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Chain formation by disordered, but correlated, hydrogen bonds in *cis*-(2*RS*,4*SR*)-2-(thiophen-2-yl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-4-ol and *cis*-(2*RS*,4*SR*)-2-(5-methylthiophen-2-yl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-4-ol

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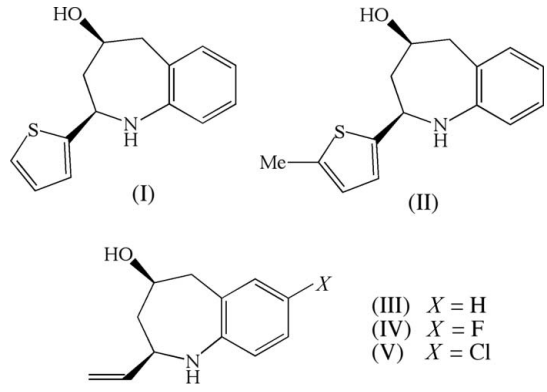
The closely related compounds *cis*-(2*RS*,4*SR*)-2-(thiophen-2-yl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-4-ol, $C_{14}H_{15}NOS$, (I), and *cis*-(2*RS*,4*SR*)-2-(5-methylthiophen-2-yl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-4-ol, $C_{15}H_{17}NOS$, (II), both crystallize with $Z' = 2$ in the space group $P\overline{1}$. In (I), the thienyl substituent in one of the two independent molecules is disordered over two sets of atomic sites having occupancies of 0.856 (2) and 0.144 (2). In both compounds, the two independent hydroxy O atoms are both within 2.8 Å of the hydroxy O atoms of two neighbouring molecules, and all of the hydroxy H atoms are disordered, each over two sites. The resulting O—H···O hydrogen bonds generate two similar but distinct $C_4^4(8)$ chains, depending upon which hydroxy H-atom sites are occupied or vacant, with full correlation of the hydroxy H-atom occupancies within each chain. Comparisons are made with the supramolecular assembly in some related compounds.

Comment

We have recently described a simple and efficient synthetic route to novel fused benzo[*b*]- and naphtho[1,2-*b*]tetrahydro-1*H*-azepines substituted at the C2 position with different aryl and alkenyl fragments (Gómez-Ayala *et al.*, 2006; Palma *et al.*, 2006; Acosta *et al.*, 2010). In addition, the potential application of these types of compounds as promising agents against the parasites *Trypanosoma cruzi* and *Leishmania chagasi* has been demonstrated (Palma *et al.*, 2009; Gómez-Ayala *et al.*, 2010). Based on these previous results and as a continuation of a systematic programme to identify new antiparasitic compounds in the tetrahydro-1-benzazepine series, we have now achieved the stereoselective synthesis of the title *cis*-2-(thiophen-2-yl)-2,3,4,5-tetrahydro-1*H*-benzazepin-4-ols, (I) and (II). We report here the molecular and supramolecular structures of (I) and (II) (Figs. 1 and 2), which we compare with the 2-vinyl-substituted analogues (III)–(V) (see Scheme), the structures of which were reported recently (Acosta *et al.*, 2009).



Compounds (I) and (II) were prepared by reduction of the corresponding 1,4-epoxy-2-*exo*-thienyl-2,3,4,5-tetrahydro-1-benzazepine derivatives, which had themselves been synthesized by a straightforward adaptation of the method used for the preparation of 2-*exo*-styryl analogues (Acosta *et al.*, 2008). Both compounds crystallize with $Z' = 2$ in the space group $P\overline{1}$, but a search for possible additional crystallographic symmetry revealed none; comparison of the atomic coordinates for corresponding pairs of atoms in the two independent molecules confirmed the absence of any additional symmetry. Moreover, in (I), although not in (II), one of the two independent molecules exhibits orientational disorder of the thienyl substituent; this alone is sufficient to preclude the possibility of any additional crystallographic symmetry in (I).

While the unit-cell repeat vectors *a*, *b* and *c* exhibit somewhat similar sets of values in (I) and (II), the unit-cell angles appear to be significantly different: these angles are all in excess of 100° in (I), while they are all less than 90° in (II), so ruling out any possibility of even approximate isomorphism. However, the cell angle β in (II) is only a little less than 90°, and if the value of this angle is artificially set to be slightly greater than 90° then the resulting reduced cell has all its angles greater than 90°, so showing much greater similarity with the unit cell of (I).

The molecules of (I) and (II) each contain two stereogenic centres and, for each compound, the asymmetric unit was selected so that the two independent molecules were of the same hand, with the *R* configuration at atoms C12 and C22. On this basis, the configuration at atoms C14 and C24 in the selected asymmetric units is *S*. Since the centrosymmetric space group $P\overline{1}$ accommodates equal numbers of the two enantiomers, both compounds are racemic with the relative configuration 2*RS*,4*SR*.

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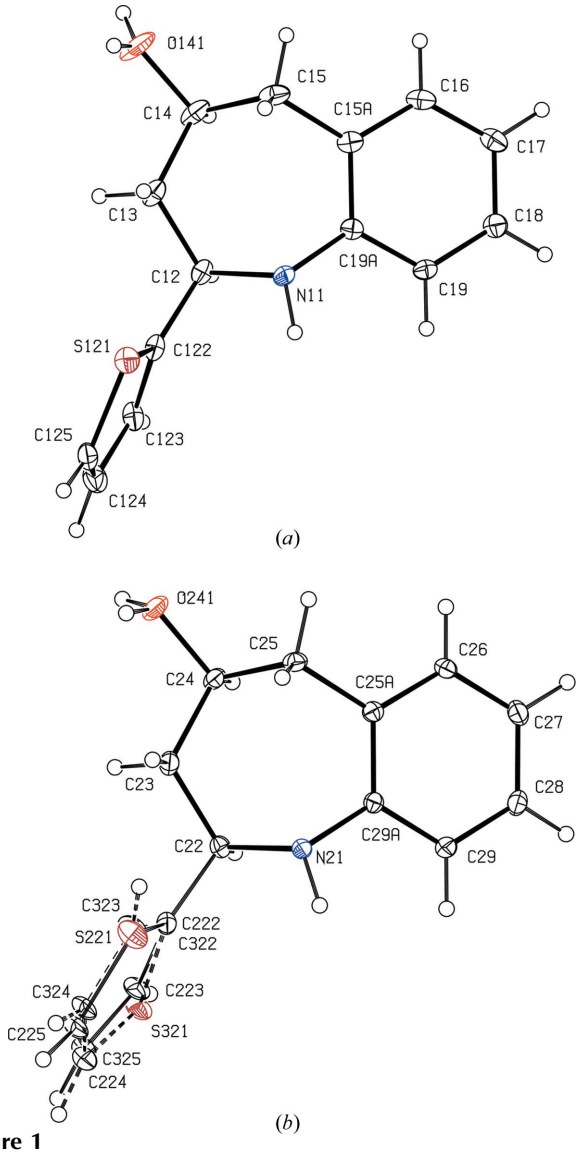

Figure 1
The molecular structures of the two independent molecules of (I), showing the atom-labelling schemes for (*a*) a molecule of type 1 and (*b*) a molecule of type 2, where the major and minor orientations of the thienyl substituent have occupancies of 0.856 (2) and 0.144 (2), respectively. The disordered hydroxy H atoms were modelled with an occupancy of 0.5, and displacement ellipsoids are drawn at the 30% probability level.

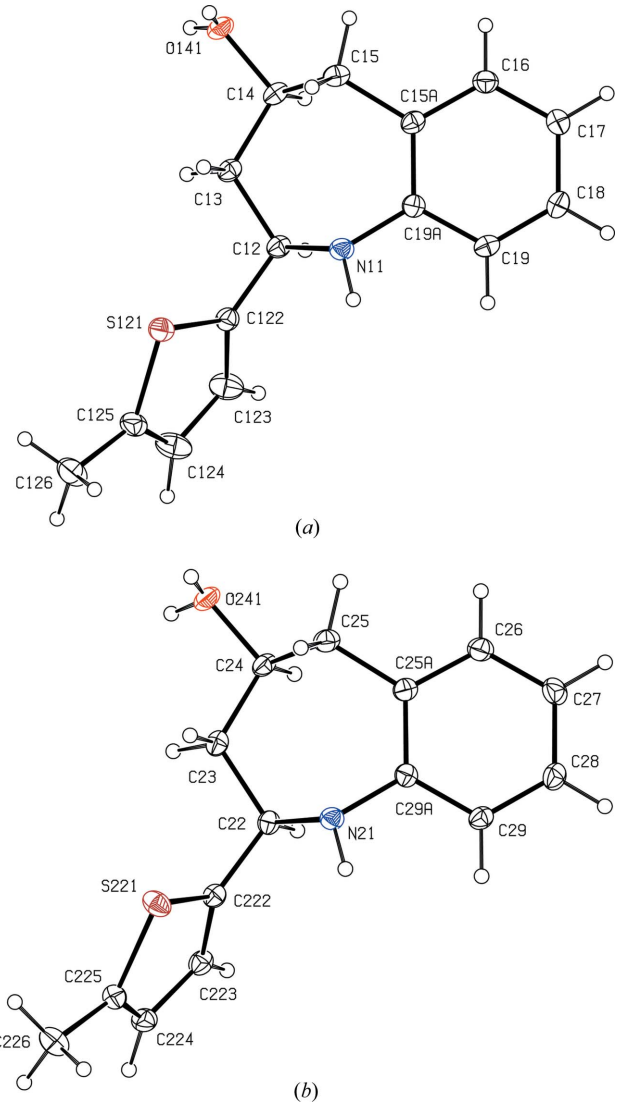

Figure 2
The molecular structures of the two independent molecules of (II), showing the atom-labelling schemes for (*a*) a molecule of type 1 and (*b*) a molecule of type 2. The disordered hydroxy H atoms were modelled with an occupancy of 0.5, and displacement ellipsoids are drawn at the 30% probability level.

As noted above, the thienyl substituent in molecule 2 of (I) (containing atom N21, see Fig. 1) exhibits orientational disorder, with refined site occupancies for the major and minor components (containing atoms S221 and S321, respectively, Fig. 1) of 0.856 (2) and 0.144 (2), respectively. The torsion angles defining the orientation of the thienyl substituents (Table 1) (*a*) confirm the approximate 180° rotation relating the major and minor orientations of the disorder components in (I), (*b*) indicate a significant difference between the two independent molecules in (II), so ruling out any possible additional symmetry, and (*c*) indicate, for the ordered molecules, a fairly similar but by no means identical conformation in both compounds.

In addition, the hydroxy H atom is disordered over two sites in each of the independent molecules of both compounds (Figs. 1 and 2, and Table 2), which has some interesting implications for the hydrogen-bonding scheme, as discussed below.

The supramolecular assembly in both compounds is dominated by O—H···O hydrogen bonds, augmented in each case by a single C—H···π(arene) hydrogen bond (Table 2). There is also a weak C—H···O interaction in (I), but the N—H bonds play no role in the hydrogen bonding. The behaviour of the O—H···O hydrogen bonds is the same for both compounds, so these interactions will be discussed first, in the specific context of (I), followed by a consideration of the other hydrogen bonds and their actions.

The disorder of the hydroxy H atoms means that at any atom O*x*41 (where $x = 1$ or 2), if the site H*x*41 is occupied, then the H*x*42 site must be vacant. Within the bimolecular unit defined by the selected asymmetric units of both (I) and (II),

atom O141 acts as hydrogen-bond donor *via* H141 to atom O241, and atom O241 acts in turn as donor *via* H241 to atom O141. However, the corresponding H141···H241 distances are only *ca* 1.16 Å in (I) and 1.13 Å in (II), so that in any specific bimolecular unit of this type, if the site H141 is occupied, the two sites H142 and H241 must be vacant, and thus the site H242 is also occupied. Similarly, if the site H141 is vacant, so too is the site H242, while the two sites H142 and H241 must both be occupied.

Similar considerations apply to the pairs of hydrogen bonds linking symmetry-related asymmetric units. Atoms O141 and O241 at (x, y, z) act as hydrogen-bond donors *via* H142 and H242, respectively, to the inversion-related atoms O141 and O241 at ($-x+1$, $-y+1$, $-z+1$) and ($-x$, $-y+1$, $-z+1$), respectively. The distances between the two inversion-related hydroxy H-atom sites across ($\frac{1}{2}$, $\frac{1}{2}$, $\frac{1}{2}$) are 1.28 Å in (I) and 1.16 Å in (II), while the corresponding H···H distances across (0, $\frac{1}{2}$, $\frac{1}{2}$) are 1.21 Å in (I) and 1.38 Å in (II). Thus, for any specific pair of inversion-related hydroxy O atoms within hydrogen-bonding range, only one of the two H-atom sites can be occupied, while the other must be vacant.

These constraints on the occupancies of the hydroxy H-atom sites give rise to two similar but distinct types of $C_4^4(8)$ chain (Bernstein *et al.*, 1995) running parallel to the [100] direction (Fig. 3). In one such chain, involving the occupied sites H141 and H242 at (x, y, z) and H142 and H241 at ($-x+1$, $-y+1$, $-z+1$), together with their equivalents by translation along [100], the O—H···O hydrogen bonds are all directed towards the negative direction of a (Fig. 3*a*). In the other chain, involving the occupied sites H142 and H241 at ($-x+1$, $-y+1$, $-z+1$), and their translational equivalents, the O—H···O hydrogen bonds are all directed towards the positive direction of a (Fig. 3*b*). Thus, within any given chain, the locations of the hydroxy H atoms within any such chain are fully correlated, but there is no necessary correlation between the senses of the hydrogen bonds in adjacent chains; the alternative directions of the hydrogen bonds in the chains are likely to be randomly distributed.

Entirely similar comments apply to the O—H···O hydrogen bonds in (II), where the O···O distances in the hydrogen bonds are all slightly longer than the corresponding distances in (I), by *ca* 2–3% (Table 2). In each compound, each hydroxy O atom has two neighbouring hydroxy O atoms from different molecules, not only within hydrogen-bonding distance but also almost equidistant (Table 2). This almost certainly underlies the twofold positional disorder of the hydroxy H atoms.

A study of the aggregation patterns of mono- and dialcohols (Taylor & Macrae, 2001), based on an analysis of data in the October 2000 Version of the Cambridge Structural Database (Allen, 2002), showed that, for the class of all secondary mono-alcohols, chains built from O—H···O hydrogen bonds and rings built from similar interactions were found with approximately equal frequency. However, when steric effects were taken into consideration, as defined by a quantity denoted SSBC (the sum of substituents on the β-C atoms), chain formation was found to be more usually associated with lower values of SSBC, while ring formation was more usually associated with higher values. For (I) and (II) discussed here, the value of SSBC is 2, the lowest value possible for a secondary mono-alcohol, so that, based on the earlier study (Taylor & Macrae, 2001), chain formation is to be expected here in preference to ring formation.

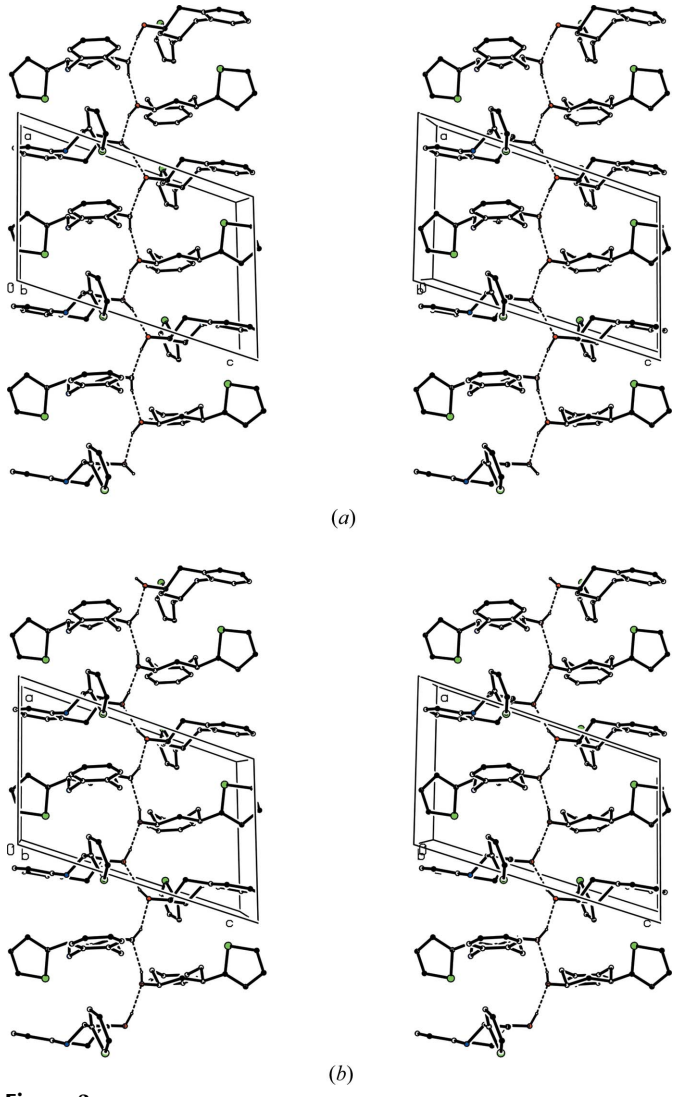

Figure 3
Stereoviews of the two hydrogen-bonded $C_4^4(8)$ chains along [100] in (I), showing (*a*) the chain resulting from the occupancy of site H141 at (x, y, z) and (*b*) the chain resulting from the occupancy of site H142 at (x, y, z). For the sake of clarity, only the major orientation of the disordered thienyl substituent is shown, and H atoms bonded to C and N atoms have all been omitted.

In addition to the O—H···O hydrogen bonds, each of the crystal structures contains a single C—H···π(arene) hydrogen bond, involving the same donor and acceptor groups in both compounds (Table 2). These interactions lie within the chains generated by the O—H···O hydrogen bonds, independent of the directionality of those bonds, and thus they do not influence the dimensionality of the hydrogen-bonded structures. It may be noted here that the metrics of the C—H···π(arene) hydrogen bond in (II) suggest that it is significantly stronger than that in (I).

The only other direction-specific intermolecular interaction is a single C—H···O hydrogen bond in (I) (Table 2), but there is no corresponding interaction in the structure of (II). The effect of this hydrogen bond is to link the chains along [100] into a sheet lying parallel to (001).

It is of interest briefly to compare the structures of the thienyl compounds (I) and (II) reported here with those of the three vinyl-substituted analogues (III)–(V) (Acosta *et al.*, 2009) (see Scheme). Compounds (III)–(V), unlike (I) and (II), are all isomorphous, but with sufficient variation in their unit-cell dimensions to influence the range of hydrogen bonds present. All three compounds crystallize in the space group $P2_1/n$ with $Z' = 1$, as opposed to $Z' = 2$ for (I) and (II), and in all of them the hydroxy H atoms are fully ordered. Unlike (I) and (II), O—H···O hydrogen bonds are absent from the structures of (III)–(V), where instead a combination of O—H···N and N—H···O hydrogen bonds generates chains of edge-fused $R_3^3(10)$ rings. When the aryl substituent X = H or F, *viz.* in (III) and (IV), the chains are linked into sheets by a single C—H···π(arene) hydrogen bond, but this is not the case in (V), where X = Cl.

The absence of any participation in hydrogen bonding by the N—H bonds in (I) and (II) may be a consequence of the greater steric demands of the thienyl substituents, as opposed to the vinyl substituents in (III)–(V).

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

	(I)	(II)
N11—C12—C122—S121	64.28 (18)	71.7 (2)
N21—C22—C222—S221	60.73 (19)	60.8 (2)
N21—C22—C322—C321	−114.9 (2)	

Table 2
Hydrogen-bond parameters (Å, °) for (I) and (II).

Cg represents the centroid of the C15*A*/C16–C19/C19*A* ring.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
(I)				
O141—H141···O241	0.81 (5)	1.92 (5)	2.684 (3)	156 (5)
O141—H142···O141^{i}	0.81 (6)	1.95 (5)	2.695 (3)	153 (6)
O241—H241···O141	0.81 (4)	1.89 (3)	2.684 (3)	164 (7)
O241—H242···O241^{ii}	0.81 (6)	1.92 (6)	2.691 (3)	158 (6)
C225—H225···O241^{iii}	0.95	2.50	3.361 (4)	151
C223—H223···*Cg*^{i}	0.95	2.93	3.705 (9)	140
(II)				
O141—H141···O241	0.82 (4)	1.94 (4)	2.763 (3)	173 (6)
O141—H142···O141^{i}	0.82 (4)	1.95 (4)	2.757 (3)	168 (4)
O241—H241···O141	0.82 (4)	1.95 (4)	2.763 (3)	177 (7)
O241—H242···O241^{ii}	0.82 (4)	2.02 (5)	2.746 (3)	149 (4)
C223—H223···*Cg*^{ii}	0.95	2.74	3.572 (2)	147

Symmetry codes: (i) $-x+1, -y+1, -z+1$; (ii) $-x, -y+1, -z+1$; (iii) $x, y+1, z$.

Experimental

For the syntheses of (I) and (II), zinc powder (15 mmol), glacial acetic acid (7.5 mmol) and concentrated hydrochloric acid (7.5 mmol) were added to a stirred and cooled (ice bath) solution of the corresponding 2-*exo*-(thiophen-2-yl)- [for (I)] or 2-*exo*-(5-methylthiophen-2-yl)-2,3,4,5-tetrahydro-1,4-epoxybenzazepine [for (II)] (1.5 mmol) in methanol (25 ml). The resulting reaction mixtures were stirred at 273 K for 15 min and then at ambient temperature for a further 1–2 h. The mixtures were filtered and the filtrates were basified to pH 8 with aqueous ammonia solution (25%), and then extracted with ethyl acetate (2 × 50 ml). The combined organic extracts were dried over anhydrous sodium sulfate and then the solvent was removed under reduced pressure. The resulting crude products were purified by silica-gel column chromatography using heptane–ethyl acetate as eluent (from 5:1 to 2:1 *v*/*v*). Crystallization from heptane–ethyl acetate (10:1 *v*/*v*) gave crystals of (I) and (II) suitable for single-crystal X-ray diffraction. For (I), colourless crystals, yield 84%, m.p. 395 K; MS (70 eV) *m*/*z* (%): 245 (M^+, 64), 227 (3), 199 (21), 139 (52), 118 (21), 107 (82), 106 (100). For (II), light-yellow crystals, yield 83%, m.p. 366 K; MS (70 eV) *m*/*z* (%): 259 (M^+, 42), 241 (1), 215 (9), 153 (100), 118 (15), 107 (70), 106 (67).

Compound (I)

Crystal data

$C_{14}H_{15}NOS$
M_r = 245.34
Triclinic, $P\overline{1}$
a = 9.5677 (6) Å
b = 9.8798 (4) Å
c = 14.7183 (11) Å
α = 104.726 (5)°
β = 104.033 (6)°
γ = 103.273 (4)°
V = 1240.95 (15) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.24 mm^{-1}
T = 120 K
0.31 × 0.16 × 0.12 mm

Data collection

Bruker–Nonius KappaCCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
T_{min} = 0.928, T_{max} = 0.971
31492 measured reflections
5703 independent reflections
4174 reflections with $I > 2\sigma(I)$
R_{int} = 0.049

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.047
$wR(F^2)$ = 0.108
S = 1.06
5703 reflections
332 parameters
14 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.30 e Å^{-3}
$\Delta\rho_{min}$ = −0.36 e Å^{-3}

Compound (II)

Crystal data

$C_{15}H_{17}NOS$
M_r = 259.37
Triclinic, $P\overline{1}$
a = 9.6764 (5) Å
b = 10.6897 (3) Å
c = 14.4433 (5) Å
α = 72.018 (3)°
β = 89.108 (3)°
γ = 72.494 (3)°
V = 1350.27 (9) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.23 mm^{-1}
T = 120 K
0.34 × 0.22 × 0.10 mm

Data collection

Bruker–Nonius KappaCCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
T_{min} = 0.927, T_{max} = 0.978
35561 measured reflections
6208 independent reflections
4151 reflections with $I > 2\sigma(I)$
R_{int} = 0.056

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.049$	H atoms treated by a mixture of independent and constrained refinement
$wR(F^2) = 0.131$	$\Delta\rho_{max} = 0.29$ e Å^{-3}
$S = 1.05$	$\Delta\rho_{min} = -0.43$ e Å^{-3}
6208 reflections	
339 parameters	
4 restraints	

It was apparent from an early stage in the refinement of (I) that in molecule 2, containing atom N21, the thienyl group was disordered over two sets of atomic sites, related to one another by a rotation of approximately 180° around the C22—C222 bond (Fig. 2). In the refinement model used for this disorder, the directly bonded distances and the one-angle nonbonded distances in the minor-occupancy component (containing atom S321) were restrained to be equal to the corresponding distances in the major-occupancy component (containing atom S221), subject to s.u. values of 0.005 and 0.01 Å, respectively. In addition, the anisotropic displacement parameter components for partially occupied atomic sites occupying similar regions of space were constrained to be equal. On this basis, the site-occupancy factors for the two components refined to values of 0.856 (2) and 0.144 (2), respectively. All H atoms bonded to C and N atoms, with the exception of those in the minor orientation component of (I), were located in difference maps; these H atoms were then treated as riding atoms. H atoms bonded to C atoms were included in geometrically idealized positions, with C—H = 0.95 (aromatic and thienyl), 0.98 (CH_3), 0.99 (CH_2) or 1.00 Å (aliphatic CH), and with $U_{iso}(H) = kU_{eq}(C)$, where $k = 1.5$ for the methyl groups, which were permitted to rotate but not to tilt, and 1.2 for all other H atoms bonded to C atoms. H atoms bonded to N atoms were permitted to ride at the positions located in difference maps, with $U_{iso}(H) = 1.2U_{eq}(N)$, giving N—H distances in the range 0.88–0.93 Å. The difference maps showed clearly that each of the hydroxy H atoms was disordered over two sites having approximately equal occupancy in every case. Thereafter, the site occupancies of H atoms bonded to O atoms were all fixed at 0.50. The atomic coordinates were refined subject to an O—H bond-length restraint of 0.82 (1) Å, with $U_{iso}(H) = 1.5U_{eq}(O)$.

For both compounds, data collection: *COLLECT* (Nonius, 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: YF3011). Services for accessing these data are described at the back of the journal.

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