Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

(–)-Parasantonic acid and its enol lactone, (+)-parasantonide: observation of the rare acid-to-acid catemeric hydrogen-bonding mode in a γ,ε-diketocarboxylic acid

Juan Zinczuk,[a]* Edmundo A. Ruveda,[a] Hugh W. Thompson[b] and Roger A. Lalancette[b]*

[a]Instituto de Quimica Organica de Sintesis (CONICET–UNR), Facultad de Ciencias Bioquimicas y Farmaceuticas, Suipacha 531, 2000 Rosario, Argentina, and [b]Carl A. Olson Memorial Laboratories, Department of Chemistry, Rutgers University, Newark, NJ 07102, USA
Correspondence e-mail: jzinczuk@fbioyf.unr.edu.ar, rogerlal@andromeda.rutgers.edu

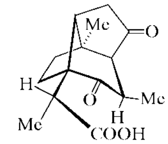
Received 4 March 2004
Accepted 7 April 2004
Online 11 May 2004

The title diketo acid, (−)-α,3a,7-trimethyl-5,8-dioxo-1,4-ethanoperhydropentalene-1-acetic acid, $C_{15}H_{20}O_4$, is shown to aggregate in the solid state as acid-to-acid hydrogen-bonded catemers, whose chains follow 2_1 screw axes from each carboxyl H atom to the C═O group of a neighboring carboxyl group [O···O = 2.672 (4) Å and O···H—O = 173°]. Two parallel counterdirectional screw-related single-strand hydrogen-bonded chains pass through the cell in the *a* direction. Two intermolecular C═O···H—C close contacts are present in this compound. Both this diketo acid and its enol lactone, (+)-parasantonide [systematic name: (−)-α,3a,7-trimethyl-5-oxo-1,4-ethenoperhydropentalene-1,8-carbolactone], $C_{15}H_{18}O_3$, have an *R* configuration at the methylated chiral center adjacent to the carboxyl group, unlike the precursor from which they are derived, *viz*. (−)-santonic acid.

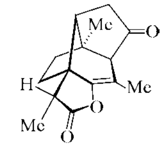
Comment

Our continuing interest in the crystal structures of solid ketocarboxylic acids lies in defining the molecular characteristics that control their various hydrogen-bonding modes. For simple keto acids, five modes are known, including two in which the ketone does not participate, *viz*. the common acid dimer and the rare acid-to-acid catemer motifs. Among factors that appear to discourage dimerization are: (i) restrictions in the conformations available and (ii) the presence of a single enantiomer. A factor that ought to favor carboxyl-to-ketone hydrogen-bonding patterns is: (iii) the presence of multiple ketone receptors for the hydrogen bond.

The title compounds are derived from a sesquiterpenoid isolate of *Artemisia*, (−)-α-santonin, whose transformations have provided rich subject material for numerous structural, analytical and synthetic studies (Cannizzaro, 1885; Woodward *et al.*, 1948; Mislow & Djerassi, 1960; Hirakura *et al.*, 1962). We have previously reported the structures of several keto acid santonin derivatives (Brunskill *et al.*, 1999, 2001, 2002; Thompson & Lalancette, 2003). We now report that the title compound, (I), embodying all of the features enumerated above, adopts the rare acid-to-acid catemeric hydrogen-bonding mode in the solid state. Like its isomer santonic acid (Brunskill *et al.*, 1999), (I) is a tricyclic γ,ε-diketo acid. It differs from santonic acid in the relative sizes of two of the rings in its tricyclic system and in the absolute configuration at the site adjacent to the carboxyl group, whose chirality is independent of the rest of the molecule. This center has an *S* configuration in santonic acid but an *R* configuration in (I) and its enol lactone, parasantonide, (II), whose structure we also report.



(I)



(II)

Fig. 1 shows the asymmetric unit of (I), with the atomic numbering scheme. The rigidity of the tricyclic framework means that conformationally significant rotations are possible only about the C1—C9 and C9—C10 bonds; the arrangement about the former is staggered, with the C9 methyl and γ-ketone groups *anti* to one another [C8—C1—C9—C11 = −176.6 (4)°]. The carboxyl group is rotated to a C1—C9—C10—O3 torsion angle of 146.0 (4)°, so that the carboxyl and γ-ketone carbonyl groups point in similar directions. The stereochemistry of the methyl group at atom C7 arises during the generation of (I), by hydrolysis of (+)-parasantonide, and evidently represents the thermodynamically favored configuration at this site (Woodward & Kovach, 1950).

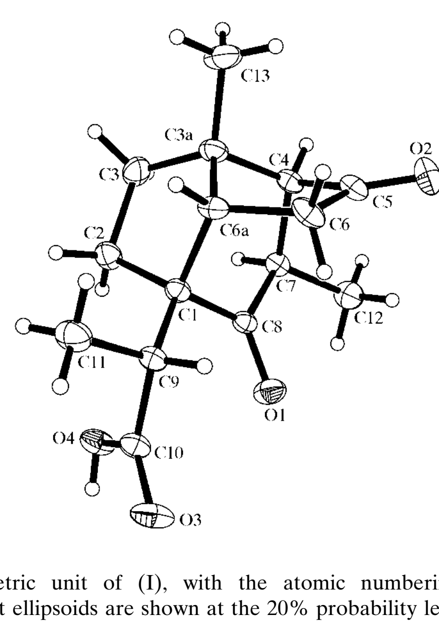


Figure 1
The asymmetric unit of (I), with the atomic numbering scheme. Displacement ellipsoids are shown at the 20% probability level.

  DOI: 10.1107/S010827010400839X

Averaging of C—O bond lengths and C—C—O angles by disorder, although common in carboxyl dimers, is not observed in any other keto acid aggregation mode, since other geometries cannot support the averaging processes involved. In (I), which is not dimeric, these C—O bond lengths are 1.227 (5) and 1.319 (5) Å, with angles of 122.1 (4) and 115.3 (3)° (Table 1). Our own survey of 56 keto acid structures that are not acid dimers gives average values of 1.20 (1) and 1.32 (2) Å, and 124.5 (14) and 112.7 (17)°, for these lengths and angles, in accordance with typical values of 1.21 and 1.31 Å, and 123 and 112°, cited for highly ordered dimeric carboxyls (Borthwick, 1980).

Fig. 2 illustrates the packing, which involves acid-to-acid catemers whose hydrogen bonding follows the 2_1 screw axis along *a*, from each carboxyl H atom to the C═O group of a neighboring carboxyl [O···O = 2.672 (4) Å and O—H···O = 173°; Table 2]. Two parallel counterdirectional single-strand chains pass through the cell in the *a* direction. This hydrogen-bonding mode is quite rare, with only three or four occurrences in the keto acid X-ray literature. Among the ~90 keto acids whose structures we have determined, this is only the second acid-to-acid catemer we have observed, the other also being a chiral non-racemate (Lalancette *et al.*, 1998), in common with all other instances that we are aware of.

We characterize the geometry of hydrogen bonding to carbonyl groups using a combination of the H···O═C angle and the H···O═C—C torsion angle. These describe the approach of the acid H atom to the receptor O atom in terms of its deviation from, respectively, C═O axiality (ideal = 120°) and planarity with the carbonyl group (ideal = 0°). In (I), the values for these two angles are 136.2 and −0.8°.

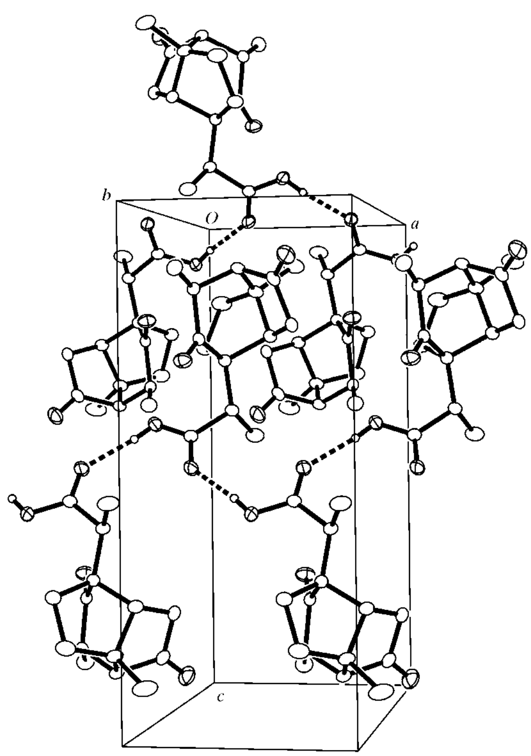


Figure 2
A partial packing diagram for (I), with extracellular molecules, illustrating the two parallel counterdirectional screw-related single-strand hydrogen-bonded chains passing through the cell in the *a* direction. All C-bound H atoms have been omitted for clarity. Displacement ellipsoids are shown at the 20% probability level.

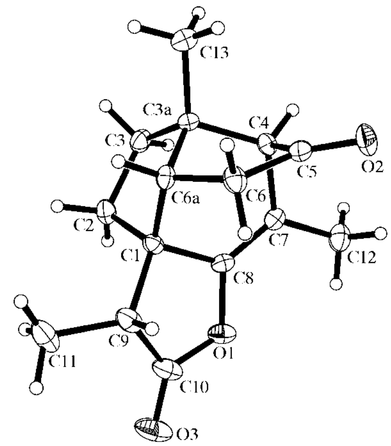


Figure 3
The asymmetric unit of (II), whose atomic numbering scheme follows that of (I). Displacement ellipsoids are shown at the 20% probability level.

Two intermolecular C═O···H—C close contacts exist for (I), involving atoms O1 (2.53 Å to H13*C*) and O3 (2.44 Å to H9*A*). These distances both lie within the 2.7 Å range we normally employ for non-bonded H···O packing interactions (Steiner, 1997). Using compiled data for a large number of C—H···O contacts, Steiner & Desiraju (1998) find significant statistical directionality, even as far out as 3.0 Å, and conclude that these are legitimately viewed as 'weak hydrogen bonds', with a greater contribution to packing forces than simple van der Waals attractions.

Fig. 3 shows the structure of (+)-parasantonide, (II), which is the synthetic precursor to (I) and is itself formed from (−)-santonic acid by acidic reflux and pyrolysis at temperatures of up to 573 K. All the major structural features of (I) may be seen in either obvious or incipient form in (II), including the *R* configuration at the C9 chiral center and the enollactone, which gives rise on hydrolysis to the carboxyl group, the γ-ketone and the stereochemistry at atom C7 in (I). The packing of (II) (Z = 4) lacks hydrogen bonding and involves no C—H···O contacts closer than 2.7 Å.

The solid-state (KBr) IR spectrum of (I) has absorption bands at 1743 (strained ε-ketone) and 1709 cm^{-1} (carboxyl C═O and γ-ketone). In $CHCl_3$ solution, the relative intensities and widths of these bands are altered, but the frequencies are unchanged.

Experimental

(−)-Santonic acid, derived from (−)-α-santonin of known absolute stereochemistry, was subjected to the acidic pyrolysis procedure described by Woodward & Kovach (1950). Crystals of (II) suitable for X-ray analysis (m.p. 376 K) were obtained from diisopropyl ether. Basic hydrolysis of (II), as described by the same source, then gave (I); crystals were obtained from methanol (m.p. 448 K).

Compound (I)

Crystal data

$C_{15}H_{20}O_4$
$M_r = 264.31$
Orthorhombic, $P2_12_12_1$
$a = 6.770$ (2) Å
$b = 13.160$ (3) Å
$c = 15.553$ (4) Å
$V = 1385.7$ (6) Å^3
$Z = 4$
$D_x = 1.267$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 30 reflections
$\theta = 2.6$–10.0°
$\mu = 0.09$ mm^{-1}
$T = 296$ (2) K
Block, colorless
0.46 × 0.25 × 0.11 mm

Data collection

Siemens *P*4 diffractometer
$2\theta/\omega$ scans
Absorption correction: numerical (*SHELXTL*; Sheldrick, 1997)
$T_{min} = 0.976$, $T_{max} = 0.990$
2846 measured reflections
1424 independent reflections
1065 reflections with $I > 2\sigma(I)$
$R_{int} = 0.048$
$\theta_{max} = 25.1°$
$h = -8 \rightarrow 8$
$k = -15 \rightarrow 15$
$l = -18 \rightarrow 18$
3 standard reflections every 97 reflections intensity variation: <3.5%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.050$
$wR(F^2) = 0.128$
$S = 1.06$
1424 reflections
173 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.049P)^2 + 0.3537P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.15$ e Å^{-3}
$\Delta\rho_{min} = -0.17$ e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.022 (4)

Table 1
Selected geometric parameters (Å, °) for (I).

O3—C10	1.227 (5)	O4—C10	1.319 (5)
O3—C10—C9	122.1 (4)	O4—C10—C9	115.3 (3)

Compound (II)

Crystal data

$C_{15}H_{18}O_3$
$M_r = 246.29$
Orthorhombic, $P2_12_12_1$
$a = 8.562$ (2) Å
$b = 11.656$ (3) Å
$c = 13.275$ (4) Å
$V = 1324.8$ (6) Å^3
$Z = 4$
$D_x = 1.235$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 33 reflections
$\theta = 2.3$–10.8°
$\mu = 0.09$ mm^{-1}
$T = 296$ (2) K
Block, colorless
0.24 × 0.17 × 0.06 mm

Data collection

Siemens *P*4 diffractometer
$2\theta/\theta$ scans
Absorption correction: numerical (*SHELXTL*; Sheldrick, 1997)
$T_{min} = 0.972$, $T_{max} = 0.990$
2891 measured reflections
1446 independent reflections
875 reflections with $I > 2\sigma(I)$
$R_{int} = 0.061$
$\theta_{max} = 25.6°$
$h = -10 \rightarrow 10$
$k = -14 \rightarrow 14$
$l = -16 \rightarrow 16$
3 standard reflections every 97 reflections intensity variation: <1.5%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.052$
$wR(F^2) = 0.093$
$S = 1.00$
1446 reflections
167 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0211P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.18$ e Å^{-3}
$\Delta\rho_{min} = -0.13$ e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.0148 (11)

Table 2
Hydrogen-bonding geometry (Å, °) for (I).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O4—H4···O3^i	0.82	1.86	2.672 (4)	172.9

Symmetry code: (i) $x - \frac{1}{2}, \frac{3}{2} - y, 2 - z$.

All H atoms for both (I) and (II) were found in electron-density difference maps but were placed in calculated positions for the C-bound H atoms (0.97 Å for the methylene H atoms, 0.98 Å for the methine H atoms and 0.96 Å for the methyl H atoms) and allowed to refine as riding on their respective C atoms [$U_{iso}(H) = 1.2U_{eq}(C)$]. The rotational parameters of all methyl groups in (II) were allowed to vary. The carboxy H atom was placed 0.82 Å from its O atom and was allowed to refine riding on its O atom with its displacement parameter fixed at 0.087 Å^2. The absolute configuration was not determinable for either (I) or (II) but is based on the reported absolute configuration of the synthetic starting material (see *Experimental*). Friedel pairs for both (I) and (II) were merged.

For both compounds, data collection: *XSCANS* (Siemens, 1996); cell refinement: *XSCANS*; data reduction: *XSCANS*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *SHELXP*97 (Sheldrick, 1997); software used to prepare material for publication: *SHELXL*97.

This paper is dedicated to Dr Eugene G. Kovach to acknowledge his long-standing interest in the chemistry of santonin derivatives. JZ and EAR thank Dr Kovach for a generous gift of santonin, and CONICET and UNR for financial support.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FR1475). Services for accessing these data are described at the back of the journal.

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