Photochemistry of Tiaprofenic Acid, a Nonsteroidal Anti-Inflammatory Drug with Phototoxic Side Effects

FRANCISCO BOSCÁ, MIGUEL A. MIRANDA[x], AND FRANKLIN VARGAS

Received August 6, 1990, from the *Departamento de Quimica and Instituto de Tecnologia Quimica UPV-CSIC, Universidad Politécnica de Valencia, Camino de Vera s/n, Apartado 22012, 46071 Valencia, Spain.* Accepted for publication March 26, 1991.

Abstract □ The phototoxic nonsteroidal anti-inflammatory drug tiaprofenic acid (**1**) is photolabile under aerobic conditions. Irradiation of a methanol solution of **1** under oxygen produces the photoproducts **2**, **3**, **4**, and **5**, and also produces a singlet oxygen as evidenced by trapping with 2,5-dimethylfuran.

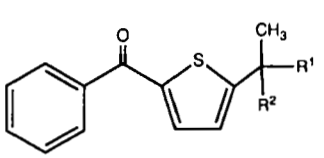
Nonsteroidal anti-inflammatory drugs (NSAIDs) have gained prominence in the last 10 years because of their efficiency in the treatment of inflammation diseases and the lack of the long-term side effects associated with corticosteroids. Tiaprofenic acid (**1**) is a NSAID with a balanced benefit:risk ratio, but whose use has been associated in some patients with the appearance of phototoxic effects such as erythema, flaring, and urticarial weal.[1-3] In a photopatch test for skin photosensitization to UV-A plus UV-B light, a significant portion of the patients gave a positive reaction to **1**.[4,5] In vitro experiments also point to the potential phototoxicity of this drug.[6]

It appears that there may be a relationship between photochemical behavior and phototoxicity. In this context, nothing is as yet known about the photochemistry of **1**. This has prompted us to examine the photolysis of **1** under a variety of conditions with two main goals: to establish the structures of the different photoproducts and to evidence the role of oxygen in these photoprocesses.

Experimental Section

Tiaprofenic acid (**1**) was irradiated for 24 h in methanol (1.00 g in 200 mL) at 20 °C by means of a pyrex immersion-well photoreactor (Applied Photophysics, parts no. 3230 + 3307), with a OSRAM HQL 400 W medium-pressure Hg lamp, under oxygen or argon atmosphere. The course of the reaction was followed by UV-Vis spectrophotometry using a Perkin-Elmer Lambda 15 instrument, as well as by gas chromatography (GC) using a Hewlett-Packard 5890 instrument, with a 25 m × 0.32 mm × 0.52 μm capillary column of cross-linked 5% phenylmethylsilicone. The solvent was then evaporated at reduced pressure, and the residue was analyzed by column chromatography (silica gel). Elution was carried out with a mixture of hexane: ethyl acetate (5:1, v/v).

The products **2**–**5** (see structure) were isolated and analyzed by ^{1}H NMR spectrometry (Varian 360 EM spectrometer), IR spectrophotometry (Perkin-Elmer 781 spectrophotometer), and mass spectrometry (Hewlett-Packard 5988 A spectrometer). Some chemical correlations were established which allowed structural assignation. Thus, benzylic bromination of **5** with *N*-bromosuccinimide in boiling carbon tetrachloride, followed by treatment of the resulting bromide with silver nitrate in aqueous acetone, gave the alcohol **4**. Alternatively, heating of the same intermediate bromide in methanol produced the methyl ether **3**.



1: R^1 = COOH, R^2 = H
2: R^1, R^2 = O
3: R^1 = OCH_3, R^2 = H
4: R^1 = OH, R^2 = H
5: R^1 = R^2 = H

Compound **2** had a mp of 115–116 °C; IR (KBr): v = 3100, 2900, 2710, 2550, 1690, 1640, 1500, 1290, 1260, 870, and 740 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 2.50 (s, 3 H, CH_3) and 7.30–8.00 (m, 7 H, aromatic); MS (70 ev): *m/z* (%) = 230 (67, M^+), 215 (100, M^+–CH_3), 187 (8), 153 (25), 105 (78), 77 (41), 51 (6).

Compound **3** showed a mp of 104–106 °C; IR (KBr): v = 3200, 3000, 2990, 2820, 1640, 1520, 1450, 1300, 1250, 1110, 880, 700, and 620 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 1.60 (d, 3 H, CH_3), 3.30 (s, 3 H, -OCH_3), 4.60 (q, 1 H, -CH), 7.00 (d, 1 H, thiophene-CH), and 7.20–7.80 (m, 6 H, aromatic); MS (70 ev): *m/z* (%) = 246 (23, M^+), 231 (100, M^+–CH_3), 215 (27, M^+–OCH_3), 141 (35), 105 (43), 77 (28), 57 (10).

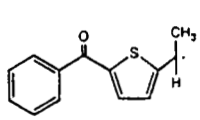
Compound **4**: IR (KBr): v = 3600, 3500–3100, 2980, 1640, 1450, 1300, 1260, 1100, 1000, 870, and 600 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 1.65 (d, 3 H, CH_3), 4.20 (s, 1 H, -OH), 5.20 (q, 1 H, -CH-), 6.80 (d, 1 H, thiophene-CH), and 7.10–7.60 (m, 6 H, aromatic); MS (70 ev): *m/z* (%) = 232 (16, M^+), 217 (100, M^+–CH_3), 215 (65, M^+–OH), 214 (30), 199 (22), 187 (13), 139 (52), 105 (25), 77 (30), 51 (5).

Compound **5**: IR (KBr): v = 3100, 3000, 2990, 1640, 1450, 1300, 1250, 1100, 1000, 860, and 600 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 1.20 (t, 3 H, CH_3), 2.70 (q, 2 H, CH_2), 6.60 (d, 1 H, thiophene-CH), and 7.10–7.60 (m, 6 H, aromatic); MS (70 ev): *m/z* (%) = 216 (60, M^+), 201 (32, M^+–CH_3), 187 (9), 173 (13), 139 (100, M^+–C_6H_5), 105 (28), 77 (25), 51 (4).

Results and Discussion

The major photoproduct of **1** in oxygenated media was the ketone **2** (yield = 94%). Its formation, together with traces of the alcohol **4**, can be explained as the result of oxygen trapping by a decarboxylated radical **6** and subsequent breakdown of an unstable hydroperoxide **7** (see structure). A similar mechanism has been proposed in the case of the closely related 2-arylpropionic acids ibuprofen,[7] naproxen,[8-10] and ketoprofen,[11,12] whose irradiation under oxygen also produces the analogous ketones as major products. Irradiation of **1** under anaerobic conditions resulted in the formation of **5** (yield = 96%), which can be explained as occurring from intermediate **6** via hydrogen abstraction from the medium. The small amounts of the methyl ether **3** might arise from the cation **8** after photoionization and subsequent homolysis of the C—C bond α to the carboxyl group.[9]

In a separate experiment, **1** was found to be capable of producing singlet oxygen. Studies repeated in the presence of 2,5-dimethylfuran ($^1O_2$ scavenger)[8,12,13] showed the formation of hexene-2,5-dione, detected by GC-MS. Thus, in principle, it could be possible that **1** photosensitizes its own oxidation, through singlet oxygenation of its enol form and subsequent decarboxylation of an intermediate, α-peroxylac-



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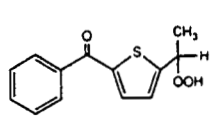

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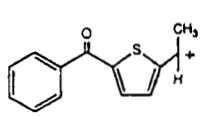

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tone or α-hydroperoxyacid, to give the ketone 2.[9] However, this possibility was easily ruled out by irradiating 1 in the presence of tetraphenylporphin (TPP) as source of singlet oxygen, using a potassium chromate solution (100 mg/L) as filter and allowing $\lambda > 400$ nm (to ensure light absorption by TPP alone and avoid direct irradiation of 1) and maintaining all other conditions the same. In this experiment, no photodegradation of 1 was observed, which means that 1 is not consumed by reaction with $^1O_2$ independently generated by TPP-sensitized photolysis.

In light of these data, the phototoxicity mechanism for 1 must involve reactions of free radical 6, stable photoproduct 2 or 5, or singlet oxygen with cell membranes following in vivo photoactivation.

References and Notes

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Acknowledgments

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