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Synthesis and Structural Analysis of (±)-Threo-ritalinic Acid

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Supporting Information: Experimental Procedures

**General techniques:** All chemicals were purchased from Aldrich, TCI or ABCR and used as received unless otherwise noted. Reported density values are for ambient temperature. (±)-Threo-methylphenidate was obtained from Ciba-Geigy.

$^1$H and $^{13}$C NMR spectra were recorded in Fourier transform mode at the field strength specified on Bruker Avance FT-NMR spectrometers. Spectra were obtained from the specified deuterated solvents in 5 mm diameter tubes. Chemical shift in ppm is quoted relative to residual solvent signals calibrated as follows: D$_2$O $\delta_H$ (H$_2$O) = 4.79 ppm. Multiplicities in the $^1$H NMR spectra are described as: s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintet, m = multiplet, b = broad; coupling constants are reported in Hz. Numbers in parentheses following carbon atom chemical shifts refer to the number of attached hydrogen atoms as revealed by the DEPT spectral editing technique.

**Chemistry**

(±)-**Threo-2-Phenyl-2-(piperidin-2-yl)acetic acid (±)-threo-ritalinic acid, (±)-threo-2):**

**Method A:** At ambient temperature, open to air one neck round bottom flask was charged with methyl 2-phenyl-2-(piperidin-2-yl)acetate (methylphenidate, 100 mg, 0.42 mmol) and hydrochloric acid (6 M, aq., 1 mL) and the resulting heterogeneous mixture was allowed to heat (oil bath temperature 130 °C) and stir over 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 aq. NaOH (4 M) to 3 to yield a white precipitate which was identified as the title compound (21 mg, 0.1 mmol, 21%): IR (neat) 2938, 1653, 1565, 1380, 1340, 1031, 710, 695 cm$^{-1}$; $^1$H NMR (D$_2$O, 400 MHz) $\delta$ ppm; $^{13}$C NMR (D$_2$O) $\delta$ ppm.

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S2
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) ppm.

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

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

References


Supporting Information: $^1$H and $^{13}$C NMR Spectra

$^1$H NMR spectra were recorded in Fourier transform mode at the field strength specified using standard 5 mm diameter tubes. Chemical shifts in ppm is quoted relative to residual solvent signals calibrated as follows: D$_2$O $\delta_H (H_2O) = 4.79$ ppm. Unless otherwise stated spectra were collected at ambient temperature.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$^1$H/$^{13}$C NMR</th>
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<tr>
<td>(s)-threo-2</td>
<td>400/100 MHz, D$_2$O</td>
<td>S5/6</td>
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<tr>
<td>(s)-threo-2</td>
<td>400/100 MHz, NaOD/D$_2$O</td>
<td>S7/8</td>
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</table>
SDM-V-033CR, D2O, 400MHz, 24.08.2012.

(±)-threo-2
C_{13}H_{17}NO_2
(219.28)

D_2O
SDM-V-033CR, D2O, 100MHz, 27.08.2012, not calibrated

(±)-threo-2
C_{13}H_{17}NO_2
(219.28)

D_2O
SDM-V-033CR, NaOD, D2O, 400MHz, 24.08.2012.

(±)-threo-2
C_{13}H_{17}NO_{2}
(219.28)

NaOD/D_{2}O

\begin{align*}
\text{ppm} & \quad 0 \quad 1 \quad 2 \quad 3 \quad 4 \quad 5 \quad 6 \quad 7 \quad 8 \quad 9 \quad 10
\end{align*}
SDM-V-033CR, NaOD/D2O, 100MHz, 27.08.2012., not calibrated

\((\pm)-\text{threo-2}\)

\(\text{C}_{13}\text{H}_{17}\text{NO}_2\)

(219.28)

NaOD/D2O
(±)-threo-2
(±)-threo-1·HCl
recrystallized from MeOH