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N-(*X*-Chlorophenyl)-4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide (with *X* = 2 and 4)

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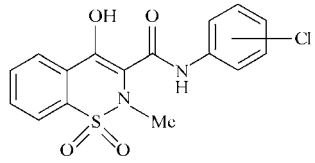
The structures of *N*-(2-chlorophenyl)-4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide and *N*-(4-chlorophenyl)-4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide, both $C_{16}H_{13}ClN_2O_4S$, are stabilized by extensive intramolecular hydrogen bonds. The 4-chloro derivative forms dimeric pairs of molecules lying about inversion centres as a result of intermolecular N—H···O hydrogen bonds, forming 14-membered rings representing an $R_2^2(14)$ motif; the 2-chloro derivative is devoid of any such intermolecular hydrogen bonds. The heterocyclic thiazine rings in both structures adopt half-chair conformations.

Comment

In recent years, there has been a rapid growth in the literature dealing with 1,2-benzothiazine-3-carboxamide 1,1-dioxide derivatives, due to their importance as analgesic and anti-inflammatory agents belonging to the oxicams, a new class of nonsteroidal anti-inflammatory drugs (NSAIDs) (Lombardino & Wiseman, 1972; Hirai *et al.*, 1997; Khalil *et al.*, 2000; Yaltirik *et al.*, 2001; Myung *et al.*, 2002). These drugs are free from steroidal side effects, although they have little effect on the progression of bone and cartilage destruction (Katzung, 1994). The search for more effective anti-inflammatory agents has led to the exploration of a wide variety of compounds that may inhibit cartilage destruction associated with NSAIDs, or at least reduce their severity. Besides great therapeutic potential, these are very motivating polyfunctional heterocyclic molecules by virtue of their dynamic structural features, including different tautomeric forms and their possible polymorphism (Banerjee & Sarkar, 2002). The crystal structures of piroxicam [an oxicam, 4-hydroxy-2-methyl-*N*-(2-pyridyl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide] and a wide variety of its derivatives have been reported (Kojić-Prodić & Ružić-Toroš, 1982; Reck *et al.*, 1988; Drebushchak *et al.*, 2006; Bordner *et al.*, 1984; Bhatt *et al.*, 2005; Hammen *et al.*, 1989; Bordner *et al.*, 1989; Chiesi-Villa *et al.*, 1998). The structures of a few derivatives of meloxicam (a 5-methyl-2-thiazolyl analogue of piroxicam) have also been reported (Fabiola *et al.*, 1998; Luger *et al.*, 1996). In continuation of our research in this important area (Siddiqui *et al.*, 2006*a*,*b*, 2007), we have synthesized analogues of piroxicam and meloxicam wherein the pyridyl ring of the former and 5-methoxy-2-thiazolyl group of the latter have been replaced by a chlorophenyl ring. A new facile procedure has been adopted that leads to an excellent yield and product purity. In this paper, we report the structures of the 2-chloro- and 4-chlorophenyl derivatives of the title compound, *viz*. (I) and (II), respectively.



(I) =2-Cl
(II)=4-Cl

The structure of (I) contains independent molecules separated by normal van der Waals distances (Fig. 1). The heterocyclic thiazine ring in (I) adopts a half-chair conformation, with atoms S1 and N1 displaced by −0.468 (3) and 0.328 (3) Å, respectively, from the plane defined by atoms C1/C6/C7/C8; the puckering parameters (Cremer & Pople, 1975) are Q = 0.522 (1) Å, θ = 117.8 (2)° and φ = 204.3 (2)°. Similar conformations of the thiazine ring have been reported in the above-mentioned structures of piroxicams and meloxicams. The conformations about the bonds C8—C9 and C9—N2 in (I) are both *EZ*, as determined by the intramolecular hydrogen bonds O1—H1O···O4 and N2—H2N···N1, resulting in graph-set patterns *S*(6) and *S*(5), respectively (Bernstein *et al.*, 1994). The intramolecular hydrogen bonds

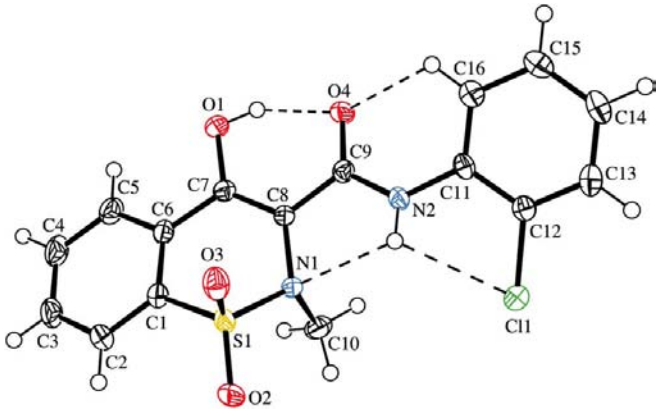


Figure 1
A drawing of the molecule of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

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N2—H2N···Cl1 and C16—H16···O4 also represent $S(5)$ and $S(6)$ motifs, respectively; details of the hydrogen-bonding geometry are given in Table 1. In the structures of oxicams, *EZ* and *ZZ* conformations about the corresponding bonds have been reported previously, depending on the environment of the drug molecules. In (I), the C10 and O3 methyl groups are axial, while atoms O1 and O2 are equatorial to the thiazine ring. Atoms N2/O4/C8/C9/C11 in (I) are essentially planar, with the maximum deviation from the plane being 0.0077 (11) Å for atom N2; the plane is inclined at 27.18 (6)° to the plane of the 2-chlorophenyl ring.

The structure of (II) (Fig. 2) contains dimeric pairs of molecules lying about inversion centres resulting from N2—H2N···O2 hydrogen bonds, thus forming 14-membered rings that can be best described in the graph-set notation as $R_2^2(14)$ (Bernstein *et al.*, 1994) (Fig. 3); the structure of (I) is devoid of any such intermolecular interactions. However, similar hydrogen-bonded dimers have been reported in piroxicams (Kojić-Prodić & Ružić-Toroš, 1982; Drebushchak *et al.*, 2006). The structure of (II) is also stabilized by extensive intramolecular interactions involving hydrogen bonds: N2—H2N···N1, O1—H1O···O4 and C12—H12···O4, representing $S(5)$, $S(6)$ and $S(6)$ motifs, respectively; details of the hydrogen-bonding geometry are given in Table 2. The thiazine ring in (II) also adopts a half-chair conformation, with atoms S1 and N1 displaced by −0.485 (5) and 0.358 (5) Å, respectively, from the plane formed by atoms C1/C6/C7/C8. The values of the puckering parameters in (II) are Q = 0.556 (2) Å, θ = 117.0 (3)° and φ = 205.1 (4)°, and these are close to the corresponding values observed in (I) and other related compounds. The conformations about the bonds C8—C9 and C9—N2 in (II) are also both *EZ*, due to the strong intramolecular hydrogen bonds O1—H1O···O4 and N2—H2N···N1. Intramolecular hydrogen bonds N2—H2N···Cl1 and C16—H16···O4 also represent $S(5)$ and $S(6)$ motifs, respectively (Table 2). The C10 and O3 methyl groups in (II) are axial, while atoms O1 and O2 are equatorial to the thiazine ring. Atoms N2/O4/C8/C9/C11 are essentially planar, with the maximum deviation from the plane being 0.053 (2) Å for atom N2. However, the chlorophenyl ring in (II) is inclined at 33.0 (2)° to the plane formed by atoms N2/O4/C8/C9/C11.

The molecular dimensions in the two structures are unexceptional and agree with the reported values for the corresponding dimensions for oxicams.

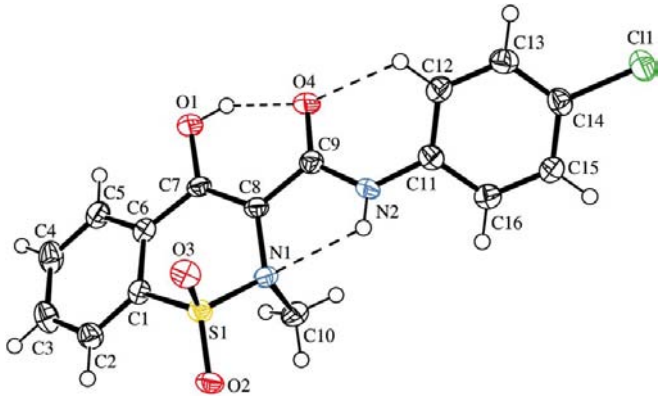

Figure 2
A drawing of the molecule of (II), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

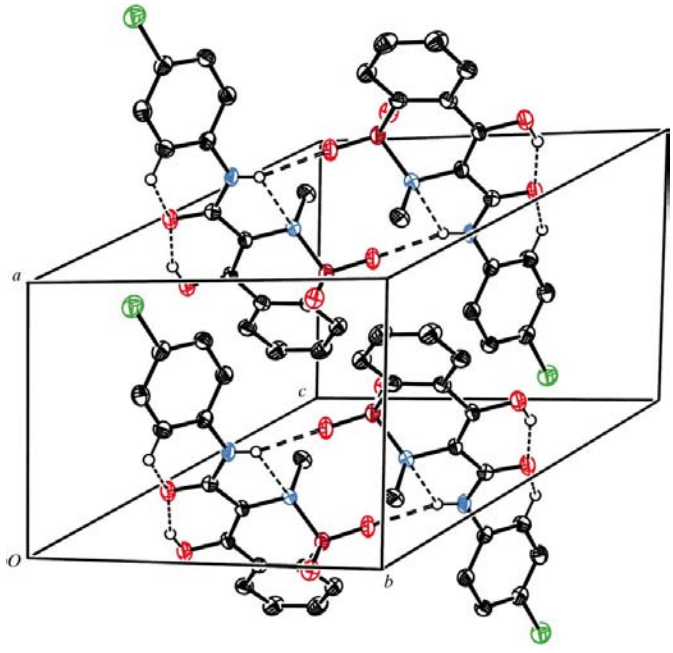

Figure 3
The unit-cell packing of (II), showing the inter- and intramolecular interactions as dashed lines. Only H atoms involved in the hydrogen bonds are shown.

Experimental

A mixture of methyl 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide (67.3 g, 250 mmol) and *o*- or *p*-chloroaniline (35.7 g, 280 mmol) in xylene (250 ml) was refluxed for 4–12 h in a Soxhlet apparatus having Linde type A_4 molecular sieves. Half of the xylene was then distilled off and the remaining contents were allowed to stand overnight at room temperature. The precipitates obtained were filtered off, washed with hexane and dried at room temperature to obtain the crystalline products (I) and (II), respectively. The products were crystallized from $CHCl_3$ solutions by slow evaporation at 313 K.

Analysis for (I): IR (neat, ν_{max}, cm^{-1}): NH 3325 (*s*), CO 1742 (*m*), SO_2 1380 and 1155; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.75 (*s*, 3H, CH_3), 7.26–7.30 (*d*, *J* = 6.8 Hz, 2H), 7.31–7.45 (*d*, *J* = 7.5 Hz, 2H), 7.69–7.73 (*m*, 2H), 7.76–7.88 (*d*, *J* = 6.8 Hz, 1H), 7.90–8.06 (*d*, *J* = 7.5 Hz, 1H), 8.21 (*s*, 1H, NH); ^{13}C NMR: δ 167.5, 157.3, 136.1, 134.7, 133.4, 132.6, 130.2, 129.1, 128.7, 126.2, 124.3, 121.7, 120.5, 118.3, 111.5, 42.3. Yield: 84.9 g (233 mmol, 93%); m.p. 457–459 K.

Analysis for (II): IR (neat, ν_{max}, cm^{-1}): NH 3337 (*s*), CO 1744 (*m*), SO_2 1341 and 1156; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.94 (*s*, 3H, CH_3), 7.30–7.31 (*d*, *J* = 6.7 Hz, 2H), 7.34–7.58 (*d*, *J* = 7.6 Hz, 2H), 7.70–7.75 (*m*, 2H), 7.76–7.90 (*d*, *J* = 6.9 Hz, 1H), 7.91–8.07 (*d*, *J* = 7.6 Hz, 1H), 8.38 (*s*, 1H, NH); ^{13}C NMR: δ 166.6, 158.2, 135.0, 134.3, 133.2, 132.5, 130.5, 129.2, 128.5, 126.8, 124.8, 121.8, 120.6, 118.0, 111.6, 40.1. Yield: 87.5 g (240 mmol, 96%); m.p. 496–498 K.

Compound (I)

Crystal data

$C_{16}H_{13}ClN_2O_4S$
M_r = 364.79
Monoclinic, $P2_1/c$
a = 7.750 (2) Å
b = 28.588 (7) Å
c = 7.5190 (10) Å
β = 106.630 (12)°
V = 1596.2 (6) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.39 mm^{-1}
T = 173 (2) K
0.22 × 0.20 × 0.11 mm

Data collection

Nonius KappaCCD diffractometer
Absorption correction: multi-scan (*SORTAV*; Blessing, 1997)
T_{min} = 0.918, T_{max} = 0.958
6588 measured reflections
3610 independent reflections
3003 reflections with $I > 2\sigma(I)$
R_{int} = 0.027

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.034
$wR(F^2)$ = 0.090
S = 1.02
3610 reflections
226 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.30 e Å^{-3}
$\Delta\rho_{min}$ = −0.37 e Å^{-3}

Table 1
Hydrogen-bond geometry (Å, °) for (I).

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1O···O4	0.87 (2)	1.75 (2)	2.563 (2)	153 (2)
N2—H2N···N1	0.85 (2)	2.29 (2)	2.733 (2)	113 (2)
N2—H2N···Cl1	0.85 (2)	2.58 (2)	2.953 (2)	108 (2)
C16—H16···O4	0.95	2.38	2.908 (2)	115

Compound (II)

Crystal data

$C_{16}H_{13}ClN_2O_4S$
M_r = 364.79
Triclinic, $P\overline{1}$
a = 7.970 (5) Å
b = 10.945 (6) Å
c = 11.133 (7) Å
α = 60.61 (3)°
β = 69.81 (3)°
γ = 86.32 (2)°
V = 787.6 (8) Å^3
Z = 2
Mo $K\alpha$ radiation
μ = 0.40 mm^{-1}
T = 173 (2) K
0.14 × 0.10 × 0.04 mm

Data collection

Nonius KappaCCD diffractometer
Absorption correction: multi-scan (*SORTAV*; Blessing, 1997)
T_{min} = 0.946, T_{max} = 0.984
6690 measured reflections
3595 independent reflections
2197 reflections with $I > 2\sigma(I)$
R_{int} = 0.057

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.050
$wR(F^2)$ = 0.127
S = 1.02
3595 reflections
224 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.34 e Å^{-3}
$\Delta\rho_{min}$ = −0.37 e Å^{-3}

Table 2
Hydrogen-bond geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1O···O4	0.88 (3)	1.74 (3)	2.560 (3)	153 (3)
N2—H2N···N1	0.80 (3)	2.27 (3)	2.734 (4)	118 (3)
N2—H2N···O2^{i}	0.80 (3)	2.30 (3)	3.006 (3)	148 (3)
C12—H12···O4	0.95	2.51	2.966 (4)	110

Symmetry code: (i) $-x, -y+1, -z+1$.

For both structures, H atoms bonded to C atoms were included in the refinements in geometrically idealized positions, with C—H = 0.98 and 0.95 Å for methyl and benzene H atoms, respectively, and with U_{iso}(H) = 1.2U_{eq}(C). H atoms bonded to N and O atoms were allowed to refine, with U_{iso}(H) = 1.2U_{eq}(parent). The final difference maps were free of chemically significant features.

For both compounds, data collection: *COLLECT* (Nonius, 1998); cell refinement: *DENZO* (Otwinowski & Minor, 1997); data reduction: *SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SAPI91* (Fan, 1991); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEPII* (Johnson, 1976); software used to prepare material for publication: *SHELXL97*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: GZ3109). Services for accessing these data are described at the back of the journal.

References

Banerjee, R. & Sarkar, M. (2002). *J. Lumin.* **99**, 255–263.
Bernstein, J., Etter, M. C. & Leiserowitz, L. (1994). *Structure Correlation*, Vol. 2, edited by H.-B. Bürgi & J. D. Dunitz, pp. 431–507. New York: VCH.
Bhatt, P. M., Ravindra, N. V., Banerjee, P. & Desiraju, G. R. (2005). *Chem. Commun.* pp. 1073–1075.
Blessing, R. H. (1997). *J. Appl. Cryst.* **30**, 421–426.
Bordner, J., Hammen, P. D. & Whipple, E. B. (1989). *J. Am. Chem. Soc.* **111**, 6572–6578.
Bordner, J., Richards, J. A., Weeks, P. & Whipple, E. B. (1984). *Acta Cryst.* C**40**, 989–990.
Chiesi-Villa, A., Rizzoli, C., Amari, G., Delcanale, M., Redenti, E. & Ventura, P. (1998). *Supramol. Chem.* **10**, 111–119.
Cremer, D. & Pople, J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354–1358.
Drebushchak, T. N., Pankrushina, N. N., Shakhtshneider, T. P. & Apenina, S. A. (2006). *Acta Cryst.* C**62**, o429–o431.
Fabiola, G. F., Pattabhi, V., Manjunatha, S. G., Rao, G. V. & Nagarajan, K. (1998). *Acta Cryst.* C**54**, 2001–2003.
Fan, H.-F. (1991). *SAPI91*. Rigaku Corporation, Tokyo, Japan.
Hammen, P. D., Berke, H., Bordner, J., Braisted, A. C., Lombardino, J. G. & Whipple, E. B. (1989). *J. Heterocycl. Chem.* **26**, 11–16.
Hirai, T., Matsumoto, S. & Kishi, I. (1997). *J. Chromatogr. B*, **692**, 375–388.
Johnson, C. K. (1976). *ORTEPII*. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.
Katzung, B. G. (1994). Editor. *Basic and Clinical Pharmacology*, 7th ed., pp. 589–590. Stampford, CT, USA: Appleton & Lange.
Khalil, S., Borham, N. & El-Ries, M. A. (2000). *Anal. Chim. Acta*, **441**, 215–219.
Kojić-Prodić, B. & Ružić-Toroš, Ž. (1982). *Acta Cryst.* B**38**, 2948–2951.
Lombardino, J. G. & Wiseman, E. H. (1972). *J. Med. Chem.* **15**, 848–849.
Luger, P., Daneck, K., Engel, W., Trummlitz, G. & Wagner, C. (1996). *Eur. J. Pharm. Sci.* **4**, 175–187.
Myung, S. P., Eun, S. C., Myung, S. L. & Soon-kyoung, K. (2002). *Bull. Korean Chem. Soc.* **23**, 1836–1838.
Nonius (1998). *COLLECT*. Nonius BV, Delft, The Netherlands.
Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, *Macromolecular Crystallography*, Part A, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.
Reck, G., Dietz, G., Laban, G., Gunter, W., Bannier, G. & Hohne, E. (1988). *Pharmazie*, **43**, 477–481.
Sheldrick, G. M. (1997). *SHELXL97*. University of Göttingen, Germany.
Siddiqui, W. A., Ahmad, S., Khan, I. U., Siddiqui, H. L. & Weaver, G. W. (2007). *Synth. Commun.* **37**, 767–773.
Siddiqui, W. A., Ahmad, S., Ullah, I. & Malik, A. (2006*a*). *J. Chem. Soc. Pak.* **28**, 583–589.
Siddiqui, W. A., Ahmad, S., Ullah, I. & Malik, A. (2006*b*). *Synth. Commun.* **37**, 767–773.
Yaltirik, M., Oral, C. K., Oral, I., Kasaboglu, G. & Cebi, V. (2001). *Turk. J. Med. Sci.* **31**, 151–154.