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4-Hydroxy-2-vinyl-2,3,4,5-tetrahydro-1-benzazepine and its 7-fluoro and 7-chloro analogues are isomorphous but not strictly isostructural

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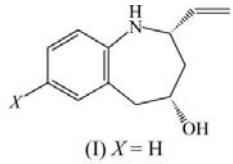
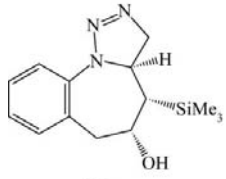
4-Hydroxy-2-vinyl-2,3,4,5-tetrahydro-1-benzazepine, $C_{12}H_{15}NO$, (I), and its 7-fluoro and 7-chloro analogues, namely 7-fluoro-4-hydroxy-2-vinyl-2,3,4,5-tetrahydro-1-benzazepine, $C_{12}H_{14}FNO$, (II), and 7-chloro-4-hydroxy-2-vinyl-2,3,4,5-tetrahydro-1-benzazepine, $C_{12}H_{14}ClNO$, (III), are isomorphous, but with variations in the unit-cell dimensions which preclude in compound (III) one of the weaker intermolecular interactions found in compounds (I) and (II). Thus the compounds are not strictly isostructural in terms of the structurally significant intermolecular interactions, although the corresponding atomic coordinates are very similar. The azepine rings adopt chair conformations. The molecules are linked by a combination of N—H···O and O—H···N hydrogen bonds into chains of edge-fused $R_3^3(10)$ rings, which in compounds (I) and (II) are further linked into sheets by a single C—H···π(arene) hydrogen bond. The significance of this study lies in its observation of isomorphism in compounds (I)–(III), and its observation of a sufficient variation in one of the cell dimensions effectively to alter the range of significant hydrogen bonds present in the crystal structures.

Comment

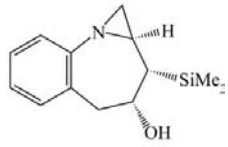
In our investigation of the use of the tetrahydro-1-benzazepine system as a scaffold for the elaboration of novel anti-parasitic compounds exhibiting new modes of action to combat both *Trypanosoma cruzi* and *Leishmania chagasi* parasites, we have recently reported a simple and efficient synthetic pathway to obtain novel *cis*-2-aryl-4-hydroxytetrahydro-1-benzazepines and *cis*-2-aryl-4-hydroxytetrahydronaphtho[1,2-*b*]azepines from readily available *ortho*-allyl-*N*-benzyl-substituted anilines (Gómez *et al.*, 2006; Yépez *et al.*, 2006). These compounds appear to be promising as anti-*Trypanosoma cruzi* and anti-*Leishmania chagasi* agents (Palma *et al.*, 2009). A part of this study, we have now developed a stereoselective synthesis of *cis*-4-hydroxy-2-vinyltetrahydro-1-benzazepines and present here the molecular and supramolecular structures of the three title compounds, (I)–(III), which belong to this class. Compounds (I)–(III) were obtained *via* the reductive cleavage of the N—O bond in the corresponding 1,4-epoxy-2-*exo*-vinyl-2,3,4,5-tetrahydro-1-benzazepines, which were themselves prepared using a method exactly equivalent to that for the 2-*exo*-styryl analogues (Acosta *et al.*, 2008). The reduction was effected using an excess of zinc powder in 80% acetic acid solution.



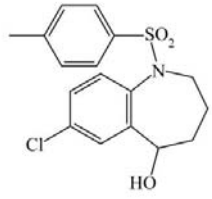
(I) X = H
(II) X = F
(III) X = Cl



(IV)



(V)



(VI)

Compounds (I)–(III) (Figs. 1–3) are isomorphous and the corresponding atomic coordinates are very similar. The unit-

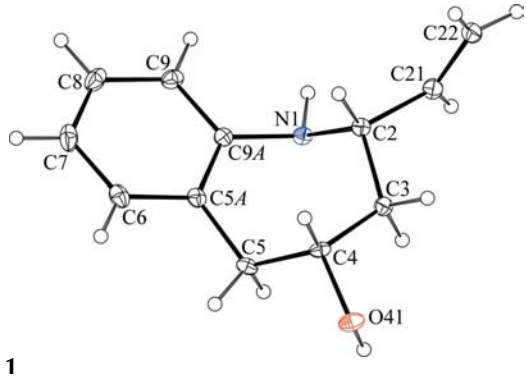


Figure 1
The molecular structure of (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level.

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cell dimensions show some interesting variations as the 7-substituent X is altered from H to F to Cl. The unit-cell dimension b decreases slightly along this series, while the dimension c shows a rather modest increase. However, the dimension a shows the largest increase, of some 1.73% from X = H to X = F, and a further 5.31% from X = F to X = Cl. The dominant effect on the dimension a of the change in substituent is readily understood in terms of the direction of the C7—X7 bonds, which are inclined at only *ca* 15° to the a direction. Hence, as X is varied from H to F to Cl with a concomitant increase in the C—X bond distance, this effects a corresponding increase in the unit-cell dimensions, predominantly in the a repeat distance. This in turn influences the longer and weaker of the direction-specific intermolecular interactions, as discussed below.

There are two stereogenic centres in each molecule, and for the selected reference molecule in each structure the configuration is 2*S*,4*R*. However, the centrosymmetric space groups mean that the compounds are all racemic, with configuration 2*SR*,4*RS*. The overall molecular conformations are defined by the shape of the azepine ring and by the orientation of the vinyl substituent relative to this ring. The ring-puckering parameters (Cremer & Pople, 1975) are very similar for compounds (I)–(III), as are the torsion angles defining the orientation of the vinyl substituent (Table 1). For each compound, the best description of the azepine ring is a chair conformation, with the hydroxy and vinyl substituents both occupying equatorial sites. The bond distances show no unexpected values.

The supramolecular aggregation is simpler in (III) than in (I) and (II), and the hydrogen-bonded structure in (III) can in fact be identified as a substructure in the isostructural pair of compounds (I) and (II); accordingly, we discuss (III) first. In (III), the aggregation is determined by the combination of two hydrogen bonds, one each of N—H···O and O—H···N types (Table 2). Amine atom N1 in the molecule at (x, y, z) acts a hydrogen-bond donor to hydroxy atom O41 in the molecule at (x, 1 + y, z), so forming by translation a $C(6)$ (Bernstein *et al.*, 1995) chain running parallel to the [010] direction. Pairs of such chains, related by the 2_1 screw axis along ($\frac{1}{4}$, y, $\frac{1}{4}$), are linked by the O—H···N hydrogen bonds to form a chain of edge-fused $R_3^3(10)$ rings running parallel to the [010] direction (Fig. 4). The only additional hydrogen bond in (III) is a C—H···O contact, which is probably too long and too weak to be structurally significant and which, in any event, lies within the chain of rings generated by the N—H···O and O—H···N hydrogen bonds.

Precisely the same type of chain of rings is generated in each of compounds (I) and (II) by exactly the same combination of hydrogen bonds (Table 2), although the C—H···O contact distances are even longer in (I) and (II). However, in these two compounds, these chains are linked by a single C—H···π(arene) hydrogen bond to form a sheet parallel to (101) (Fig. 5). A similar type of contact is present in (III), but now the H···Cg^{iv} and C···Cg^{iv} distances [symmetry code: (iv) $-x+1, -y+1, -z$] are much longer than those in (I) and (II), to the extent that this contact cannot be regarded as structurally significant in (III). The steady elongation of the H···Cg^{iv} and C···Cg^{iv} distances from (I) to (II) (Table 2) is a consequence of the increased offset of the inversion-related molecules involved, itself a direct consequence of the increased unit-cell dimension a which, as noted above, appears to be directly associated with the alignment of the C7—X7 bond. Accordingly, the series (I)–(III) presents examples of isomorphous compounds whose cell dimensions vary suffi-

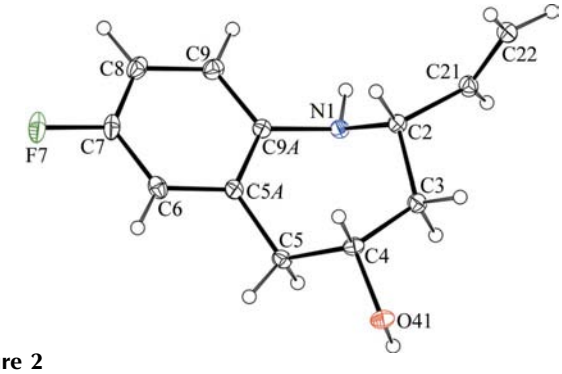

Figure 2
The molecular structure of (II), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level.

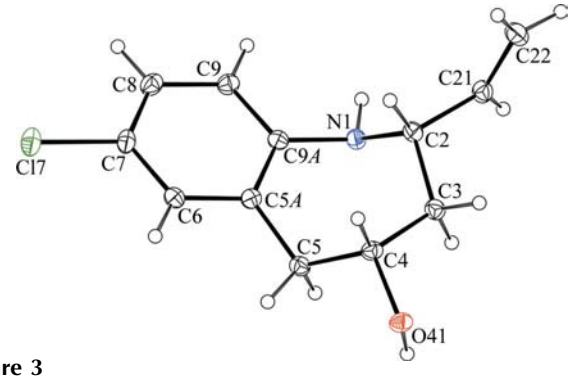

Figure 3
The molecular structure of (III), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level.

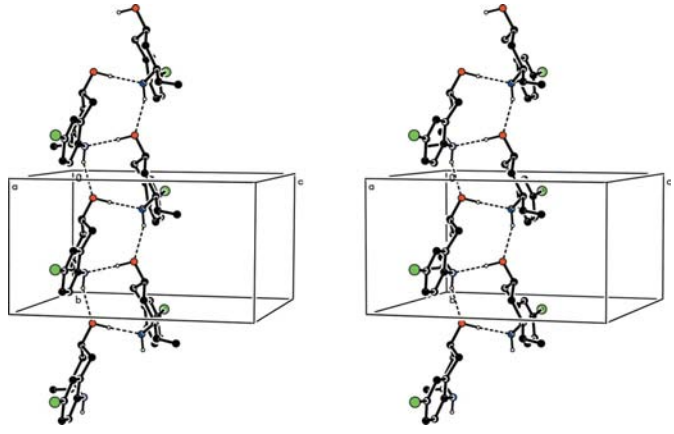

Figure 4
A stereoview of part of the crystal structure of (III), showing the formation of a hydrogen-bonded chain of edge-fused $R_3^3(10)$ rings parallel to [010]. For the sake of clarity, H atoms bonded to C atoms have been omitted.

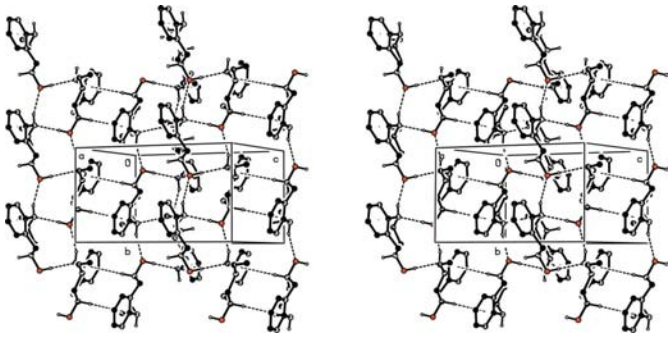

Figure 5
A stereoview of part of the crystal structure of (I), showing the formation of a hydrogen-bonded sheet parallel to (101). For the sake of clarity, H atoms bonded to C atoms but not involved in the motif shown have been omitted. An entirely equivalent sheet is formed in compound (II).

ciently between the extreme members of the series to take a weak, but structurally significant, intermolecular interaction outside the range of significance as the critical cell dimension increases.

The structures of only a rather small number of 2,3,4,5-tetrahydro-1-benzazepines carrying a hydroxy substituent on the azepine ring are recorded in the Cambridge Structural Database (CSD, September 2008 update; Allen, 2002). The majority of these [CSD refcodes: DOJJER (Coda *et al.*, 1986), RAYYAR (Guzikowski *et al.*, 1996), SIJMIH (Floyd *et al.*, 1990), SIJMON (Floyd *et al.*, 1990), YUCTOF (Kimball *et al.*, 1993) and YUCVUN (Kimball *et al.*, 1993)] carry other hydrogen-bonding functional groups on this ring, such as ring carbonyl groups, or pendent acyl or carboxyl groups. However, two 4-hydroxy-1-benzazepines have been reported, *viz*. compounds (IV) (AFOKUB; Ducray *et al.*, 2001*a*) and (V) (AFOLAI; Ducray *et al.*, 2001*b*). Unfortunately, no atom coordinates are available for the 5-hydroxy compound (VI) (FABJAU; Matsubara *et al.*, 2001).

While compound (IV) crystallizes as a single enantiomorph in space group $P2_12_12_1$, (V) crystallizes as a racemate in $P2_1/n$. In (IV), where the configuration at the C atom carrying the hydroxy substituent is *R*, as in compounds (I)–(III), the azepine ring adopts a chair conformation, but folded in the opposite sense to that in compounds (I)–(III), so that the hydroxy group in (IV) occupies an axial site, as opposed to the equatorial site in each of (I)–(III). However, the $SiMe_3$ group in (IV) occupies an equatorial site. In (V), by contrast, the azepine ring has a twist-boat conformation, although with the OH and $SiMe_3$ substituents again in axial and equatorial sites, respectively. In each of (IV) and (V), the molecules are linked into simple chains by a single O—H···N hydrogen bond. In (IV), molecules related by translation are linked into *C*(7) chains, and in (V), molecules related by a 2_1 screw axis are linked into *C*(6) chains, but C—H···π(arene) interactions are absent from the structures of both (IV) and (V).

Experimental

Samples of 1,4-epoxy-2-*exo*-vinyltetraydro-1-benzazepine and its 7-fluoro and 7-chloro derivatives were prepared using a simple modification of the method described recently (Acosta *et al.*, 2008) for the synthesis of the analogous 2-*exo*-(*E*)-styryl compounds. An eightfold molar excess of zinc powder was added to a solution in 80% aqueous acetic acid of 1,4-epoxy-2-*exo*-vinyltetrahydro-1-benzazepine for (I) or its 7-fluoro and 7-chloro derivatives for (II) and (III), respectively. The reaction mixtures were stirred at 350–353 K for 8–10 h. The mixtures were then filtered, and the filtrates were neutralized with aqueous ammonia solution to pH 8 and then extracted with ethyl acetate (3 × 50 ml). In each case, the organic phase was then dried over anhydrous sodium sulfate; after removal of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel using heptane/ethyl acetate (10:1 to 2:1 *v*/*v*) as eluant. Crystallization from heptane gave crystals of compounds (I)–(III) suitable for single-crystal X-ray diffraction. For (I), colourless crystals, yield 82%, m.p. 376 K; MS (70 eV) *m*/*z* (%): 189 (91), 172 (11), 170 (33), 162 (8), 146 (26), 145 (28), 144 (100), 130 (65), 118 (92), 117 (54), 107 (11), 106 (46). For (II), colourless crystals, yield 93%, m.p. 400 K; MS (70 eV) *m*/*z* (%): 207 (60), 190 (7), 188 (21), 180 (7), 164 (27), 163 (27), 162 (90), 148 (67), 136 (100), 135 (55), 125 (13), 124 (45). For (III), colourless crystals, yield 87%, m.p. 391 K; MS (70 eV) *m*/*z* (%): 223 (M^+, ^{35}Cl, 100), 206 (21), 204 (30), 196 (7), 180 (58), 179 (37), 178 (94), 164 (57), 152 (68), 151 (46), 141 (11), 140 (44).

Compound (I)

Crystal data

$C_{12}H_{15}NO$
M_r = 189.25
Monoclinic, $P2_1/n$
a = 10.3466 (13) Å
b = 7.488 (3) Å
c = 13.227 (9) Å
β = 92.94 (2)°
V = 1023.4 (8) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.08 mm^{-1}
T = 120 (2) K
0.39 × 0.36 × 0.08 mm

Data collection

Bruker–Nonius KappaCCD diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
T_{min} = 0.978, T_{max} = 0.994
23550 measured reflections
2360 independent reflections
1626 reflections with $I > 2\sigma(I)$
R_{int} = 0.066

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.053
$wR(F^2)$ = 0.112
S = 1.11
2360 reflections
127 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.27 e Å^{-3}
$\Delta\rho_{min}$ = −0.25 e Å^{-3}

Compound (II)

Crystal data

$C_{12}H_{14}FNO$
M_r = 207.24
Monoclinic, $P2_1/n$
a = 10.5258 (13) Å
b = 7.4501 (13) Å
c = 13.251 (2) Å
β = 93.441 (2)°
V = 1037.2 (3) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.10 mm^{-1}
T = 120 (2) K
0.10 × 0.07 × 0.02 mm

Data collection

Bruker–Nonius APEXII CCD diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2007)
T_{min} = 0.981, T_{max} = 0.998
11679 measured reflections
2365 independent reflections
1850 reflections with $I > 2\sigma(I)$
R_{int} = 0.046

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.056$	136 parameters
$wR(F^2) = 0.113$	H-atom parameters constrained
$S = 1.10$	$\Delta\rho_{max} = 0.25$ e Å^{-3}
2365 reflections	$\Delta\rho_{min} = -0.24$ e Å^{-3}

Compound (III)

Crystal data

$C_{12}H_{14}ClNO$	$V = 1103.45$ (19) Å^3
$M_r = 223.69$	$Z = 4$
Monoclinic, $P2_1/n$	Mo $K\alpha$ radiation
$a = 11.0850$ (7) Å	$\mu = 0.32$ mm^{-1}
$b = 7.4214$ (10) Å	$T = 120$ (1) K
$c = 13.4588$ (11) Å	0.56 × 0.41 × 0.05 mm
$\beta = 94.721$ (8)°	

Data collection

Bruker–Nonius KappaCCD diffractometer	25737 measured reflections
	2535 independent reflections
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)	1691 reflections with $I > 2\sigma(I)$
	$R_{int} = 0.064$
$T_{min} = 0.841$, $T_{max} = 0.984$	

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.051$	136 parameters
$wR(F^2) = 0.141$	H-atom parameters constrained
$S = 1.12$	$\Delta\rho_{max} = 0.40$ e Å^{-3}
2535 reflections	$\Delta\rho_{min} = -0.35$ e Å^{-3}

Table 1
Ring-puckering parameters (Å, °) and selected torsion angles (°) for compounds (I)–(III).

Ring-puckering parameters are defined for the atom sequence N1—C2—C3—C4—C5—C5*A*—C9*A*.

Parameter	(I)	(II)	(III)
φ_2	169.8 (3)	169.7 (3)	173.9 (4)
φ_3	231.2 (2)	230.9 (2)	231.1 (2)
Q	0.744 (2)	0.748 (2)	0.734 (2)
N1—C2—C21—C22	138.18 (19)	135.5 (2)	132.4 (3)

Table 2
Hydrogen bonds and short intermolecular contacts (Å, °) for compounds (I)–(III).

Cg represents the centroid of the C5*A*/C6–C9/C9*A* ring.

Compound	D—H···A	D—H	H···A	D···A	D—H···A
(I)	N1—H1···O41^{i}	0.95	2.26	3.154 (3)	156
	O41—H41···N1^{ii}	0.90	2.09	2.987 (3)	173
	C5—H51···O41^{iii}	0.99	2.65	3.523 (3)	147
	C4—H4···Cg^{iv}	1.00	2.79	3.749 (3)	161
(II)	N1—H1···O41^{i}	0.88	2.28	3.123 (2)	159
	O41—H41···N1^{ii}	0.86	2.14	2.995 (2)	173
	C5—H51···O41^{iii}	0.99	2.62	3.503 (2)	149
	C4—H4···Cg^{iv}	1.00	2.84	3.805 (2)	163
(III)	N1—H1···O41^{i}	0.95	2.21	3.113 (3)	159
	O41—H41···N1^{ii}	1.00	2.00	3.002 (2)	176
	C5—H51···O41^{iii}	0.99	2.59	3.805 (2)	163
	C4—H4···Cg^{iv}	1.00	3.05	4.045 (3)	176

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

All H atoms were located in difference maps and then treated as riding atoms. H atoms bonded to N or O atoms were permitted to ride at the positions deduced from the difference maps, giving N—H distances of 0.88–0.95 Å and O—H distances of 0.86–1.00 Å, with U_{iso}(H) values set at $1.2U_{eq}$(N) or $1.5U_{eq}$(O). H atoms bonded to C atoms were permitted to ride in geometrically idealized positions, with C—H distances of 0.95 (aromatic and vinyl), 0.99 (aliphatic CH_2) or 1.00 Å (aliphatic CH), all with U_{iso}(H) values of $1.2U_{eq}$(C).

For all compounds, data collection: *COLLECT* (Hooft, 1999); cell refinement: *DIRAX*/*LSQ* (Duisenberg *et al.*, 2000) for (I) and (III), and *DENZO* (Otwinowski & Minor, 1997) and *COLLECT* for (II); data reduction: *EVALCCD* (Duisenberg *et al.*, 2003) for (I) and (III), and *DENZO* and *COLLECT* for (II); program(s) used to solve structure: *SIR2004* (Burla *et al.*, 2005); program(s) used to refine structure: *OSCAIL* (McArdle, 2003) and *SHELXL97* (Sheldrick, 2008); molecular graphics: *PLATON* (Spek, 2003); software used to prepare material for publication: *SHELXL97* and *PRPKAPPA* (Ferguson, 1999).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GG3188). Services for accessing these data are described at the back of the journal.

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