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Diastereomers of 4-(2-hydroxyphenyl)-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepine

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The crystal structure of the title compound is composed of diastereomers of 4-(2-hydroxyphenyl)-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepine, $C_{21}H_{19}NOS$, that are cocrystallized. The asymmetric unit contains two molecules. One S and two C atoms of the heterocyclic ring in one molecule are disordered, resulting in two different conformers. The H atoms at the chiral centers in the ordered molecule are *trans* with respect to each other, *cis* in the other conformer. The average bond distances are: $S-Csp^3$ 1.825 (2), $S-Csp^2$ 1.778 (8), $N-Csp^3$ 1.495 (5), $N-Csp^2$ 1.415 (8), $O-C_{aromatic}$ 1.380 (7), Csp^3-Csp^3 1.533 (14), $Csp^3-C_{aromatic}$ 1.52 (2) and $C-C_{aromatic}$ 1.382 (13) Å. The structure is stabilized by strong intra- and intermolecular hydrogen bonds.

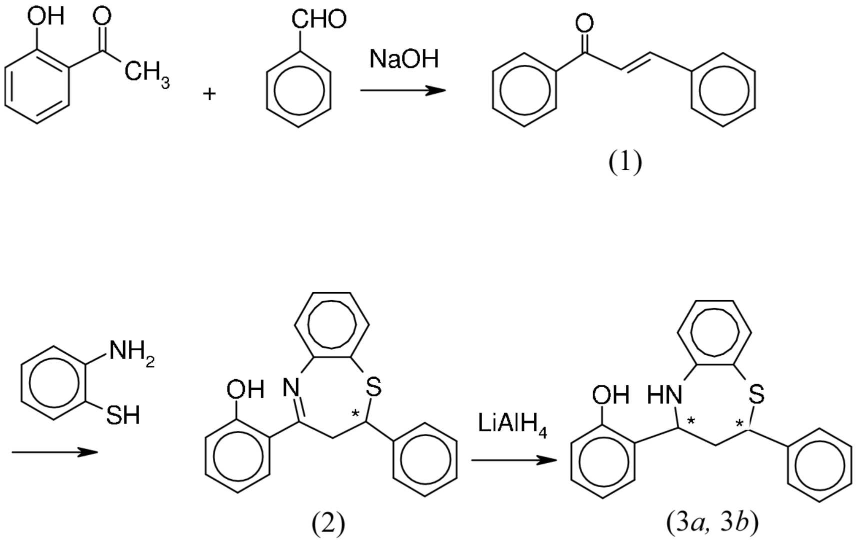
Key indicators

Single-crystal X-ray study
T = 170 K
Mean σ(C–C) = 0.005 Å
R factor = 0.068
wR factor = 0.148
Data-to-parameter ratio = 17.2

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

Comment

With the advances in pharmaceutical chemistry, benzothiazepine seven-membered-ring systems containing both nitrogen and sulfur in addition to carbon in the ring have become increasingly important in heterocyclic chemistry. Substituted benzothiazepines are specially known for their calcium antagonistic activity (Kugita *et al.*, 1971; Sato *et al.*, 1971; Abe *et al.*, 1988), anti-HIV activity (Grandolini *et al.*, 1999), anticancer (Sharma *et al.*, 1997) and antihypertensive activity (Karnail *et al.*, 1987). For example, Diltiazem is an accepted drug for the treatment of cardiovascular disorders (Kurokawa *et al.*, 1991).



In our efforts towards the synthesis of novel benzothiazepines of clinical importance, condensation of *o*-hydroxyacetophenone with benzaldehyde led to the formation of a

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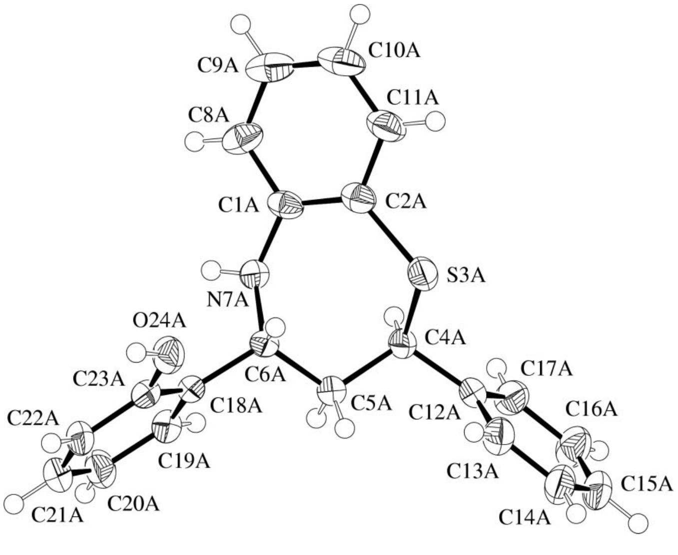

Figure 1
*ORTEP*II (Johnson, 1976) drawing of molecule *A* of (3), with displacement ellipsoids plotted at the 50% probability level.

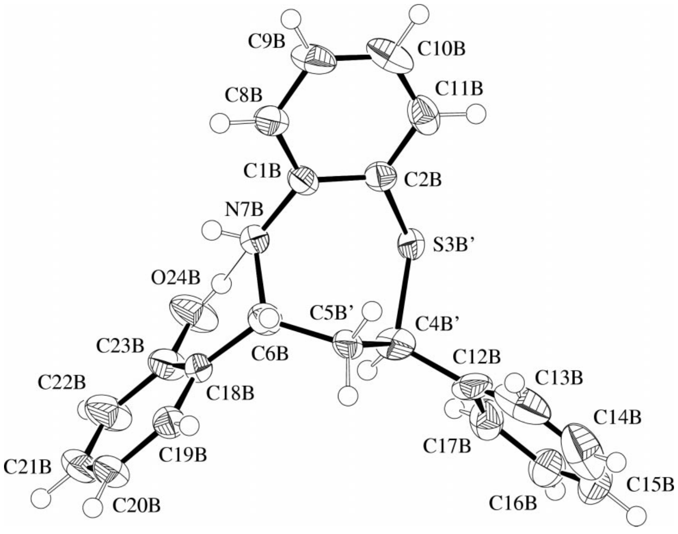

Figure 3
*ORTEP*II (Johnson, 1976) drawing of molecule *B*′ of (3), with displacement ellipsoids plotted at the 50% probability level.

chalcone, (1). The reaction of (1) with *o*-aminothiophenol produced dihydro-1,5-benzothiazepine (2). Reaction of (2) with LAH (lithium aluminium hydride) gave a crude product which, on crystallization, led to colorless crystals containing diastereomeric benzothiazepines [(3*a*) and (3*b*); see Scheme]. In this paper, we report the structure of the diastereomers of 4-(2-hydroxyphenyl)-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepine, (3), which display different conformations in the solid state.

The asymmetric unit of (3) is composed of two molecules represented by atomic labels C1*A*–O24*A* (molecule *A)* and C1*B*–O24*B* (molecule *B*), respectively. The H atoms attached to both chiral centers, C4*A* and C6*A*, in molecule *A* are *trans* with respect to each other (Fig. 1). On the other hand, in molecule *B*, three atoms, S3, C4 and C5, are disordered over sites S3*B*, C4*B*, C5*B* and S3*B*′, C4*B*′, C5*B*′, with site-occupancy factors 0.606 (3) and 0.394 (3), respectively, giving rise to two distinct conformations of the heterocyclic ring, resulting in a major (molecule *B*, Fig. 2) and a minor (molecule *B*′, Fig. 3) conformer. The H atoms attached to the chiral C atoms (C4*B*/C4*B*′ and C6*B*) are *cis* in the major (molecule *B*) and *trans* in the minor (molecule *B*′) conformers. In other words, molecules *A* and *B*′ have the same relative conformation, which is different from the conformation of molecule *B*. The three conformers are distinguished by the conformation of the central seven-membered heterocyclic ring. The heterocyclic ring in molecule *A* is in a distorted twist conformation with C4*A* and C6*A* 0.887 (4) and 0.827 (4) Å, respectively, on either side of the plane formed by the rest of the atoms of the heterocyclic ring; maximum deviation of any atom from the plane formed by the remaining atoms of the ring is 0.018 (2) Å. On the other hand, the heterocyclic ring adopts a chair conformation for the major conformer (molecule *B*) with atoms S3*B*, C4*B*, C6*B* and N7*B* forming a plane wherein C5*B* lies below this plane [0.722 (6) Å] and C1*B* and C2*B* above the plane [1.083 (4) and 1.099 (5) Å, respectively]. The heterocyclic ring in the minor conformer (molecule *B*′) adopts a boat conformation, with atoms S3*B*′, C4*B*′, C6*B* and N7*B* forming a plane, while atoms C1*B*, C2*B* and C5*B*′ lie 0.943 (6), 1.225 (5) and 0.689 (9) Å, respectively, above this plane. The conformations of the central rings in these conformers are probably influenced by the presence of the heteroatoms (S and N) in the ring, as well as by the exocyclic phenyl substituents attached to the chiral C atoms in the three molecules.

The phenol substituent is involved in intra- and intermolecular interactions. In molecule *A*, the phenol ring is positioned in such a way that the hydroxyl residue is closer to atom C6*A*. Thus, there exists bonding of the type C—H···O within this molecule [H6*A*···O24*A* 2.38 (3), C6*A*···O24*A*

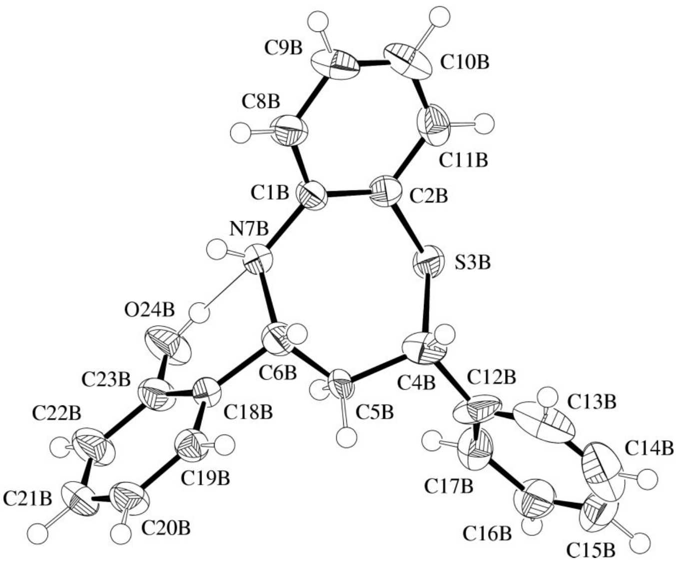

Figure 2
*ORTEP*II (Johnson, 1976) drawing of molecule *B* of (3), with displacement ellipsoids plotted at the 50% probability level.

2.839 (5) Å and C—H···O 108 (2)°]. Conversely, in both of the other conformers, molecules *B* and *B*′, the phenol ring is 'flipped', and thus the hydroxyl residue is close to the N atom of the seven-membered ring. The intramolecular interaction within these molecules consists of the hydrogen bonding between atoms O24*B* and N7*B* [H24*B*···N7*B* 2.02 (3), O24*B*···N7*B* 2.706 (4) Å and O—H···N 140 (3)°]. The structure is stabilized by intermolecular hydrogen bonds between hydroxyl groups in a linear bonding mode [H24*A*···O24*B* 2.09 (4), O24*A*···O24*B* 2.873 (4) Å and O—H···O 171 (4)°]. It is interesting to note that the H atoms bonded to N atoms are not involved in hydrogen bonding and that the closest contact is between H7*B* and both hydroxyl O atoms [H7*B*···O24*A* 2.75 (3) and H7*B*···O24*B* 2.76 (3) Å]; atom H7*A* shows no such environment.

An examination of the mean-planes calculations reveals that all the phenyl groups are individually planar [within the range 0.005 (3)–0.020 (3) Å], as expected. The conformational differences in the diastereomers are further evident from the orientation of the phenyl rings in the three molecules. The phenyl substituents attached to C4*A* and C6*A* in molecule *A* are almost at right angles to the aromatic ring fused to the heterocyclic ring, with angles between planes of 86.04 (10) and 78.60 (10)°, respectively. Somewhat similar, but significantly different, values were found for both molecules (*B* and B′), the corresponding angles between planes being 61.79 (13) and 86.98 (11)°, respectively.

The average bond distances for the diastereomers are: S—Csp^3 1.825 (2), S—Csp^2 1.778 (8), N—Csp^3 1.495 (5), N—Csp^2 1.415 (8), O—$\text{C}_{\text{aromatic}}$ 1.380 (7), Csp^3—Csp^3 1.533 (14), Csp^3—$\text{C}_{\text{aromatic}}$ 1.52 (2) and C—$\text{C}_{\text{aromatic}}$ 1.382 (13) Å. A search of the October 2001 release of the Cambridge Structural Database (Allen & Kennard, 1993) revealed only eight structures consisting of a heterocyclic seven-membered ring containing both nitrogen and sulfur, analogous to that in (3).

Experimental

Condensation of *o*-hydroxyacetophenone (0.01 mol) with benzaldehyde (0.01 mol) in the presence of sodium hydroxide and rectified spirit led to the formation of chalcone (1). The reaction of chalcone (1) (0.02 mol) with *o*-aminothiophenol (0.02 mol) in acidified methanol led to dihydro-1,5-benzothiazepine (2). Reaction of dihydro-1,5-benzothiazepine (2) (0.01 mol) was then carried out with lithium aluminium hydride (0.02 mol) in dry THF under argon. A crude product was obtained which, on crystallization, led to the isolation of (3) ($C_{21}H_{19}NOS$, 1.06 g, 32%); m.p. 363 K. MS(EI): m/e (relative intensity): 333 (M^+).

Crystal data

$C_{21}H_{19}NOS$
$M_r = 333.43$
Monoclinic, $P2_1/c$
$a = 10.3404\ (1)$ Å
$b = 36.9797\ (7)$ Å
$c = 9.4929\ (1)$ Å
$\beta = 108.993\ (1)$°
$V = 3432.32\ (8)$ Å^3
$Z = 8$
$D_x = 1.291$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 12187 reflections
$\theta = 1.0$–27.5°
$\mu = 0.20$ mm^{-1}
$T = 170\ (2)$ K
Block, colorless
0.15 × 0.15 × 0.15 mm

Data collection

Nonius KappaCCD diffractometer
ω and φ scans
Absorption correction: multi-scan (*SORTAV*; Blessing, 1997)
$T_{\min} = 0.97$, $T_{\max} = 0.97$
23647 measured reflections
7825 independent reflections
3496 reflections with $I > 2\sigma(I)$
$R_{\text{int}} = 0.088$
$\theta_{\max} = 27.6$°
$h = -13 \rightarrow 13$
$k = -47 \rightarrow 47$
$l = -12 \rightarrow 11$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.068$
$wR(F^2) = 0.148$
$S = 1.01$
7825 reflections
456 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.051P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max} < 0.001$
$\Delta\rho_{\max} = 0.45$ e Å^{-3}
$\Delta\rho_{\min} = -0.53$ e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

C1*A*—N7*A*	1.407 (4)	C2*B*—S3*B*	1.765 (3)
C2*A*—S3*A*	1.778 (3)	C2*B*—S3*B*′	1.792 (3)
S3*A*—C4*A*	1.822 (3)	S3*B*—C4*B*	1.829 (3)
C6*A*—N7*A*	1.490 (4)	S3*B*′—C4*B*′	1.827 (3)
C23*A*—O24*A*	1.377 (4)	C6*B*—N7*B*	1.502 (4)
C1*B*—N7*B*	1.424 (4)	C23*B*—O24*B*	1.391 (4)
C2*A*—S3*A*—C4*A*	103.97 (14)	C2*B*—S3*B*—C4*B*	98.72 (19)
C1*A*—N7*A*—C6*A*	119.4 (3)	C2*B*—S3*B*′—C4*B*′	113.7 (4)

Table 2
Hydrogen-bonding geometry (Å, °).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O24*A*—H24*A*···O24*B*$^{\text{i}}$	0.81 (3)	2.07 (3)	2.871 (3)	168 (3)
O24*B*—H24*B*···N7*B*	0.77 (3)	2.06 (3)	2.706 (4)	141 (3)
C6*A*—H6*A*···O24*A*	1.00	2.36	2.841 (4)	108

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

Three atoms in the heterocyclic ring of one of the molecules were disordered over sites S3*B*/S3*B*′, C4*B*/C4*B*′ and C5*B*/C5*B*′; partial site-occupancy factors were allowed to refine for the unprimed and primed atoms with some restrained bond lengths. The rest of the atoms in the disordered molecule did not seem to be affected by the disorder in the heterocyclic ring. Most of the H atoms were included at geometrically idealized positions, with C—H distances in the range 0.95–1.00 Å, in a riding mode, with isotropic displacement parameters 1.2 times the equivalent isotropic displacement parameters of the atoms to which they were bonded. The H atoms involved in hydrogen-bonding interactions and those bonded to N atoms were located from difference maps and were allowed to refine with an overall isotropic displacement parameter. The final difference Fourier map was essentially featureless, with the three highest peaks in the vicinity of atoms S3*B*′ and C4*B* and between C4*B*′and C5*B* , in the range 0.35–0.55 e Å^{-3}.

Data collection: *COLLECT* (Hooft, 1998); cell refinement: *HKL DENZO* (Otwinowski & Minor, 1997); data reduction: *SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SAPI*91 (Fan, 1991); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*II (Johnson, 1976); software used to prepare material for publication: *SHELXL*97.

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