A Novel Photoisomerzation of 1,2-Benzothiazine 1,1-dioxides to 1,3-Benzothiazine 1,1-dioxides

Ibrahim Elghamry*‡, Dietrich Döpp and Gerald Henkel

Institute of Chemistry, University Duisburg-Essen, D-47048 Duisburg, Germany
e-mail: elghamry@hotmail.com

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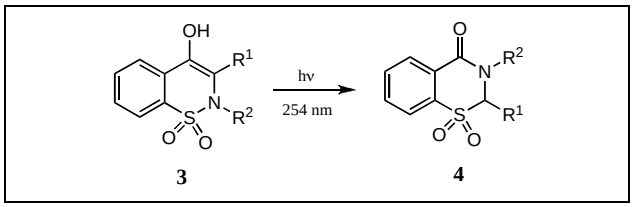

3 **4**

A novel facile photoconversion of 4-hydroxy-1,2-bezothiazine 1,1-dioxides (**3a-e**) into 4-*oxo*-1,3-2*H*-benzothiazine 1,1-dioxides (**4a-e**) and 4-hydroxy-2-methyl-*N*-(pyridin-2-yl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide (PRX) into *N*-methyl saccharin (**2**) upon 254 nm irradiation in methanol or acetonitrile is reported. The structures of the products have been elucidated by spectroscopic methods and single crystal X-ray structure determination for **4a** and **4d**.

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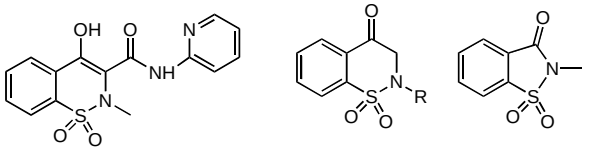
INTRODUCTION

Piroxicam (4-hydroxy-2-methyl-*N*-(pyridin-2-yl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide) (PRX-Scheme 1), is a non-steroidal anti-inflammatory drug (NSAID) used for treatment of arthritis [1-3]. It belongs to the *oxicams* group of chemicals, which have the 1,2-thiazine 1,1-dioxide as a main nucleus fused with either benzene or heterocycles ring systems. Shortly after the PRX became widely available for the therapeutic use it was associated with development of adverse light-induced biological effects, which were demonstrated mainly as a phototoxicity [4-8].

The implication of the photoproducts of the drug in the phototoxicity has been suggested in the literature [9]. Therefore, it has been reported that the phototoxicity of PRX is a result of the preferential synthesis and accumulation of 2-methyl-4-oxo-2*H*-1,2-benzothiazine 1,1-dioxide (**1**) (Scheme 1) in human skin cells. The latter compound is a minor metabolite of PRX, and has been reported to be phototoxic to Lymphocytes *in vivo* [4,5].



PRX **1** **2**

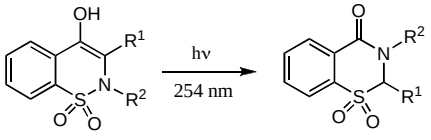
a, R = H
b, R = Me

Scheme 1

The photodegradation of PRX into *N*-methyl saccharin (**2**) and *N*-(2-pyridyl) oxamic acid by direct irradiation under aerobic conditions has been reported [10]. This was explained in terms of a plausible mechanism *via* a dioxetane intermediate [10,11]. The physicochemical studies have shown that PRX has twelve possible tautomers, which result from the unusual fast intra-molecular proton transfer from the hydroxyl group of the benzothiazine ring either to the *ortho*-carbonyl, the amide nitrogen, the benzothiazine ring nitrogen, or the pyridine ring nitrogen [11-14]. While a previous study has also reported that a similar behavior was noticed for methyl 4-hydroxy-2-methyl-1,2-benzothiazine-1,1-dioxide 3-carboxylate (**3a**), which is used as one of the PRX precursors [15,16]. Therefore, these results prompted us to study the photoreactivity of PRX precursors and analogues.

RESULTS AND DISCUSSION

Herein we report a new photoisomerization of the 3-substituted 4-hydroxy-1,2-benzothiazines **3a-e** into 2-substituted 4-*oxo*-1,3-benzothiazines **4a-e**. Therefore, the 1,2-benzothiazine 1,1-dioxides **3a-e** were prepared using literature procedures [17] and were subjected to 254 nm photolysis experiments in methanol using a low-pressure mercury lamp (15 W input) for the period listed in Table 1. A single photoproduct was obtained in moderate yields varying from 50% to 75% (Scheme 2, Table 1) which was demonstrated to be the 2-substituted 4-*oxo*-1,3-2*H*-benzothiazine 1,1-dioxide **4**. Interestingly, the author has recently reported a related ring system was obtained *via* a new photochemical ring expansion of *N*-alkyl 1,2-benzothiazole 1,1-dioxides [18].



3 **4**

Scheme 2

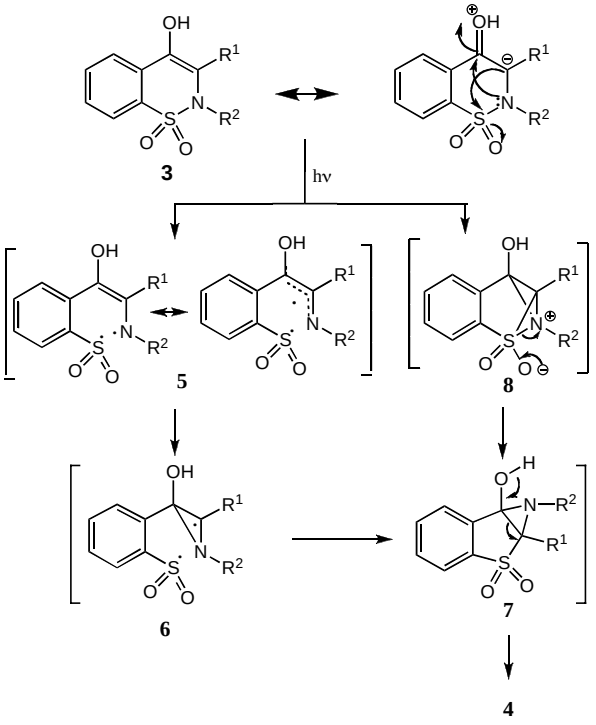
Table 1

Photoconversion of 1,2-benzothiazine 1,1-dioxide 3 to 1,3-benzothiazine 1,1-dioxide 4.

3, 4	R^1	R^2	Period of irradiation (h)	Yield of 4 (%)[a]
a	CO_2Me	H	7	54
b	CN	H	6	75
c	COPh	H	15	50
d	CN	CH_3	7	60
e	CO_2Me	CH_3	7	55

[a] Based on the consumed starting material.

The rationale explaining the possible pathways of this photoisomerization is depicted in Scheme 3. Thus, photoexcited **3** first undergoes S-N bond homolysis [19-23] to give biradical **5** which can undergo cyclization to form a more stable captodative aziridine radical [24,25] **6** (R^1 = CO_2Me, CN, COPh). Then, subsequent bond formation between S and C_3 gives rise the bicyclic intermediate **7**. The latter is an analogous to intermediates suggested to rationalize the phototranspositions of methylisothiazoles to methylthiazoles [26] and of 2-phenylthiophene to 3-phenylthiophene [27]. Intermediate **7** in turn undergoes subsequent C-C bond cleavage with protonation at C-2 to form the final isolable photoisomerization product **4**. Alternatively, **3** may first be photocyclized to give the tricyclic zwitterionic intermediate **8** [26]. Final S-N bond rupture results in the aforementioned bicyclic intermediate **7** which proceeds to product **4**.



Scheme 3

To investigate the scope and limitation of this photoisomerization and the role of the R^1 group, the 3,4-dihydro-1,2-benzothiazine (**1a**) and the *N*-methyl derivative (**1b**) were prepared [28] and subjected to photolysis under the same conditions and the course of the reaction was monitored by NMR. Unsurprisingly photoisomerization was not observed and the substrates were recovered without change after irradiation for 24 hours. Therefore the presence of R^1 (electron-withdrawing) is proven to be essential for the photoisomerization which enhances the formation and stabilization of either or both of the intermediate **6** and **8** (Scheme 3). Furthermore, it was noticed that there was no effect on the photoisomerization, whether with respect to the yield or the nature of the photoproduct when the photolysis was carried out in aprotic (acetonitrile) or protic (methanol) solvents.

The structure of the photoisomerization products **4a-e** was delineated primarily from the mass spectral and ^1H / ^{13}C NMR data but was firmly supported by a single crystal X-ray structure determination for compounds **4a** and **4d** (Fig 1 and 2). The spectral data of the photoisomerization products revealed new signals attributed to formation of a new stereogenic centre at C-2. Thus, ^{13}C-NMR and ^1H-NMR spectra reveal signals at δ = 46.1- 75.3, 159.8-168.5 and 5.75-7.15 ppm attributed to the new asymmetric carbon in the 1,3-benzothiazine ring at C-2, the new ring carbonyl at C-4 and the proton bonded to the stereogenic carbon, respectively. Also, a signal is observed at 1675-1699 cm^{-1} in the IR spectra is assigned to the new amidic carbonyl.

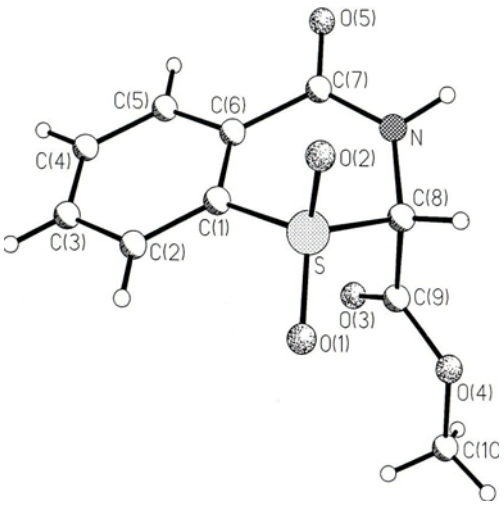


Figure 1. ORTEP-plot of molecular structure **4a** in the crystal. The crystallographic numbering does not reflect the systematic number.

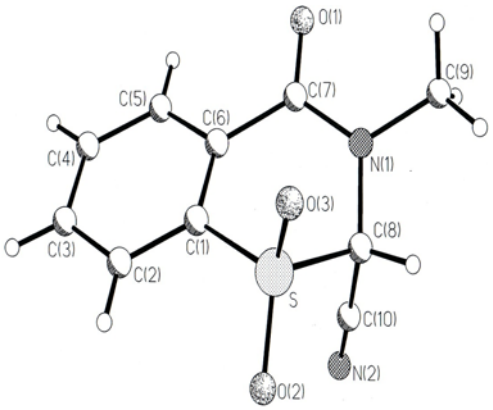


Figure 2. ORTEP-plot of molecular structure **4d** in the crystal. The crystallographic numbering does not reflect the systematic number.

Table 2

Selected bond lengths and angles of compounds **4a** and **4d** in the crystal. The crystallographic numbering does not reflect systematic numbering.

Cpd	Bond length [Å]	Bond angles [^ o]
4a	S-C(1) 1.756 (16)	C(1)-S-C(8) 99.82 (7)
	S-C(8) 1.813 (15)	S-C(8)-N 109.47 (10)
	C(8)-N 1.444 (19)	C(7)-N-C(8) 126.53 (13)
	C(8)-C(9) 1.533 (2)	N-C(7)-C(6) 118.83 (13)
	N-C(7) 1.354 (2)	
	O(5)-C(7) 1.234 (19)	
	O(3)-C(9) 1.199 (19)	
4d	S-C(1) 1.763 (5)	C(1)-S-C(8) 98.62 (2)
	S-C(8) 1.22 (5)	S-C(8)-N(1) 109.81 (3)
	C(8)-N(1) 1.448 (6)	C(7)-N(1)-C(8)122.83 (4)
	C(8)-C(10)1.501 (7)	N(1)-C(7)-C(6)121.23 (4)
	C(6)-C(7) 1.497 (7)	
	C(10)-N(2)1.122 (6)	
	C(9)-N(1) 1.462 (6)	
	O(1)-C(7) 1.228 (6)	
	O(3)-C(9) 1.199 (19)	

A preliminary result from our laboratory indicated that one of the aerobic photodegradation products of PRX was isolated in 40% yield and identified as *N*-methylsaccharin (**2**) after subjecting the PRX to photolysis for seven hours using a low-pressure mercury lamp with continuous argon purging. However, it has been reported that PRX is photostable under inert atmosphere where the aerobic photodegradation was only explained in terms of singlet oxygen involvement in the process [5, 10, 29].

Finally, a new photoisomerization of 4-hydroxy 3-substituted 1,2 -benzothiazine 1,1-dioxides (**3a-e**) into 4-oxo-2-substituted 1,3-bezothiazine 1,3-dioxides (**4a-e**) was achieved in reasonable yields and a rationale for this transformation has been proposed. Thus, based on the above mentioned photoisomerzation and the degradation of PRX under inert conditions it is likely that PRX degrades into **2** *via* 1, 3 –benzothiazine intermediate. Therefore, further studies in this direction are under way.

EXPERIMENTAL

General. All commercially available solvents and reagents were purchased from commercial sources and used without further purification unless otherwise noted. NMR spectra were recorded on a Bruker WM 300 and DRX 500 spectrometers (300 MHz and 500 MHz, respectively for ^{1}H, 75 and 125 MHz, respectively, for ^{13}C) using TMS as internal standard and the deuterated solvent as lock. IR spectra were obtained by using a Perkin-Elmer 983 spectrophotometer. Electron impact ionisation mass spectrometry (EIMS) was performed on a Varian AMD 604 instrument using 70 eV ionization energy. Melting points are uncorrected. All the chromatographic separations were performed on 48 x 20 cm glass plates covered with an air-dry layer (1 cm thick) of silica gel (Merck Kiesegel PF254).

General Photolysis Procedure. Samples of **7a-e** (1.0 mmol each) in methanol (or acetonitrile) (100 ml) were irradiated for the period listed (see Table 1) using a quartz immersion well in connection with a Hanau TNN 15 low-pressure mercury lamp (15 W input) with continuous argon purging. After concentration the residue was subjected to chromatography on two silica gel plates each with EtOAc-hexane (1:1). The R_f values of the appropriate zones are given below.

Methyl 3,4-dihydro-1,1-dioxide-5-*oxo*-1,3-2*H*-benzothiazine 2-carboxlate (4a). R_f 0.51 Colourless crystals (from acetone) mp 198-199 °C, ir: NH 3191, C=O 1758, C=O 1677, SO_2 1326, 1203 cm^{-1}; ^{1}H nmr: (DMSO) δ: 3.75 (s, 3H, CH_3), 5.75 (d, *J* = 6.0,1H, *H*C-2), 7.85 (m, 3H, Ar-H), 8.15 (m, 1H, Ar-H), 9.21ppm (d, *J* = 6.0, 1H, NH); ^{13}C nmr: (DMSO) δ: 54.1 (OCH_3), 72.5 (C-2), 122.9 (Ar-CH), 128.9 (Ar-Cq), 129.5, 133.5, 134.1 (Ar-CH), 136.2 (Ar-Cq), 161.1 (C=O, ring), 164.5 ppm (C=O, ester); ei ms: m/z 256 (M^+ + 1). *Anal*. Calcd. for $C_{10}H_9NO_5S$: C, 47.05; H, 3.55; N, 5.49. Found: C, 46.91; H, 3.45; N, 5.29.

2-Cyano-3,4-dihydro-1,1-dioxide-1,3-2*H*-benzothiazin-4-one (4b). R_f 0.42 Colourless crystals (from ethanol) mp 175 °C, ir: NH 3220, C=O 1675, SO_2 1340, 1150 cm^{-1}; ^{1}H nmr (DMSO) δ: 7.15 (d, *J* = 6.0, 1H, *H*C-2), 8.13 (m, 4H, Ar-H), 10.35 ppm (d, *J* = 6.0, 1H, NH); ^{13}C nmr (DMSO) δ: 60.9 (C-2), 113.1 (CN), 117.5 123.5 (Ar-CH), 126.9 (Ar-Cq), 130.5 (Ar-CH), 134.4 (Ar-Cq), 135.5 (Ar-CH), 160.5 ppm (C=O), ei ms: m/z 222 (M^+). *Anal*. Calcd. for $C_9H_6N_2O_3S$: C, 48.64; H, 2.72; N, 12.61. Found: C, 48.56; H, 2.55; N, 12.54.

2-Benzoyl-3,4-dihydro-1,1-dioxide-1,3-2*H*-benzothiazin-4-one (4c). R_f 0.51 Colourless crystals (benzene/n-hexane 3:1) mp 218-219 °C; ir: NH 3264, C=O 1734, C=O 1699, SO_2 1375, 1179 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 5.81 (s, 1H, *H*C-2), 7.52 (m,4H, Ar-H), 8.05 (m, 4H, Ar-H), 8.38 (m, 1H, Ar-H), 9.92 ppm (s, 1H, NH); ^{13}C nmr ($CDCl_3$)) δ: 46.1 (C-2), 127.4, 128.7, 129.8, 130.2 (Ar-CH), 131.4, 131.9(Ar-Cq), 133.9 (Ar-CH), 134.3 (Ar-Cq), 135.6, 136.6 (Ar-CH), 168.5 (C=O, ring), 191.3 ppm (C=O, ketonic); ei ms: m/z 302 (M^+ +1). *Anal*. Calcd. for $C_{15}H_{11}NO_4S$: C, 59.79; H, 3.68; N, 4.65. Found: C, 59.68; H, 3.67; N, 4.54.

2-Cyano-3,4-Dihydro-1,1-dioxide-N-methyl-1,3-2*H*-benzothiazin-4-one (4d). R_f 0.48 Colourless crystals (acetone) mp 200-201 °C; ir: C=O 1675, SO_2 1340, 1150 cm^{-1}; ^{1}H nmr (DMSO) δ: 3.10 (s, 3H, CH_3), 6.54 (s, 1H, *H*C-2), 7.98 ppm (m, 4H, Ar-H); ^{13}C nmr (DMSO) δ: 35.8 (*C*H_3), 66.1 (C-2), 112.4 (CN), 117.8, (Ar-Cq), 123.7, 126.7, 134.6 (Ar-CH), 135.1 (Ar-Cq), 135.7 (Ar-CH), 159.8 ppm (C=O); ei ms m/z 336 (M^+).

Anal Calcd. for $C_{10}H_8N_2O_3S$: C, 50,84; H, 3.41; N, 11.86. Found: C, 50.77; H, 3.32; N, 11.78.

Methyl 3,4-dihydro-1,1-dioxide-*N*-methyl-5-oxo-1,3-2*H*-benzothiazine-2-carboxlate (4e). R_f 0.50 Colourless crystals (acetone) mp 205-206°C; ir: C=O 1760, C=O 1679, SO_2 1330, 1210 cm^{-1}; ^1H nmr (DMSO) δ: 2.95 (s, 3H,CH_3), 3.65 (s, 3H, CH_3), 5.94 (s, 1H, *H*C-2), 7.85 (m, 2H, Ar-H), 8.21 ppm (m, 2H, Ar-H); ^{13}C nmr (DMSO) δ: 29.2 (*C*H_3), 54.3 (*C*H_3), 75.3 (C-2), 123.5, (Ar-CH) 128.0 (Ar-Cq), 129.5, 132.9, 133.2 (Ar-CH), 136.9 (Ar-Cq), 166.2 (C=O ring), 169.1 ppm (C=O ester); ei ms: m/z 270 (M^+ + 1). *Anal*. Calcd for $C_{11}H_{11}NO_5S$: C, 49.06; H, 4.12; N, 5.20: Found: C, 48.95; H, 4.10; N, 5.19.

Photolysis of Piroxicam. A solution of 0.14 g (0.50 mmol) of Piroxicam in methanol (100 ml) was irradiated for 7 hours using a quartz immersion well in connection with a Hanau TNN 15 low-pressure mercury lamp (15 W input) with continuous argon purging. After concentration the residue was subjected to chromatography on two silica gel plates with EtOAc- hexane (1:1).

***N*-Methylsaccharin (2).** R_f 0.50, Colourless crystals (from methanol) mp 128 °C (lit [30] 130 °C, lit [31] 131 °C); ir: C=O 1739, SO_2 1325, 1174 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 3.39 (s, 3H, methyl-H), 7.95 ppm (m, 4H, aryl-H); ^{13}C nmr ($CDCl_3$) δ: 23.2 (CH_3), 121.0, 125.2 (Ar-CH) 127.6 (Ar-Cq), 134.4, 134.7 (Ar-CH), 137.6 (Ar-Cq), 158.8 ppm (C=O).

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‡ Current address, Misr International University, faculty of pharmacy, department of pharmaceutical organic chemistry, P.O. Box 1 Heliopolis 11341, Cairo, Egypt.

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