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(2*R**,4*S**)-2-(Pyridin-3-yl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-4-ol: a three-dimensional framework built from O—H···N, C—H···O and C—H···π(arene) hydrogen bonds

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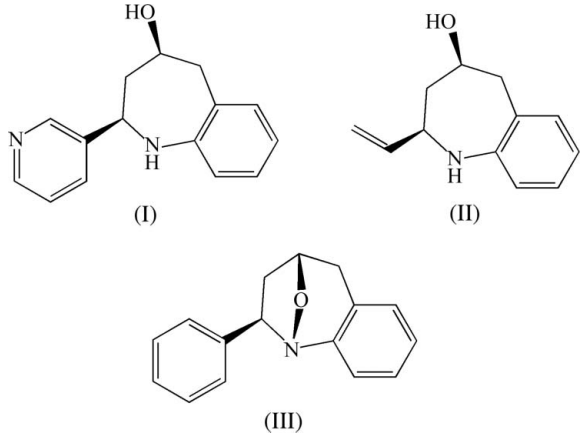
The title compound, $C_{15}H_{16}N_2O$, crystallizes in the space group $P2_12_12_1$ with $Z' = 1$. The seven-membered ring adopts a chair-type conformation with the hydroxy and pyridyl substituents in equatorial sites. Molecules are linked into a three-dimensional framework structure by a combination of O—H···N, C—H···O and C—H···π(arene) hydrogen bonds, but N—H···O and N—H···π(arene) interactions are absent from the structure. Comparisons are made with some related compounds.

Comment

The chemistry of tetrahydro-1-benzazepine systems has been extensively investigated, and many examples of this class have been the targets in synthetic investigations because of their known biological properties, such as nonpeptide arginine vasopressin antagonists for both V1A and V2 receptors (Tsunoda *et al.*, 2005), inhibitors of cyclin-dependent kinases (Kunick *et al.*, 2006), agents against HIV-1 infection (Seto *et al.*, 2005) and antipsychotic agents (Zhao *et al.*, 2003). The growing interest in tetrahydro-1-benzazepines has recently been boosted by their high potential value as agents against promastigotes and amastigotes of *Leishmania mexicana* (Knockaert *et al.*, 2002), and as inhibitors of *Trypanosoma cruzi* dihydrofolate reductase (Zuccotto *et al.*, 2001). As an extension of our current work towards the synthesis of bioactive compounds containing the tetrahydro-1-benzazepine ring system, we recently reported the synthesis and antiparasitic activity of a new series of *cis*-2-aryl-4-hydroxytetrahydronaphtho[1,2-*b*]azepines against *Trypanosoma cruzi* and *Leishmania chagasi* parasites (Palma *et al.*, 2009). Here we report the structure of the title hydroxybenzazepine compound, (I) (Fig. 1), and we compare compound (I) with its close analogues 2-vinyl-2,3,4,5-tetrahydro-1-benzazepin-4-ol, (II), and 2-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-epoxy-1-benzazepine, (III), whose structures have been reported recently (Acosta *et al.*, 2009; Gómez *et al.*, 2010). The constitution of compound (I) differs from that of (II) in that the pendent substituent is a 3-pyridyl group in (I) as opposed to a vinyl group in (II); the constitution of (I) differs from that of (III) in that the pendent substituent is a 3-pyridyl group in (I) as opposed to a phenyl group in (III) and the amino-alcohol functionality in (I) is the reduction product of a 1,4-epoxy bridge as found in compound (III). The reductive cleavage of the N—O bond in such an epoxy bridge is readily accomplished by the use of zinc powder in 80% acetic acid, as employed in the preparation of compound (I).



Compound (I) crystallizes in the space group $P2_12_12_1$ with only one enantiomorph present in any given crystal. It was not possible to establish the absolute configuration of the molecules in the crystal selected for data collection, and the asymmetric unit was selected to be a molecule having the *R* configuration at atom C2; on this basis the configuration at atom C4 is *S*. However, the method of synthesis employed for compound (I), *i.e.* reduction of a racemic precursor under

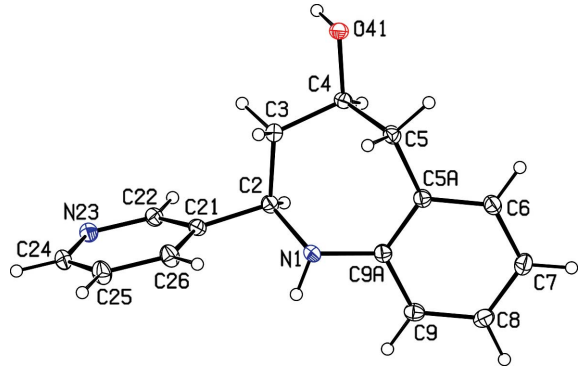


Figure 1
The molecular structure of the (2*R*,4*S*) enantiomer of compound (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level.

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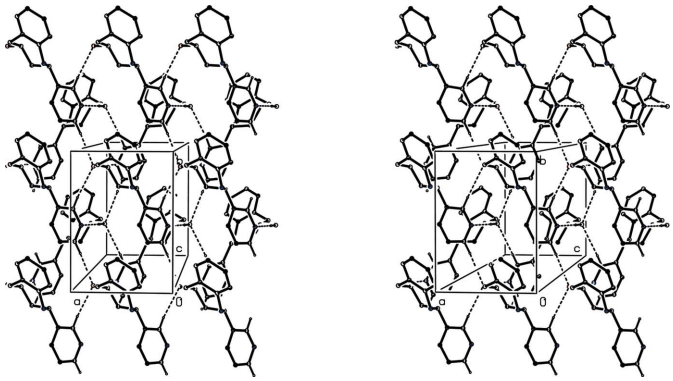

Figure 2
A stereoview of part of the crystal structure of compound (I), showing the formation of a sheet lying parallel to (001) and built from O—H···N and C—H···O hydrogen bonds. For the sake of clarity, H atoms not involved in the motifs shown have been omitted.

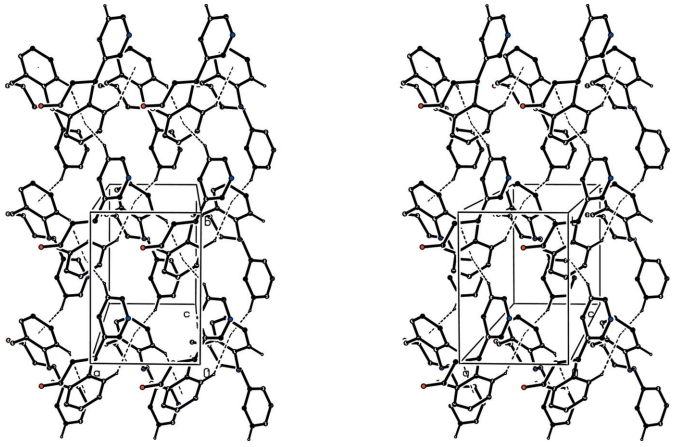

Figure 3
A stereoview of part of the crystal structure of compound (I), showing the formation of a sheet lying parallel to (001) and built from C—H···π(arene) hydrogen bonds. For the sake of clarity, H atoms not involved in the motifs shown have been omitted.

conditions which do not induce enantioselectivity, suggests that compound (I) should be formed as a racemic mixture, so that conglomerate crystallization has subsequently occurred. The crystallization behaviour of (I) may be contrasted with that of compounds (II) and (III), which crystallize as true racemates in the space groups $P2_1/n$ and Cc, respectively (Acosta *et al.*, 2009; Gómez *et al.*, 2010).

The seven-membered ring in compound (I) adopts a chair-type conformation with both the pyridyl and the hydroxy substituents in equatorial sites. The bond distances and the interbond angles present no unusual values.

The molecules of compound (I) are linked into a three-dimensional framework structure by a combination of O—H···N, C—H···O and C—H···π(arene) hydrogen bonds (Table 1). The two independent C—H···O hydrogen bonds necessarily have a common acceptor atom, while the two C—H···π(arene) hydrogen bonds utilize as acceptors the two faces of the fused aryl ring. These two interactions subtend

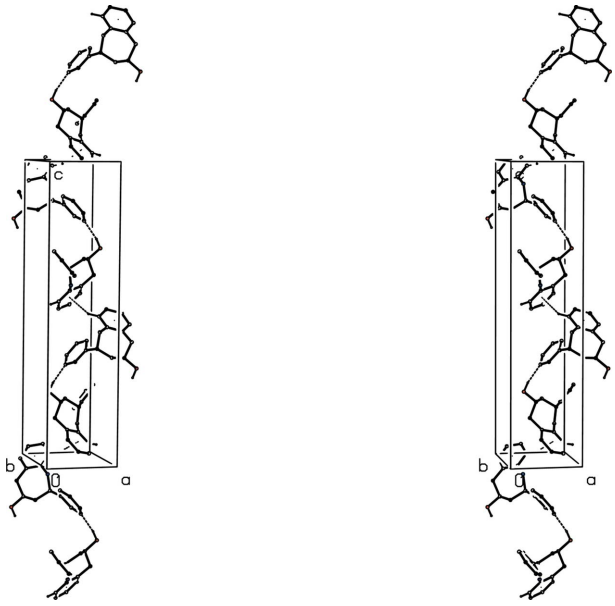

Figure 4
A stereoview of part of the crystal structure of compound (I), showing the formation of a chain running parallel to [001] and built from alternating O—H···N and C—H···π(arene) hydrogen bonds. For the sake of clarity, H atoms not involved in the motifs shown have been omitted.

angles at the ring centroid, denoted Cg, whose values are close to 180°; thus the angles H25^{i}···Cg···H9^{ii} and C25^{i}···Cg···C9^{ii} [symmetry codes: (i) x, $y+1$, z; (ii) $x+\frac{1}{2}$, $-y+\frac{3}{2}$, $-z+1$] are 151 and 157.6 (2)°, respectively. It is striking that, although four C—H bonds are involved in hydrogen-bond formation, including three of the four C—H bonds of the pyridyl ring (Table 1), the N—H bond does not participate at all in the intermolecular hydrogen bonding. There are no potential acceptors within hydrogen-bonding range of the N1 atom and, in fact, all of the non-H atoms within 3.6 Å of the N1 atom are components of the same molecule.

Although the hydrogen-bonded framework, based on five independent hydrogen bonds, is somewhat complex overall, its formation can readily be analysed using the substructure approach (Ferguson *et al.*, 1998*a*,*b*; Gregson *et al.*, 2000), in terms of three substructures, two of them two-dimensional while the third substructure is one-dimensional.

The first substructure is built from the O—H···N and C—H···O hydrogen bonds. Acting individually, these three hydrogen bonds, having atoms O41, C22 and C24, respectively, as the donors, form chains of types $C(8)$, $C(7)$ and $C(9)$ (Bernstein *et al.*, 1995), respectively, running parallel to the [010], [100] and [110] directions. Acting together, these three hydrogen bonds form a sheet parallel to (001) and lying in the domain $0.5 < z < 1.0$ (Fig. 2); two such sheets pass through each unit cell.

In the second substructure, the two C—H···π(arene) hydrogen bonds combine to form another type of sheet. Acting individually, the hydrogen bonds having atoms C9 and C25 as the donors form chains running parallel to the [100] and [010] directions, respectively. In combinations these two interactions generate a sheet lying parallel to (001) but now in

the domain $0.3 < z < 0.7$ (Fig. 3); again, two sheets of this type pass through each unit cell.

The linking of the sheets is most simply understood in terms of the third substructure. Of the five independent hydrogen bonds (Table 1), three link molecules which are related to one another by translation; by contrast, the O—H···N hydrogen bond and the C—H···π(arene) hydrogen bond utilizing atom C9 as the donor, respectively, link molecules related by the 2_1 screw axes along $(\frac{1}{2}, y, \frac{3}{4})$ and $(x, \frac{3}{4}, \frac{1}{2})$. The combination of these two hydrogen bonds, acting alternately, generates a chain running parallel to the [001] direction (Fig. 4). This chain along [001] links together all of the sheets, of both types, parallel to (001), so that the combination of the three substructures generates a three-dimensional framework structure.

It is of interest briefly to compare the molecular aggregation in compound (I) with that in compounds (II) and (III). In the crystal structure of compound (II) (Acosta *et al.*, 2009), a combination of N—H···O and O—H···N hydrogen bonds links the molecules into a chain of edge-fused $R_3^3(10)$ rings, while a single C—H···π(arene) hydrogen bond links chains of this type into a sheet. Thus, by contrast with compound (I), the N—H bond in compound (II) participates in the intermolecular hydrogen bonding, presumably because the steric shielding of the N—H unit afforded by the vinyl substituent in compound (II) is less than that provided by the pyridyl substituent in compound (I). There are neither N—H nor O—H bonds in compound (III), so that the intermolecular aggregation in (III) is necessarily different from that in compounds (I) and (II). Compound (III) crystallizes with $Z' = 2$ in the space group *Cc* (Gómez *et al.*, 2010), and molecules related by translation are linked by C—H···π(arene) hydrogen bonds to form two independent chains running antiparallel to one another and each containing only one type of molecule.

Experimental

Zinc powder (0.8 mmol) was added to a solution of racemic (2*RS*,4*SR*)-2-*exo*-(pyridin-3-yl)-1,4-epoxy-2,3,4,5-tetrahydro-1-benzazepine (0.1 mmol) in 80% acetic acid (15 ml). The resulting mixture was stirred at 318 K for 3 h. The mixture was filtered, and the filtrate was neutralized with aqueous ammonia solution to pH = 8 and then extracted with ethyl acetate (3 × 50 ml). The combined extracts were dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure to give the crude product which was purified by column chromatography on silica gel using heptane–ethyl acetate (10:1 to 1:1 *v*/*v*) as eluent. Recrystallization from heptane–ethyl acetate (1:4 *v*/*v*) gave colourless crystals suitable for single-crystal X-ray diffraction (yield 86%, m.p. 403–404 K). MS (70 eV) *m*/*z* (%): 240 (M^+, 74), 221 (13), 195 (61), 130 (11), 118 (100), 106 (74), 91 (21), 77 (16).

Crystal data

$C_{15}H_{16}N_2O$
$M_r = 240.30$
Orthorhombic, $P2_12_12_1$
$a = 6.0318$ (9) Å
$b = 8.3396$ (10) Å
$c = 25.361$ (4) Å
$V = 1275.7$ (3) Å^3
$Z = 4$
Mo $K\alpha$ radiation
$\mu = 0.08$ mm^{-1}
$T = 120$ K
0.40 × 0.22 × 0.20 mm

Data collection

Bruker–Nonius KappaCCD diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
$T_{min} = 0.969$, $T_{max} = 0.984$
10571 measured reflections
1714 independent reflections
1453 reflections with $I > 2\sigma(I)$
$R_{int} = 0.034$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.035$
$wR(F^2) = 0.086$
$S = 1.11$
1714 reflections
163 parameters
H-atom parameters constrained
$\Delta\rho_{max} = 0.16$ e Å^{-3}
$\Delta\rho_{min} = -0.22$ e Å^{-3}

Table 1
Hydrogen-bond geometry (Å, °).

Cg is the centroid of the C5A/C6–C9/C9A ring.

D—H···A	D—H	H···A	D···A	D—H···A
O41—H41···N23^{i}	0.86	1.94	2.786 (2)	168
C22—H22···O41^{ii}	0.95	2.47	3.288 (2)	145
C24—H24···O41^{iii}	0.95	2.49	3.436 (2)	175
C9—H9···Cg^{iv}	0.95	2.83	3.633 (2)	143
C25—H25···Cg^{v}	0.95	2.77	3.633 (2)	151

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

All H atoms were located in difference maps and subsequently treated as riding atoms in geometrically idealized positions, with C—H distances = 0.95 (aromatic and heteroaromatic), 0.99 (CH_2) or 1.00 Å (aliphatic CH), N—H = 0.88 Å and O—H = 0.86 Å, and with $U_{iso}(H) = kU_{eq}$(carrier), where $k = 1.5$ for hydroxy atom H41 and 1.2 otherwise. In the absence of significant resonant scattering, the values of the Flack *x* parameter (Flack, 1983) and the Hooft *y* parameter (Hooft *et al.*, 2008), *viz.* 0.2 (15) and 0.6 (7), respectively, were indeterminate (Flack & Bernardinelli, 2000). Accordingly, the Friedel-equivalent reflections were merged prior to the final refinements, and the asymmetric unit was arbitrarily selected as having the *R* configuration at atom C2, and hence the *S* configuration at atom C4.

Data collection: *COLLECT* (Hooft, 1999); cell refinement: *DIRAX*/*LSQ* (Duisenberg *et al.*, 2000); data reduction: *EVALCCD* (Duisenberg *et al.*, 2003); program(s) used to solve structure: *SIR2004* (Burla *et al.*, 2005); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *PLATON* (Spek, 2009); software used to prepare material for publication: *SHELXL97* and *PLATON*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK3404). Services for accessing these data are described at the back of the journal.

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