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# Preparation and structural analysis of (±)-*threo*-ritalinic acid

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Hydrolysis of the methyl ester (±)-*threo*-methyl phenidate afforded the free acid in 40% yield, *viz.* (±)-*threo*-ritalinic acid, $C_{13}H_{17}NO_2$. Hydrolysis and subsequent crystallization were accomplished at pH values between 5 and 7 to yield colourless prisms which were analysed by X-ray crystallography. Crystals of (±)-*threo*-ritalinic acid belong to the $P2_1/n$ space group and form intermolecular hydrogen bonds. An antiperiplanar disposition of the H atoms of the (HOOC−)CH−$CH_{py}$ group (py is pyridine) was found in both the solid (diffraction analysis) and solution state (NMR analysis). It was also determined that (±)-*threo*-ritalinic acid conforms to the minimization of negative *gauche*$^+$–*gauche*$^-$ interactions.

**Keywords: crystal structure; (±)-*threo*-ritalinic acid; (±)-*threo*-methyl phenidate; hydrolysis; Ritalin®; *gauche*$^+$–*gauche*$^-$ interactions.**

## 1. Introduction

(±)-*threo*-Methyl phenidate hydrochloride, denoted (±)-*threo*-**1**·HCl (see Fig. 1), which is also known as Ritalin® (Novartis), is a stimulant and the worldwide drug of choice for children and adults affected by attention deficit hyperactivity disorder (ADHD) but it is also used for the treatment of narcolepsy and cancer-related fatigue (Leonard *et al.*, 2004). The therapeutic effects of enhanced attention, organization, planning, motivation and motor control arise from blocking of the re-uptake of dopamine into the presynaptic neurons of the basal ganglia and frontal cortex (Ding *et al.*, 1997; Kimko *et al.*, 1999; Scahill *et al.*, 2004). The (*R*,*R*)-*threo*-stereoisomer of **1** is the biologically active isomer (Szporny & Görög, 1961) and the major metabolite of **1** is *threo*-α-phenylpiperidine-2-acetic acid (*threo*-ritalinic acid, *threo*-**2**). The enzymatic hydrolysis of Ritalin® by the human enzyme carboxyl esterase 1A1 (CES1A1), mainly present in the liver and fatty tissue, has a stereochemical preference for the (*S*,*S*)-enantiomer (Hendley *et al.*, 1972; Patrick *et al.*, 1987; Srinivas *et al.*, 1993; Sun *et al.*, 2004; Thomsen *et al.*, 2012). (±)-*threo*-**2** shows low lipophilicity (logP 1.88) compared to (±)-*threo*-**1** (logP 3.31) and has modest pharmacological activity (Letzel *et al.*, 2010).

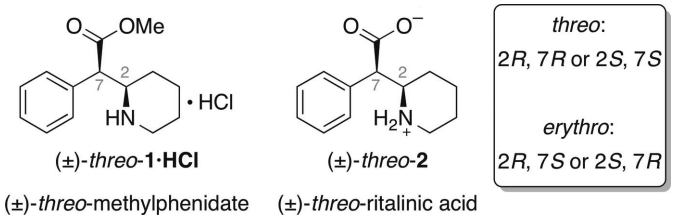


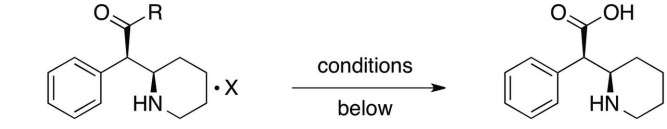

**Figure 1**
The structures of (±)-*threo*-ritalinic acid [(±)-*threo*-**2**] and its methyl ester [(±)-*threo*-**1**·HCl].

## 2. Experimental

### 2.1. Synthesis and crystallization

Three methods for the preparation of 2-phenyl-2-(piperidin-2-yl)acetic acid (ritalinic acid, **2**) are described.

**2.1.1. Method A**. At ambient temperature and open to air, a one-necked round-bottomed flask was charged with methyl 2-phenyl-2-(piperidin-2-yl)acetate (methyl phenidate; 100 mg, 0.42 mmol) and hydrochloric acid (6 *M*, aqueous, 1 ml) and the resulting heterogeneous mixture was allowed to heat (oil bath temperature 403 K) and was stirred for 1.3 h, during which time the mixture became colourless and completely homogeneous. After this time, the mixture was allowed to cool to ambient temperature and the pH was adjusted using aqueous NaOH (4 *M*) to 3 to yield a white precipitate which was identified as the title compound (yield 21 mg, 0.1 mmol, 21%). IR (neat): 2938, 1653, 1565, 1380, 1340, 1031, 710, 695 cm$^{-1}$; $^1$H NMR ($D_2O$, 400 MHz): δ 7.46–7.39 (*m*, 3H, Ph), 7.33–7.30




| Entry | SM | Reagent | Temp. (°C) | Time (h) | pH | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | **3·x$H_2O$** | aq. HCl | 110 | 7 | - | 0 |
| 2 | **3·x$H_2O$** | aq. $H_2SO_4$ | 85 | 8.5 | - | 0 |
| 3 | **3·x$H_2O$** | aq. NaOH/ MeOH | 130 | 23 | - | 0 |
| 4 | **1·HCl** | aq. HCl | 130 | 1.5 | 6 | 22 |
| 5 | **1·HCl** | aq. KOH/EtOH | rt | 20 | 5 | 40 |
| 6 | **1·HCl** | LiOH·$H_2O$/ THF:$H_2O$ | rt | 20 | 7 | 36 |

**Figure 2**
The synthesis of (±)-*threo*-**2** from (±)-*threo*-**1**·HCl.

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**Table 1**
Experimental details.

| | |
|---|---|
| Crystal data | |
| Chemical formula | $C_{13}H_{17}NO_2$ |
| $M_r$ | 219.28 |
| Crystal system, space group | Monoclinic, $P2_1/n$ |
| Temperature (K) | 100 |
| $a, b, c$ (Å) | 13.495 (3), 5.6335 (12), 15.721 (4) |
| $\beta$ (°) | 109.368 (8) |
| $V$ (Å$^3$) | 1127.5 (4) |
| $Z$ | 4 |
| Radiation type | Mo $K\alpha$ |
| $\mu$ (mm$^{-1}$) | 0.09 |
| Crystal size (mm) | 0.14 × 0.05 × 0.02 |
| Data collection | |
| Diffractometer | Bruker APEXII CCD diffractometer |
| Absorption correction | Multi-scan (*SADABS*; Bruker, 2006) |
| $T_{min}$, $T_{max}$ | 0.988, 0.998 |
| No. of measured, independent and observed [$I > 2\sigma(I)$] reflections | 10280, 2603, 1482 |
| $R_{int}$ | 0.097 |
| (sin $\theta/\lambda)_{max}$ (Å$^{-1}$) | 0.652 |
| Refinement | |
| $R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, $S$ | 0.065, 0.143, 1.12 |
| No. of reflections | 2603 |
| No. of parameters | 213 |
| H-atom treatment | All H-atom parameters refined |
| $\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å$^{-3}$) | 0.27, −0.28 |

Computer programs: *APEX2* (Bruker, 2006), *SAINT* (Bruker, 2006), *SHELXS97* (Sheldrick, 2008), *OLEX2* (Dolomanov *et al.*, 2009), *SHELXL97* (Sheldrick, 2008), *PLATON* (Spek, 2009), *ORTEPIII* (Johnson & Burnett, 1996) and *SHELXTL* (Sheldrick, 2008).

(*m*, 2H, Ph), 3.61 (*d*, *J* = 9.3 Hz, 1H, H7) 3.55 (*ddm*, *J* = 2.8, 9.3 Hz, 1H, H2), 3.47 (*dm*, *J* = 12.8 Hz, 1H, H6e), 3.04 (*td*, *J* = 3.2, 12.8 Hz, 1H, H6a), 1.87–1.80 (*m*, 2H, H5 and H4), 1.63–1.61 (*m*, 2H, H3 and H5), 1.46–1.40 (*m*, 2H, H3 and H4); $^{13}$C NMR ($D_2O$, 100 MHz): δ 178.1 (0, C14), 136.8 (0, C8), 129.1 (1, 2C, C9 and C13), 128.4 (1, 2C, C10 and C12), 127.8 (1, C11), 59.2 (1, C2), 56.6 (1, C7), 44.9 (2, C6), 26.6 (2, C3), 22.0 (2, C5), 21.4 (2, C4). $^1$H NMR (NaOD/$D_2O$, 400 MHz): δ 7.34–7.25 (*m*, 5H, Ph), 3.22 (*d*, *J* = 10.3 Hz, 1H, H7), 2.95 (*ddm*, *J* = 2.3, 10.4 Hz, 2H, H2 and H6e overlapped), 2.59 (*td*, *J* = 2.8, 11.9 Hz, 1H, H6a), 1.60–1.49 (*m*, 2H, H4 and H5), 1.35–1.22 (*m*, 1H, H5), 1.20–1.07 (*m*, 2H, H3 and H4), 0.94–0.81 (*m*, 1H, H3); $^{13}$C NMR (NaOD/$D_2O$, 100 MHz): δ 180.5 (0, C14), 139.1 (0, C8), 128.6 (1, 2C, C9 and C13), 128.4 (1, 2C, C10 and C12), 127.0 (1, C11), 61.6 (1, C7), 58.5 (1, C2), 45.8 (2, C6), 28.6 (2, C3), 24.6 (2, C5), 23.7 (2, C4).

**2.1.2. Method B**. A round-bottomed flask at ambient temperature and open to air was charged with methyl 2-phenyl-2-(piperidin-2-yl)acetate (methyl phenidate; 104 mg, 0.44 mmol) and ethanol (absolute, 0.95 ml). The heterogeneous mixture was treated with aqueous KOH (20 wt%, 0.95 ml) to give a clear mixture which was allowed to stir for a further 19.3 h, after which time the EtOH was removed and the crude mixture treated with hydrochloric acid (4 *M*, aqueous) dropwise until the precipitate started to form at pH 5. The precipitate was washed with ice-cold water and dried to afford the title compound (yield 39.5 mg, 0.18 mmol, 40%) as colourless prisms.

**2.1.3. Method C**. A round-bottomed flask at ambient temperature and open to air was charged with methyl 2-phenyl-2-(piperidin-2-yl)acetate (methyl phenidate; 151 mg, 0.64 mmol) and a tetrahydrofuran–water (7.5:1 *v*/*v*) mixture (1 ml) was added followed by lithium hydroxide monohydrate (105 mg, 2.5 mmol). The resulting heterogeneous mixture was allowed to stir for a further 19.3 h, during which time the mixture formed two phases. After this time, the THF was removed and the crude mixture was diluted with water (1 ml) and treated with hydrochloric acid (4 *M*, aqueous) to adjust the pH to 7. After *ca* 5 min, a precipitate started to form. Colourless prisms were collected, washed with ice-cold water and dried to afford the title compound (yield 50.8 mg, 0.23 mmol, 36%). These crystals were used for the crystal structure analysis.

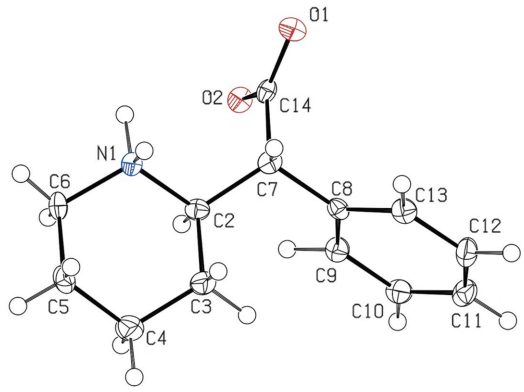


**Figure 3**
The molecular structure of (±)-*threo*-**2**, with displacement ellipsoids drawn at the 50% probability level for non-H atoms.

### 2.2. Refinement

Crystal data, data collection and structure refinement details are summarized in Table 1. All atoms could be localized and refined with reliable geometry, *i.e.* non-H atoms anisotropically and H atoms isotropically.

## 3. Results and discussion

The crystal structure of (±)-*threo*-**1**·HCl is reported to be challenging due to the significant atomic disorder observed (Glaser *et al.*, 1998) also by us[1], and other salts of (±)-*threo*-**1** and its derivatives have been reported (Froimowitz *et al.*, 1998; Glaser *et al.*, 1998; Steinberg *et al.*, 2011). We recently needed a sample of clinically relevant (±)-*threo*-**2** and in the course of its preparation we performed X-ray diffraction and NMR solution-state analysis which we now report.

The synthesis of (±)-*threo*-**2** has been described previously (Frigerio *et al.*, 2006) and it was accomplished in four steps from commercially available benzonitrile and 2-bromopyridine employing Rh-catalyzed reduction of the pyridine ring. For our purposes, commercially available amide and the methyl ester were obtained and the synthesis was envisioned

[1] In our laboratory, we obtained crystals of (±)-*threo*-**1**·HCl from MeOH (space group $Pna2_1$, $a$ = 20.781, $b$ = 9.198, $c$ = 7.378 Å); disorder and twinning did not allow satisfactory refinement of the structure. The structure was deposited with the Cambridge Structural Database under the deposition number 956413.

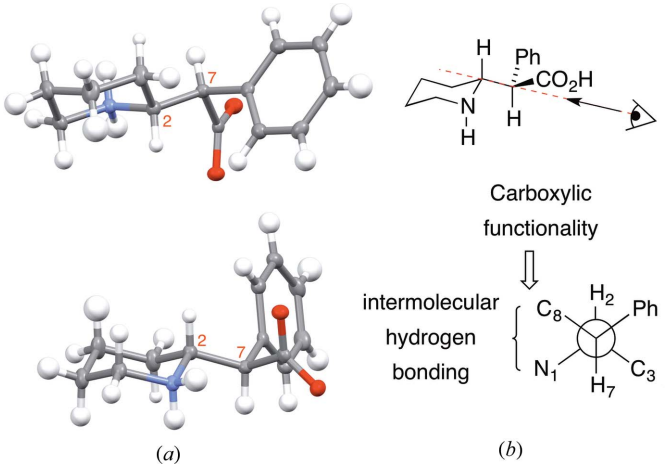


**Figure 4**
(*a*) The crystal structure of (±)-*threo*-**2**, showing the chair conformation of the piperidine ring and the antiperiplanar disposition of atoms H2 and H7. (*b*) A Newman projection of (±)-*threo*-**2** with the minimal number of *gauche*$^+$–*gauche*$^-$ interactions.

*via* the hydrolysis of the amide or the ester, respectively (Fig. 2). Acid- and base-promoted amide hydrolysis [for general acid-promoted amide hydrolysis, see: Fernandes *et al.* (2009); for conditions for acid hydrolysis of (±)-**2** amide, see: Frigerio *et al.* (2006); Jain *et al.* (2011)], contrary to literature reports, in our hands failed to yield a product even under harsh reaction conditions (Fig. 2, entries 1–3). As expected, hydrolysis of methyl ester (±)-*threo*-**1**·HCl [LiOH/THF/$H_2O$ (method C, §2.1.3) (Iliev *et al.*, 2006), KOH/EtOH (method B, §2.1.2) (Kato *et al.*, 2003) and synthesis of various (±)-**2** derivatives *via* ester hydrolysis (Misra *et al.*, 2010)] proceeded smoothly yielding the desired (±)-*threo*-**2** in moderate yields (entries 4–6). The yields are provided for the isolated product after crystallization. While at a pH of 5–6 the product crashed out of solution rapidly, at pH 7, crystallization was significantly slower, resulting in higher quality prisms.

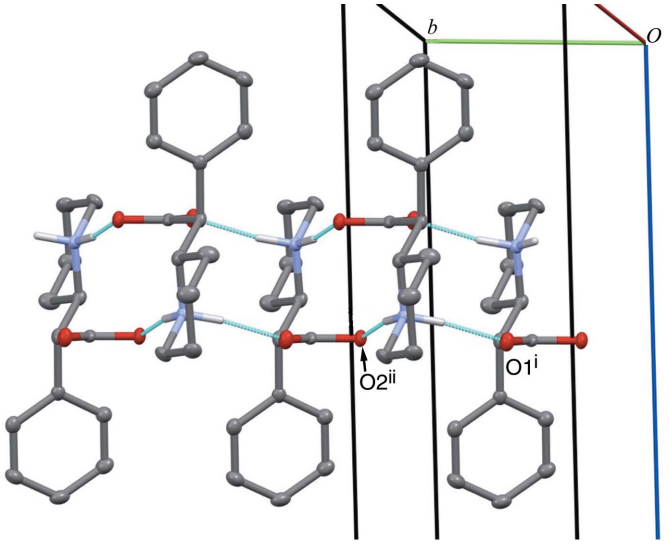


**Figure 5**
The intermolecular hydrogen bonding observed in (±)-*threo*-**2**, indicating the structural parameters of the observed bonding. The symmetry codes are as in Table 2.

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

| *D*—H···*A* | *D*—H | H···*A* | *D*···*A* | *D*—H···*A* |
|---|---|---|---|---|
| N1—H1*A*···O1$^{i}$ | 0.96 (3) | 1.73 (3) | 2.682 (3) | 172 (2) |
| N1—H1*B*···O2$^{ii}$ | 1.00 (4) | 1.74 (3) | 2.730 (3) | 171 (3) |

Symmetry codes: (i) $-x+2, -y+1, -z+1$; (ii) $-x+2, -y, -z+1$.

The X-ray crystal structure analysis revealed a monoclinic crystal system (space group $P2_1/n$) (Fig. 3). Despite the relatively small crystal size (0.14 × 0.05 × 0.02 mm), all atoms could be localized and refined with reliable geometry (non-H atoms were refined anisotropically and H atoms isotropically). The asymmetric unit contains the zwitterionic form of the molecule (Fig. 3) and the crystal quality allowed localization and refinement of all H atoms. Furthermore, the crystal structure reveals identical C—O bond lengths of 1.259 (3) and 1.260 (3) Å, which are typical for a carboxylate group.

In the crystal structure of (±)-*threo*-**2**, the piperidine ring adopts a chair conformation (Fig. 4) and the carboxylic acid group is disposed equatorially, similar to an observation made for a series of α-alkyl analogues of **1** reported by others (Froimowitz *et al.*, 1998; Glaser *et al.*, 1998; Steinberg *et al.*, 2011). Furthermore, in analogy to other *threo*-**1** derivatives, an antiperiplanar disposition of the H atoms of C2 and C7 was found, and the H2—C2—C7—H7 torsion angle of 174 (2)° (Fig. 4*a*) is in agreement with an average torsion angle of 175° for other α-alkyl methyl phenidates.

Steinberg and co-workers also describe avoidance of negative *gauche*$^+$–*gauche*$^-$ interactions between the pairs of bonds C2—C7/C7—C8 and C7—C8/C8—C9 which governs the conformational arrangement of substituents (Steinberg *et al.*, 2011). Under the same criteria, and in the absence of a methylene unit between atom C7 and the carboxylic acid group (C14 in this work and also described for some derivatives of Ritalin®; Glaser *et al.*, 1998), the carboxylic acid functionality in (±)-*threo*-**2** conforms to a synclinal position with respect to piperidine atom N1. This is the result of minimization of *gauche*$^+$–*gauche*$^-$ interactions in (±)-*threo*-**2** (Fig. 4*b*). The N1—C2—C7—C14 torsion angle is −63.3 (3)°, which in turn facilitates the intermolecular hydrogen bonding (or is facilitated by the hydrogen bonding). The crystal structure is characterized by two intermolecular hydrogen bonds (Table 2; indicated with dashed lines in Fig. 5) formed as *R*2 dimers and *C*2 chains. The two first level $R_2^2(12)$ patterns (Etter *et al.*, 1990) form two dimers with hydrogen bonding between N1···O1$^{i}$ and N1···O2$^{ii}$ over two crystallographic symmetry centres and a secondary chain pattern in the direction of the *b* axis (Fig. 5). In the structures of salts of (±)-*threo*-**1** and its derivatives, hydrogen bonding was observed between the ammonium H atoms and chloride counter-ions (Froimowitz *et al.*, 1998), resulting in a different crystal cell-packing motif, but maintaining an analogous conformation of the piperidine ring. Although (±)-*threo*-**2** exhibits similar properties, further comparison is limited due to the presence

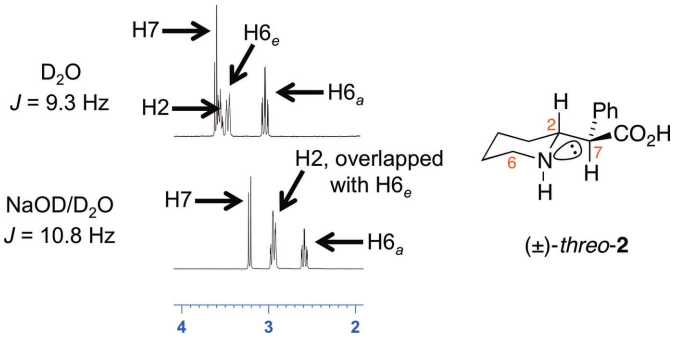


**Figure 6**
NMR analysis of (±)-*threo*-**2** in (*a*) $D_2O$ and (*b*) $NaOD/D_2O$.

of countrer-ions in reported structures of other (±)-*threo*-**1** analogues. For instance, hydrogen bonding between the piperidine N atom and the chloride anion in (±)-*threo*-**1**·HCl is 3.06 (1) or 3.34 (3) Å (see *Supplementary data* for a displacement ellipsoid plot and a hydrogen-bond diagram), significantly longer than in (±)-*threo*-**2** [2.682 (3) and 2.730 (3) Å].

Furthermore, the NMR structural data obtained for (±)-*threo*-**2** provided new insight into the geometry of (±)-*threo*-**2** in the solution state. The proton NMR analysis of (±)-*threo*-**2** was performed in $D_2O$ and $D_2O$/NaOD (the solution was prepared by addition of two drops of NaOD). NMR analysis was not performed in $CH_2Cl_2$, which was employed for derivatives of (±)-*threo*-**1** due to poor solubility of (±)-*threo*-**2**. Under the basic pH conditions, hydrogen bonding is disturbed resulting in the upfield proton shift (the opposite effect, *i.e.* downfield proton shift, was observed at acidic pH for a series of biquinolyl molecules; Blakemore *et al.*, 2008). Both NMR spectra are characterized by a H7 doublet and H2 which shows a small coupling constant as a result of 1,3-diaxial coupling with atom H6a. The analysis revealed coupling constants of 9.3 ($D_2O$) and 10.8 Hz ($D_2O$/NaOD) for adjacent H2 and H7 protons, suggesting an antiperiplanar arrangement[2] in the solution state (Fig. 6). This finding is in agreement with our solid-state structure in which antiperiplanar positions of H2 and H7 were also found, suggesting that minimization of *gauche*$^+$–*gauche*$^-$ interactions and the synclinal orientation of piperidine atom N1 and the carboxylic acid group allows for hydrogen bonding.

In conclusion, solid- and solution-state structure analysis of (±)-*threo*-**2** has been reported showing some interesting features of this important Ritalin® metabolite. Although chemically relatively simple, the crystal structure analysis of (±)-*threo*-**2** revealed intermolecular hydrogen bonding which is enabled by the minimization of *gauche*$^+$–*gauche*$^-$ interactions also resulting in an N1—C2—C7—C14 torsion angle of −63.3 (3)°. Additionally, an antiperiplanar arrangement of atoms H2 and H7 has been confirmed in both the solid and solution states.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: FM3004). Services for accessing these data are described at the back of the journal.

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[2] Based on the Karplus equation, coupling constant $J$ is 7–11 Hz for $\theta = 0°$ and $J$ = 8–15 Hz for $\theta = 180°$. Based on the coupling constant observed in $^1$H NMR of (±)-*threo*-**2**, $\theta \neq 90°$.

# supplementary materials

*Acta Cryst.* (2013). C**69**, 1225-1228 [doi:10.1107/S010827011302595X]

## Preparation and structural analysis of (±)-*threo*-ritalinic acid

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### Computing details

Data collection: *APEX2* (Bruker, 2006); cell refinement: *SAINT* (Bruker, 2006); data reduction: *SAINT* (Bruker, 2006); program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: OLEX2 (Dolomanov *et al.*, 2009) and *SHELXL97* (Sheldrick, 2008); molecular graphics: *PLATON* (Spek, 2009) and *ORTEPIII* (Johnson & Burnett, 1997); software used to prepare material for publication: *SHELXTL* (Sheldrick, 2008).

### (*R*,*R*)-2-Phenyl-2-(piperidin-2-yl)acetic acid

*Crystal data*

$C_{13}H_{17}NO_2$
$M_r = 219.28$
Monoclinic, $P2_1/n$
Hall symbol: -P 2yn
$a = 13.495$ (3) Å
$b = 5.6335$ (12) Å
$c = 15.721$ (4) Å
$\beta = 109.368$ (8)°
$V = 1127.5$ (4) Å$^3$
$Z = 4$
$F(000) = 472$
$D_x = 1.292$ Mg m$^{-3}$
Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
Cell parameters from 895 reflections
$\theta = 3.2$–$24.3°$
$\mu = 0.09$ mm$^{-1}$
$T = 100$ K
Rod, colourless
0.14 × 0.05 × 0.02 mm

*Data collection*

Bruker APEXII CCD diffractometer
Radiation source: fine-focus sealed tube
Graphite monochromator
$\varphi$ and $\omega$ scans
Absorption correction: multi-scan (*SADABS*; Bruker, 2006)
$T_{min} = 0.988$, $T_{max} = 0.998$
10280 measured reflections
2603 independent reflections
1482 reflections with $I > 2\sigma(I)$
$R_{int} = 0.097$
$\theta_{max} = 27.6°$, $\theta_{min} = 2.8°$
$h = -17 \rightarrow 17$
$k = -7 \rightarrow 6$
$l = -20 \rightarrow 20$

*Refinement*

Refinement on $F^2$
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)] = 0.065$
$wR(F^2) = 0.143$
$S = 1.12$
2603 reflections
213 parameters
0 restraints
Primary atom site location: structure-invariant direct methods
Secondary atom site location: difference Fourier map
Hydrogen site location: difference Fourier map
All H-atom parameters refined
$w = 1/[\sigma^2(F_o^2) + (0.0513P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.007$
$\Delta\rho_{max} = 0.27$ e Å$^{-3}$
$\Delta\rho_{min} = -0.28$ e Å$^{-3}$

*Special details*

**Geometry**. All e.s.d.'s (except the e.s.d. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell e.s.d.'s are taken into account individually in the estimation of e.s.d.'s in distances, angles and torsion angles; correlations between e.s.d.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell e.s.d.'s is used for estimating e.s.d.'s involving l.s. planes.

**Refinement**. Refinement of $F^2$ against ALL reflections. The weighted *R*-factor *wR* and goodness of fit *S* are based on $F^2$, conventional *R*-factors *R* are based on *F*, with *F* set to zero for negative $F^2$. The threshold expression of $F^2 > \sigma(F^2)$ is used only for calculating *R*-factors(gt) *etc*. and is not relevant to the choice of reflections for refinement. *R*-factors based on $F^2$ are statistically about twice as large as those based on *F*, and *R*- factors based on ALL data will be even larger.

*Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)*

| | *x* | *y* | *z* | $U_{iso}$*/$U_{eq}$ |
|---|---|---|---|---|
| O1 | 1.10921 (14) | 0.2562 (3) | 0.61033 (13) | 0.0188 (5) |
| O2 | 0.99451 (14) | −0.0390 (3) | 0.59486 (12) | 0.0173 (5) |
| N1 | 0.84435 (17) | 0.3000 (4) | 0.42549 (15) | 0.0149 (5) |
| H1A | 0.867 (2) | 0.458 (6) | 0.418 (2) | 0.037 (9)* |
| H1B | 0.903 (3) | 0.195 (6) | 0.423 (2) | 0.049 (10)* |
| C2 | 0.8278 (2) | 0.2914 (5) | 0.51527 (18) | 0.0162 (6) |
| H2 | 0.803 (2) | 0.131 (5) | 0.5193 (18) | 0.017 (7)* |
| C3 | 0.7376 (2) | 0.4585 (6) | 0.5116 (2) | 0.0238 (7) |
| H3A | 0.725 (2) | 0.446 (5) | 0.573 (2) | 0.031 (8)* |
| H3B | 0.759 (2) | 0.623 (6) | 0.507 (2) | 0.025 (8)* |
| C4 | 0.6384 (2) | 0.3989 (6) | 0.4352 (2) | 0.0265 (7) |
| H4A | 0.615 (2) | 0.235 (6) | 0.449 (2) | 0.035 (9)* |
| H4B | 0.579 (2) | 0.509 (5) | 0.4344 (19) | 0.030 (8)* |
| C5 | 0.6590 (2) | 0.4042 (6) | 0.34566 (19) | 0.0214 (7) |
| H5A | 0.599 (2) | 0.345 (5) | 0.300 (2) | 0.021 (8)* |
| H5B | 0.676 (2) | 0.569 (5) | 0.3305 (19) | 0.024 (8)* |
| C6 | 0.7487 (2) | 0.2388 (5) | 0.3486 (2) | 0.0197 (6) |
| H6A | 0.766 (2) | 0.254 (5) | 0.295 (2) | 0.021 (8)* |
| H6B | 0.731 (2) | 0.075 (5) | 0.3593 (19) | 0.024 (8)* |
| C7 | 0.9294 (2) | 0.3550 (5) | 0.58976 (18) | 0.0160 (6) |
| H7 | 0.948 (2) | 0.514 (5) | 0.5718 (18) | 0.017 (7)* |
| C8 | 0.9128 (2) | 0.3658 (4) | 0.68055 (18) | 0.0147 (6) |
| C9 | 0.8648 (2) | 0.1789 (5) | 0.71042 (19) | 0.0187 (6) |
| H9 | 0.837 (2) | 0.043 (5) | 0.6660 (18) | 0.019 (7)* |
| C10 | 0.8501 (2) | 0.1864 (5) | 0.7927 (2) | 0.0202 (6) |
| H10 | 0.814 (2) | 0.046 (6) | 0.814 (2) | 0.038 (9)* |
| C11 | 0.8852 (2) | 0.3802 (5) | 0.8488 (2) | 0.0222 (7) |
| H11 | 0.877 (2) | 0.380 (5) | 0.907 (2) | 0.038 (9)* |
| C12 | 0.9339 (2) | 0.5657 (5) | 0.82067 (19) | 0.0228 (7) |
| H12 | 0.958 (2) | 0.705 (5) | 0.858 (2) | 0.023 (8)* |
| C13 | 0.9474 (2) | 0.5600 (5) | 0.73721 (19) | 0.0189 (6) |
| H13 | 0.977 (2) | 0.698 (5) | 0.712 (2) | 0.036 (9)* |
| C14 | 1.0181 (2) | 0.1778 (5) | 0.59797 (17) | 0.0144 (6) |

*Atomic displacement parameters (Å²)*

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{12}$ | $U^{13}$ | $U^{23}$ |
|---|---|---|---|---|---|---|
| O1 | 0.0162 (10) | 0.0149 (10) | 0.0247 (11) | −0.0001 (8) | 0.0061 (8) | 0.0016 (8) |
| O2 | 0.0217 (10) | 0.0107 (9) | 0.0200 (11) | −0.0004 (8) | 0.0076 (8) | 0.0008 (8) |
| N1 | 0.0172 (12) | 0.0129 (12) | 0.0143 (12) | −0.0006 (10) | 0.0050 (10) | 0.0001 (9) |
| C2 | 0.0154 (14) | 0.0159 (14) | 0.0182 (15) | 0.0004 (12) | 0.0067 (12) | 0.0027 (11) |
| C3 | 0.0189 (16) | 0.0322 (18) | 0.0205 (17) | 0.0060 (14) | 0.0068 (13) | −0.0013 (14) |
| C4 | 0.0204 (17) | 0.036 (2) | 0.0229 (17) | 0.0062 (15) | 0.0062 (13) | 0.0031 (14) |
| C5 | 0.0198 (16) | 0.0242 (17) | 0.0154 (15) | 0.0022 (13) | −0.0007 (13) | 0.0010 (12) |
| C6 | 0.0222 (16) | 0.0194 (16) | 0.0148 (15) | −0.0038 (13) | 0.0024 (12) | −0.0057 (12) |
| C7 | 0.0186 (14) | 0.0115 (14) | 0.0193 (15) | −0.0013 (12) | 0.0083 (12) | 0.0002 (11) |
| C8 | 0.0124 (13) | 0.0139 (14) | 0.0155 (14) | 0.0024 (11) | 0.0016 (11) | 0.0014 (11) |
| C9 | 0.0200 (15) | 0.0180 (15) | 0.0177 (15) | 0.0010 (12) | 0.0057 (12) | 0.0008 (12) |
| C10 | 0.0186 (15) | 0.0230 (15) | 0.0193 (16) | 0.0016 (13) | 0.0068 (12) | 0.0050 (13) |
| C11 | 0.0256 (16) | 0.0267 (17) | 0.0146 (15) | 0.0067 (13) | 0.0071 (13) | 0.0043 (13) |
| C12 | 0.0271 (17) | 0.0225 (16) | 0.0165 (15) | 0.0013 (14) | 0.0044 (13) | −0.0044 (13) |
| C13 | 0.0194 (15) | 0.0155 (14) | 0.0203 (15) | 0.0040 (12) | 0.0044 (12) | 0.0023 (12) |
| C14 | 0.0199 (15) | 0.0130 (14) | 0.0120 (14) | −0.0015 (11) | 0.0075 (12) | 0.0003 (11) |

*Geometric parameters (Å, º)*

| | | | |
|---|---|---|---|
| O1—C14 | 1.260 (3) | C5—C6 | 1.517 (4) |
| O2—C14 | 1.259 (3) | C6—H6A | 0.95 (3) |
| N1—H1A | 0.96 (3) | C6—H6B | 0.98 (3) |
| N1—H1B | 1.00 (4) | C7—H7 | 0.99 (3) |
| N1—C2 | 1.501 (3) | C7—C8 | 1.518 (4) |
| N1—C6 | 1.487 (3) | C7—C14 | 1.530 (4) |
| C2—H2 | 0.97 (3) | C8—C9 | 1.397 (4) |
| C2—C3 | 1.524 (4) | C8—C13 | 1.390 (4) |
| C2—C7 | 1.522 (4) | C9—H9 | 1.02 (3) |
| C3—H3A | 1.04 (3) | C9—C10 | 1.373 (4) |
| C3—H3B | 0.98 (3) | C10—H10 | 1.04 (3) |
| C3—C4 | 1.511 (4) | C10—C11 | 1.385 (4) |
| C4—H4A | 1.02 (3) | C11—H11 | 0.95 (3) |
| C4—H4B | 1.01 (3) | C11—C12 | 1.382 (4) |
| C4—C5 | 1.522 (4) | C12—H12 | 0.97 (3) |
| C5—H5A | 0.95 (3) | C12—C13 | 1.384 (4) |
| C5—H5B | 1.00 (3) | C13—H13 | 1.01 (3) |
| | | | |
| H1A—N1—H1B | 105 (3) | N1—C6—H6B | 105.9 (16) |
| C2—N1—H1A | 107.4 (19) | C5—C6—H6A | 110.3 (16) |
| C2—N1—H1B | 113 (2) | C5—C6—H6B | 110.3 (16) |
| C6—N1—H1A | 109.6 (19) | H6A—C6—H6B | 113 (2) |
| C6—N1—H1B | 108 (2) | C2—C7—H7 | 103.7 (16) |
| C6—N1—C2 | 113.4 (2) | C2—C7—C14 | 113.1 (2) |
| N1—C2—H2 | 104.6 (16) | C8—C7—C2 | 110.9 (2) |
| N1—C2—C3 | 108.1 (2) | C8—C7—H7 | 111.0 (15) |
| N1—C2—C7 | 109.8 (2) | C8—C7—C14 | 107.6 (2) |
| C3—C2—H2 | 106.8 (16) | C14—C7—H7 | 110.7 (15) |

| | | | |
|---|---|---|---|
| C7—C2—H2 | 114.2 (16) | C9—C8—C7 | 121.0 (2) |
| C7—C2—C3 | 112.9 (2) | C13—C8—C7 | 120.8 (2) |
| C2—C3—H3A | 107.3 (16) | C13—C8—C9 | 118.2 (3) |
| C2—C3—H3B | 109.3 (17) | C8—C9—H9 | 116.1 (15) |
| H3A—C3—H3B | 106 (2) | C10—C9—C8 | 121.4 (3) |
| C4—C3—C2 | 112.2 (3) | C10—C9—H9 | 122.3 (15) |
| C4—C3—H3A | 110.6 (16) | C9—C10—H10 | 120.5 (18) |
| C4—C3—H3B | 110.8 (18) | C9—C10—C11 | 119.9 (3) |
| C3—C4—H4A | 106.6 (18) | C11—C10—H10 | 119.6 (17) |
| C3—C4—H4B | 111.3 (17) | C10—C11—H11 | 119.0 (19) |
| C3—C4—C5 | 110.2 (3) | C12—C11—C10 | 119.4 (3) |
| H4A—C4—H4B | 105 (2) | C12—C11—H11 | 121.6 (19) |
| C5—C4—H4A | 112.1 (17) | C11—C12—H12 | 121.0 (16) |
| C5—C4—H4B | 111.3 (17) | C11—C12—C13 | 120.8 (3) |
| C4—C5—H5A | 108.8 (17) | C13—C12—H12 | 118.2 (17) |
| C4—C5—H5B | 111.4 (16) | C8—C13—H13 | 116.6 (17) |
| H5A—C5—H5B | 110 (2) | C12—C13—C8 | 120.3 (3) |
| C6—C5—C4 | 110.4 (3) | C12—C13—H13 | 123.0 (17) |
| C6—C5—H5A | 106.3 (16) | O1—C14—O2 | 124.6 (2) |
| C6—C5—H5B | 109.4 (16) | O1—C14—C7 | 118.7 (2) |
| N1—C6—C5 | 110.6 (2) | O2—C14—C7 | 116.7 (2) |
| N1—C6—H6A | 107.1 (17) | | |

| | | | |
|---|---|---|---|
| N1—C2—C3—C4 | 56.2 (3) | C6—N1—C2—C7 | 179.7 (2) |
| N1—C2—C7—C8 | 175.7 (2) | C7—C2—C3—C4 | 177.8 (3) |
| N1—C2—C7—C14 | −63.3 (3) | C7—C8—C9—C10 | 179.6 (3) |
| C2—N1—C6—C5 | 57.8 (3) | C7—C8—C13—C12 | −178.6 (3) |
| C2—C3—C4—C5 | −57.1 (4) | C8—C7—C14—O1 | −99.4 (3) |
| C2—C7—C8—C9 | 51.1 (3) | C8—C7—C14—O2 | 78.2 (3) |
| C2—C7—C8—C13 | −130.5 (3) | C8—C9—C10—C11 | −1.4 (4) |
| C2—C7—C14—O1 | 137.8 (2) | C9—C8—C13—C12 | −0.1 (4) |
| C2—C7—C14—O2 | −44.6 (3) | C9—C10—C11—C12 | 0.7 (4) |
| C3—C2—C7—C8 | 55.1 (3) | C10—C11—C12—C13 | 0.3 (4) |
| C3—C2—C7—C14 | 176.0 (2) | C11—C12—C13—C8 | −0.5 (4) |
| C3—C4—C5—C6 | 55.6 (4) | C13—C8—C9—C10 | 1.1 (4) |
| C4—C5—C6—N1 | −55.7 (4) | C14—C7—C8—C9 | −73.0 (3) |
| C6—N1—C2—C3 | −56.8 (3) | C14—C7—C8—C13 | 105.4 (3) |

*Hydrogen-bond geometry (Å, º)*

| *D*—H···*A* | *D*—H | H···*A* | *D*···*A* | *D*—H···*A* |
|---|---|---|---|---|
| N1—H1*A*···O1$^{i}$ | 0.96 (3) | 1.73 (3) | 2.682 (3) | 172 (2) |
| N1—H1*B*···O2$^{ii}$ | 1.00 (4) | 1.74 (3) | 2.730 (3) | 171 (3) |

Symmetry codes: (i) −*x*+2, −*y*+1, −*z*+1; (ii) −*x*+2, −*y*, −*z*+1.