, as well as by uv spectroscopy. The final reaction solution was concentrated by solvent removal (under partial vacuum and a warm water bath) to yield a solid product which was recrystallized from methyl alcohol to yield greater than 85% of clear, glassy needles. Methanol solutions of C-8353 held in the dark and under gentle refluxing (with subsequent recrystallization) yielded only starting material.

Photolysis of C-8353 in Water. Photolysis in water under similar conditions as described above yielded a great deal of polymer(s). Irradiation of a 0.5% solution of C-8353 at 360 nm for 42 hr resulted in the formation of several products, as determined by tlc. The photolyzed solutions were extracted with ethyl ether, dried over anhydrous sodium sulfate, and chromatographed on a silicic acid column. This procedure allowed the isolation of one product of increased polarity which could also be isolated by extraction of the photoreaction with methylene chloride, and recrystallization of the residue from ethyl ether or benzene. The only other characterized photoproduct was resolved by tlc. Aqueous solutions of C-8353 did not decompose when held in the dark.

Photolysis of C-8353 in Acetone. The photodecomposition of C-8353 was also studied in acetone. Aliquots taken during the reaction were analyzed by glpc and tlc.

Photolysis of C-10015 in Methanol. The photolysis of C-10015 was studied in methanol to determine the chemical specificity of the decomposition and rearrangement involving the unsubstituted dioxolane ring of C-8353. Photolysis of C-10015 in methanol was carried out at 253.7 and 300 nm, using a mixture of the *cis* and *trans* isomers. Product formation was followed by glpc and tlc.

Preparation of 3-Methyl-2H-1,3-Benzoxazine-2,4-(3H)-dione (IV). This compound was synthesized according to the procedures of Rekker and Nauta (R. F. Rekker and W. T. Nauta, 1964). Recrystallization of the solid product from methanol yielded approximately 85% IV, mp 146° C (lit. 140° C).

Preparation of 2-(1,3-Dioxolane-2-yl)-Phenol (III). A mixture of 61 g of salicylaldehyde, 41 g of ethylene glycol, 0.25 g of zinc chloride, 0.4 ml of concentrated phosphoric acid, and 150 ml of benzene was refluxed until no more water was separated (azeotropically). The reaction mixture was washed with water, and the benzene was decanted off and dried over anhydrous magnesium sulfate. Concentration of this benzene layer yielded an impure product which, upon recrystallization, yielded pure III. Compound III may be alternatively named as phenol-*o*-(1,3-dioxolane-2-yl).

From III, the carbamate I may be prepared easily by the base catalyzed (triethylamine) reaction of methyl isocyanate with III in toluene.

Hydrolysis of 2-N-Methylcarbamyl-Benzaldehyde (XII). Hydrolysis of XII was achieved by heating approximately 10 mg of XII in 20 ml of 1M hydrochloric acid at 100° C for 10 min. Analysis by glpc and tlc showed the total conversion of XII to salicylaldehyde.

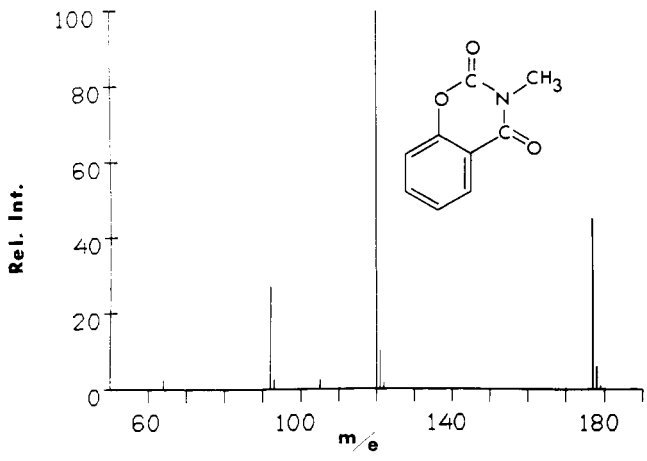


Figure 1. Mass spectrum of IV at 70 eV

RESULTS AND DISCUSSION

Major Photoproduct of C-8353 (I) in Methyl Alcohol. Photolysis of C-8353 in methanol at 253.7 and 300 nm yielded, upon recrystallization from methanol, a pure product in greater than 85% yield. The mp was 148° C, and the elemental analysis showed the loss of the equivalent of C_2H_6O. The analysis (calcd: 61.02% C; 3.98% H; 7.91% N and found: 61.33% C; 4.02% H; 7.94% N) was consistent with the empirical formula of $C_9H_7NO_3$.

The mass spectrum of the photoproduct (Figure 1) confirmed the elemental composition—judged by molecular weight and isotopic abundance. The presence of a strong peak at *m/e* 120 (P-57) was initially suggestive of a substituted N-methylcarbamate, but there was no ion present at *m/e* 57 $(O{=}C{=}N{-}CH_3)^+$.

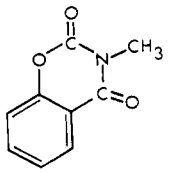
The ir spectrum of this product was different from the spectrum of I in several major respects: (1) the strong N—H stretching at 3330 cm^{-1} present in C-8353 was absent in the photoproduct; (2) the strong C=O stretching at 1725 cm^{-1} appeared as a multiplet of at least two carbonyl absorbances in the product; and (3) the aliphatic C—H stretching in the 2870–3000 cm^{-1} region was greatly diminished in the product's spectrum. Absorbances characteristic of esters and/or alcohols were not present.

The nmr spectrum of the photoproduct in methylene chloride -d_2 showed the presence of only two types of protons, based on observed chemical shifts. A singlet appeared at τ 6.6. Integration assigned three hydrogens to this signal. It was assigned as a methyl with no adjacent hydrogens. The other absorbance appeared as a complex multiplet at

τ 2.0–3.0. Integration showed the contribution of four protons, due to the nonequivalent hydrogens of the phenyl ring.

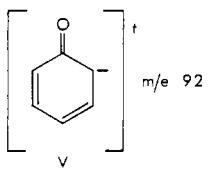
These data suggested that photochemical scission of the dioxolane ring had occurred, followed by the intramolecular cyclization to yield the six-membered benzoxazine derivative (IV).

The ir spectrum of a synthesized sample (Rekker and Nauta, 1964) and the isolated photoproduct were identical. Thus, the major photolysis product of C-8353 in methanol may be assigned the structure 3-methyl-2H-1,3-benzoxazine-2,4-(3H)-dione (IV).

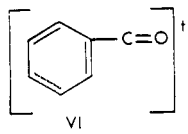


IV

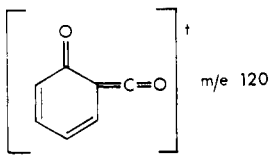
A reexamination of the mass spectral fragmentation pattern was consistent with structure IV. The following assignments were made to the major ions present in the mass spectrum of IV:



V m/e 92



VI m/e 105



VII m/e 120

Photoproducts of C-8353 in Water. One phenolic product was resolved by tlc after the irradiation of I in water at 360 nm. Chromogenic tests indicated it was a phenol (Stahl, 1965). It co-chromatographed on tlc (three solvent systems) with an authentic sample of 2-(1,3-dioxolane-2-yl)-phenol (III). Chromatography did not allow quantitation of this product.

The other isolable water photoproduct was obtained by column chromatography of an ethyl ether extract of the reaction solution, or by recrystallization of the material obtained by methylene chloride extraction of the final reaction solution. The product had an mp of 135° C. Elemental analysis indicated the loss of C_2H_4O had occurred as the result of photolysis. The empirical formula was determined to be $C_9H_9NO_3$ (calcd: 60.33% C; 5.02% H; 7.82% N and found: 60.49% C; 5.06% H; 7.80% N).

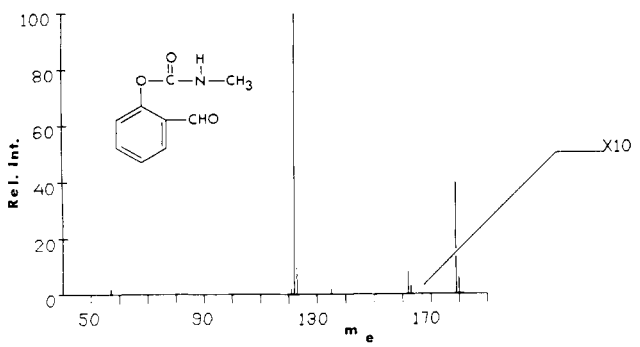
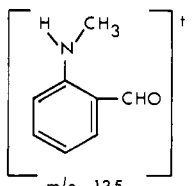


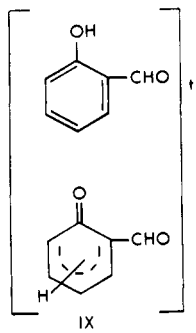
Figure 2. Mass spectrum of XII at 13 eV

Mass spectrometry (Figure 2) showed a molecular ion at *m/e* 179 and an isotopic abundance in agreement with the elemental composition. The fragmentation pattern at 13 eV was quite diagnostic of a substituted phenylcarbamate (Benson and Damico, 1968). The ion at *m/e* 135 (P-44) could be obtained by elimination of CO_2 and rearrangement to VIII. The base peak appears at *m/e* 122 (P-57) and is assigned a structure equivalent to IX. A proposed H migration mechanism, leading to the formation of X, is discounted because of the large abundance of IX. The *m/e* 57 molecular fragment is seen in the spectrum, and is assigned structure XI.

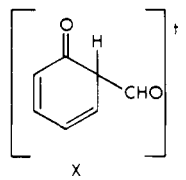


m/e 135 (P-44)

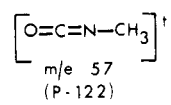
VIII



IX m/e 122 (P-57)



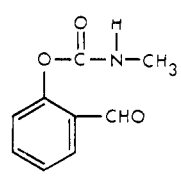
X



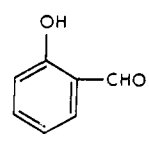
XI m/e 57 (P-122)

The ir spectrum of this water photoproduct was characterized by the presence of a strong N-H stretching absorbance, a decrease in intensity in the methylene region of absorbance, and multiple carbonyl absorbances in the 1700 cm^{-1} region.

From these data it was hypothesized that the photochemical cleavage of the dioxolane ring had occurred, with the generation of the benzaldehyde derivative of the carbamate, XII. Attempts made to synthesize this photoproduct from the known phenolic analog, XIII, were fruitless; however, it was hydrolyzed by acid to yield salicylaldehyde (XIII) (2-hydroxybenzaldehyde), as determined by tlc and glpc. The glpc retention time of this hydrolysis product, determined to be free of I by tlc, was identical to that of authentic XIII. Therefore, this photolysis product of I in water is 2-N-methylcarbamyl-benzaldehyde (XIII).

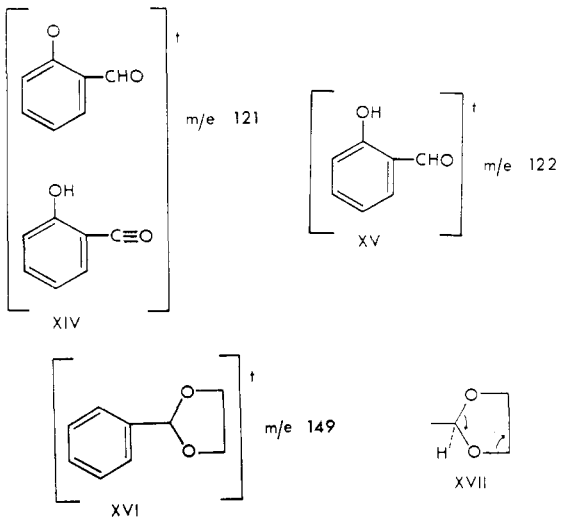


XII



XIII

Mass spectral analysis of I via the direct inlet system disclosed an interesting phenomenon—the thermal degradation of the carbamate moiety, forming methyl isocyanate and the substituted phenol, III. This phenolic derivative was analyzed by mass spectrometry (Figure 3). Prominent ions are given the following assignments: It is believed that cleavage of the dioxolane ring occurs by a stepwise electron shift, schematically represented in XVII.



Photolysis of I in Acetone. Photolysis of I in acetone at 253.7 nm resulted in the formation of two major products. One of them behaves chromatographically as the product isolated from methanol. Further irradiation of these acetone solutions resulted in the formation of secondary products that were not eluted by glpc. The irradiation of I in methanol at 360 nm did not result in a photochemical reaction.

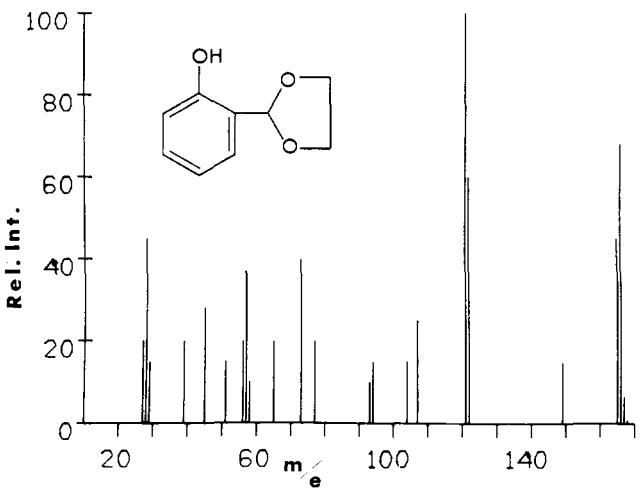


Figure 3. Mass spectrum of III at 70 eV (abundances greater than 10% base peak represented)

Photolysis of C-10015 (II). Photolysis of C-10015 (II) did occur in methanol solution at 253.7 nm. Analysis by glpc showed that IV was not formed under these conditions. No products were identified.

SUMMARY AND CONCLUSIONS

Compound C-8353 (I) undergoes a solution-phase photochemical reaction in methyl alcohol and in water. A benzoxazine derivative (IV) is formed in greater than 85% yield in methanol, and multiple products are formed in water—two that are isolable being the benzaldehyde derivative (XII) and the substituted phenol (III). Studies indicate that these reactions may be of significance in determining the persistence of this compound under field conditions.

A photochemical mechanism has not been proposed for these reactions; however, studies with the 4,5-dimethyl-1,3-dioxolane-2-yl analog (II) indicate that formation of the benzoxazine product in methanol is specific to the unsubstituted dioxolane ring of I. Mechanistic studies, utilizing N-substituted and dioxolane-substituted analogs, are planned.

Mass spectral fragmentation patterns of these systems appear to be quite straightforward and very applicable to problems of structural elucidation.

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