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Photolysis of 3-Hydroxyisoxazoles

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Photolysis of 3-hydroxy-5-phenylisoxazole in methanol with a low-pressure mercury lamp afforded 5-phenyl-4-oxazolin-2-one, together with small amounts of benzoic acid and benzoylacetamide. Similarly, 3-hydroxy-5-methylisoxazole in distilled water afforded 5-methyl-4-oxazolin-2-one as the major product. Both isoxazoles were stable in sunlight for up to 20 days.

3-Hydroxy-5-methylisoxazole is a plant-protecting agent[1] widely used under the name of Hymexazol, or Tachigaren,® and 3-hydroxy-5-phenylisoxazole is a metabolite or hydrolyzate of a registered insecticide, Isoxathion[2] [O, O-diethyl, O-(5-phenyl-3-isoxazolyl) phosphorothioate]. The present work deals with the photolysis of these 3-hydroxyisoxazoles.

Extensive studies on the photolysis of isoxazoles have shown that a major photolytic pathway is the rearrangement of the isoxazole nucleus to the corresponding oxazoles.[3~7] This general rule has been extended to 3-hydroxyisoxazoles by Göth *et al.*,[8] who showed that ibotenic acid and 3-hydroxy-5-methylisoxazole are converted by ultraviolet light to muscazone and 5-methyl-4-oxazolin-2-one, respectively; the latter compound was not isolated, but was determined by NMR spectrometry of the reaction mixture.

On the other hand, muscazone together with ibotenic acid has been isolated from *Amanita muscaria*.[9] Göth *et al.*[8] have pointed out that the muscazone is not a photochemical artifact derived from ibotenic acid during the isolation procedure, but is biosynthesized by the fungus, although it has not been clarified whether the latter is a precursor to the former.

From these studies, together with the known similarity between the photodecomposition products and metabolites of various kinds of pesticides,[10,11] a photolytic study on 5-methyl-, and 5-phenyl-3-hydroxyisoxazoles appeared important not only from the standpoint of environmental toxicology, but also to afford useful information for metabolic studies on Hymexazol and Isoxathion. Thus, the present work was undertaken on photolysis under sunlight and ultraviolet light. It was found that both compounds were stable in sunlight, but were readily photolyzed by ultraviolet light.

3-Hydroxy-5-phenylisoxazole (I) in methanol was irradiated with 253.7 nm light at room temperature while nitrogen was passed through the solution. The reaction was monitored by UV spectrometry. The longer wavelength absorption of the isoxazole (I) [λ_{max}^{MeOH} nm(ε): 259(18,800)] gradually disappeared and a new absorption appeared at *ca.* 275 nm. The strength of this absorption reached a maximum after 6 hr. Chromatography of the reaction mixture afforded a major and at least four minor products in addition to I. Further irradiation afforded several new products.

The major product was 5-phenyl-4-oxazolin-2-one (IV), and its melting point and IR spectrum were in accord with the reported data.[12] It was stable on heating in ethanol, and was derivatized to α-benzoylaminoacetophenone by the method of Strumza *et al.*[13]

Among the minor products, benzoic acid(VI) and benzoylacetamide(V) were isolated and identified by comparison of the IR and MS spectra with those of authentic samples; other products were not identified. Although in many instances azirine derivatives have been isolated as intermediates of the photorearrangement of isoxazoles, we could not isolate

the α-lactam (III).

The formation of benzoylacetamide (V) suggests the presence of a diradical intermediate (II) and a radical proton probably derived from the solvent, methanol. The mechanism of formation of benzoic acid (VI) is unclear and no detailed sequence study has been done; however, it is unlikely that benzoylacetamide (V) is responsible for the formation of benzoic acid, because V was quite stable under irradiation with 253.7 nm light in methanol.

Similarly, photolysis of 3-hydroxy-5-methylisoxazole (VII) in distilled water with 253.7 nm light afforded a major and at least two minor products. The major product was indeed 5-methyl-4-oxazolin-2-one (IX), and its NMR spectrum was identical with that reported by Göth *et al.*[8] Other products were not identified. Again, we could not isolate the α-lactam (VIII), nor could we confirm the formation of acetoacetamide or acetic acid. The pH of the sample solution was unchanged during irradiation, and an attempt to detect acetate ions with lanthanum nitrate[14] was unsuccessful because 3-hydroxy-5-methylisoxazole (VII) was also colored blue to purple by the reagent.

In connection with the objectives of this study, it should be noted that metabolic studies have revealed a striking analogy between the major products of photolysis and metabolism: 5-methyl- and 5-phenyl-4-oxazoline-2-one were detected in "unsterilized" soils treated with Hymexazol[15] and Isoxathion, or 3-hydroxy-5-phenylisoxazole,[16] respectively. 5-Phenyl-4-oxazolin-2-one was also found to be produced as a metabolite of 3-hydroxy-5-phenylisoxazole in rat liver homogenates.[17]

EXPERIMENTAL

Melting points were taken on a Yanagimoto microscopic hotstage and are uncorrected. Mass spectra were taken with a JEOL JMS-O1SG spectometer. The light sources were an Ishii low-pressure mercury lamp (30W) and an Ushio high-pressure mercury lamp (100W). Benzoylacetamide was prepared by the reported procedure.[18] Thin-layer chromatography was conducted with Merck precoated silica gel GF_{254} (0.25 mm).

3-Hydroxy-5-phenylisoxazole (I)

(a) The isoxazole (400 mg) was irradiated in methanol (200 ml) under nitrogen with a low-pressure mercury lamp for 6 hr. The solvent was removed and the residue was chromatographed on plates with a hexane-ethylformate (1: 1) solvent system. A major (*Rf*: 0.30) and at least four minor products in addition to unreacted I (*Rf*: 0.44) were detected. The separated products were extracted from the silica gel with acetone, and each was rechromatographed in the same solvent system. The major product, obtained as pale yellow needles in 18% yield (72 mg) after recrystallization from ethanol, was determined to be 5-phenyl-4-oxazolin-2-one (IV) on the basis of the following data: mp 217~218°C (lit. mp 216~217°C,[12] 223~224°C[13]). *Anal.* Found: C, 67.06; H, 4.29; N, 8.84. Calcd. for $C_9H_7NO_2$: C, 67.07; H, 4.38; N, 8.69%. MS *m/e*: 161 (M^+), 117, 106, 105, 90, 89. IR ν_{max}^{KBr} cm^{-1}: 3190, 3140, 1740, 1720. NMR δ (60 MHz, d_6-DMSO): 7.2~7.7 (6H, multiplet, aromatic and H-C (4)), 10.8 (1H, broad, NH). UV λ_{max}^{MeOH} nm (ε): 275 (21,200).

Two minor products (*Rf*: 0.51 and 0.16) were benzoic acid (VI) (yield: 15 mg) and benzoylacetamide (V) (yied: *ca.* 3 mg), respectively; others (*Rf*: 0.68 and 0.08, yield: 8 and 6 mg, respectively) were not identified.

Benzoic acid (VI): mp 119°C (from ethyl ether). *Anal.* Found: C, 68.29; H, 4.92. Calcd. for $C_7H_8O_2$: C, 68.84; H, 4.95 %. IR ν_{max}^{KBr} cm^{-1}: 3200~2500 (OH), 1685 (C=O). MS *m/e*: 122 (M^+), 105, 77.

Benzoylacetamide (V): IR ν_{max}^{KBr} cm^{-1}: 3430 (NH), 1680 (C=O), 1640 (C=O). MS *m/e*: 163 (M^+), 105, 77.

(b) For irradiation with sunlight, samples were prepared by dissolving 400 mg of the isoxazole (I) in 200 ml of methanol and dispersing the solution in 800 ml of distilled water. Irradiation was carried out for up to 20 days in 1-liter Erlenmeyer flasks (Iwaki #7740, Pyrex®) covered with a beaker to prevent contamination. After removing methanol, the remaining suspension was extracted with ethyl ether. The ether extract was chromatographed on plates. However, no product was detected and recovery of the starting compound was nearly quantitative.

3-Hydroxy-5-methylisoxazole (VII)

(a) The isoxazole (600 mg) was irradiated in distilled water (200 ml) with a low-pressure mercury lamp for 8 hr. Nitrogen was passed through the solution from 30 min before initiation until the termination of irradiation. The reaction mixture was lyophilized and the residue was chromatographed on plates with ethyl ether. A major (*Rf*: 0.46) and at least two minor products were detected in addition to VII (*Rf*: 0.85). The separated products were extracted from the silica gel with a mixture of ethyl ether and methanol (10: 1), and each was rechromatographed in the same solvent

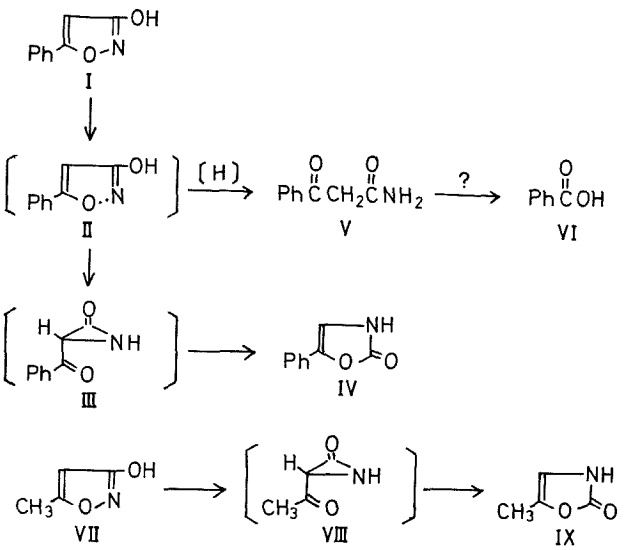

FIG. 1.

system.

The major product, obtained as colorless needles in 11% yield (66 mg) after recrystallization from ethyl ether, was determined to be 5-methyl-4-oxazolin-2-one (IX) on the basis of the following data: mp 78~79°C. *Anal.* Found: C, 48.59; H, 4.95; N, 14.09. Calcd. for $C_4H_5NO_2$: C, 48.48; H, 5.09; N, 14.14%. MS *m/e*: 99 (M^+), 71, 54, 43. IR ν_{max}^{Nujol} cm^{-1}: 3150 (NH), 1730 (C=O). NMR δ (60 MHz, D_2O): 2.10 (3H, doublet, J=1.5 Hz, CH_3–C (5)), 6.47 (1H, quartet, J=1.5 Hz, H–C (4)).

Other products (*Rf*: 0.16 and 0.06; yield: 5 and 12 mg, respectively) were not identified. The latter product apparently decomposed during the isolation procedure since rechromatography afforded two new spots.

(b) A solution of 5.0 g of the isoxazole (VII) in 1 liter of distilled water was irradiated under nitrogen with a high-pressure mercury lamp in a quartz immersion well for 12 hr. Water was removed by lyophilization, and the residue was washed with ethyl ether to separate ether-soluble and ether-insoluble polymeric materials. The ether was removed, and the residue was subjected to silica gel column chromatography with ethyl ether to give 4.8% (240 mg) of 5-methyl-4-oxazolin-2-one (IX) together with several unidentified materials. Approximately 30% of the starting compound was recovered.

(c) A solution of 600 mg of the isoxazole (VII) in 1 liter of distilled water was placed in a 1-liter Erlenmeyer flask (Iwaki #7740). The flask was covered with a beaker and placed outdoors in sunlight for 20 days. Water was removed by lyophilization, and the residue was chromatographed on plates. However, no product was detected besides the starting compound.

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