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rac-(*Z*)-2-(2-Thienylmethylene)-1-azabicyclo[2.2.2]octan-3-ol

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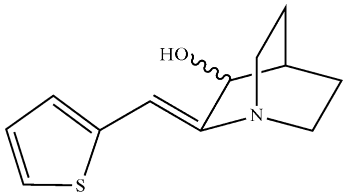
The asymmetric unit of the racemic form of the title compound, $C_{12}H_{15}NOS$, contains four crystallographically independent molecules. The olefinic bond connecting the 2-thienyl and 1-azabicyclo[2.2.2]octan-3-ol moieties has *Z* geometry. Strong hydrogen bonding occurs in a directed co-operative $O—H\cdots O—H\cdots O—H\cdots O—H$ $R_4^4(8)$ pattern that influences the conformation of the molecules. Co-operative $C—H\cdots\pi$ interactions between thienyl rings are also present. The average dihedral angle between adjacent thienyl rings is 87.09 (4)°.

Comment

Radiation therapy prevents cancer cells from growing and dividing, but can also damage normal cells. Radio-sensitizers are drugs that sensitize cancer cells to radiation therapy. Recent research in our laboratory has focused on the discovery of molecules that can either sensitize a tumour to radiation without affecting healthy tissue, or that can shield normal cells from radiation damage. Recently, we have reported (Sekhar *et al.*, 2007) the radio-sensitizing activity of *N*-aryl-substituted *rac*-(*Z*)-2-(1*H*-indol-3-ylmethylene)-1-azabicyclo[2.2.2]octan-3-ols. In addition to these indole analogues, we have also synthesized 1-azabicyclo[2.2.2]octan-3-ols linked to non-indolic systems, in order to compare their radio-sensitizing activities with those of the indole analogues. The title compound, (I), was prepared by the base-catalyzed reaction of thiophene-2-carbaldehyde with 1-azabicyclo[2.2.2]octan-3-one and subsequent reduction to the corresponding secondary alcohol. In order to confirm the double-bond geometry, and to determine the molecular conformation in the crystal structure, the X-ray analysis of compound (I) has been carried out, and the results are presented here.

The asymmetric unit of (I) contains four crystallographically independent molecules, (I*A*)–(I*D*), with almost identical bond lengths and angles. The molecular structure and atom-numbering scheme of molecule (I*A*) are shown in Fig. 1, and selected bond lengths and angles are listed in Table 1.



(I)

The title molecule comprises a 1-azabicyclo[2.2.2]octan-3-ol moiety and a 2-thienyl group linked by a C5═C6 bond that has *Z* geometry. In this *Z* isomer, the C1—C5 bond is *trans* with respect to the C6—C10 bond. The double bond has a nearly planar atomic arrangement, since the r.m.s. deviation from the best plane passing through atoms N1, C6, C10, C5 and C1 is 0.0061 (10) Å for (I*A*), 0.0972 (10) Å for (I*B*), 0.1943 (10) Å for (I*C*) and 0.2500 (10) Å for (I*D*). The geometries of the four molecules in the asymmetric unit are essentially the same, so only molecule *A* is discussed in detail here.

The bond angles around atoms C5*A* and C6*A* deviate from 120° and this is in general agreement with our earlier observation for a similar type of compound (Sonar *et al.*, 2004). The angles N1*A*—C6*A*—C10*A*, C6*A*═C5*A*—C1*A* and C5*A*═C6*A*—C10*A* [114.02 (15), 126.55 (17) and 125.26 (17)°, respectively] are distorted as a consequence of the strain induced by the double-bond linkage at C5*A*═C6*A*. The azabicyclic system exhibits small distortions in geometry compared with standard tetrahedral values. The angles C6*A*—N1*A*—C7*A*, C10*A*—C9*A*—C11*A* and C9*A*—C11*A*—C12*A* [107.28 (14), 107.41 (15) and 107.79 (14)°, respectively] are all smaller than the ideal tetrahedral value of 109.5°, while the angles N1*A*—C7*A*—C8*A*, O1*A*—C10*A*—C9*A* and N1*A*—C12*A*—C11*A* [111.32 (15), 113.84 (14) and 112.05 (14)°, respectively] are all slightly larger than the tetrahedral value. The C4═C1—C5═C6 torsion angles [170.67 (19),

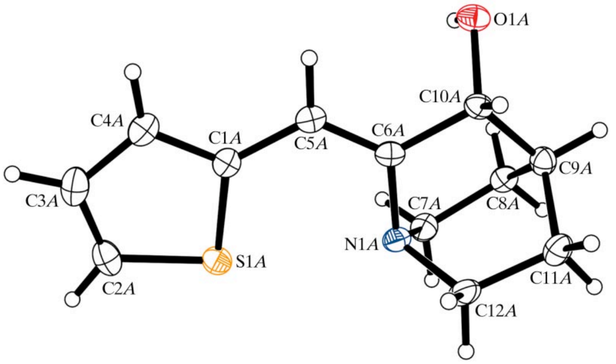


Figure 1
A view of molecule (I*A*), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii. The numbering schemes for molecules *B*, *C* and *D* are identical to the numbering scheme for molecule *A*.

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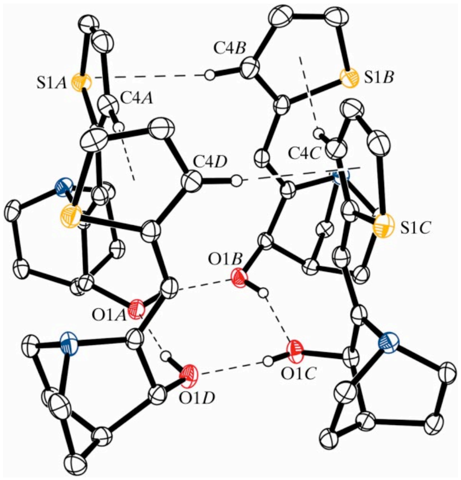

Figure 2
A view of molecules (I*A*)–(I*D*). H atoms have been omitted for clarity, except for those involved in π interactions and O—H···O hydrogen bonds (dashed lines).

173.55 (19), 173.41 (19) and 170.85 (19)° for molecules *A*, *B*, *C* and *D*, respectively] indicate a deviation of the 2-thienyl ring from the plane of the double bond connecting it to the azabicyclic ring in these molecules. This small deviation facilitates a weak conjugation between the C5═C6 double bond and the 2-thienyl ring. This is also evident from the C1—C5 bond lengths [1.456 (3), 1.455 (3), 1.458 (3) and 1.451 (3) Å in molecules *A*, *B*, *C* and *D*, respectively].

Strong hydrogen bonds and weaker C—H···π interactions (Fig. 2) present in the crystal structure of (I) effectively group sets of four molecules together into roughly cylindrical units. Within each group, all molecules possess the same absolute configuration and are related to other groups of opposite hand *via* crystallographic inversion centres. The donor–acceptor direction of the $R_4^4(8)$ hydrogen-bonded motif comprising O1*A*—H1*A*···O1*B*—H1*B*···O1*C*—H1*C*···O1*D*—H1*D*···O1*A* (Table 2) is opposite from the directionality around the C—H···π-linked thienyl rings [(ring *A*)—H4*A*···(ring *D*)—H4*D*···(ring *C*)—H4*C*···(ring *B*)—H4*B*···(ring *A*)]. These C—H···π interactions, C4*A*···(ring *B*), C4*B*···(ring *C*), C4*C*···(ring *D*) and C4*D*···(ring *A*), with distances of 3.551 (2), 3.531 (2), 3.554 (2) and 3.565 (2) Å, respectively, effectively lock the thiophene rings into a single conformation. The dihedral angles between successive rings are *A*/*B* = 89.24 (4)°, *B*/*C* = 86.64 (4)°, *C*/*D* = 85.08 (4)° and *D*/*A* = 87.39 (4)°.

Experimental

The title compound was prepared according to the previously reported procedure of Sonar *et al.* (2004). Crystallization from ethyl acetate afforded colourless crystals. ^{1}H NMR (CDCl$_3$): δ 1.47–1.89 (*m*, 5H), 2.05 (*s*, 1H), 2.74–3.00 (*m*, 4H), 4.34 (*s*, 1H), 6.59 (*s*, 1H), 6.97 (*d*, 2H), 7.25 (*d*, 1H); ^{13}C NMR (CDCl$_3$): δ 19.07, 25.37, 31.09, 46.64, 47.77, 70.61, 116.83, 125.47, 126.95, 127.49, 138.53, 149.20.

Crystal data

$C_{12}H_{15}NOS$
$M_r = 221.32$
Monoclinic, $P2_1/n$
$a = 14.7933$ (3) Å
$b = 20.0349$ (4) Å
$c = 14.8243$ (3) Å
$\beta = 90.2820$ (7)°
$V = 4393.61$ (15) Å^3
$Z = 16$
Mo *K*α radiation
$\mu = 0.27$ mm^{-1}
$T = 90.0$ (2) K
0.38 × 0.35 × 0.03 mm

Data collection

Nonius KappaCCD area-detector diffractometer
Absorption correction: multi-scan (*SCALEPACK*; Otwinowski & Minor, 1997)
$T_{\min} = 0.906$, $T_{\max} = 0.992$
37339 measured reflections
10043 independent reflections
7113 reflections with $I > 2\sigma(I)$
$R_{\rm int} = 0.058$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.044$
$wR(F^2) = 0.114$
$S = 1.04$
10043 reflections
545 parameters
H-atom parameters constrained
$\Delta\rho_{\max} = 0.31$ e Å^{-3}
$\Delta\rho_{\min} = -0.34$ e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

S1*A*—C1*A*	1.7350 (19)	S1*C*—C1*C*	1.7357 (19)
O1*A*—C10*A*	1.431 (2)	O1*C*—C10*C*	1.431 (2)
C6*A*—C10*A*	1.523 (2)	C6*C*—C10*C*	1.519 (3)
S1*B*—C1*B*	1.7348 (19)	S1*D*—C1*D*	1.7373 (19)
O1*B*—C10*B*	1.435 (2)	O1*D*—C10*D*	1.430 (2)
C6*B*—C10*B*	1.516 (2)	C6*D*—C10*D*	1.522 (2)
C6*A*—C5*A*—C1*A*	126.55 (17)	C6*C*—C5*C*—C1*C*	126.38 (18)
C5*A*—C6*A*—C10*A*	125.26 (17)	C5*C*—C6*C*—C10*C*	125.30 (17)
N1*A*—C6*A*—C10*A*	114.02 (15)	N1*C*—C6*C*—C10*C*	114.31 (15)
C6*B*—C5*B*—C1*B*	127.41 (17)	C6*D*—C5*D*—C1*D*	127.25 (17)
C5*B*—C6*B*—C10*B*	125.22 (17)	C5*D*—C6*D*—C10*D*	125.02 (17)
N1*B*—C6*B*—C10*B*	114.17 (15)	N1*D*—C6*D*—C10*D*	114.52 (15)
S1*A*—C1*A*—C5*A*—C6*A*	−8.6 (3)	S1*C*—C1*C*—C5*C*—C6*C*	−4.6 (3)
S1*B*—C1*B*—C5*B*—C6*B*	−7.6 (3)	S1*D*—C1*D*—C5*D*—C6*D*	−7.1 (3)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O1*A*—H1*A*···O1*B*	0.84	1.97	2.7734 (18)	161
O1*B*—H1*B*···O1*C*	0.84	2.02	2.8124 (18)	157
O1*C*—H1*C*···O1*D*	0.84	1.97	2.7812 (18)	163
O1*D*—H1*D*···O1*A*	0.84	1.97	2.7795 (18)	162

H atoms were found in a difference Fourier map and subsequently placed in idealized positions with constrained C—H distances of 0.95 (Csp^2—H), 0.99 (CH$_2$) and 1.00 Å (CH), and with O—H = 0.84 Å. $U_{\rm iso}$(H) values were set at either 1.2$U_{\rm eq}$ or 1.5$U_{\rm eq}$ (OH only) of the parent atom.

Data collection: *COLLECT* (Nonius, 1999); cell refinement: *SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO-SMN* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *XP* in *SHELXTL/PC* (Sheldrick, 1995); software used to prepare material for publication: *SHELXL97* and local procedures.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: HJ3044). Services for accessing these data are described at the back of the journal.

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