2-(2-Naphthyloxy)acetate derivatives. II. A new class of antiamnesic agents

S. Thamotharan, V. Parthasarathi, P. Gupta, D. P. Jindal, P. Piplani and Anthony Linden

2-(2-Naphthyloxy)acetate derivatives. II. A new class of antiamnesic agents

S. Thamotharan,^{a} V. Parthasarathi,^{a*} P. Gupta,^{b}
D. P. Jindal,^{b}† and P. Piplani^b and Anthony Linden^c

^{a}Department of Physics, Bharathidasan University, Tiruchirappalli 620 024, India,
^{b}University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh
160 014, India, and ^{c}Institute of Organic Chemistry, University of Zürich,
Winterthurerstrasse 190, CH-8057 Zürich, Switzerland
Correspondence e-mail: vpsarati@yahoo.com

The title compounds, 4-(2-naphthyloxymethylcarbonyl)-
morpholine, $C_{16}H_{17}NO_3$, (I), and 4-methyl-1-(2-naphthyloxy-
methylcarbonyl)piperazine, $C_{17}H_{20}N_2O_2$, (II), are potential
antiamnesics. The morpholine ring in (I) and the piperazine
ring in (II) adopt chair conformations. In (I), the molecules are
linked by weak intermolecular C—H···O interactions into
chains that have a graph-set motif of $C(10)$, while in (II), the
molecules are linked by weak intermolecular C—H···O
interactions that generate two $C(7)$ graph-set motifs. The
dihedral angle between the naphthalene moiety and the best
plane through the morpholine ring is 20.62 (4)° in (I), while
the naphthalene moiety is oriented nearly perpendicular to
the mean plane of the piperazine ring in (II).

Comment

The conformation of molecules with antiamnesic activity has
attracted considerable interest (Amato *et al.*, 1991), and the
present structure determinations are part of our research
program on biologically active 2-(2-naphthyloxy)acetate
derivatives. We report here the preparation and the X-ray
crystal structures of 4-(2-naphthyloxymethylcarbonyl)mor-
pholine, (I), and 1-(2-naphthyloxymethylcarbonyl)-4-methyl-
piperazine, (II), both of which are new classes of antiamnesic
agents (Thamotharan *et al.*, 2003, and references therein).

(I)   (II)
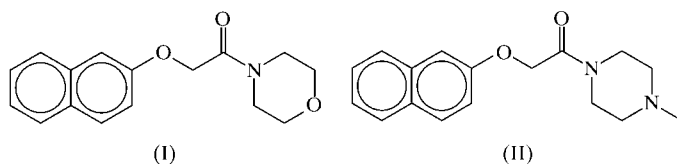
Views of the molecules of (I) and (II), with the atomic
numbering schemes, are shown in Figs. 1 and 2, respectively.

† Deceased.

The corresponding bond lengths and angles in (I) and (II)
are essentially equivalent and are comparable to those in
the related structures 1-(2-naphthyloxymethylcarbonyl)piperi-
dine and 3-methyl-1-(2-naphthyloxymethylcarbonyl)piperidine
(Thamotharan *et al.*, 2003). In the molecule of (I), the central
C2/O11/C12/C13/N14 fragment is planar, with a maximum
deviation of 0.023 (1) Å for atom C13. In contrast, only the
O11/C12/C13/N14 segment is planar in (II), while atom C2 is
twisted about the O11—C12 bond so that it lies almost
perpendicular to the O11/C12/C13/N14 plane (Table 3). In (I),
the central unit is almost coplanar with the naphthalene
moiety, the angle between the planes being 3.67 (7)°, while the
dihedral angle between the central unit and the naphthalene
moiety in (II) is 76.94 (15)°. The central unit is twisted
27.79 (14)° out of the mean plane of the piperazine ring in (II),
whereas it is twisted 21.73 (6)° out of the best plane passing
through the morpholine ring in (I). The C2—O11—C12—C13
and O11—C12—C13—N14 torsion angles show that the
central unit has an antiperiplanar conformation in (I), while
the corresponding torsion angles in (II) represent synclinal
and antiperiplanar conformations, respectively.

The morpholine ring in (I) has a chair conformation
[the Cremer & Pople (1975) puckering parameters are
$Q = 0.550$ (1) Å, $q_2 = 0.045$ (1) Å, $q_3 = 0.548$ (1) Å, $\theta =
4.7$ (1)° and $\varphi_2 = 345.8$ (19)° for the atom sequence O17—
C16—C15—N14—C19—C18]. The dihedral angle between
the naphthalene moiety and the morpholine ring is 20.62 (4)°.
In (II), the puckering parameters of the piperazine ring
[$Q = 0.5585$ (3) Å, $q_2 = 0.016$ (3) Å, $q_3 = 0.558$ (3) Å, $\theta =
0.7$ (3)° and $\varphi_2 = 131$ (10)° for the atom sequence N14—C15—
C16—N17—C18—C19] are indicative of a chair conformation,
and the methyl substituent at atom N17 is in an equatorial
position. The sum of the angles around N17 is 331°, revealing
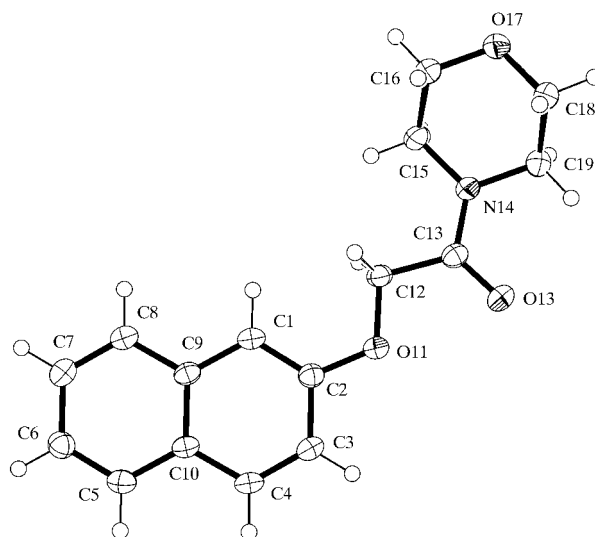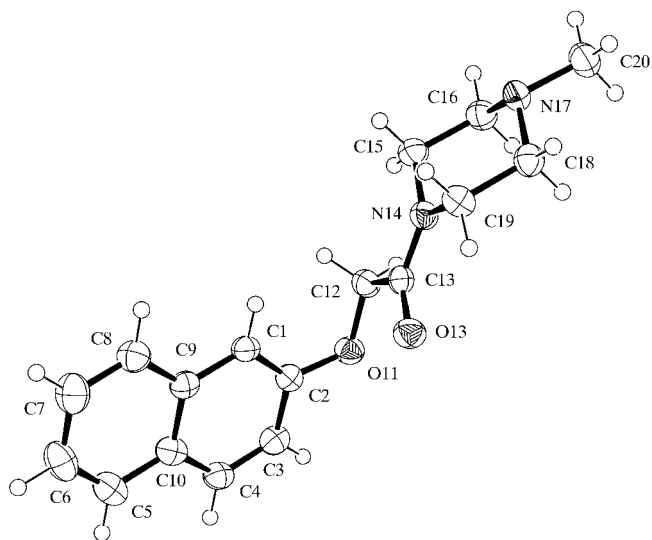an essentially pyramidal geometry at atom N17. In contrast,

Figure 1
A view of the molecule of (I), showing the atom-labelling scheme.
Displacement ellipsoids are drawn at the 50% probability level and H
atoms are represented by circles of arbitrary radii.

organic compounds

Figure 2
A view of the molecule of (II), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are represented by circles of arbitrary radii.

atom N14 in (I) and (II) does not exhibit a pyramidal geometry because of the amide-type cojugation with carbonyl atom O13. The sum of the angles around atom N14 in (I) and (II) is 360° (Tables 1 and 3). The naphthalene moiety is oriented nearly perpendicular to the mean plane of the piperazine ring.

The exocyclic C1—C2—O11 and C13—N14—C15 angles deviate significantly from the usual value of 120° (Tables 1 and 3), perhaps as a result of steric repulsion [H1···H121 = 2.21 Å (2.10 Å), H121···H151 = 2.25 Å (H121···H152 = 2.26 Å) and H122···H151 = 2.17 Å (H122···H152 = 2.11 Å); the values in parentheses correspond to (II)].

As can be seen from Table 2, in (I), atom C1 acts as a donor in a weak intermolecular C—H···O interaction with atom O17 of an adjacent molecule. This interaction links the molecules into chains that run parallel to the c axis and have a graph-set motif of $C(10)$ (Bernstein *et al.*, 1995).

In (II), atom C1 acts as a donor for a weak intermolecular C—H···O interaction with carbonyl atom O13 of an adjacent molecule (Table 4). This interaction produces a continuous chain that runs parallel to the c axis and has a graph-set motif of $C(7)$. In addition, atom C5 is involved in an intermolecular C—H···O interaction with atom O11 of a different molecule. This interaction links the molecules into a continuous chain that runs parallel to the a axis and has a graph-set motif of $C(7)$ (Bernstein *et al.*, 1995).

Experimental

For the preparation of (I), methyl 2-(2-naphthyloxy)acetate (0.5 g) was reacted with morpholine. The oily product obtained was treated with water, and the resulting precipitate was filtered off, dried and crystallized from acetone to afford crystals of (I) (yield 0.532 g,

84.8%; m.p. 416–418 K). For the preparation of (II), methyl 2-(2-naphthyloxy)acetate (0.5 g) was reacted with *N*-methylpiperazine. The oily product obtained was treated with water, and the resulting precipitate was filtered off, dried and crystallized from ethanol to afford crystals of (II) (yield 0.514 g, 78.17%; m.p. 383–385 K).

Compound (I)

Crystal data

$C_{16}H_{17}NO_3$	$D_x = 1.378$ Mg m^{-3}
$M_r = 271.31$	Mo $K\alpha$ radiation
Monoclinic, $P2_1/n$	Cell parameters from 4035
$a = 10.5594\ (2)$ Å	reflections
$b = 9.2956\ (2)$ Å	$\theta = 2.0$–$30.0°$
$c = 14.1012\ (3)$ Å	$\mu = 0.10$ mm^{-1}
$\beta = 109.0917\ (9)°$	$T = 160\ (2)$ K
$V = 1307.98\ (5)$ Å^3	Prism, colourless
$Z = 4$	$0.28 \times 0.25 \times 0.23$ mm

Data collection

Nonius KappaCCD diffractometer	$R_{int} = 0.060$
φ and ω scans with κ offsets	$\theta_{max} = 30.0°$
37 467 measured reflections	$h = 0 \rightarrow 14$
3815 independent reflections	$k = 0 \rightarrow 13$
2574 reflections with $I > 2\sigma(I)$	$l = -19 \rightarrow 18$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.089P)^2$
$R[F^2 > 2\sigma(F^2)] = 0.051$	$\quad + 0.0564P]$
$wR(F^2) = 0.148$	where $P = (F_o^2 + 2F_c^2)/3$
$S = 1.03$	$(\Delta/\sigma)_{max} < 0.001$
3815 reflections	$\Delta\rho_{max} = 0.36$ e Å^{-3}
181 parameters	$\Delta\rho_{min} = -0.26$ e Å^{-3}
H-atom parameters constrained	

Table 1
Selected bond and torsion angles (°) for (I).

C13—N14—C15	125.35 (11)	C15—N14—C19	113.52 (10)
C13—N14—C19	120.73 (10)	C1—C2—O11	125.24 (11)
C2—O11—C12—C13	177.19 (10)	O11—C12—C13—N14	178.29 (10)

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

D—H···A	D—H	H···A	D···A	D—H···A
C1—H1···O17^i	0.95	2.42	3.3359 (15)	161

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

Compound (II)

Crystal data

$C_{17}H_{20}N_2O_2$	Mo $K\alpha$ radiation
$M_r = 284.35$	Cell parameters from 1547
Orthorhombic, $Pca2_1$	reflections
$a = 13.7560\ (3)$ Å	$\theta = 2.0$–$25.0°$
$b = 12.7389\ (2)$ Å	$\mu = 0.08$ mm^{-1}
$c = 8.5031\ (2)$ Å	$T = 160\ (2)$ K
$V = 1490.05\ (5)$ Å^3	Plate, colourless
$Z = 4$	$0.23 \times 0.13 \times 0.07$ mm
$D_x = 1.268$ Mg m^{-3}	

Data collection

Nonius KappaCCD diffractometer	$R_{int} = 0.079$
ω scans with κ offsets	$\theta_{max} = 25.0°$
17 668 measured reflections	$h = -16 \rightarrow 16$
1414 independent reflections	$k = -15 \rightarrow 15$
1169 reflections with $I > 2\sigma(I)$	$l = -10 \rightarrow 10$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0575P)^2]$
$R[F^2 > 2\sigma(F^2)] = 0.039$	where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.095$	$(\Delta/\sigma)_{max} < 0.001$
$S = 1.06$	$\Delta\rho_{max} = 0.18$ e Å^{-3}
1414 reflections	$\Delta\rho_{min} = -0.16$ e Å^{-3}
192 parameters	Extinction correction: $SHELXL97$
H-atom parameters constrained	Extinction coefficient: 0.014 (3)

Table 3
Selected bond and torsion angles (°) for (II).

C13—N14—C15	126.0 (2)	C18—N17—C20	109.9 (2)
C13—N14—C19	121.2 (2)	C16—N17—C20	110.7 (2)
C15—N14—C19	112.4 (2)	C1—C2—O11	125.1 (2)
C18—N17—C16	110.0 (2)		
C2—O11—C12—C13	84.0 (3)	O11—C12—C13—N14	175.6 (2)

Table 4
Hydrogen-bonding geometry (Å, °) for (II).

D—H$\cdots$A	D—H	H$\cdots$A	$D\cdots$A	D—H$\cdots$A
C1—H1$\cdots$O13^{ii}	0.95	2.55	3.471 (3)	163
C5—H5$\cdots$O11^{iii}	0.95	2.49	3.236 (3)	135

Symmetry codes: (ii) $\frac{1}{2} - x, y, z - \frac{1}{2}$; (iii) $\frac{1}{2} + x, 1 - y, z$.

For compound (I), all H atoms were placed in idealized positions (C—H = 0.95–0.99 Å) and constrained to ride on their parent atoms, with U_{iso}(H) values of 1.2U_{eq}(C). For compound (II), methyl H atoms were constrained to an ideal geometry (C—H = 0.98 Å), with U_{iso}(H) values of 1.5U_{eq}(C), but were allowed to rotate freely about the C—C bond. All remaining H atoms were placed in idealized positions (C—H = 0.95–0.99 Å) and constrained to ride on their parent atoms, with U_{iso}(H) values of 1.2U_{eq}(C). Although the molecule is achiral, the structure possesses a polar axis. Because of the absence of any

significant anomalous scatterers in the compound, attempts to confirm the absolute structure by refinement of the Flack (1983) parameter in the presence of 1099 sets of Friedel equivalents led to an inconclusive value (Flack & Bernardinelli, 2000) of −0.1 (15) for this parameter. Therefore, the absolute direction of the polar axis was assigned arbitrarily and the Friedel pairs were merged before the final refinement. Reflection 110 was partially obscured by the beam stop and was omitted.

For both compounds, data collection: *COLLECT* (Nonius, 2000); cell refinement: *DENZO–SMN* (Otwinowski & Minor, 1997); data reduction: *DENZO–SMN* and *SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR*92 (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: *PARST*97 (Nardelli, 1995) and *PLATON* (Spek, 2003).

References

Altomare, A., Cascarano, G., Giacovazzo, C., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1994). *J. Appl. Cryst.* **27**, 435.
Amato, M. E., Bandoli, G., Grassi, A., Marletta, A. & Perly, B. (1991). *Eur. J. Med. Chem.* **26**, 443–448.
Bernstein, J., Davis, R. E., Shimoni, L. & Chang, N.-L. (1995). *Angew. Chem. Int. Ed. Engl.* **34**, 1555–1573.
Cremer, D. & Pople, J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354–1358.
Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.
Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
Flack, H. D. & Bernardinelli, G. (2000). *J. Appl. Cryst.* **33**, 1143–1148.
Nardelli, M. (1995). *J. Appl. Cryst.* **28**, 659.
Nonius (2000). *COLLECT.* Nonius BV, Delft, The Netherlands.
Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, *Macromolecular Crystallography*, Part A, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.
Sheldrick, G. M. (1997). *SHELXL97*. University of Göttingen, Germany.
Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.
Thamotharan, S., Parthasarathi, V., Malik, R., Jindal, D. P., Piplani, P. & Linden, A. (2003). *Acta Cryst.* C**59**, o422–o425.