

Absolute configuration and conformational disorder of a tricyclic thiosemicarbazone derivative

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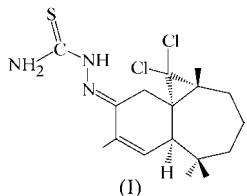
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The title compound, (1*S*,3*R*,8*R*)-2,2-dichloro-3,7,7,10-tetramethyltricyclo[6.4.0.0^{1,3}]dodecan-11-one thiosemicarbazone, C₁₇H₂₅Cl₂N₃S, has two disordered conformations of the cycloheptane moiety and a screw-boat conformation for the cyclohexene ring. The absolute configuration was established.

Comment

Thiosemicarbazone compounds exhibit well known pharmacological activities, such as selective inhibition of the herpes virus (Blumenkopf *et al.*, 1992) and inhibition of the human immunodeficiency virus (HIV) (Teitz *et al.*, 1994). Within the framework of the evaluation of Moroccan natural resources, we have undertaken the synthesis and characterization of such compounds. The dichlorocyclopropanation (Auhmani *et al.*, 2002; Eljamili *et al.*, 2002) of β -himachalene (Plattier & Teisseire, 1974), a major sesquiterpene isolated from the essential oil of *Atlantical Cedrus*, followed by oxidation using *N*-bromosuccinimide and condensation with thiosemicarbazide, led to the title compound, (I). The structure of (I) was elucidated by ¹H and ¹³C NMR spectroscopy and the absolute configuration established by single-crystal X-ray diffraction analysis.



The overall shape of the molecule of (I) can be described as two domains, *viz.* a globular hydrophobic core consisting of three substituted fused rings and an elongated hydrophilic thiosemicarbazone tail (Fig. 1). The absolute configuration of (I) was established without ambiguity from the anomalous

dispersion of the S and Cl atoms and confirmed that stereochemistry of the ring junction atoms as C1(*S*), C3(*R*) and C8(*R*) (Fig. 1). The cyclohexene ring is distorted and the puckering parameters (Cremer & Pople, 1975) show that its conformation is close to that of a screw-boat; the θ and φ angles calculated for the atom sequence C8–C9–C10–C11–C12–C1 are 67.7 (2) and 324.4 (3)°, respectively. The thiosemicarbazone substituent on the cyclohexene ring adopts a planar zigzag conformation, with the N–H bond *cis* to the C=N double bond and *trans* to the terminal NH₂ group. This latter group forms a single hydrogen bond with the S atom of a symmetry-related molecule at $(-\frac{1}{2} + x, \frac{1}{2} - y, 1 - z)$ (Table 1). The two remaining potential N–H donors are not involved in any inter- or intramolecular interactions and thus the hydrogen-bonding network within the crystal structure of (I) can be described as an extended chain along [100] (Fig. 2).

Interestingly, the solid-state structure of (I) reveals the presence of conformational disorder for the cycloheptane ring. Both the chair and boat conformations have been trapped randomly during the crystallization process and the chair conformation occurs in 63.6 (6)% of the molecules. The chair conformation of seven-membered rings is known to be more stable than the boat conformation by a few kcal mol⁻¹ (Elieil *et al.*, 1994; 1 kcal mol⁻¹ = 4.184 kJ mol⁻¹). Thus, the relative proportion of both conformers observed within the crystal of (I) may reflect the statistical partitioning of the two populations of cycloheptane structures corresponding to different energetic states.

Another point of interest is the comparison of the molecular structure of (I) with that of its parent compound, (II) (*i.e.* without the thiosemicarbazone substituent), which was reported by Auhmani *et al.* (1999). In this latter structure, no conformational disorder was observed and the cycloheptane ring adopts a boat conformation. The superposition of the boat conformation of (I) with compound (II) shows that they fit remarkably well; the r.m.s. deviation calculated with all pairs of corresponding C and Cl atoms of the three- and seven-membered rings, including the methyl substituents, is 0.070 Å. The main difference between the conformations of the two

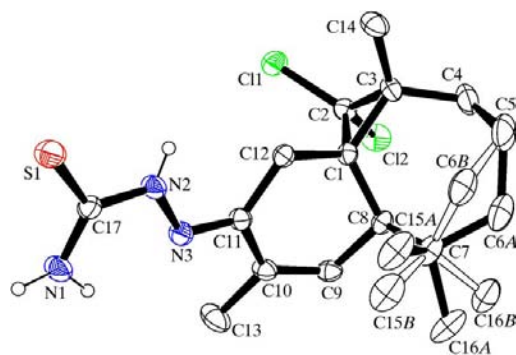


Figure 1

A view of (I), showing the atom-labelling scheme. Both cycloheptane ring conformations are depicted; the minor boat conformation is drawn with open bonds. Displacement ellipsoids are drawn at the 30% probability level. H atoms bonded to C atoms have been omitted for clarity.

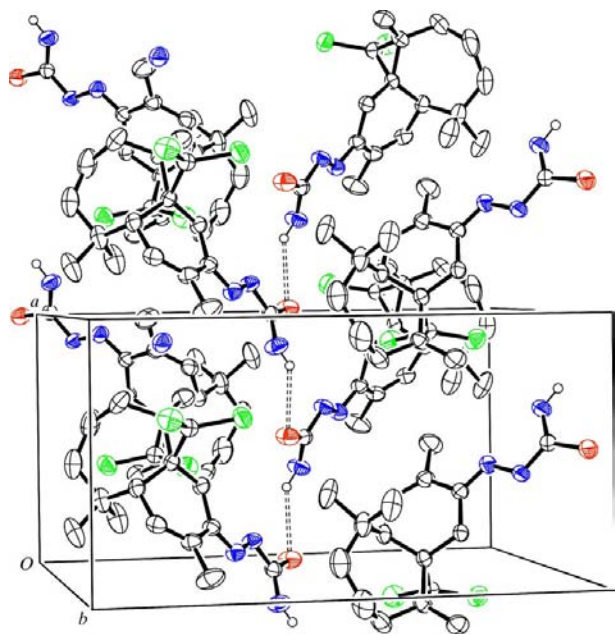


Figure 2
A view of the crystal packing of (I), showing the hydrogen-bonding network. Only the chair conformation of the cycloheptane is represented.

molecules is observed for the cyclohexene ring. The θ and φ puckering parameters for the cyclohexene ring of (II) [with the same reference atoms as used for (I)] are 53.5 (4) and 277.1 (4)°, respectively, and describe a distorted conformation between that of an envelope and a half-chair. The different hybridization character of the C atom, which bears the thiosemicarbazone moiety in (I) (sp^2 hybridization) and two H atoms in (II) (sp^3 hybridization) is responsible for this difference in ring conformation. On the basis of the superposition described above, we calculated the distance between C11 in (I) and its equivalent in (II) and found it to be 0.638 Å, while the five remaining atoms of the cyclohexene ring fit well (the mean distance between corresponding C atoms is 0.108 Å).

Experimental

The dichlorocyclopropanation of β -himachalene, a major sesquiterpene isolated from the essential oil of *Cedrus atlanticus*, was carried out using 1 equivalent of chloroform and excess sodium hydroxide in phase-transfer catalysis liquid–solid at 273 K for 2 h. The product obtained was dissolved in tetrahydrofuran (50 ml) and oxidized with 2 equivalents of *N*-bromosuccinimide at 273 K for 1 h. The condensation of an equimolar quantity of the resultant ketone with thiosemicarbazide and several drops of hydrochloric acid in ethanol gave (I) in 60% yield after heating under reflux for 5 h. Suitable crystals were obtained by evaporation of a hexane solution at 277 K. $^1\text{H NMR}$ (CDCl_3): δ 9.80, 8.00, 7.40 (3H, NH_2 and NH), 0.89 (3H, s), 1.01 (3H, s), 1.2–1.8 (6H, m), 4.90 (1H, d, $J = 7.9$ Hz), 1.82 (3H, s), 1.83 (3H, s), 2.60 (2H, AB system, $J = 18.3$ Hz); $^{13}\text{C NMR}$ (CDCl_3): δ 31.06 (C-1), 77.57 (C-2), 31.64 (C-3), 29.81 (C-4), 18.09 (C-5), 21.38 (C-6), 39.12 (C-7), 45.66 (C-8), 136.10 (C-9), 133.10 (C-10), 147.52 (C-11), 34.06 (C-12), 25.63 (C-13), 18.09 (C-14), 16.59 (C-15), 14.24 (C-16), 179.24 (C=O).

Crystal data

$\text{C}_{17}\text{H}_{25}\text{Cl}_2\text{N}_3\text{S}$
 $M_r = 374.38$
Orthorhombic, $P2_12_12_1$
 $a = 8.6379$ (2) Å
 $b = 13.3638$ (3) Å
 $c = 16.3161$ (3) Å
 $V = 1883.49$ (7) Å³
 $Z = 4$
 $D_x = 1.32$ Mg m⁻³

Data collection

Nonius KappaCCD area-detector diffractometer
 φ scans
22028 measured reflections
3671 independent reflections
3499 reflections with $I > 2\sigma(I)$

Refinement

Refinement on F^2
 $R[F^2 > 2\sigma(F^2)] = 0.029$
 $wR(F^2) = 0.072$
 $S = 1.08$
3671 reflections
237 parameters
H-atom parameters constrained
 $w = 1/[\sigma^2(F_o^2) + (0.029P)^2 + 0.5086P]$
where $P = (F_o^2 + 2F_c^2)/3$

Mo $K\alpha$ radiation
Cell parameters from 22028 reflections
 $\theta = 1.3$ – 26.0°
 $\mu = 0.46$ mm⁻¹
 $T = 293$ (2) K
Prism, colourless
 $0.6 \times 0.6 \times 0.4$ mm

$R_{\text{int}} = 0.036$
 $\theta_{\text{max}} = 26.0^\circ$
 $h = -10 \rightarrow 10$
 $k = -16 \rightarrow 16$
 $l = -19 \rightarrow 20$

$(\Delta/\sigma)_{\text{max}} < 0.001$
 $\Delta\rho_{\text{max}} = 0.16$ e Å⁻³
 $\Delta\rho_{\text{min}} = -0.18$ e Å⁻³
Extinction correction: *SHELXL97* (Sheldrick, 1997)
Extinction coefficient: 0.033 (3)
Absolute structure: Flack & Bernardinelli (1999, 2000), with 1566 Friedel pairs
Flack parameter: -0.04 (5)

Table 1

Hydrogen-bond geometry (Å, °).

$D-H \cdots A$	$D-H$	$H \cdots A$	$D \cdots A$	$D-H \cdots A$
$\text{N1}-\text{H1B} \cdots \text{S1}^i$	0.86	2.59	3.348 (2)	147

Symmetry code: (i) $x - \frac{1}{2}, -y + \frac{1}{2}, -z + 1$.

All H atoms were placed in geometrically idealized positions and constrained to ride on their parent atoms, with C–H distances in the range 0.93–0.98 Å, N–H = 0.86 Å and $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{parent atom})$. Additionally, the methyl groups were allowed to rotate freely about their parent C–C bond. The disordered atoms in the cycloheptane ring were refined using the SADI, DELU and SAME instructions of *SHELXL97* (Sheldrick, 1997) with an effective standard deviation of 0.005 in order to restrain the geometric parameters to chemically reasonable values. The site-occupancy factors of the chair and boat conformations refined to 0.636 (5) and 0.364 (5), respectively.

Data collection: *KappaCCD Server Software* (Nonius, 1997); cell refinement: *DENZO* and *SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO* and *SCALEPACK*; program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997); software used to prepare material for publication: *SHELXL97*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: LN1186). Services for accessing these data are described at the back of the journal.

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