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Derivatives of 4-(2-hydroxylphenyl)-2-phenyl-2,3-dihydro-1,5-benzothiazepine

Masood Parvez,[a]* Sumaira Umbreen[b] and Farzana Latif Ansari[b]

[a]Department of Chemistry, The University of Calgary, 2500 University Drive NW, Calgary, Alberta, Canada T2N 1N4, and [b]Department of Chemistry, Quaid-i-Azam University, Islamabad 45320, Pakistan
Correspondence e-mail: parvez@ucalgary.ca

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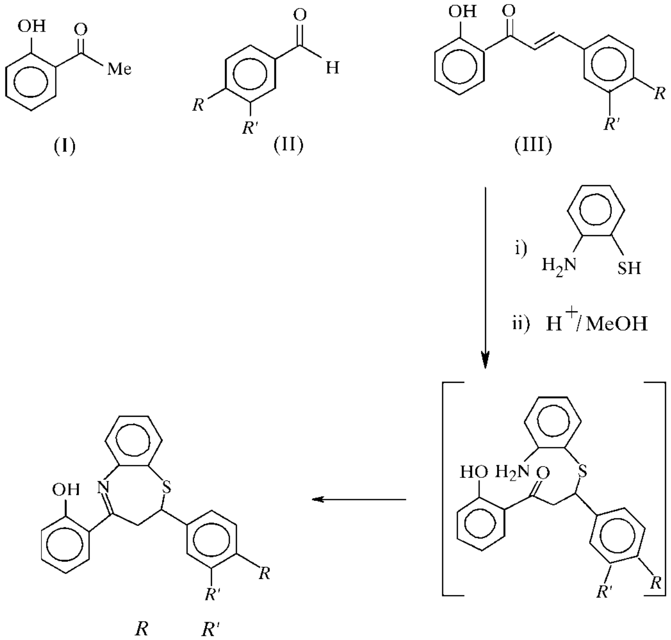
In the structures of 2-(4-chlorophenyl)-4-(2-hydroxyphenyl)-2,3-dihydro-1,5-benzothiazepine, $C_{21}H_{16}ClNOS$, 4-(2-hydroxyphenyl)-2-(4-tolyl)-2,3-dihydro-1,5-benzothiazepine, $C_{22}H_{19}NOS$, and 4-(2-hydroxyphenyl)-2-(3-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepine, $C_{22}H_{19}NO_2S$, the central seven-membered heterocyclic rings adopt twist-boat conformations in which the N atoms are involved in strong intramolecular hydrogen bonds with the hydroxyl H atoms, resulting in six-membered rings.

Comment

Many chemotherapeutic applications have been associated with benzothiazepine derivatives such as diltiazem, which is used as a calcium channel blocker (Chaffman & Brogden, 1985), an angiotensin-converting enzyme inhibitor (Itoh *et al.*, 1986), and an anticonvulsant and tranquilizing agent (Bock *et al.*, 1989). Calcium channel blockers are important cardiovascular drugs for the management of angina pectoris and hypertension and may have applications in additional therapeutic areas (Godfraind *et al.*, 1986). The importance of the methoxyphenyl moiety in biologically active compounds belonging to the benzothiazepine series of drugs has also been reported (Pant *et al.*, 1994). Following these studies and continuing our investigations in this area (Ansari *et al.*, 2002), we have reacted 2-hydroxyacetophenone, (I), with substituted benzaldehydes, (II) (see *Scheme*; $R = Cl$, CH_3 or H, and $R' = H$, H or OCH_3, respectively). The reaction yielded chalcones, (III), which on treatment with *o*-aminothiophenol in equimolar quantities in acidified methanol led to the formation of the 2-(4-chlorophenyl)-, 2-(4-tolyl)- and 2-(3-methoxyphenyl)- derivatives, (IV*a*)–(IV*c*), respectively, of 4-(2-hydroxyphenyl)-2-phenyl-2,3-dihydro-1,5-benzothiazepine. In this paper, we report the crystal structures of (IV*a*)–(IV*c*).

Figs. 1–3 show the structures of (IV*a*)–(IV*c*), respectively, and selected geometric parameters are given in Tables 1, 3 and 5. In all three structures, the central seven-membered heterocyclic rings adopt twist-boat conformations, such that atoms C1, C5, C6 and N7 are essentially planar and the remaining atoms lie above this plane. The distances of the remaining atoms of the heterocyclic ring from the planes in (IV*a*)–(IV*c*) are, respectively, 0.997 (4), 0.983 (3) and 0.983 (3) Å for atom C2, 2.287 (3), 2.283 (2) and 2.268 (4) Å for atom S3, and 1.393 (4), 1.388 (3) and 1.375 (2) Å for atom C4. In each structure, the C1/C5/C6/N7 plane (plane 1) is coplanar with the hydroxyphenyl ring. Atoms C1 and O24 lie on opposite sides of plane 1, their maximum deviations from the plane being 0.181 (2), 0.1307 (12) and 0.1531 (11) Å for C1, and 0.095 (2), 0.0591 (11) and 0.0590 (10) Å for O24, for compounds (IV*a*)–(IV*c*), respectively. Moreover, the C12–C17 phenyl ring (plane 2) is almost coplanar with plane 1 in (IV*a*) [the angle between the mean planes is 3.48 (12)°] and is inclined at 18.39 (7) and 65.88 (5)° in (IV*b*) and (IV*c*), respectively. The angles between the mean planes formed by the C1/C2/C8–C11 (plane 3) and C12–C17 (plane 4) phenyl rings are 51.3 (9), 63.68 (5) and 64.05 (6)°, respectively, while the C18–C23 phenyl ring (plane 5) is oriented with respect to plane 3 at angles of 52.94 (9), 48.71 (6) and 52.49 (5)° in compounds (IV*a*)–(IV*c*), respectively.).



	R	*R′*
(IV*a*)	Cl	H
(IV*b*)	Me	H
(IV*c*)	H	OMe

In all three structures, atom N7 is involved in intramolecular hydrogen bonds with the hydroxy H atom, resulting in a six-membered ring; details of the hydrogen-bonding geometry are provided in Tables 2, 4 and 6 for (IV*a*)–(IV*c*), respectively. Note that in (IV*b*), atom S3 is involved in a short intramol-

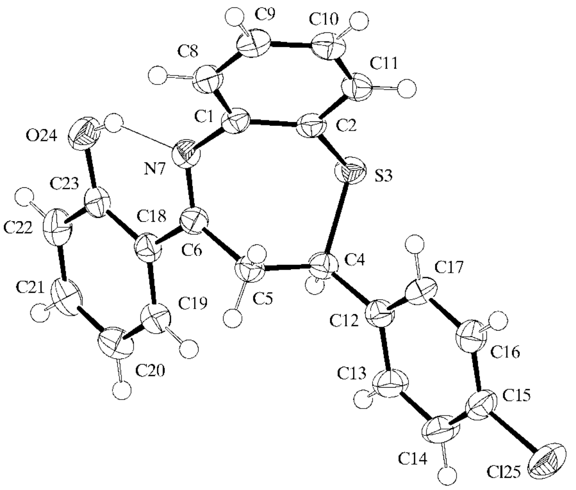


Figure 1
*ORTEP*II (Johnson, 1976) drawing of (IV*a*), with displacement ellipsoids plotted at the 50% probability level.

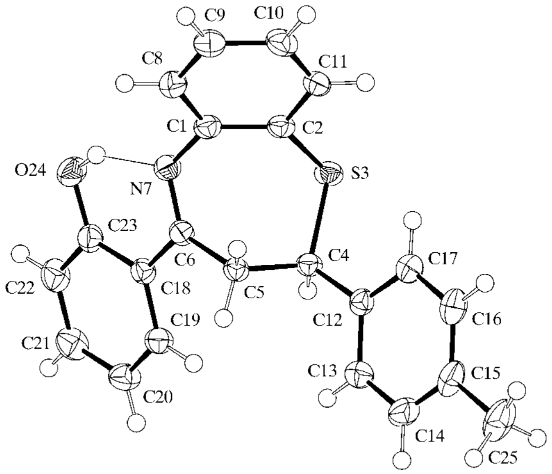


Figure 2
*ORTEP*II (Johnson, 1976) drawing of (IV*b*), with displacement ellipsoids plotted at the 50% probability level. Only three of the disordered methyl H atoms are shown.

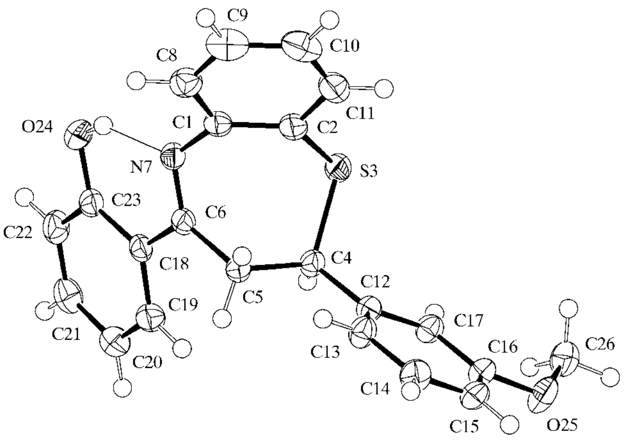


Figure 3
*ORTEP*II (Johnson, 1976) drawing of (IV*c*), with displacement ellipsoids plotted at the 50% probability level.

ecular contact with a phenyl H atom (S3···H17 = 2.78 Å). The corresponding contact in (IV*a*) is 2.91 Å, while (IV*c*) displays no such contact. Crystal-packing forces and the orientation of the phenyl rings are probably responsible for these differences.

The molecular dimensions in the three structures are unexceptional. A search of the November 2002 release of the Cambridge Structural Database (Allen, 2002) showed only five structures containing a heterocyclic seven-membered ring analogous to that in (IV*a*)–(IV*c*).

Experimental

The syntheses of compounds (III) (see *Scheme*) were carried out according to the procedures described by Furniss *et al.* (1989). Aqueous solutions of NaOH (60.0 ml, 4.0 *M*) were added to rectified spirit (35.0 ml) in conical flasks fitted with mechanical stirrers. The flasks were cooled in an ice bath and freshly distilled (I) (0.01 mol) was added to each. To these solutions were added, with stirring, substituted benzaldehydes, (II) (0.01 mol). The temperature was maintained at ~298 K and the reaction mixtures were stirred vigorously for 2–3 h until the mixtures became thick. The reaction mixtures were maintained at 273–277 K overnight. The solid masses thus obtained were neutralized with HCl and the precipitates were crystallized from aqueous ethanol. The benzothiazepine derivatives, (IV*a*)–(IV*c*), were synthesized according to the procedure reported by Svetlik *et al.* (1989). To the corresponding solutions of (III) (0.02 mol) in dry methanol (100–150 ml), which were acidified with concentrated HCl (five drops), was added *o*-aminothiophenol (0.02 mol). The mixtures were refluxed until crystalline solids separated out. After cooling, solid benzothiazepine derivatives were collected, washed with ether and cold methanol, and recrystallized from aqueous ethanol.

Compound (IV*a*)

Crystal data

$C_{21}H_{16}ClNOS$
$M_r = 365.86$
Monoclinic, $P2_1/c$
$a = 18.036\ (9)$ Å
$b = 4.836\ (2)$ Å
$c = 19.790\ (11)$ Å
$\beta = 97.02\ (2)^\circ$
$V = 1713.2\ (15)$ Å^3
$Z = 4$

$D_x = 1.419$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 9054 reflections
$\theta = 4.1$–25.0°
$\mu = 0.35$ mm^{-1}
$T = 173\ (2)$ K
Needle, yellow
0.15 × 0.08 × 0.06 mm

Data collection

Nonius KappaCCD area-detector diffractometer
ω and φ scans
Absorption correction: multi-scan (*SORTAV*; Blessing, 1997)
$T_{\min} = 0.901$, $T_{\max} = 0.982$
9054 measured reflections

2987 independent reflections
2093 reflections with $I > 2\sigma(I)$
$R_{\rm int} = 0.064$
$\theta_{\max} = 25.0^\circ$
$h = -21 \rightarrow 20$
$k = -5 \rightarrow 5$
$l = -23 \rightarrow 23$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.044$
$wR(F^2) = 0.113$
$S = 1.02$
2987 reflections
227 parameters
H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.058P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max} = 0.001$
$\Delta\rho_{\max} = 0.21$ e Å^{-3}
$\Delta\rho_{\min} = -0.32$ e Å^{-3}

Table 1
Selected geometric parameters (Å, °) for (IV*a*).

C1—N7	1.418 (3)	C6—N7	1.295 (3)
C2—S3	1.776 (3)	C15—Cl25	1.743 (3)
S3—C4	1.836 (2)	C23—O24	1.349 (3)
C2—S3—C4	103.99 (12)	C6—N7—C1	121.0 (2)

Table 2
Hydrogen-bonding geometry (Å, °) for (IV*a*).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O24—H24···N7	0.84	1.80	2.543 (3)	146

Compound (IV*b*)

Crystal data

$C_{22}H_{19}NOS$
$M_r = 345.44$
Monoclinic, $P2_1/c$
$a = 4.8678\ (11)$ Å
$b = 17.563\ (3)$ Å
$c = 20.129\ (5)$ Å
$\beta = 93.078\ (8)°$
$V = 1718.4\ (6)$ Å^3
$Z = 4$

$D_x = 1.335$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 8207 reflections
$\theta = 3.6$–$30.0°$
$\mu = 0.20$ mm^{-1}
$T = 173\ (2)$ K
Needle, yellow
0.22 × 0.12 × 0.08 mm

Data collection

Nonius KappaCCD area-detector diffractometer
ω and φ scans
Absorption correction: multi-scan (*SORTAV*; Blessing, 1997)
$T_{\min} = 0.906$, $T_{\max} = 0.988$
8207 measured reflections

4972 independent reflections
3195 reflections with $I > 2\sigma(I)$
$R_{\rm int} = 0.037$
$\theta_{\max} = 30.0°$
$h = -6 \rightarrow 6$
$k = -21 \rightarrow 24$
$l = -28 \rightarrow 28$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.046$
$wR(F^2) = 0.121$
$S = 0.99$
4972 reflections
228 parameters
H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.0547P)^2 + 0.2349P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max} = 0.001$
$\Delta\rho_{\max} = 0.23$ e Å^{-3}
$\Delta\rho_{\min} = -0.32$ e Å^{-3}

Table 3
Selected geometric parameters (Å, °) for (IV*b*).

S3—C2	1.7696 (17)	N7—C6	1.2952 (19)
S3—C4	1.8368 (15)	N7—C1	1.4128 (19)
O24—C23	1.3427 (19)		
C2—S3—C4	103.23 (7)	C6—N7—C1	120.37 (13)

Table 4
Hydrogen-bonding geometry (Å, °) for (IV*b*).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O24—H24···N7	0.84	1.80	2.5489 (17)	147

Compound (IV*c*)

Crystal data

$C_{22}H_{19}NO_2S$
$M_r = 361.44$
Monoclinic, $P2_1/c$
$a = 11.973\ (2)$ Å
$b = 16.224\ (4)$ Å
$c = 9.250\ (3)$ Å
$\beta = 94.437\ (9)°$
$V = 1791.4\ (8)$ Å^3
$Z = 4$

$D_x = 1.340$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 7583 reflections
$\theta = 3.7$–$27.5°$
$\mu = 0.20$ mm^{-1}
$T = 173\ (2)$ K
Needle, yellow
0.35 × 0.08 × 0.07 mm

Data collection

Nonius KappaCCD area-detector diffractometer
ω and φ scans
Absorption correction: multi-scan (*SORTAV*; Blessing, 1997)
$T_{\min} = 0.908$, $T_{\max} = 0.990$
7583 measured reflections

4081 independent reflections
3007 reflections with $I > 2\sigma(I)$
$R_{\rm int} = 0.031$
$\theta_{\max} = 27.5°$
$h = -15 \rightarrow 15$
$k = -21 \rightarrow 21$
$l = -11 \rightarrow 12$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.040$
$wR(F^2) = 0.107$
$S = 1.02$
4081 reflections
237 parameters
H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.050P)^2 + 0.404P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max} < 0.001$
$\Delta\rho_{\max} = 0.23$ e Å^{-3}
$\Delta\rho_{\min} = -0.36$ e Å^{-3}

Table 5
Selected geometric parameters (Å, °) for (IV*c*).

C1—N7	1.414 (2)	C6—N7	1.297 (2)
C2—S3	1.775 (2)	C23—O24	1.351 (2)
S3—C4	1.848 (2)		
C2—S3—C4	104.57 (7)	C6—N7—C1	121.32 (13)

Table 6
Hydrogen-bonding geometry (Å, °) for (IV*c*).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O24—H24···N7	0.84	1.81	2.5489 (18)	147

For the three structures, the H atoms were located from difference Fourier syntheses and were included in the refinements at idealized positions, with C—H distances of 0.95–1.00 Å and an O—H distance of 0.84 Å, and with $U_{\rm iso}$ values of 1.5 (hydroxyl H atoms) or 1.2 (the remaining H atoms) times the $U_{\rm eq}$ values of the parent atoms. The methyl H atoms in (IV*b*) were disordered over six sites and were included in the refinement using the DFIX 123 command in *SHELXL*97 (Sheldrick, 1997). The final difference maps were free of any chemically significant features.

For all three compounds, data collection: *COLLECT* (Hooft, 1998); cell refinement: *HKL DENZO* (Otwinowski & Minor, 1997); data reduction: *HKL 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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Supplementary data for this paper are available from the IUCr electronic archives (Reference: FR1416). Services for accessing these data are described at the back of the journal.

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