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rac-5-Diphenylacetyl-2,2,4-trimethyl-2,3,4,5-tetrahydro-1,5-benzothiazepine and *rac*-5-formyl-2,2,4-trimethyl-2,3,4,5-tetrahydro-1,5-benzothiazepine

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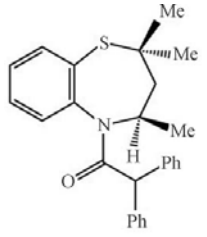
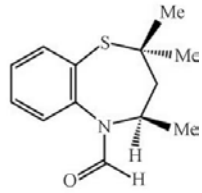
rac-5-Diphenylacetyl-2,2,4-trimethyl-2,3,4,5-tetrahydro-1,5-benzothiazepine, $C_{26}H_{27}NOS$, (I), and *rac*-5-formyl-2,2,4-trimethyl-2,3,4,5-tetrahydro-1,5-benzothiazepine, $C_{13}H_{17}NOS$, (II), are both characterized by a planar configuration around the heterocyclic N atom. In contrast with the chair conformation of the parent benzothiazepine, which has no substituents at the heterocyclic N atom, the seven-membered ring adopts a boat conformation in (I) and a conformation intermediate between boat and twist-boat in (II). The molecules lack a symmetry plane, indicating distortions from the perfect boat or twist-boat conformations. The supramolecular architectures are significantly different, depending in (I) on C—H···O interactions and intermolecular S···S contacts, and in (II) on a single aromatic π–π stacking interaction.

Comment

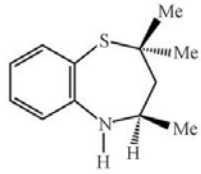
1,5-Benzothiazepine is a versatile pharmacophore found in a number of clinically used drugs. The biological function of such drugs is quite varied, and ranges from calcium antagonist activity observed for diltiazem, (+)-*cis*-3-acetoxy-5-(2,2-dimethylaminoethyl)-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one, and clentiazem, (+)-*cis*-3-acetoxy-8-chloro-5-(2,2-dimethylaminoethyl)-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one, to CNS-depressant behaviour observed for thiazesim, (+)-5-(2,2-dimethyl aminoethyl)-2-phenyl-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one. Replacement of the 3-acetyl group of diltiazem with a methyl group gives a more potent analogue of diltiazem. Further, TA 933, which has an inverted stereochemistry with respect to the substituents at the 2 and 3 positions of diltiazem, is a more active vasorelaxant (Bariwal *et al.*, 2008). Dihydro-1,5-benzothiazepines containing phenyl substituents at the 2 and 4 positions are potent antibacterial agents (Micheli *et al.*, 2001). Therefore, the configuration and conformation of 1,5-benzothiazepines are of interest and importance.



(I)



(II)



(III)

The conformational effects of substituents in the seven-membered ring are pronounced, as indicated by the existence of the chair conformation in 2,2,4-trimethyl-2,3,4,5-tetrahydro-1,5-benzothiazepine, (III) (Muthukumar *et al.*, 2004), and the twist-boat conformation in 2,4-diphenyl-2,3,4,5-tetrahydrobenzothiazepine (Laavanya *et al.*, 2002). Subtle electronic effects can introduce distortions in the ideal conformations, *viz.* chair, twist-chair, boat and twist-boat. In the solid state, the conformation of *rac*-5-diphenylacetyl-2,2,4-trimethyl-2,3,4,5-tetrahydro-1,5-benzothiazepine, (I), is a distorted twist-boat and that of *rac*-5-formyl-2,2,4-trimethyl-2,3,4,5-tetrahydro-1,5-benzothiazepine, (II), is intermediate between boat and twist-boat forms. The molecules of compounds (I)–(III) are all chiral, raising the possibility that they could crystallize in an enantiopure form in noncentrosymmetric space groups, as required for nonlinear optical properties (Long, 1995). All three compounds were obtained by synthetic methods and are racemates. However, only (III) crystallizes in a noncentrosymmetric space group, *viz.* $P2_1$ (Muthukumar *et al.*, 2004).

The molecules of these compounds could, in principle, be linked in the solid state by one or more noncovalent forces, *viz.* C—H···*X*, N—H···*X* (*X* = O or S), S···S, C—H···π and π···π interactions. The presence or absence of these interactions can affect the molecular conformation and supramolecular structure of these crystals. We report here the crystal and molecular structures of (I) and (II) and compare them with those of (III). Analysis of the Cambridge Structural Database (CSD, Version 5.29; Allen, 2002) reveals 75 reported crystal structures of 1,5-benzothiazepine derivatives, six of which belong to the diltiazem family, and 11 1,5-benzothiazepines which contain neither ring oxo groups nor extra fused rings, which are akin to compounds (I)–(III).

Compounds (I) and (II) crystallize as racemates and for each compound the reference molecules were selected to have an *R* configuration at C4 (Figs. 1 and 2). The bond lengths and angles of (I) and (II) are unexceptional. As expected, the

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C—S bond lengths in (I) are unequal [1.7603 (16) and 1.8518 (18) Å], and in (II) [1.7577 (15) and 1.8536 (13) Å]. The means of the bond angles around the ring N atom are 119.98 (8) and 119.82 (6)° for (I) and (II), respectively, signifying planarity of the N atom, as expected. The C4—C3—C2—C12 and C4—C3—C2—C13 torsion angles of (I) are −177.45 (19) and −55.2 (2)°, respectively, and the corresponding torsion angles for (II) are −173.65 (12) and −50.89 (17)°, respectively, indicating in both molecules that the two methyl groups are not isoclinal but assume equatorial and axial orientations. The C2—C3—C4—C14 torsion angles of (I) and (II) are 178.41 (15) and −179.07 (11)°, respectively, confirming the equatorial orientations of the methyl group bonded to C4. Additional selected torsion angles for (I)–(III) are listed in Table 1.

In each of (I) and (II), the carbonyl group is *exo* oriented with respect to the N5—C6 bond and the benzene ring. The S and N atoms are coplanar with the benzene ring in molecule (I), while in (II) and (III), although the N atom is essentially coplanar with the benzene ring, the S atom deviates significantly from the ring plane [0.227 (1) Å in (II) and 0.211 (1) Å in (III)]. Table 1 indicates the absence of a mirror plane in all the molecules and the considerable distortion from the four distinct conformations of the seven-membered ring. Comparison of the standard values of all the four forms (Hendrickson, 1967) revealed that the conformations of (I) and (II) are clearly nonchair and that of (III) is chair. A transition from chair to boat form occurs as a result of *N*-acylation.

Ring-puckering parameters can be used to infer the conformational preferences of the molecules (Cremer & Pople, 1975). The four ring-puckering parameters required to discern the conformation of the seven-membered ring for each of the molecules are given in Table 2. Detailed puckering analysis of the seven-membered ring on the basis of the four puckering parameters indicates six conformations derived from the four fundamental conformations discussed above. They are contained in three pseudorotational manifolds, *viz.* chair–twist-chair, boat–twist-boat and sofa–twist-sofa–sofa–boat forms. The puckering amplitudes q_2 and q_3 for (I) and (II) are close to 1.15 and 0, respectively, which are the values ascribed to both boat and twist-boat forms (Boessenkool & Boeyens, 1980) of the seven-membered ring. From the puck-

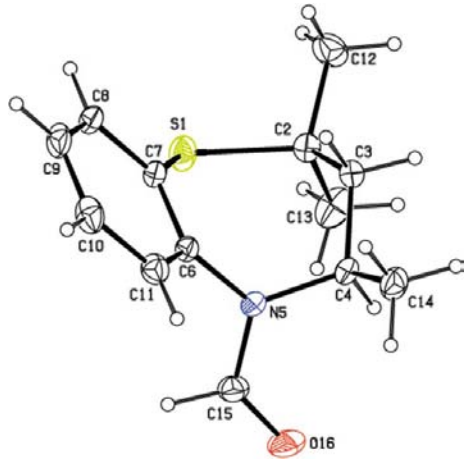

Figure 2
The molecule of (II), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

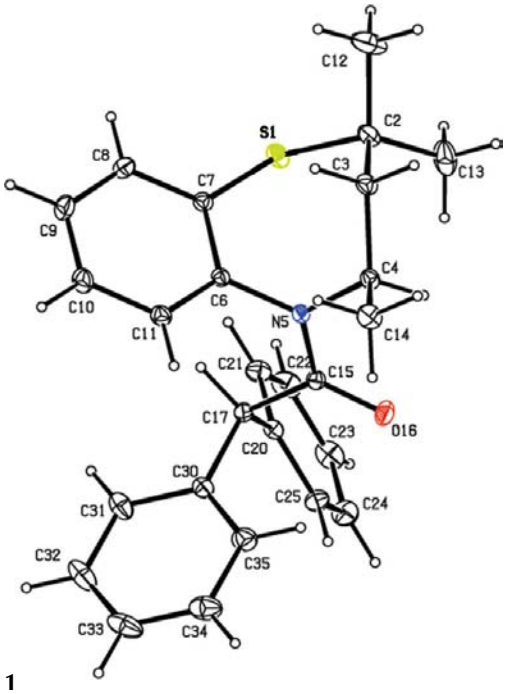

Figure 1
The molecule of (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

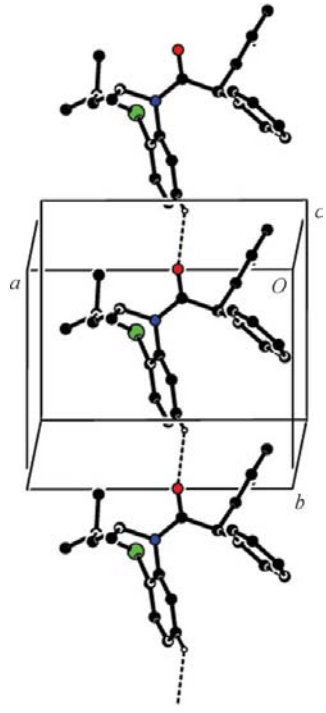

Figure 3
Part of the crystal structure of (I), showing the hydrogen-bonded chain along [010]. For clarity, H atoms bonded to C atoms have been omitted.

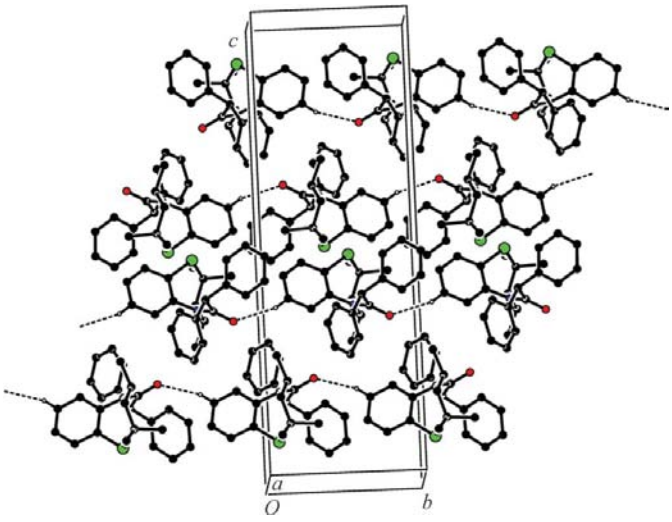

Figure 4
Part of the crystal structure of (I), showing the S···S contacts (green/grey in the electronic version of the paper) between the hydrogen-bonded chains. For clarity, most H atoms bonded to C atoms have been omitted.

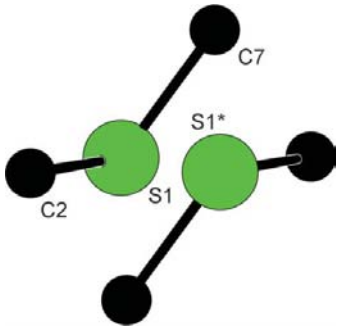

Figure 5
Part of the crystal structure of (I), showing the relative orientation of bonds around adjacent S atoms. The S atom marked with an asterisk (*) is at the symmetry position $(-x+1, -y+1, -z+1)$.

ering angles φ_2 and φ_3 (Table 2), the conformation of (I) is found to be twist-boat, and that of (II) is intermediate between the twist-boat and boat forms.

In (I), molecules are linked by a C—H···O hydrogen bond (Table 3), forming a chain parallel to the [010] axis (Fig. 3). There are short S···S contacts [3.376 (6) Å] between adjacent antiparallel chains, involving the S atoms at (x, y, z) and $(1-x, 1-y, 1-z)$ (Fig. 4). The pair of bonds around the S atom are uneclipsed with respect to those of the other S atom, signifying a nonparallel orientation (Fig. 5) of the S-atom *p*-type lone pairs, promoting close contacts between the S-atom *s*-type lone pairs (Ozturk *et al.*, 1994).

The structure of (II) contains neither S···S nor C—H···O interactions; instead, the molecules are linked by an aromatic π–π interaction. The aryl rings in the molecules at (x, y, z) and $(1-x, 1-y, -z)$ are parallel with an interplanar spacing of 3.5390 (6) Å. The ring–centroid distance is 3.8597 (9) Å. These parameters are comparable with the corresponding values reported for similar interactions (Portilla *et al.*, 2005; Delgado *et al.*, 2006). This interaction generates a centrosymmetric dimer (Fig. 6). By contrast, the molecules of (III)

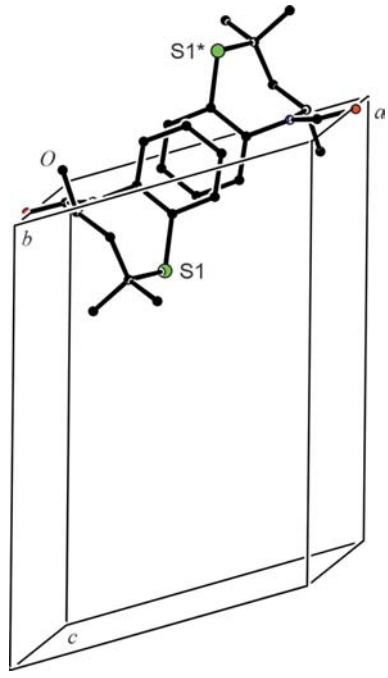

Figure 6
Part of the crystal structure of (II), showing the formation of a centrosymmetric π-stacked dimer. For clarity, all H atoms have been omitted. The S atom marked with an asterisk (*) is at the symmetry position $(-x+1, -y+1, -z)$.

are linked by an N—H···S hydrogen bond (Muthukumar *et al.*, 2004). It is noted that the three molecules are in different conformations and exhibit differences in intermolecular interactions. The packing indices (%) follow the order (III) 68.6 > (II) 67.2 > (I) 64.5, signifying a lack of close packing in (I) compared with the other two. This is substantiated by the lowest density for (I) despite its high molecular weight; the density (in Mg m^{-3}) order is (II) 1.255 > (III) 1.219 > (I) 1.182. The melting points (K), which depend upon crystal packing forces, follow the order (I) 398 > (III) 358 > (II) 337. The melting point of (II) is low, much lower than (III), indicating weaker intermolecular interactions in the former. As shown by AM1 calculations, the stable conformations of isolated molecules of (I)–(III) are similar to those established through X-ray analysis. We conclude that the conformations of the three benzothiazepines depend upon their molecular structures and crystal packing effects cause subtle distortions in conformation. We further conclude that in the structures of the crystals studied here the packing interactions are determined by the molecular conformations.

Experimental

Compound (I) was obtained by the acetylation of the parent 2,2,4-trimethyl-2,3,4,5-tetrahydrobenzothiazepine, (III), using diphenylacetyl chloride in a 1:1 molar ratio in the presence of triethylamine in a benzene medium. The product was isolated as a single crystal by slow evaporation from a solution in 95% ethanol (yield 54%, m.p. 398–400 K). Compound (II) was prepared by the formylation of (III) in a benzene medium using the same base and acetic formic anhydride as formylating agent, adopting the reported procedure of

Muthukumar (2001). The latter was prepared *in situ* by warming a mixture of acetic anhydride and 85% formic acid in a 1:1 molar ratio. Repeated recrystallization by the slow and spontaneous evaporation of the solvent at room temperature from a solution in petroleum ether afforded colourless single crystals (yield 89%, m.p. 337–339 K).

Compound (I)

Crystal data

$C_{26}H_{27}NOS$
M_r = 401.55
Monoclinic, $P2_1/c$
a = 10.2731 (2) Å
b = 8.5637 (2) Å
c = 25.6968 (6) Å
β = 93.2180 (10)°
V = 2257.13 (9) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.16 mm^{-1}
T = 296 K
0.30 × 0.02 × 0.02 mm

Data collection

Bruker Kappa APEXII CCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Bruker, 1999)
T_{min} = 0.954, T_{max} = 0.997
25865 measured reflections
5164 independent reflections
3691 reflections with $I > 2\sigma(I)$
R_{int} = 0.031

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.042
$wR(F^2)$ = 0.117
S = 1.03
5164 reflections
289 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.23 e Å^{-3}
$\Delta\rho_{min}$ = −0.31 e Å^{-3}

Compound (II)

Crystal data

$C_{13}H_{17}NOS$
M_r = 235.34
Monoclinic, $P2_1/n$
a = 9.6038 (8) Å
b = 9.9485 (8) Å
c = 13.6818 (11) Å
β = 107.713 (2)°
V = 1245.23 (18) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.24 mm^{-1}
T = 296 K
0.29 × 0.12 × 0.10 mm

Data collection

Bruker Kappa APEXII CCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Bruker, 1999)
T_{min} = 0.934, T_{max} = 0.977
17043 measured reflections
4056 independent reflections
2895 reflections with $I > 2\sigma(I)$
R_{int} = 0.024

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.041
$wR(F^2)$ = 0.124
S = 1.06
4056 reflections
165 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.36 e Å^{-3}
$\Delta\rho_{min}$ = −0.38 e Å^{-3}

The formyl H atom in (II) was located in a difference map and then freely refined, giving a C—H distance of 1.009 (18) Å. All other H atoms were treated as riding atoms, with C—H = 0.95 (aromatic), 0.98 (CH_3), 0.99 (CH_2) or 1.00 Å (aliphatic CH). Individual isotropic displacement parameters were refined for all H atoms.

For both compounds, data collection: *APEX2* (Bruker, 2004); cell refinement: *APEX2* and *SAINT* (Bruker, 2004); data reduction: *SAINT* and *XPREP* (Bruker, 2004); program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *PLATON* (Spek, 2009); plane calculations: *PARST* in *WinGX* (Farrugia, 1999); software used to prepare material for publication: *PLATON*.

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

	(I)	(II)	(III)
N5—C6—C7—S1	3.51 (19)	8.26 (17)	−6.53 (19)
C6—C7—S1—C2	−61.14 (14)	−57.55 (12)	62.97 (13)
C7—S1—C2—C3	17.01 (15)	7.64 (11)	−70.33 (13)
S1—C2—C3—C4	63.58 (19)	68.82 (13)	63.33 (14)
C2—C3—C4—N5	−57.90 (19)	−55.25 (15)	−67.82 (17)
C3—C4—N5—C6	−41.69 (18)	−44.92 (15)	90.42 (16)
C4—N5—C6—C7	78.68 (17)	74.34 (15)	−69.68 (18)

Table 2
Ring-puckering parameters (Å, °) for (I)–(III).

	(I)	(II)	(III)
q_2	1.1591 (14)	1.1111 (12)	0.4783 (14)
q_3	0.0650 (15)	0.0313 (12)	0.7083 (14)
φ_2	151.43 (8)	146.09 (7)	332.25 (18)
φ_3	168.6 (14)	129.0 (2)	44.74 (12)

Table 3
Hydrogen-bond geometry (Å, °) for (I).

D—H···A	D—H	H···A	D···A	D—H···A
C10—H10···O16^{i}	0.95	2.43	3.263 (2)	146

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

Supplementary data for this paper are available from the IUCr electronic archives (Reference: GD3302). Services for accessing these data are described at the back of the journal.

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