4-(2-Hydroxyphenyl)-2-phenyl-2,3-dihydro-1*H*-1,5-benzodiazepine and the 2-(2,3-dimethoxyphenyl)-, 2-(3,4-dimethoxyphenyl)- and 2-(2,5-dimethoxyphenyl)-substituted derivatives

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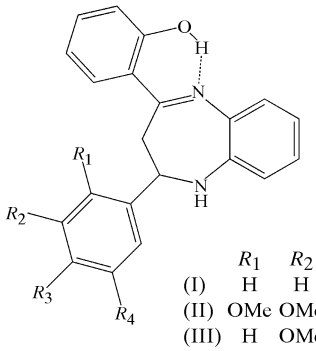
The 1,5-benzodiazepine ring system exhibits a puckered boat-like conformation for all four title compounds [4-(2-hydroxyphenyl)-2-phenyl-2,3-dihydro-1*H*-1,5-benzodiazepine, $C_{21}H_{18}N_2O$, (I), 2-(2,3-dimethoxyphenyl)-4-(2-hydroxyphenyl)-2,3-dihydro-1*H*-1,5-benzodiazepine, $C_{23}H_{22}N_2O_3$, (II), 2-(3,4-dimethoxyphenyl)-4-(2-hydroxyphenyl)-2,3-dihydro-1*H*-1,5-benzodiazepine, $C_{23}H_{22}N_2O_3$, (III), and 2-(2,5-dimethoxyphenyl)-4-(2-hydroxyphenyl)-2,3-dihydro-1*H*-1,5-benzodiazepine, $C_{23}H_{22}N_2O_3$, (IV)]. The stereochemical correlation of the two C_6 aromatic groups with respect to the benzodiazepine ring system is pseudo-equatorial–equatorial for compounds (I) (the phenyl group), (II) (the 2,3-dimethoxyphenyl group) and (III) (the 3,4-dimethoxyphenyl group), while for (IV) (the 2,5-dimethoxyphenyl group) the system is pseudo-axial–equatorial. An intramolecular hydrogen bond between the hydroxyl OH group and a benzodiazepine N atom is present for all four compounds and defines a six-membered ring, whose geometry is constant across the series. Although the molecular structures are similar, the supramolecular packing is different; compounds (I) and (IV) form chains, while (II) forms dimeric units and (III) displays a layered structure. The packing seems to depend on at least two factors: (i) the nature of the atoms defining the hydrogen bond and (ii) the number of intermolecular interactions of the types O—H···O, N—H···O, N—H···π(arene) or C—H···π(arene).

Comment

Continuing our search for supramolecular synthons of importance in the crystal engineering of substituted aromatic compounds (Donoso-Tauda *et al.*, 2006), our group has focused considerable interest on the crystalline properties of benzodiazepines, particularly in their packing by intermolecular hydrogen bonding. Benzodiazepines are well studied because of their pharmacological properties, with their antifungal, antibacterial, analgesic, tranquilizing and anticonvulsant activities well established (Di Braccio *et al.*, 2001; Michaelidou & Hadjipavlou-Litina, 2005). Additionally, the chemistry and structure of 1,5-benzodiazepines have become increasingly interesting, owing to their potential as cocrystals in supramolecular chemistry, showing ladder or brick superstructures formed *via* hydrogen-bonding networks (Thakuria *et al.*, 2006).



	R_1	R_2	R_3	R_4
(I)	H	H	H	H
(II)	OMe	OMe	H	H
(III)	H	OMe	OMe	H
(IV)	OMe	H	H	OMe

The structures of the title compounds, (I)–(IV) (Fig. 1), are constructed around a central benzodiazepine C_5N_2 seven-membered ring, which is fused with a benzene ring at atoms C10 and C11. The heterocycle is substituted in all cases at position 4 with an *o*-hydroxyphenyl group, and also with a phenyl [for (I)] or a dimethoxyphenyl [for (II)–(IV)] ring at position 2, as summarized in the scheme. The least-squares plane defined by the C6–C11 aromatic ring plus atoms N1 and N5 defines an acute angle with the plane defined by atoms C2, C3 and C4 [85.0 (1)° for (I), 78.7 (2)° for (II), 89.3 (3)° for (III) and 87.0 (1)° for (IV)]; the benzodiazepine ring system has a puckered boat-like conformation for all four compounds. This has also been noted in two related benzodiazepines, *viz.* 2,4-bis(2,5-dipropoxyphenyl)-2,3-dihydro-1*H*-1,5-benzodiazepine (Hormaza *et al.*, 2004) and 2-methyl-4-*p*-tolyl-2,3-dihydro-1,5-benzodiazepine (Qi *et al.*, 1985). Bond distances are similar for all four compounds and comparable to literature values (Qi *et al.*, 1985; Braun *et al.*, 2000). Although some significant differences are observed in the torsion angles for the benzodiazepine ring systems [*e.g.* N1—C2—C3—C4 ranges from 44.7 (4)° in (III) to 76.0 (4)° in (II); Tables 1, 3, 5 and 7] the boat-like conformation of the heterocycle is conserved across the series. The substituted benzene rings occupying positions 2 and 4 in the 1,5-benzodiazepine ring system display, respectively, a pseudo-equatorial–equatorial correlation for compounds (I), (II) and (III) (*e.g.* Hormaza *et al.*, 2004), and pseudo-axial–equatorial correlation for (IV). The dihedral angles between the C18–C23 least-squares plane and the *o*-hydroxyphenyl plane (C12–C17) are 46.8 (1), 66.1 (1), 37.4 (2) and 4.0 (1)° for (I)–(IV), respectively.

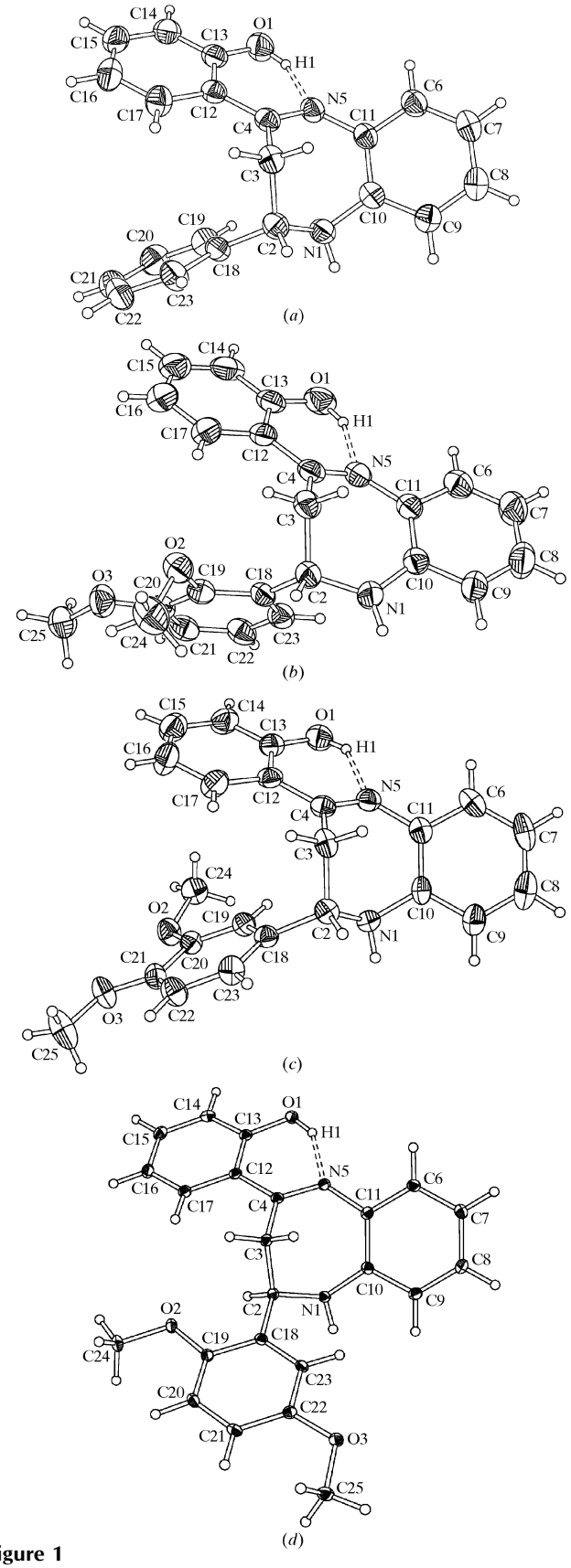


Figure 1
The molecular structures of (*a*) (I), (*b*) (II), (*c*) (III) and (*d*) (IV), showing the atom-numbering schemes. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

Figure 2
The molecular packing for (*a*) (I) [symmetry codes: (*A*) $x, y+1, z$; (*B*) $x, y-1, z$], (*b*) (II) [symmetry code: (*A*) $-x, -y+1, -z+2$], (*c*) (III) [symmetry codes: (*A*) $-x+1, -y+2, -z$; (*B*) $x-\frac{1}{2}, -y+\frac{3}{2}, z-\frac{1}{2}$] and (*d*) (IV) [symmetry codes: (*A*) $x, -y+\frac{1}{2}, z-\frac{1}{2}$; (*D*) $x, -y+\frac{1}{2}, z+\frac{1}{2}$]. Some of the H atoms have been omitted for clarity.

The hydroxyl H atom on the *o*-hydroxyphenyl substituent (H1) forms an intramolecular O—H···N hydrogen bond with atom N5 for (I)–(IV) (Tables 2, 4, 6 and 8). The intramolecular hydrogen bond is rather insensitive to the remainder of the molecule or the different packing modes. This intramolecular bond has been also been described in the synthetic precursor 2-hydroxy chalcone (Srivastava & Verma, 1990). An important consequence of this hydrogen bond is that the N5/C4/C12/C13/O1/H1 six-membered ring is significantly planar in all cases. This planarity is reflected in the low value measured for the N5—C4—C12—C13 torsion angle (Tables 1, 3, 5 and 7).

Despite the close structural similarity between the compounds, their packing modes, arising from N—H···O, N—H···π(arene) or C—H···π(arene) interactions, differ considerably. As in Fig. 2(*a*), the C—H···π(arene) interactions give a supramolecular chain along the *b* axis. Molecules of (II) and (III) form supramolecular dimers by means of N—H···π(arene) and C—H···O—CH_3 interactions, respectively, as depicted in Figs. 2(*b*) and 2(*c*). In the case of (III), the dimers are also connected by means of N—H···O hydrogen bonds, leading to a two-dimensional suprastructure. The amine NH group in (IV) interacts with a methoxy substituent in a neighbouring molecule, leading to a chain along the *c* axis (Fig. 2*d*).

As previously stated (Desiraju, 2002), the relative magnitude of intramolecular interactions could be listed as C—H···π(arene) weaker than N—H···π(arene) and both still weaker than the N—H···O interaction. In this context, the relatively low melting point measured for (I) (379–382 K) could be understood in terms of the weak C—H···π(arene) interaction stabilizing the packing. Conversely, in (III) (with the highest melting point, 440–441 K), stronger N—H···O interactions are present in addition to the C—H···π(arene) interactions. In the same way, (II) and (IV) exhibit intermediate melting points (around 429 K).

Experimental

A methanol (40 ml) solution of the appropriate 3-(dimethoxyphenyl)-1-(2-hydroxyphenyl)prop-2-enone (0.704 mmol) and 1,2-diaminobenzene (1.056 mmol) was heated under reflux for 24 h. Concentration *in vacuo* followed by column chromatographic purification (silica gel 60, ethyl acetate–hexane 1:10) of the reaction mixture afforded a yellow solid that on recrystallization from methanol gave yellow crystals of (I)–(IV) [(I): yield 60%, m.p. 379–382 K; (II): yield 15%, m.p. 427–428 K; (III): yield 21%, m.p. 439.5–440.7 K; (IV): yield 21%, m.p. 429–430 K].

Compound (I)

Crystal data

$C_{21}H_{18}N_2O$
M_r = 314.37
Monoclinic, $C2/c$
a = 24.855 (4) Å
b = 7.6825 (11) Å
c = 19.455 (3) Å
β = 118.824 (2)°
V = 3254.7 (9) Å^3
Z = 8
Mo $K\alpha$ radiation
μ = 0.08 mm^{-1}
T = 298 (2) K
0.30 × 0.27 × 0.21 mm

Data collection

Siemens SMART CCD area-detector diffractometer
Absorption correction: part of the refinement model (ΔF) (*SADABS* in *SAINT-NT*; Bruker, 1999)
T_{min} = 0.977, T_{max} = 0.983
9815 measured reflections
2893 independent reflections
1696 reflections with $I > 2\sigma(I)$
R_{int} = 0.055

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.055
$wR(F^2)$ = 0.139
S = 1.02
2893 reflections
222 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.16 e Å^{-3}
$\Delta\rho_{min}$ = −0.12 e Å^{-3}

Table 1
Selected torsion angles (°) for (I).

C10—N1—C2—C3	32.0 (3)	C3—C4—N5—C11	4.0 (3)
N1—C2—C3—C4	51.1 (3)	N5—C4—C12—C13	−2.2 (3)
C2—C3—C4—N5	−76.3 (3)	N1—C2—C18—C23	149.0 (2)

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

*Cg*1 is the centroid of the C6–C11 ring.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O1—H1···N5	0.82	1.79	2.514 (3)	147
C23—H23···*Cg*1^{i}	0.93	2.62	3.480 (2)	155

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

Compound (II)

Crystal data

$C_{23}H_{22}N_2O_3$
M_r = 374.43
Triclinic, $P\overline{1}$
a = 8.250 (2) Å
b = 9.889 (3) Å
c = 12.272 (3) Å
α = 108.697 (4)°
β = 90.973 (5)°
γ = 90.594 (5)°
V = 948.1 (4) Å^3
Z = 2
Mo $K\alpha$ radiation
μ = 0.09 mm^{-1}
T = 298 (2) K
0.30 × 0.18 × 0.11 mm

Data collection

Siemens SMART CCD area-detector diffractometer
Absorption correction: part of the refinement model (ΔF) (*SADABS* in *SAINT-NT*; Bruker, 1999)
T_{min} = 0.974, T_{max} = 0.990
5882 measured reflections
3329 independent reflections
1625 reflections with $I > 2\sigma(I)$
R_{int} = 0.040

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.062
$wR(F^2)$ = 0.179
S = 0.98
3329 reflections
259 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.16 e Å^{-3}
$\Delta\rho_{min}$ = −0.20 e Å^{-3}

Table 3
Selected torsion angles (°) for (II).

C10—N1—C2—C3	−22.7 (5)	C3—C4—N5—C11	−0.6 (5)
N1—C2—C3—C4	76.0 (4)	N5—C4—C12—C13	−7.7 (5)
C2—C3—C4—N5	−65.1 (4)	N1—C2—C18—C23	−13.2 (4)

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

Cg2 is the centroid of the C12–C17 ring.

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1···N5	0.82	1.78	2.514 (4)	147
N1—H1N···$Cg2^{i}$	0.90 (4)	2.60 (4)	3.445 (4)	159 (3)

Symmetry code: (i) $-x, -y+1, -z+2$.

Compound (III)

Crystal data

$C_{23}H_{22}N_2O_3$
M_r = 374.43
Monoclinic, $P2_1/n$
a = 5.5372 (8) Å
b = 23.144 (3) Å
c = 15.131 (2) Å
β = 99.520 (3)°
V = 1912.4 (4) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.09 mm^{-1}
T = 300 (2) K
0.37 × 0.07 × 0.06 mm

Data collection

Siemens SMART CCD area-detector diffractometer
Absorption correction: part of the refinement model (ΔF) (*SADABS* in *SAINT-NT*; Bruker, 1999)
T_{min} = 0.969, T_{max} = 0.995
11881 measured reflections
3400 independent reflections
1703 reflections with $I > 2\sigma(I)$
R_{int} = 0.105

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.086
$wR(F^2)$ = 0.167
S = 1.04
3400 reflections
259 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.15 e Å^{-3}
$\Delta\rho_{min}$ = −0.16 e Å^{-3}

Table 5
Selected torsion angles (°) for (III).

C10—N1—C2—C3	38.8 (5)	C3—C4—N5—C11	8.4 (6)
N1—C2—C3—C4	44.7 (4)	N5—C4—C12—C13	−1.5 (6)
C2—C3—C4—N5	−76.8 (5)	N1—C2—C18—C23	136.1 (4)

Table 6
Hydrogen-bond geometry (Å, °) for (III).

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1···N5	0.82	1.76	2.494 (5)	148
N1—H1N···$O1^{i}$	0.91 (3)	2.20 (3)	3.017 (4)	150 (3)
C8—H8···$O3^{ii}$	0.93	2.48	3.385 (6)	163
C15—H15···$O2^{iii}$	0.93	2.64	3.501 (5)	154

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

Compound (IV)

Crystal data

$C_{23}H_{22}N_2O_3$
M_r = 374.43
Monoclinic, $P2_1/c$
a = 10.5071 (3) Å
b = 20.3901 (6) Å
c = 8.7280 (3) Å
β = 102.390 (2)°
V = 1826.34 (10) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.09 mm^{-1}
T = 296 (2) K
0.50 × 0.50 × 0.35 mm

Data collection

Bruker APEXII diffractometer
Absorption correction: part of the refinement model (ΔF) (*SADABS* in *SAINT-NT*; Bruker, 1999)
T_{min} = 0.956, T_{max} = 0.969
12443 measured reflections
4181 independent reflections
3367 reflections with $I > 2\sigma(I)$
R_{int} = 0.033

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.039
$wR(F^2)$ = 0.126
S = 1.10
4181 reflections
338 parameters
20 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.30 e Å^{-3}
$\Delta\rho_{min}$ = −0.31 e Å^{-3}

Table 7
Selected torsion angles (°) for (IV).

C10—N1—C2—C3	25.97 (16)	C3—C4—N5—C11	10.16 (18)
N1—C2—C3—C4	54.54 (13)	N5—C4—C12—C13	−4.52 (18)
C2—C3—C4—N5	−81.63 (15)	N1—C2—C18—C23	27.89 (17)

Table 8
Hydrogen-bond geometry (Å, °) for (IV).

Cg3 is the centroid of the C18–C23 ring.

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1···N5	0.82	1.81	2.5443 (14)	148
N1—H1N···$O3^{i}$	0.892 (16)	2.311 (16)	3.201 (2)	177
C24—H24B···$Cg3^{ii}$	0.996 (9)	2.744 (13)	3.5462 (16)	140 (1)

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

H atoms attached to C atoms were included at calculated positions and treated as riding atoms for (I)–(III) using *SHELXL97* (Sheldrick, 1997) default values; for (IV), these were refined with the C—H distances restrained to be 0.93 Å for aromatic and 0.99 Å for aliphatic H atoms. In all four compounds, hydroxy atom H1 was treated as a riding atom, and amino atom H1N was refined with isotropic displacement parameters. Analysis of the diffraction pattern suggests that the rather high R factor obtained for (III) could be attributed to poor crystal quality.

For compounds (I)–(III), data collection: *SMART-NT* (Bruker, 2001); cell refinement: *SAINT-NT* (Bruker, 1999); data reduction: *SAINT-NT*; program(s) used to solve structure: *SHELXTL-NT* (Bruker, 2000); program(s) used to refine structure: *SHELXTL-NT*; molecular graphics: *SHELXTL-NT*; software used to prepare material for publication: *SHELXTL-NT*. For compound (IV), data collection: *SMART-NT*; cell refinement: *SAINT-NT*; data reduction: *SAINT-NT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3* (Farrugia, 1997); software used to prepare material for publication: *WinGX* (Farrugia, 1999).

The authors gratefully acknowledge Universidad Andrés Bello (UNAB) for financial support through grant DI 41-04 awarded to CAE, and thank Dr M. T. Garland, Universidad de Chile, and Therry Roisnel, University of Rennes, for data collection. ODT is grateful to UNAB for a graduate fellowship. AV acknowledges FONDECYT (grant No. 11060176) and Universidad Andrés Bello (grant No. DI-20-06/R).

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