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Keto–enol tautomerism in crystals of 3-[hydroxy(phenyl)methyl]-2,5,7-trimethyl-2,3-dihydropyrido[3,2-e]-[1,2]thiazin-4-one 1,1-dioxide and 3-(1-hydroxyethylidene)-2,5,7-trimethyl-2,3-dihydropyrido[3,2-e][1,2]-thiazin-4-one 1,1-dioxide

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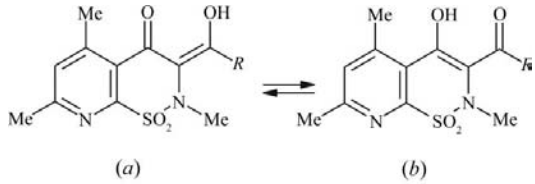
In the crystal structures of the title compounds, $C_{17}H_{16}N_2O_4S$, (I), and $C_{12}H_{14}N_2O_4S$, (II), the co-existence of both possible keto/enol (4-keto and 4-hydroxy) tautomers, with visible predominance of the 4-keto form, is observed. The tautomeric equilibrium is stabilized by strong intramolecular O—H···O hydrogen bonding. The ^{13}C NMR spectra recorded for (I) and (II), and theoretical calculations at the RHF SCF *ab initio* 6–31G** level, show the same tautomeric equilibrium in solution and the gaseous phase. The partially saturated thiazine rings in the pyrido[3,2-*e*][1,2]thiazine rings systems of (I) and (II) adopt a diplanar conformation. The molecular packing in (I) is influenced by weak intermolecular C—H···O hydrogen bonding and C—H···π interactions. In the crystal structure of (II), the molecules are linked by a combination of O—H···O hydrogen bonding and C—H···π and π–π interactions.

Comment

In recent papers, we reported the synthesis of 3-acyl-4-oxo/hydroxy-2-substituted-pyrido[3,2-*e*][1,2]thiazine 1,1-dioxides prepared for pharmaceutical reasons (Zawisza & Malinka, 1986; Malinka *et al.*, 2002, 2004). For the β-dicarbonyl grouping incorporated into the structure of the thiazine ring, the 4-hydroxy tautomeric form [(*b*), see scheme] was assigned as predominant on the basis of spectral data (IR and ^{1}H NMR). On the other hand, 3-acyl-4-oxo/hydroxy-2-substituted-pyrido[3,2-*e*][1,2]thiazine 1,1-dioxides show reactivity toward nucleophiles, such as primary aliphatic amines, with formation of 4-oxo-enamines, whose structures were confirmed by X-ray analysis (Malinka *et al.*, 2004). In order to determine the keto/enol tautomeric equilibrium within a series of pyridothiazines, X-ray crystal structure determinations and theoretical calculations were undertaken using 3-[hydroxy(phenyl)methyl]-2,5,7-trimethyl-2,3-dihydropyrido-[3,2-*e*][1,2]thiazin-4-one 1,1-dioxide, (I), and 3-(1-hydroxy-ethylidene)-2,5,7-trimethyl-2,3-dihydropyrido[3,2-*e*][1,2]thiazin-4-one 1,1-dioxide, (II) (Figs. 1 and 2, respectively), as model compounds.



Difference electron-density maps for (I) and (II) revealed the position of the H atom in the vicinity of atom O11, clearly indicating that both molecules exist as the O4-keto/O11-enol form, (*a*), with the hydroxy and carbonyl groups involved in a strong intramolecular O11—H11···O4 (Tables 2 and 4) resonance-assisted hydrogen bond (Gilli *et al.*, 1989). Moreover, the O11—C11, O4—C4, C3—C4 and C3—C11 bond lengths in (I) (Table 1) and (II) (Table 3), nominally corresponding to hydroxy, carbonyl, single and double bonds, respectively, have values characteristic of the delocalization of

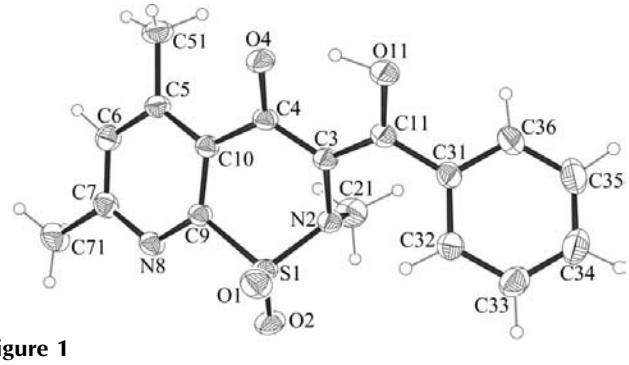


Figure 1
A view of (I*a*), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

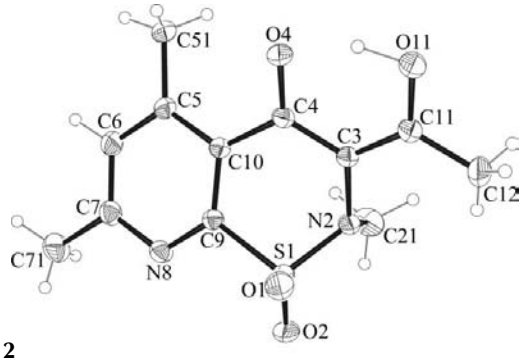


Figure 2
A view of (II*a*), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

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π electrons in the O4/C4/C3/C11/O11 system. Notwithstanding, a residual electronic density in Fourier maps (Fig. 3) of 0.15 e Å^{-3} for (I) and 0.16 e Å^{-3} for (II) is observed at distances of 0.729, 0.889 and 1.884 Å in (I), and 0.710, 0.896 and 1.906 Å in (II) from atoms O4, H11 and O11, respectively. Thus, the possibility of desmotropism (Foces-Foces *et al.*, 1997), *i.e.* the co-existence in the crystalline state of the O4-keto/O11-enol form, (*a*), and a small amount of the O4-enol/O11-keto form, (*b*), cannot be precluded.

Because of the keto–enol tautomerism, the C—O bonds clearly differ in length from single and double bonds. The O11—C11 bonds are significantly shorter than expected for the Csp^2—O2 bond in enols [1.333 (17) Å], while the O4—C4 bonds are longer than expected for Csp^2═O1 in ketones [1.210 (8) Å; Allen *et al.*, 1987]. The C—O bonds in the similar structure of methyl 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide [a precursor in the synthesis of piroxicam, a nonsteroidal and anti-inflammatory agent (Golič & Leban, 1987)] are more differentiated, with C—O bond lengths of 1.352 (9) and 1.234 (9) Å for the hydroxy and carbonyl groups, respectively.

In solution, the ^{13}C NMR (DMSO) spectrum of (I) shows the presence of both tautomers (*a*) and (*b*), with the predominance of one of them indicated by the non-equivalent splitting of some signals. The splittings 176.00 and 176.13, 162.45 and 163.13, 151.40 and 151.72, 133.82 and 133.60, 132.43 and 132.78, 130.30 and 130.80, and 121.62 and 121.44 p.p.m. can be ascribed to seven C atoms (C3, C4, C10, C11, C31, C32 and C36) having different structural surroundings in molecules of tautomers (*a*) and (*b*). The ^{13}C NMR ($CDCl_3$) spectrum of (II) exhibits only one group of signals, corresponding to one tautomeric form in solution. The change of the ^{13}C NMR spectrum of the keto–enol pair with changing solvent is observed, for example, for the keto–enol tautomerism in fluorinated β-diketones (Salman *et al.*, 1990) and phenylpyruvic acids (Carpy *et al.*, 2000).

Theoretical calculations at the RHF SCF *ab initio* 6–31G** level (Bylaska *et al.*, 2006; Kendall *et al.*, 2000) show that form (*a*) of (I) and (II) obtained after energy minimization and geometry optimization in the gaseous phase is more energetically stable than form (*b*), with a small difference in the energy between the (*b*) and (*a*) forms of 1.195 and 1.537 kcal mol^{-1} for (I) and (II), respectively. Thus, the populations of the tautomers (*a*) and (*b*) in vacuum estimated using a nondegenerate Boltzmann distribution are in the ratio 0.87:0.13 in (I) and 0.93:0.07 in (II). In solution [DMSO (ε = 46.7) for (I) and $CHCl_3$ (ε = 4.81) for (II); COSMO model (Klamt & Schüürmann, 1993)], the energy difference between forms (*b*) and (*a*) is 0.150 kcal mol^{-1} for (I) and 0.847 kcal mol^{-1} for (II), indicating the predominance of form (*a*) over form (*b*), with population ratios of 0.88:0.12 and 0.81:0.19 for (I) and (II), respectively. The results of theoretical calculations for (I) and (II) do not include the co-existence of both possible keto–enol (*a*) and (*b*) forms in the gaseous phase and solution, indicating the O4-keto/O11-enol form, (*a*), as predominant, and are in good agreement with X-ray and ^{13}C NMR experimental data. The theoretical data showed also that the third possible O4-keto/O11-keto/CH_2 tautomeric form of (I) and (II) is the most stable form. However, this tautomeric form is not present in the crystalline state, probably because of the impossibility of forming intra- or (and) intermolecular O—H···O hydrogen bonds to stabilize the crystal and molecular structures.

In the pyrido[3,2-*e*][1,2]thiazine ring systems of (I*a*) and (II*a*), the aromatic pyridine rings are planar within 0.008 (1) and 0.006 (1) Å, respectively, while the partially saturated thiazine rings exist in a diplanar conformation with an asymmetry parameter $\Delta C_2^{S1,N2}$ of 14.01 (15)° in (I*a*) and 9.31 (13)° in (II*a*) (Duax & Norton, 1975), and S1—C9—C10—C4 and N2—C3—C4—C10 torsion angles close to 0° (Tables 1 and 3). The substituent atoms O1 and C21 in both molecules occupy axial positions, and all other substituents occupy equatorial

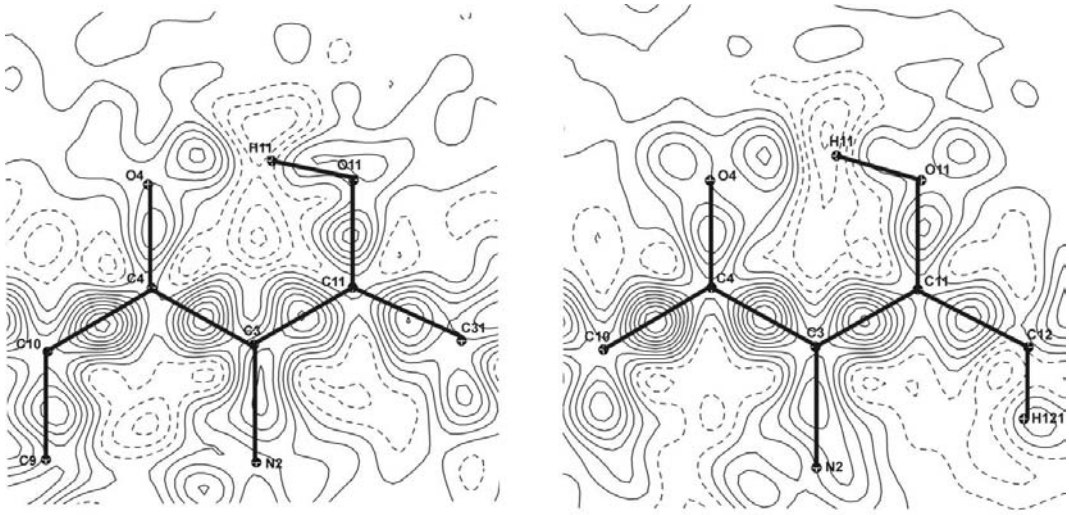

Figure 3
Difference Fourier maps calculated for the O4-keto and O11—H11-enol groups involved in the intramolecular hydrogen bond (*a*) in (I*a*) and (*b*) in (II*a*). Solid lines indicate positive values and dashed lines indicate negative values of difference electron density, with a contour level of 0.04 e Å^{-3}.

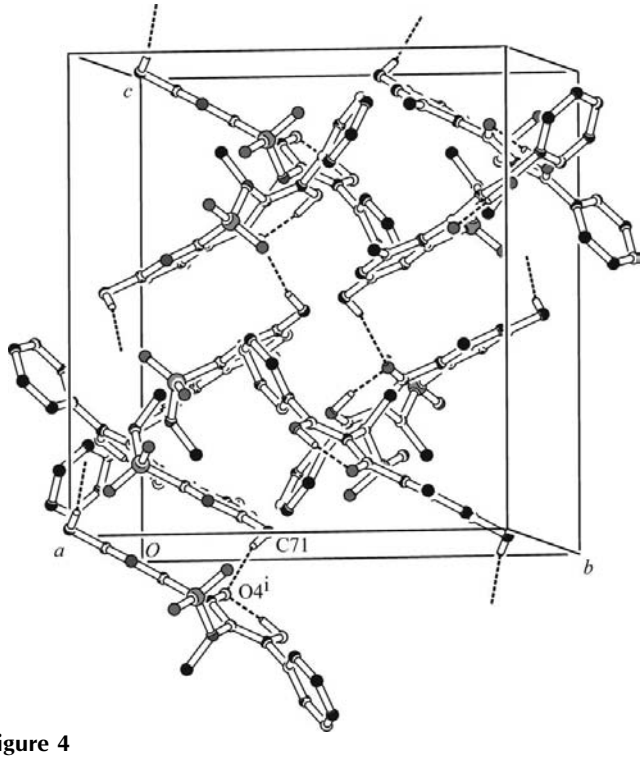

Figure 4
The molecular packing of (I*a*), viewed down the *a* axis. Dashed lines indicate intermolecular hydrogen bonds. [Symmetry code: (i) $x+\frac{1}{2}$, $-y+\frac{1}{2}$, $-z$.]

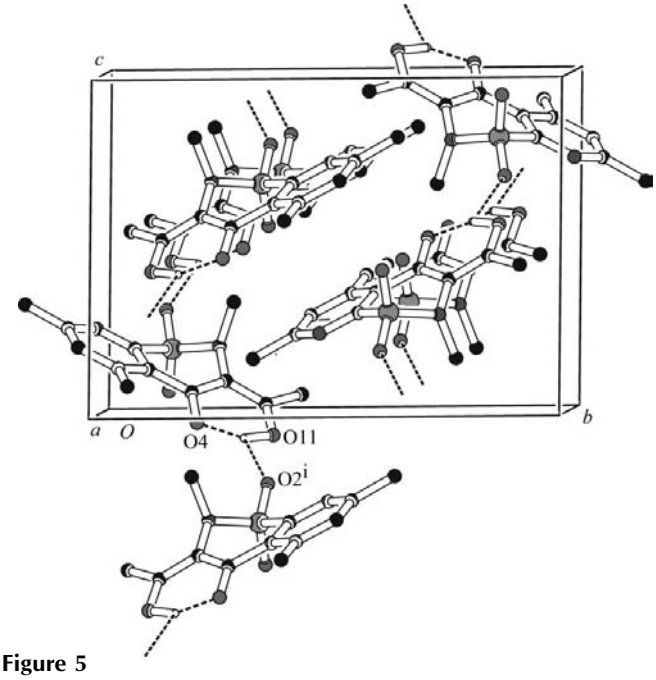

Figure 5
The molecular packing of (II*a*), viewed down the *a* axis. Dashed lines indicate intermolecular hydrogen bonds. [Symmetry code: (i) $x+\frac{1}{2}$, $-y+\frac{1}{2}$, $z-\frac{1}{2}$.]

positions with respect to the plane of the thiazine ring. Atoms N2 have a flattened pyramidal configuration, the sum of the angles around N2 being 342.61 (18)° in (I*a*) and 345.45 (16)° in (II*a*); these values are intermediate between sp^3- and sp^2-hybridization as a result of the weak conjugation of the lone pair at N2 with the C10/C4/O4/C3/C11 π-electron system. The marked deviation from sp^2-hybridization and four different substituents at atom N2 cause the chirality of the molecules of (I*a*) and (II*a*). A similar effect is observed for four close analogues containing the pyridothiazine ring system (Malinka *et al.*, 2004; Karczmarzyk & Malinka, 2005, 2006), but there is only one case (5*H*-2,4-dimethyl-6-phenyl-8,9-dihydropyrido-[3′,2′:5,6][1,2]thiazino[3,2-*c*][1,4]oxazin-5-one 11,11-dioxide) where this results in the separation of the enantiomers during the process of crystallization. The presence of bulky 2-methyl and 3-[hydroxy(phenyl)methyl] [in (I*a*)] and 3-(1-hydroxyethylidene) [in (II*a*)] substituents on adjacent positions of the thiazine ring is the cause of asymmetry in the O11—C11—C31 and C3—C11—C31 angles in (I*a*) (Table 1) and the O11—C11—C12 and C3—C11—C12 angles in (II*a*) (Table 3), and of the distortion of the molecule of (I*a*) as a whole from a planar conformation, the C3—C11—C31—C32 torsion angle being −46.7 (2)°.

The molecular packing in the crystal structure of (I*a*) (Fig. 4) is influenced by a weak intermolecular C—H···O hydrogen bond, specified as *C*(8) (Bernstein *et al.*, 1995), linking molecules related by a 2_1 axis into molecular chains along the [100] direction (Table 2). Additionally, the C21—H212 bond of the methyl group is oriented towards the centroid *CgA* of the benzene ring of a neighbouring molecule related by a *b*-glide plane. This interaction connects the hydrogen-bonded chains into sheets parallel to the (001) plane.

The packing of molecules in the crystal structure of (II*a*) (Fig. 5) is governed by a combination of a very weak O—H···O hydrogen bond, specified as *C*(7), and a C—H···π(pyridine, *CgB*) interaction, linking the molecules related by *n*-glide planes into molecular chains parallel to the [101] direction (Table 3). Significant π–π interactions are observed in the packing. Pairs of pyridine rings belonging to inversion-related molecules partially overlap, with a centroid-to-centroid separation of 4.0364 (7) Å, a perpendicular distance of 3.738 Å and a slippage of 1.523 Å.

In conclusion, the crystal and molecular structures of (I) and (II), as well as their ^{13}C NMR spectra and theoretical calculations in solution and the gaseous phase, confirm the co-existence of the O4-keto/O11-enol, (*a*), and O4-enol/O11-keto, (*b*), tautomeric forms, with a visible predominance of the former. This tautomeric equilibrium is stabilized by a strong intramolecular O—H···O hydrogen bond. The above data should be taken into consideration when analysing the structure/bioactivity relationship within series of 3-acyl-4-oxopyrido[3,2-*e*][1,2]thiazines tested pharmacologically, both previously and in the future.

Experimental

The syntheses of (I) and (II) and their analytical data (IR and ^{1}H NMR) were described by Zawisza & Malinka (1986). Crystals suitable for X-ray diffraction analysis were grown by slow evaporation of benzene and propan-1-ol solutions of (I) and (II), respectively. For (I*a*), ^{13}C NMR (DMSO): δ 185.71, 176.00, 162.45, 155.57, 151.40, 133.82, 132.43, 130.30, 129.16, 128.67, 128.37, 121.62, 117.37, 111.58,

24.61, 22.54, 22.41. For (I*b*), ^{13}C NMR (DMSO): δ 185.71, 176.13, 163.13, 155.57, 151.72, 133.60, 132.78, 130.80, 129.16, 128.67, 128.37, 121.44, 117.37, 111.58, 24.61, 22.54, 22.41. For (II), ^{13}C NMR ($CDCl_3$): δ 195.72, 172.21, 163.24, 153.22, 151.33, 130.33, 121.33, 118.24, 40.29, 24.43, 22.62, 21.93.

Compound (I)

Crystal data

$C_{17}H_{16}N_2O_4S$
M_r = 344.38
Orthorhombic, *Pbca*
a = 12.9699 (4) Å
b = 15.2714 (5) Å
c = 16.6176 (6) Å
V = 3291.42 (19) Å^3
Z = 8
Mo *K*α radiation
μ = 0.22 mm^{-1}
T = 293 (2) K
0.44 × 0.26 × 0.18 mm

Data collection

Bruker SMART APEXII CCD diffractometer
Absorption correction: multi-scan (*SADABS*; Bruker, 2005)
T_{min} = 0.873, T_{max} = 0.961
54023 measured reflections
4042 independent reflections
3459 reflections with $I > 2\sigma(I)$
R_{int} = 0.020

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.039
$wR(F^2)$ = 0.129
S = 1.08
4042 reflections
220 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.30 e Å^{-3}
$\Delta\rho_{min}$ = −0.27 e Å^{-3}

Table 1
Selected geometric parameters (Å, °) for (I).

O4—C4	1.2636 (16)	C3—C11	1.3906 (18)
O11—C11	1.3070 (16)	C3—C4	1.4216 (18)
O11—C11—C31	115.44 (12)	C3—C11—C31	123.97 (12)
N2—C3—C4—C10	5.38 (19)	C3—C11—C31—C32	−46.7 (2)
S1—C9—C10—C4	−4.56 (17)		

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

CgA is the centroid of the benzene ring.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O11—H11···O4	1.00 (2)	1.58 (2)	2.5083 (17)	154 (2)
C71—H712···O4^{i}	0.96	2.53	3.472 (2)	167
C21—H212···*CgA*^{ii}	0.96	2.97	3.817 (2)	148

Symmetry codes: (i) $x+\frac{1}{2}, -y+\frac{1}{2}, -z$; (ii) $-x-\frac{1}{2}, y-\frac{1}{2}, z$.

Compound (II)

Crystal data

$C_{12}H_{14}N_2O_4S$
M_r = 282.31
Monoclinic, $P2_1/n$
a = 8.9023 (2) Å
b = 14.3095 (3) Å
c = 10.6151 (2) Å
β = 105.817 (2)°
V = 1301.03 (5) Å^3
Z = 4
Mo *K*α radiation
μ = 0.26 mm^{-1}
T = 293 (2) K
0.42 × 0.35 × 0.26 mm

Data collection

Bruker SMART APEXII CCD diffractometer
Absorption correction: multi-scan (*SADABS*; Bruker, 2005)
T_{min} = 0.846, T_{max} = 0.935
18200 measured reflections
3097 independent reflections
2924 reflections with $I > 2\sigma(I)$
R_{int} = 0.015

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.034
$wR(F^2)$ = 0.113
S = 1.00
3097 reflections
175 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.34 e Å^{-3}
$\Delta\rho_{min}$ = −0.24 e Å^{-3}

Table 3
Selected geometric parameters (Å, °) for (II).

O4—C4	1.2717 (14)	C3—C11	1.3948 (18)
O11—C11	1.3001 (17)	C3—C4	1.4234 (16)
O11—C11—C12	115.69 (13)	C3—C11—C12	123.31 (13)
N2—C3—C4—C10	2.76 (18)	S1—C9—C10—C4	−2.29 (15)

Table 4
Hydrogen-bond geometry (Å, °) for (II).

CgB is the centroid of the pyridine ring.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O11—H11···O4	1.05 (3)	1.55 (3)	2.5139 (17)	152 (2)
O11—H11···O2^{i}	1.05 (3)	2.59 (3)	3.0074 (19)	103.3 (16)
C12—H122···*CgB*^{ii}	0.96	2.97	3.820 (2)	149

Symmetry codes: (i) $x+\frac{1}{2}, -y+\frac{1}{2}, z-\frac{1}{2}$; (ii) $x-\frac{3}{2}, -y-\frac{1}{2}, z-\frac{3}{2}$.

For both compounds, the O-bound H atom involved in the intramolecular hydrogen bond was located by difference Fourier synthesis and refined freely. The remaining H atoms were positioned geometrically and treated as riding on their C atoms, with C—H distances of 0.93 (aromatic) and 0.96 Å (CH_3). All H atoms were assigned U_{iso}(H) values of $1.5U_{eq}$(O,C).

For both compounds, data collection: *APEX2* (Bruker, 2005); cell refinement: *SAINT* (Bruker, 2005); data reduction: *SAINT*; program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1993); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997); software used to prepare material for publication: *SHELXL97* and *WinGX* (Farrugia, 1999).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SF3092). Services for accessing these data are described at the back of the journal.

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