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Structural Studies of 2-Pentyl/Pentenyl-Substituted Methyl 4-Hydroxy-2*H*-1,2-Benzothiazine-3-Carboxylate-1,1-Dioxide

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Abstract

Crystal structures of methyl 2-pentyl-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate-1,1-dioxide **1** and methyl 2-pentenyl-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate-1,1-dioxide **2** have been determined after their synthesis from saccharin. **1** and **2** crystallize in a monoclinic and orthorhombic crystal system, respectively. The asymmetric unit of both contains one molecule of each compound and shows intramolecular O-H···O interactions generating six membered ring motifs $S^1_1(6)$. Intermolecular hydrogen bonding interactions have been observed in the molecule with the pentyl side chain. The thiazine ring in both molecules adopts a half chair conformation with a r.m.s. deviation of 0.2049 Å and 0.2161 Å.

Keywords: 1,2-benzothiazine, single crystal, structure studies, X-rays, oxicam

Introduction

Structural studies of medicinal compounds and their intermediates have long been investigated to confirm the exact spatial arrangements of various atoms and groups on the main skeleton. 1,2-Benzothiazine nucleus was spotlighted after the introduction of an anti-inflammatory drug, Piroxicam® [1] in 1971 which is a member of oxicam family (**Figure 1**). It is known that Piroxicam® (4-hydroxy-2-methyl-*N*-pyridin-2-yl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide) exhibits polymorphism during the recrystallization process [2]. Structural and solid-state changes of the same molecule in its crystalline form under mechanical stress have also been observed using various techniques, out of which single crystal X-ray diffraction proves the best for the characterization of the enolic nature of the hydroxyl group and for the pyramidal nature of the sulfonamide nitrogen [3].

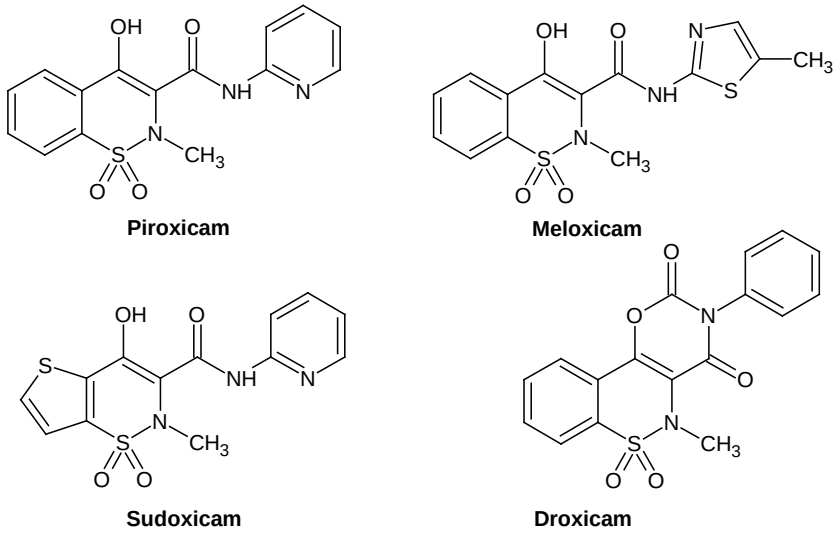
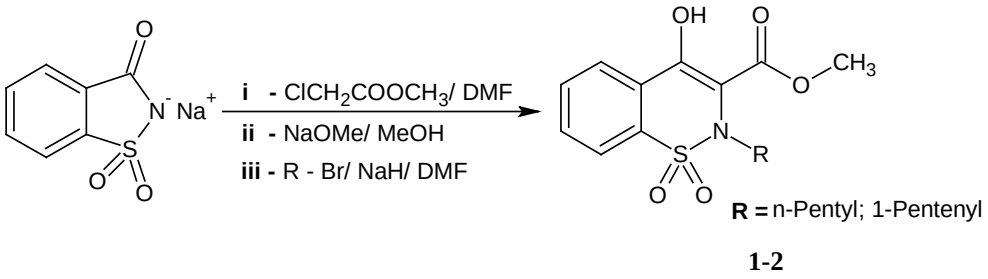


Figure 1 Structures of a few commercially available oxicams.



1-2

Scheme 1 Synthesis of *N*-alkylated derivatives of methyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide.

In continuation of our on-going research on the synthesis of various benzothiazine derivatives [4-10], the synthesis and crystal structures of methyl 2-pentyl-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate-1,1-dioxide **1** and methyl 2-pentenyl-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate-1,1-dioxide **2** are presented in this paper (**Scheme 1**).

Materials and methods

All the chemicals were purchased from Merck, BDH or Fluka and used without purification. However, solvents were purified through distillation. X-ray diffraction data were collected at 100 (2) K on a Siemens SMART three-circle X-ray diffractometer equipped with an APEX II CCD detector (Bruker-AXS) and an Oxford cryosystems 700 cryostream, using a MoKα radiation (0.71073 Å) source and a graphite monochromator. The data were corrected for Lorentz and polarization effects and for absorption using multi-scan methods [11,12].

General procedure for the synthesis of *N*-alkyl derivatives of methyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate-1,1-dioxide

A mixture of methyl chloroacetate (6.32 g, 5.84 mmol), sodium saccharin (8.00 g, 3.74 mmol) and dimethylsulfoxide (20 mL) was heated on a water bath in an inert atmosphere for a period of 20 min followed by cooling of the reaction mixture

to room temperature. Sodium methoxide (2.4 g; 4.32 mmol) was added to the reaction mixture and the contents were kept stirred at the same temperature. The reaction was cooled to 0 °C after 30 min and sodium hydride (3.76 g, 7.84 mmol) was added. After a period of 10 min, the temperature of the reaction mixture was again maintained at 20 °C, followed by dropwise addition of the respective halide (6.72 mmol). After 15 min, the contents were poured over a mixture of crushed ice (100 g) and concentrated hydrochloric acid (10 mL). The precipitates thus obtained were filtered, dried and crystallized from ethylacetate [8].

Results and discussion

Both the compounds under discussion are N-substituted derivatives of methyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide, a precursor used in the synthesis of drugs [1,5-8]. Crystallographic data and refinement details are available in **Tables 1** and **2**. It is interesting that the molecule with pentyl group crystallized in monoclinic crystal system while with alkene was orthorhombic. The methyl ester moiety is directly attached to the C-8 carbon atoms in the structures (**Figures 2**). Values of root mean square (r. m. s.) deviation for the methyl ester moiety are 0.0088 Å and 0.0021 Å (**Table 3**) respectively, which clearly indicate their planer behavior. Thiazine rings (C1/C6/C7/C8/N1/S1) in both derivatives adopt a half chair conformation and are in accordance with the already published data [13], r. m. s. deviations for these are 0.2049 Å and 0.2161 Å. The two fused rings in the molecules are twisted at 12.75(8)° and 16.63(5)°. Greater deviation in the thiazine ring is observed with the pentenyl substitution at the nitrogen atom; also, it caused a small increase in dihedral angles between the two fused rings. Dihedral angles for methyl ester and *N*-alkyl groups with respect to thiazine (C1/C6/C7/C8/N1/S1) and the aromatic (C1/C2/C3/C4/C5/C6) rings are given in (**Table 2**). Intramolecular hydrogen bonding in the crystal structures of methyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate-1,1-dioxide and its derivatives is a typical feature [13] and the same has been observed here. Both the molecules are involved in the formation of 6 membered (C7/O1/H1O/O4/C9/C8) ring motifs [14] $S^1_1(6)$ through O-H···O intramolecular hydrogen bonding interactions between the hydroxyl group at the thiazine ring and carbonyl group of the methyl ester. The r. m. s. deviation for the ring motifs for **1** is 0.0192 Å, while for **2** this is 0.0139 Å with a maximum deviation from C9 = –0.0336 (12) Å and O4 = 0.0215 (11) Å for **1** and C9 = 0.0204 (9) Å & O4 = –0.0136 (57) Å for **2**.

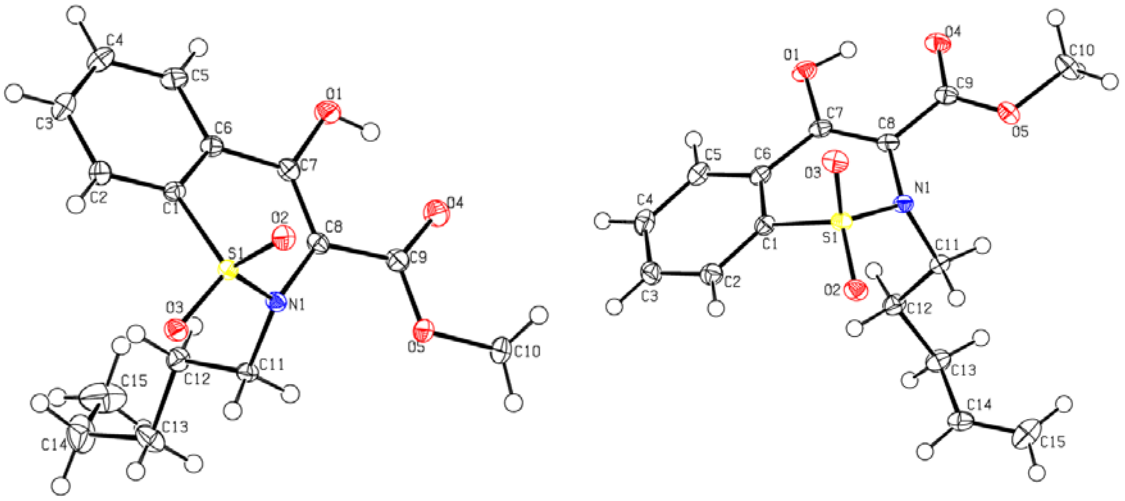


Figure 2 Ortep diagrams for **1** and **2**, thermal ellipsoids drawn at 50 % probability level.

Table 1 Crystallographic parameters of structure **1** and **2**.

Parameter	1	2
Empirical Formula	$C_{15}H_{19}N_1O_5S_1$	$C_{15}H_{17}N_1O_5S_1$
Formula Weight	325.4	323.4
Temperature/K	173(2)	173(2)
Wavelength / Å	0.71073	0.71073
Crystal System, Space group	Monoclinic, *P21*/c	Orthorhombic, *Pbca*
Unit cell dimensions		
***a*/(Å)**	8.6015(66)	8.5604(4)
α/(°)	90.00	90.00
***b*/(Å)**	17.5314(12)	12.8093(7)
β/(°)	111.241(3)	90.00
***c*/(Å)**	10.9781(18)	27.0807(15)
γ/(°)	90.00	90.00
Volume/ Å^3	1542.99(7)	2969.47(3)
Z, Calculated density/(g·cm^{-3})	4, 1.40	8, 1.45
Absorption coefficient/ mm^{-1}	0.233	0.242
***F*(000)**	687.9	1359.8
Crystal size/ mm	0.38×0.22×0.19	0.47×0.18×0.12
Reflection collected/unique	13800/3861	25148/3677
R_1	0.036	0.034
R_{int}	0.027	0.033
$\omega R2$	0.093	0.091

Table 2 Comparison of dihedral angles between different moieties of **1** and **2**.

Moiety 1	Moiety 2	1	2
Phenyl ring (C1-C6)	Thiazine ring	12.75(8)°	16.63(5)°
Methylester	Phenyl ring (C1-C6)	12.13(13)°	16.67(5)°
Methylester	Thiazine ring	14.94(11)°	13.34(8)°
N-alkyl	Thiazine ring	85.01 (5)°	78.65 (10)°

Table 3 Comparison of root mean square (r. m. s.) deviation of different moieties in **1** and **2**.

Moiety	1	2
Methylester	0.0088 Å	0.0021 Å
Thiazine ring	0.2049 Å	0.2161 Å
Six membered ring motif (C7/O1/H1O/O4/C9/C8)	0.0192 Å	0.0139 Å

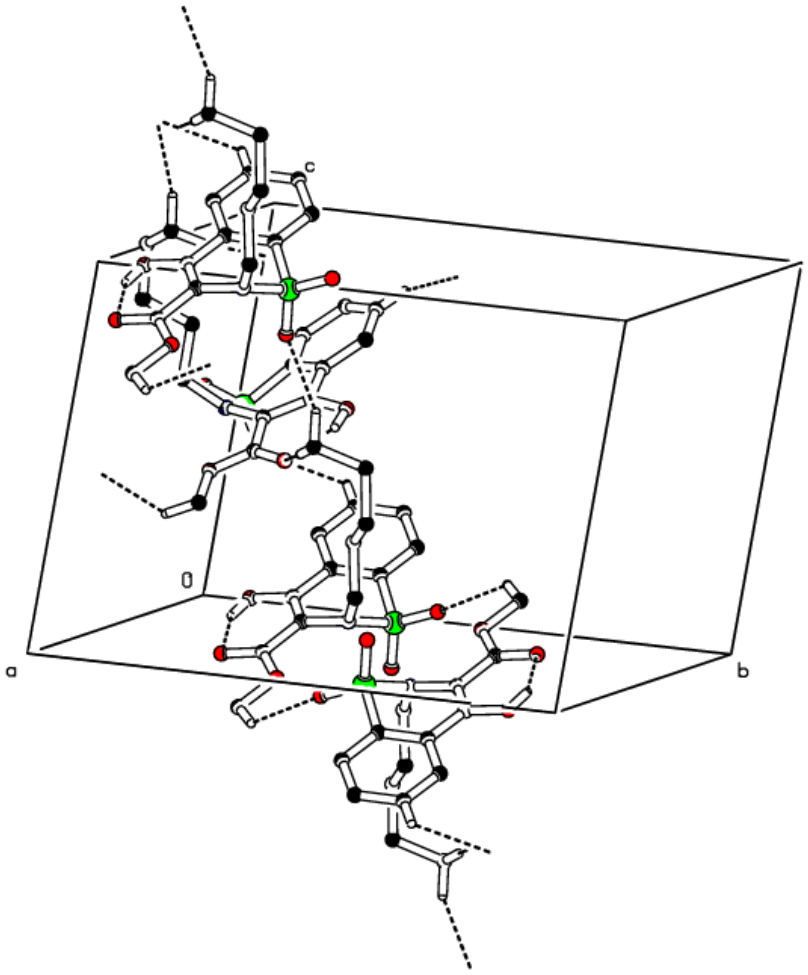


Figure 3 Unit cell packing diagram for **1** showing the hydrogen bonding using dashed lines.

Table 4 Hydrogen bonding interactions in **1** and **2**.

D---H	A	d(D---H) Å	d(H…A) Å	d(D…A) Å	<(D---H...A) (°)	Symmetry code
1						
O1---H1	O4	0.84	1.80	2.563	150.0	-
C4---H4	O2	0.93	2.56	3.221	128.2	x, ½-y, ½+z
C10---H10B	O3	0.96	2.50	3.173	127.0	1-x, 1-y, -z
C15---H15A	O4	0.96	2.54	3.466	163.1	x, ½-y, ½+z
C15---H15B	O2	0.96	2.56	3.423	149.6	x, ½-y, ½+z
2						
O1---H1	O4	0.992	1.718	2.567	151.74	-

Intermolecular hydrogen bonding interactions

The molecules exhibit intramolecular hydrogen bonding interactions but only **1** showed weak symmetry related intermolecular hydrogen bonding (**Table 4**, **Figure 3**).

Conclusions

In the present work, the crystal structures of two derivatives of 1,2-benzothiazine 1,1-dioxide have been determined. Both the structures show similarities and variations in inter- and intra-molecular hydrogen bonding, r. m. s. deviations and dihedral angles.

Supplementary details

The crystallographic files for the compounds have been deposited in CCDC and may be obtained by CCDC numbers, 847166 for **1** and 847167 for **2**.

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