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(1′*R*,3*S*)-2-Oxo-1-(1′-phenylethyl)piperidine-3-carboxylic acid: a case of a very strong intramolecular hydrogen bond

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Key indicators

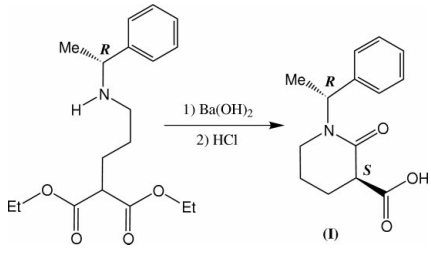
Single-crystal X-ray study
T = 296 K
Mean σ(C–C) = 0.007 Å
R factor = 0.044
wR factor = 0.132
Data-to-parameter ratio = 8.2

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

The title compound, $C_{14}H_{17}NO_3$, exhibits a very strong C═O···H—O intramolecular hydrogen bond, characterized by an O···H separation of 1.39 (7) Å and an O—H···O angle of 153 (5)°.

Comment

We are currently interested in the preparation of enantiopure 2-oxo-piperidines (Roa *et al.*, 2004), since they are useful starting materials for the asymmetric synthesis of some complex alkaloids and related compounds. As part of this project, we have synthesized (1′*R*)-2-oxo-1-(1′-phenylethyl)-piperidine-3-carboxylic acid (Micouin *et al.*, 1996), as an epimeric mixture at C3, by cyclization of an enantiopure malonic acid diethyl ester derivative (see *Experimental*). This epimeric mixture was purified and the main product, (I), was isolated and crystallized. Although modern NMR techniques are available for the assignment of absolute configuration (Seco *et al.*, 2004), we completed the characterization of (I) with a crystallographic study.



(I)

For (I) (Fig. 1), the absolute configuration at C3 is *S*, on the basis of the known configuration at C1′. The six-membered ring of the piperidine moiety exhibits the expected geometry (Table 1). The 2-oxo group induces a significant shortening of the formal σ bond N1—C2 [1.327 (5) Å], indicating a strong participation of the enolate tautomer in the solid state. This is also reflected in the bond length observed for the carbonyl group, C2═O7 = 1.252 (4) Å. Such a geometry is common for 2-piperidones (*e.g.* Forns *et al.*, 1999; Kende *et al.*, 2001; Christoffers *et al.*, 2003) and related bicyclic compounds (*e.g.* Amat *et al.*, 2003; Roa *et al.*, 2003). The geometry of the carboxylic acid group is also as expected and the position of the H atom of this group was reliably determined from the diffraction data.

The most striking feature of (I) is the very strong intramolecular hydrogen bond formed between the O—H group at C8 and the O atom of the carbonyl group at C2 (Fig. 1 and Table 2). This unusually short contact is greatly favoured by

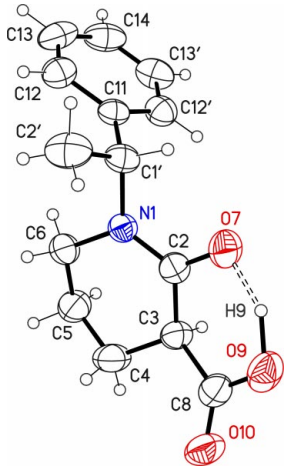


Figure 1
The structure of (I), with displacement ellipsoids at the 50% probability level. Atom H9 is represented as a sphere of arbitrary radius, although an isotropic displacement parameter was refined for this atom. The dashed line indicates the strong intramolecular hydrogen bond.

the conformation of the piperidine ring, bringing atoms O7 and O9 into much closer contact than the sum of their van der Waals radii [O7···O9 2.495 (5) Å]. The six-membered C2/C3/C8/O9/H9/O7 ring formed in this way should minimize the free energy for (I). Such a conformation is similar to that found in enol tautomers of 1,3-propanediones and 3-substituted pentane-2,4-diones. Diffraction studies (Emsley, 1980; Emsley *et al.*, 1989) have shown that, for these compounds, the O···H separations range from 1.32 to 1.70 Å, comparable with the O···H separation of 1.39 (7) Å observed in (I). Even shorter contacts have been observed for related compounds, for instance O···H = 1.27 Å in the case of 2-carboxy-3-hydroxyphenalenone (Sugawara *et al.*, 1992).

As expected, the lengthening of the covalent O9—H9 bond [1.17 (7) Å] places atom H9 close to the midpoint of the formal donor and acceptor atoms, giving some hydroxyl character to atom O7. This structural feature has an important consequence for the reactivity of (I), in that reduction of the carbonyl functionality at C2 should be facilitated. In contrast, the same reaction carried out with the epimer (1′*R*,3*R*), *i.e.* with the carboxylic group in the axial position at C3, should require stronger conditions, since the conformation of the 2-piperidone then precludes the formation of an intramolecular hydrogen bond. This prediction assumes that the hydrogen bond for (I) also exists in solution, a reasonable hypothesis when considering the strength of this contact. This assumption is also supported by spectroscopic data; indeed, we were unable to detect a ^{1}H NMR signal for H9. We attribute this lack of signal to a very efficient spin–spin relaxation mechanism with a neighbouring nucleus, resulting in severe line broadening for H9. This is in agreement with the strong localization observed for H9 in the solid state, as reflected in the small displacement parameter for this atom, U_{iso} = 0.136 (19) Å^2. These observations allow one, for instance, to discount the possibility of formation of hydrogen-bonded dimers in solution for (I), at least in polar solvents (Moulton & Zaworotko, 2001).

In conclusion, (I) is a clear illustration of the 'resonance-assisted hydrogen bond' concept, first introduced by Gilli and co-workers (Gilli *et al.*, 1989; Jeffrey, 1997). The 2-piperidone, *via* its enolic form, assists the formation of an intramolecular hydrogen bond, which, in turn, increases the contribution of this tautomer. We hope that this feedback phenomenon will provide a potential entry to the synthesis of enantiomerically pure 3-substituted piperidines.

Experimental

To a solution of $Ba(OH)_2$ (0.515 g, 3.012 mmol) in MeOH (300 ml) was added a solution of 2-[3*R*-(1-phenylethylamino)propyl]malonic acid diethyl ester (0.807 g, 2.51 mmol) in MeOH (10 ml). The mixture was stirred for 4 h at 293 K. The mixture was then treated with HCl to give pH = 6–7 and the solvent was removed *in vacuo*, giving a viscous oil, which was washed with a CH_2Cl_2–MeOH mixture (3:1). The resulting solution was filtered and the solvent removed *in vacuo*, giving an epimeric mixture of (1′*R*)-2-oxo-1-(1′-phenylethyl)-piperidine-3-carboxylic acid (yield 60%) and a byproduct, identified as (1′*R*)-(1′-phenylethyl)-2-oxo-piperidine. Separation by flash chromatography (CH_2Cl_2–MeOH, 95:5) afforded (I) as the main product (yield from starting material 40%). Single crystals were obtained from a solution in diethyl ether–CH_2Cl_2 (2:1). Analysis: $[\alpha]_D^{20}$ = +20 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, δ, p.p.m.): 1.68 (*d*, 3H, H2′), 1.70–1.90 (*m*, 2H, H5), 2.00–2.35 (*m*, 2H, H4), 2.80–3.00 (*m*, 1H, H6), 3.20 (*m*, 1H, H6), 3.37 (*m*, 1H, H3), 6.05 (*q*, 1H, H1′), 7.10.1–7.30 (*m*, 5H, Ph); ^{13}C NMR (100.6 MHz, $CDCl_3$, δ, p.p.m.): 15.50 (C2′), 21.76 (C5), 23.27 (C4), 42.25 (C6), 45.10 (C3), 51.56 (C1′), 126–128 (5C, Ph), 138.70 (C-*ipso*), 169.20 (C8), 170.30 (C2).

Crystal data

$C_{14}H_{17}NO_3$
M_r = 247.29
Orthorhombic, $P2_12_12_1$
a = 6.1413 (11) Å
b = 10.2111 (12) Å
c = 21.174 (3) Å
V = 1327.8 (3) Å^3
Z = 4
D_x = 1.237 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 52 reflections
θ = 3.9–10.6°
μ = 0.09 mm^{-1}
T = 296 (1) K
Plate, colourless
0.60 × 0.30 × 0.08 mm

Data collection

Bruker *P*4 diffractometer
$2\theta/\omega$ scans
2838 measured reflections
1382 independent reflections
779 reflections with $I > 2\sigma(I)$
R_{int} = 0.036
θ_{max} = 25.0°
$h = -7 \rightarrow 6$
$k = -1 \rightarrow 12$
$l = -25 \rightarrow 1$
3 standard reflections
every 97 reflections
intensity decay: 2.5%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.044
$wR(F^2)$ = 0.132
S = 0.98
1382 reflections
168 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0691P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.16 e Å^{-3}
$\Delta\rho_{min}$ = −0.13 e Å^{-3}
Extinction correction: *SHELXTL-Plus* (Sheldrick, 1998)
Extinction coefficient: 0.023 (5)

Table 1
Selected geometric parameters (Å, °).

N1—C2	1.327 (5)	C4—C5	1.456 (6)
N1—C6	1.476 (5)	C5—C6	1.456 (6)
N1—C1′	1.477 (5)	O7—H9	1.39 (7)
C2—O7	1.252 (4)	C8—O9	1.316 (6)
C2—C3	1.517 (6)	C8—O10	1.211 (5)
C3—C4	1.497 (6)	O9—H9	1.17 (7)
C3—C8	1.517 (6)		
C2—N1—C6	123.3 (3)	C5—C4—C3	112.9 (4)
C2—N1—C1′	119.3 (3)	C4—C5—C6	114.6 (4)
C6—N1—C1′	117.3 (3)	C5—C6—N1	114.9 (4)
O7—C2—N1	121.2 (4)	C2—O7—H9	102 (2)
O7—C2—C3	119.0 (4)	O10—C8—O9	121.4 (4)
N1—C2—C3	119.7 (3)	O10—C8—C3	121.5 (5)
C4—C3—C8	112.5 (4)	O9—C8—C3	117.1 (5)
C4—C3—C2	114.5 (4)	C8—O9—H9	105 (3)
C8—C3—C2	114.3 (4)		

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O9—H9···O7	1.17 (7)	1.39 (7)	2.495 (4)	153 (5)

Atom H9 was found in a difference map and was refined freely. No evidence for disorder was found for this site. H atoms bonded to C atoms were placed in idealized positions, with C—H distances of 0.93 for aromatic CH, 0.96 for methyl CH_3, 0.97 for methylene CH_2 and 0.98 Å for methine CH, and refined using a riding model, with $U_{iso}(H) = 1.2U_{eq}(C)$ for aromatic CH, methine CH and methylene CH_2, and $1.5U_{eq}(C)$ for methyl CH_3. In the absence of significant anomalous scattering effects, Friedel pairs were merged. The absolute configuration was assigned on the basis of the known configuration of the starting material.

Data collection: *XSCANS* (Siemens, 1996); cell refinement: *XSCANS*; data reduction: *XSCANS*; program(s) used to solve structure: *SHELXTL-Plus* (Sheldrick, 1998); program(s) used to refine structure: *SHELXTL-Plus*; molecular graphics: *SHELXTL-Plus*; software used to prepare material for publication: *SHELXTL-Plus*.

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