

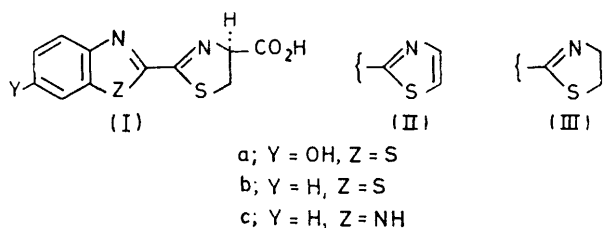
Photochemical Decarboxylation of 2-Phenyl- Δ^2 -thiazoline-4-carboxylic Acid¹

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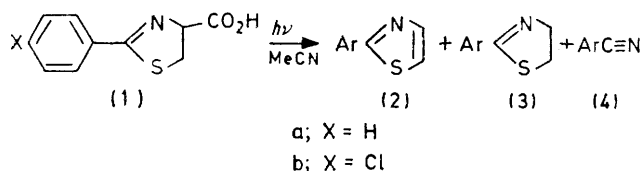
Irradiation of 2-phenyl- and 2-(*p*-chlorophenyl)- Δ^2 -thiazoline-4-carboxylic acid in acetonitrile leads in each case to the corresponding thiazole, thiazoline, and benzonitrile. 2-Phenyl- Δ^2 -thiazoline is transformed photochemically into the corresponding thiazole and nitrile. A mechanistic discussion is presented.

PHOTODECARBOXYLATION of various carboxylic acids has been reported,²⁻⁹ and the mechanisms are generally classified as: (a) radical type,^{2,3} (b) molecular reaction or zwitterion type,⁴⁻⁶ and (c) exciplex or excited charge-transfer complex type.⁷

Although there have been several reports on the photodecarboxylation of dihydroaromatic carboxylic acids,^{3,5,8,9} insufficient information is available to establish the mechanism. White *et al.* briefly commented on the photochemical decomposition of firefly luciferin (Ia) in dimethyl sulphoxide to give decarboxy-dihydroxyluciferin (IIa).⁸ Sato examined substituent and pH effects on the photodecarboxylation of the luciferin analogues (Ia—c), but did not obtain mechanistic evidence.^{†10}



We report here the photoreactions of 2-phenyl- (Ia) and 2-(*p*-chlorophenyl)- Δ^2 -thiazoline-4-carboxylic acid (Ib) to give the corresponding thiazolines (3a and b), thiazoles (2a and b), and nitriles (4a and b). Mechanistic discussions are presented on the basis of product analysis and pH effect.



† When irradiated in methanol, compounds (Ia and b) gave the corresponding decarboxy-dehydrogenated products (IIa and b) in 50 and 7.4% yield, respectively, based on the starting materials, whereas (Ic) gave exclusively a decarboxylated product (IIIc) in 10.2% yield. The effect of pH on the photoreaction of (Ia) was observed by u.v. spectroscopy. The ratio of (IIIa) to (IIa) decreased as the pH decreased: in methanol the ratio was 3 : 7; in methanol-water (3 : 1) 4 : 6; and in methanol-4% ammonia 3 : 7. In methanol-N-sulphuric acid the yield of (IIIa) was quantitative.

¹ Presented in part at the 32nd Annual Meeting of the Chemical Society of Japan, Tokyo, April 1975.

² T. O. Meiggs and S. I. Miller, *J. Amer. Chem. Soc.*, 1972, **94**, 1989; F. Chau, C. Gibbons, and D. Barton, *Canad. J. Chem.*, 1972, **50**, 2017.

³ G. D. Weatherby and D. O. Carr, *Biochemistry*, 1970, **9**, 344; G. Cauzzo and G. Joli, *J. Org. Chem.*, 1972, **37**, 1429.

RESULTS AND DISCUSSION

The carboxylic acid (Ia) (3.86mm) or (Ib) (4.27mm) in acetonitrile was irradiated under nitrogen with a low-pressure mercury lamp (30 W; immersion type) at 10–15 °C for 110 or 230 min, respectively. The mixture was then evaporated *in vacuo*, and the residue subjected to preparative thick-layer chromatography on silica gel. The products were identified as the starting material (Ia or b), the thiazole (2a or b), the thiazoline (3a or b), and the nitrile (4a or b) by comparison (i.r. and n.m.r. spectra and/or g.l.c.) with authentic samples. A polymer was also produced.

The results are summarized in the Table, together with

Results of photolyses and/or thermolyses of compounds (Ia and b) and (3a)

Starting material	With or without light	Reaction time (min)	Consumption (%)	Products (%)		
				(2)	(3)	(4)
(Ia)	a	110	34.5	6.5	29	5 ^c
	b	2.5	100		100 ^d	
(Ib)	a	230	56.2	2.5	14	19
	b	2.5	100		100 ^d	
(3a)	a	240	30.0	17		55 ^c

^a With light at 10–15° °. ^b Without light at 250 °C. Isolated yields based on consumed starting material. ^d Determined by g.l.c.

those of the thermal decomposition of the acids (Ia and b). Although thermal decarboxylation occurs at 250 °C to yield quantitatively the corresponding thiazoline

⁴ P. A. Leermakers and G. F. Vesley, *J. Org. Chem.*, 1963, **28**, 160; G. F. Vesley, *J. Phys. Chem.*, 1964, **68**, 2364; C. P. Joshua and G. E. Lewis, *Tetrahedron Letters*, 1966, 4533; R. W. Hay and M. J. Taylor, *Chem. Comm.*, 1966, 525; J. D. Margerum, *J. Amer. Chem. Soc.*, 1965, **87**, 3772; J. D. Margerum and R. G. Brault, *ibid.*, 1966, **88**, 4733; J. D. Margerum and C. T. Petrusis, *ibid.*, 1969, **91**, 2467; A. W. Bradshaw and O. L. Chapman, *ibid.*, 1967, **89**, 2372; C. Azuma and A. Sugimori, *Kogyo Kagaku Zasshi*, 1969, **72**, 239; P. H. McFarlane and D. W. Russell, *Tetrahedron Letters*, 1971, 725; R. J. Moser and E. V. Brown, *J. Org. Chem.*, 1972, **37**, 3938.

⁵ J. F. Biellmann, H. J. Callot, and W. R. Pilgrim, *Tetrahedron*, 1972, **28**, 5911.

⁶ (a) F. Takeuchi, T. Sugiyama, T. Fujimori, K. Seki, Y. Harada, and A. Sugimori, *Bull. Chem. Soc. Japan*, 1974, **47**, 1245; (b) F. R. Stermitz and W. H. Huang, *J. Amer. Chem. Soc.*, 1970, **92**, 1446; 1971, **93**, 3427.

⁷ P. S. Davidson, S. Korkut, and P. R. Steiner, *Chem. Comm.*, 1971, 1052; R. S. Davidson and P. R. Steiner, *ibid.*, p. 1115; *J. Chem. Soc. (C)*, 1971, 1682; R. S. Davidson, K. Harrison, and P. R. Steiner, *ibid.*, 1971, 3480; R. S. Davidson and P. R. Steiner, *J.C.S. Perkin II*, 1972, 1357; D. R. G. Brimage, R. S. Davidson, and P. R. Steiner, *J.C.S. Perkin I*, 1973, 526; J. Libman, *J. Amer. Chem. Soc.*, 1975, **97**, 4139.

⁸ E. H. White, F. McCapra, and G. F. Field, *J. Amer. Chem. Soc.*, 1963, **85**, 337.

⁹ Y. Kanaoka, E. Sato, and O. Yonemitsu, *Chem. and Ind.*, 1968, 1250.

¹⁰ M. Sato, Dissertation, Nagoya University, 1969.

(3a or b) as the only product, no dark reactions were appreciable at room temperature.

The lower yields of photoproducts isolated from (1b) than from (1a) may be due to polymerization of (1b), beginning with a photo-dechlorination.¹¹

Product composition as a function of irradiation time for the photoreaction of (1a) in acetonitrile is shown in Figure 1. The yield of (2a) and (3a) increases with irradiation time to a maximum and then decreases. The decrease in yield can be explained by a further photoreaction of (2a) and (3a). In fact, when irradiated for 240 min under similar conditions, the thiazoline (3a) gave the nitrile (4a) (55%) and the thiazole (2a) (17%).¹² The thiazole (2a) also undergoes a photoreaction, but the decomposition products have not been identified. These facts eliminate the possibility of production of the nitrile (4a) *via* the thiazole (2a). The photoreaction of (2a) was faster than that of (3a), which might explain its earlier maximum. The yield of (4a) increases with

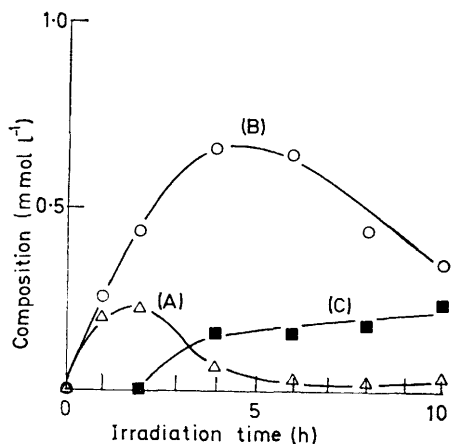


FIGURE 1 Product composition as a function of irradiation time in the photoreaction of the acid (1a) in acetonitrile: (A) the thiazole (2a), (B) the thiazoline (3a), and (C) the nitrile (4a)

decrease in the yield of (3a), in accord with the formation of the former from the latter.

Irradiation of the acid (1a) in the presence of octane-1-thiol increases the yield of the thiazoline (3a), but that of the thiazole (2a) was substantially decreased. Thus, when (1a) (12.1 m) was irradiated in acetonitrile for 3 h, the yield of (3a) was 0.60 m whereas in the presence of the thiol (48 m) the yield was 0.86 m. In both experiments the yield of nitrile (4a) was 0.1 m, and the yields of (2a) were 0.15 m and nearly zero, respectively. These facts suggest the presence of thiazoline radical (5) as an intermediate. Since the ratio of (2a) to (4a) in the photo-

¹¹ For the photodechlorination *via* an electron transfer reaction, see (a) C. Pac, T. Tosa, and H. Sakurai, *Bull. Chem. Soc. Japan*, 1972, **45**, 1169; (b) M. Ohashi, K. Tsujimoto, and K. Seki, *J.C.S. Chem. Comm.*, 1973, 384.

¹² (a) 2-Substituted Δ^2 -thiazolines to the corresponding nitriles: T. Matsuura and Y. Ito, *J.C.S. Chem. Comm.*, 1972, 896; Abstracts Annual Symposium on Photochemistry of Japan, Osaka, October 1972, p. 2B20; (b) 2-substituted Δ^2 -imidazolines to the corresponding imidazoles: T. Matsuura and Y. Ito, *Chem. Letters*, 1972, 431; *Bull. Chem. Soc. Japan*, 1974, **47**, 1724; T. Matsuura, Y. Ito, and I. Saito, *ibid.*, 1973, **46**, 3805.

reaction of (1a) is considerably different from that in the photolysis of (3a), we suppose that additional reaction pathway(s) to (2a) exist [*e.g.* direct formation from (1a)].

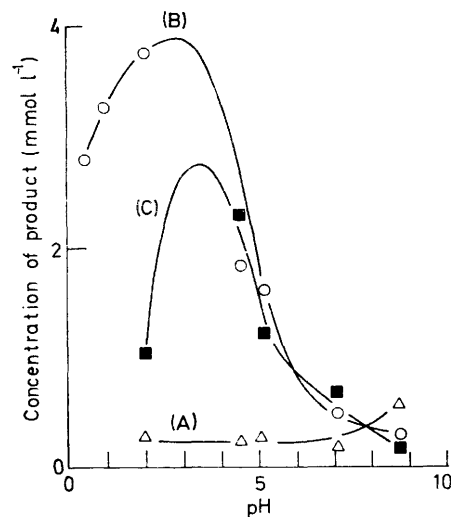
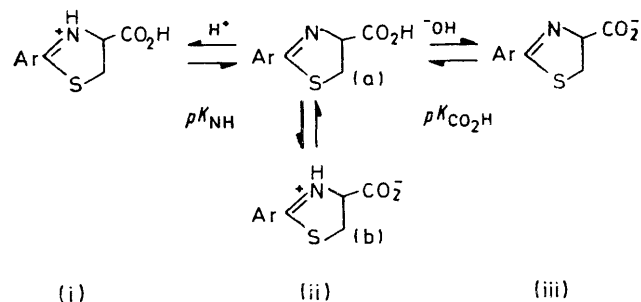


FIGURE 2 Effect of pH on the photoreaction of the acid (1a): (A) the thiazole (2a), (B) the thiazoline (3a), and (C) the nitrile (4a)

The effect of pH on the photoreaction of the acid (1a) in acetonitrile is shown in Figure 2. Yields of (3a) and (4a) increased in order acidic > neutral > alkaline media, but show maxima at pH 3–4. The acid (1a) showed pK_{NH} at 2.9 ± 0.2 and pK_{CO_2H} at 4.0 ± 0.2 , from which isoelectric point (*pI*) was calculated to be 3.5 ± 0.2 .¹³ This *pI* value suggests that the species (ii) is predominant at pH 3–4. No dark decomposition of (3a) and (4a) below pH 3 was observed, which shows that the decrease in their yields in strongly acidic media is not due to acid-catalysed hydrolysis,¹⁴ but probably to the photochemical stability of a conjugate acid (i) of (1a). Similarly, the relatively low yields of (3a) and (4a) in alkaline media may result from the stability of a



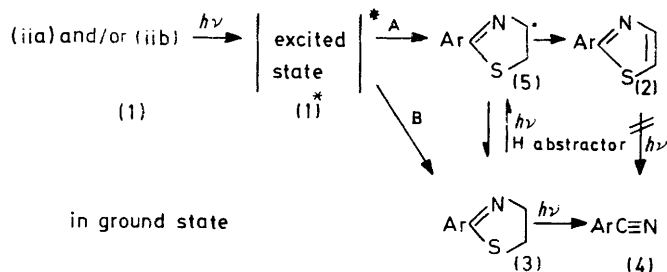
conjugate base (iii) of (1a). On the basis of the pH–yield profile and the *pI* value, the structures (ii) and (b) appear to play an important role in the present photo-decarboxylation. Similar tendencies have been ob-

¹³ See ref. 6b and C. Tanford, *Adv. Protein Chem.*, 1962, **17**, 69.

¹⁴ (a) A. Bruylants and E. F. Medicis, in 'The Chemistry of the Carbon-Nitrogen Double Bond,' ed. S. Patai, Interscience, New York, 1970, pp. 478 and 501; (b) R. J. Moser and E. V. Brown, *J. Org. Chem.*, 1972, **37**, 3938, and references cited therein.

served in the photodecarboxylations of pyridine carboxylic acids^{6a} and pyridyl acetic acid.^{6b}

On the basis of the foregoing facts, possible reaction pathways are outlined in the Scheme. We prefer route A as a main pathway, to give (2) and (3) via the thiazoline radical (5), rather than B, which produces (3) directly, because of the enhancement in the yield of (3) in the presence of thiol.



SCHEME

EXPERIMENTAL

The following instruments were used: JASCO IR-G (i.r.), Shimadzu UV-200 (u.v.), JEOL JNM-MH-100 (100 MHz n.m.r.), and JEOL D-100 (mass) spectrometers; Yanagimoto Yanaco G-1800F gas-liquid chromatograph, and Hitachi-Horiba M-5 pH meter. Spectral data are given as follows: i.r. ν_{\max} in cm^{-1} ; u.v. λ_{\max} in nm (ϵ in parentheses); n.m.r. δ values (tetramethylsilane as internal standard) and J in Hz; and mass spectra in m/e . G.l.c. was performed with a 2.5 mm \times 2 m stainless steel column of 10% Silicone SE-GE-31 on Diasolid L (60–80 mesh) [column temperature, 210 °C; injection temperature, 165 °C; and carrier gas (N_2) at 15–16 ml min^{-1}]. Preparative thick-layer chromatography (p.l.c.) was carried out on glass plates (20 \times 20 cm) with Merck Kieselgel PF₂₅₄ (thickness 2.2 mm) in *n*-hexane-acetone (3 : 1) as developer.

Benzonitrile (4a) and benzamide were purchased from Nakarai Chem. Co. and *p*-chlorobenzonitrile (4b) from Wako Pure Chem. Co. Cysteine, cysteamine, and 2-aminoacetaldehyde diethyl acetal were purchased from Tokyo Chem. Ind. Co. (Thiobenzoyl)thioacetic acid and (*p*-chlorothiobenzoyl)thioacetic acid were prepared according to the method of Kurzer *et al.*,¹⁵ the former as fine red prisms (from benzene-*n*-hexane), m.p. 121–123° (lit.,¹⁶ 125°) and the latter as reddish orange leaflets (from benzene-*n*-hexane), m.p. 120–121° (lit.,¹⁷ 115–117°). Acetonitrile was distilled over phosphorus pentoxide, and then from potassium carbonate before use. The thiazolinecarboxylic acids (1a and b) and the corresponding thiazolines (3a and b) were prepared by condensation of the corresponding dithioates (5a and b) with cysteine or cysteamine as described in our previous paper.¹⁷ The acid (1a) formed needles (from ether), m.p. 121.5–122.5° (lit.,¹⁷ 116–122.5°; lit.,¹⁸ 122°); λ_{\max} (MeCN) 243 (8 300); ν_{\max} (KBr) 3 450br, m, 2 470m, 1 730s, 1 605s, and 1 570m; δ [(CD₃)₂SO] 3.56 (1 H, d, J 9), 3.60 (1 H, d, J 9), 5.24 (1 H, t, J 9), 7.48 (3 H, m), and 7.76 (2 H, m). 2-*p*-Chlorophenyl- Δ^2 -thiazoline-4-carboxylic acid (1b) formed leaflets (from

ethanol), m.p. 169–171°; λ_{\max} (MeCN) 251 (10 300); ν_{\max} (KBr) 3 430br, m, 2 470m, 1 725s, 1 600s, and 1 560m; δ [(CD₃)₂SO] 3.65 (1 H, d, J 8.8), 3.68 (1 H, d, J 8.8), 5.32 (1 H, t, J 8.8), 7.56 (2 H, d, J 8.2), and 7.82 (2 H, d, J 8.2) (Found: C, 49.8; H, 3.25; N, 5.65. C₁₀H₈ClNO₂S requires C, 49.7; H, 3.35; N, 5.8%; m/e 241 (M^+)). The thiazoline (3a) was a liquid, b.p. 126–128° at 7.5 mmHg (lit.,¹⁷ 129–130.5° at 10 mmHg; lit.,¹⁹ 110° at 5 mmHg); λ_{\max} (MeCN) 241 (15 000); ν_{\max} (KBr) 1 605s. 2-*p*-Chlorophenyl- Δ^2 -thiazoline (3b) formed pale yellow leaflets (from ethanol), m.p. 50–52°; λ_{\max} (MeCN) 248 (18 500); ν_{\max} (KBr) 1 605s; δ (CDCl₃) 3.44 (2 H, t, J 8.4), 4.46 (2 H, t, J 8.4), 7.39 (2 H, d, J 8.6), and 7.79 (2 H, d, J 8.6) (Found: C, 54.45; H, 3.8. C₉H₈ClNS requires C, 54.7; H, 4.05%; m/e 179 (M^+)).

2-Phenylthiazole (2a) was prepared according to the method of Lawson *et al.*,²⁰ and 2-(*p*-chlorophenyl)thiazole (2b) was prepared similarly, by condensation of (5a) or (5b) with 2-aminoacetaldehyde diethyl acetal followed by cyclization with polyphosphoric acid. The former was obtained as a liquid, b.p. 130° at 12 mmHg (lit.,²⁰ 267–269° at 732 mmHg); λ_{\max} (EtOH) 286 (17 000); ν_{\max} (neat) 1 650; δ (CDCl₃) 7.16 (1 H, d, J 3.2), 7.30 (3 H, m), 7.72 (1 H, d, J 3.2), and 7.90 (2 H, m); and the latter as crystals (from petroleum), m.p. 37–38° (yield 17.6%); λ_{\max} (MeCN) 290 (21 300); ν_{\max} (KBr) 1 480, 1 090, 975, 825, and 630; δ (CDCl₃) 7.31 (1 H, d, J 3.2), 7.38 (2 H, d, J 9.2), 7.83 (1 H, d, J 3.2), and 7.88 (2 H, d, J 9.2) (Found: C, 55.25; H, 3.3. C₉H₈NSCl requires C, 55.25; H, 3.1%; m/e 195 (M^+)).

General Procedure for Preparative Scale Irradiations of the Carboxylic Acids (1a and b).—The acid (1a) in acetonitrile (200 mg in 250 ml; 3.86mm) was irradiated with a low-pressure mercury lamp [Eiko-sha Halös PIL-30 (30 W); immersion type] at 10–15 °C under nitrogen for 110 min. The mixture was then evaporated *in vacuo* below 45 °C and chromatographed (p.l.c.). Elution with methanol and evaporation *in vacuo* below 45 °C gave four compounds, identical (i.r. and n.m.r. spectra and/or g.l.c.) with authentic samples of (1a), (2a), (3a), and (4a). Similarly the acid (1b) in acetonitrile (231.5 mg in 225 ml; 4.27mm) gave compounds (2b), (3b), and (4b). The results are summarized in the Table.

No detectable reaction took place without u.v. light under similar conditions.

Effect of pH on the Photoreaction of the Acid (1a).—Small-scale irradiations of (1a) were carried out as follows. To 2 ml portions of solutions (15.1mm) of (1a) in acetonitrile were added 0.5 ml of (a) acetonitrile, (b) aqueous 0.1M citrate-phosphate or phosphate buffer (pH 3, 4, and 8), (c) aqueous 0.1N-hydrochloric acid, and (d) aqueous 15% hydrochloric acid, respectively, to give 12.1mm-solutions of (1a) whose pH values were measured as (a) *ca.* 7, (b) 4.45, 5.10, and 8.69, (c) *ca.* 2, and (d) <1. The solutions were placed in quartz tubes and flushed with nitrogen for 30 min, then irradiated externally with a high-pressure mercury lamp [Eiko-sha Halös PIH-300 (300 W)] at 10–15 °C. The reactions were monitored by g.l.c. (after neutralization with alkali when acidic). The remaining starting material (1a) was estimated by measuring the optical density of the alkaline extract of each mixture. The progress of a reaction under

¹⁵ F. Kurzer and A. Lawson, *Org. Synth.*, Coll. Vol. V, 1973, p. 1046.

¹⁶ K. A. Jensen and C. Pedersen, *Acta Chem. Scand.*, 1961, **15**, 1087.

¹⁷ N. Suzuki and Y. Izawa, *Tetrahedron Letters*, 1974, 1863.

¹⁸ J. C. Crawhall and D. F. Elliott, *J. Chem. Soc.*, 1951, 2071.

¹⁹ J. C. Sheehan and J. J. Ryan, *J. Amer. Chem. Soc.*, 1951, **73**, 4367.

²⁰ A. Lawson and C. E. Searle, *J. Chem. Soc.*, 1957, 1556.

conditions (a) is shown in Figure 1. The pH dependence is illustrated in Figure 2.

Isoelectric point (pI) and pK determinations were performed by titrating the acid (1a) in water with standard base or acid (0.02N-NaOH or HCl).⁶

Photoreaction of the Thiazoline (3a) in Acetonitrile.—A solution (12.1mM) of (3a) in acetonitrile was irradiated similarly in a quartz cell, and the products were analysed by g.l.c. The results are given in the Table.

Photolysis of the Thiazole (2a) in Acetonitrile.—A solution of (2a) (12.1mM) in acetonitrile was irradiated similarly in a quartz cell, and the reaction was monitored by g.l.c. Compound (2a) decreased gradually with time, and had disappeared after 3 h. Only a small amount of benzamide was detected.

Thermolysis of the Acids (1a and b).—The acid (1a) (50 mg) in a flask equipped with a reflux condenser was heated at 240–250 °C for 2.5 min. The resulting liquid showed i.r. and n.m.r. spectra identical with those of the thiazoline (3a). The yield was almost quantitative.

In a similar manner, compound (1b) gave the thiazoline (3b), quantitatively.

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