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1-[2-(4-Nitrophenoxy)acetyl]pyrrolidin-2-one: an antiamnesic agent

S. Thamotharan,[a] V. Parthasarathi,[a]* R. Malik,[b] D. P. Jindal,[b]† 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

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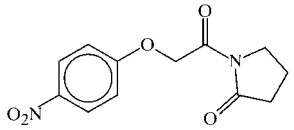
The title compound, $C_{12}H_{12}N_2O_5$, is a potential antiamnesic agent. The pyrrolidinone ring has an envelope conformation, and the central moiety is almost coplanar with the planes of the phenyl and pyrrolidinone rings. In the crystal structure, weak intermolecular C—H···O interactions link the molecules into a complex network that can be described by $R_2^2(X)$ rings (X = 16, 20 and 26) and a $C(12)$ chain.

Comment

The conformations of molecules with antiamnesic activity have attracted considerable interest (Amato, Bandoli, Grassi *et al.*, 1991). This paper is intended to further develop our studies on the conformational properties of cognition activators. Cognition activators are drugs currently employed for the symptomatic treatment of pathological brain aging phenomena, which are usually referred to as senile cognitive decline or age-associated memory impairment (Gamzu *et al.*, 1989; Bandoli *et al.*, 1992). In the light of the growing incidence of such illnesses among the older population, several families of compounds are being tested in laboratory and clinical trials. The nootropics (mind-targeted) family is the forerunner in the field (Giurgea, 1982), and the key feature of this family is the presence of the pyrrolidin-2-one ring. This moiety is a requisite for several active compounds currently used in therapy (piracetam, oxyracetam and pramiracetam). The ring-extended *N*-analogues of 2-pyrrolidinone, namely 3-aryl-2-piperazinone compounds, have been found to possess the characteristic nootropic pharmacological profile (Amato, Bandoli, Grassi *et al.*, 1991). The present paper reports the structure and conformation of the title compound, (I), which were determined in order to continue the investigation of a new class of antiamnesic agents (Thamotharan *et al.*, 2003*a*,*b*,*c*, 2003).

The pyrrolidine ring in nootropics typically has a half-chair (C_2, twist-envelope) conformation (Bandoli, Nicolini, Lumbroso *et al.*, 1987; Bandoli, Nicolini, Pappalardo *et al.*, 1987; Amato *et al.*, 1990; Amato, Bandoli, Dolmella *et al.*, 1991). In (I) (Fig. 1), however, the five-membered pyrrolidinone ring exhibits an envelope conformation, with atom C13 as the flap, a pseudorotation angle, Δ, of 86.6 (1)° and a maximum torsion angle, φ_m, of 31.5 (1)° for the atom sequence N10—C11—C12—C13—C14 (Rao *et al.*, 1981). The dihedral angle between the mean planes through the phenyl and pyrrolinone rings is 6.41 (3)°. The mean plane of the central moiety, C1—O7—C8—C9—N10, is oriented at angles of 2.16 (4) and 6.37 (5)° with respect to the planes of the phenyl and pyrrolidinone rings, respectively. The nitro group is almost coplanar with the adjacent phenyl ring. The slightly enlarged exocyclic O7—C1—C2 bond angle [124.69 (9)°] probably results from a repulsive interaction between the H atoms on atoms C2 and C8 (H2···H81 = 2.30 Å and H2···H82 = 2.25 Å). Otherwise, the bond lengths and angles show no unusual features. The C1—O7—C8—C9 [−176.59 (8)°] and O7—C8—C9—N10 [−178.72 (8)°] torsion angles show that the central moiety has an antiperiplanar conformation.



(I)

In the crystal structure, atoms C3 and C12 act as donors for weak intermolecular C—H···O interactions (Table 1) with carbonyl atom O11 of the pyrrolidinone ring and atom O16 of the nitro group of a neighbouring centrosymmetrically related molecule, respectively. Each interaction links the molecules individually into dimers that have graph-set motifs (Bernstein *et al.*, 1995) of $R_2^2(20)$ and $R_2^2(26)$, respectively (Fig. 2). Atom C5 is involved in an intermolecular C—H···O interaction with another carbonyl O atom (O9) of a different neighbouring centrosymmetrically related molecule. This interaction produces loops that have a graph-set motif of $R_2^2(16)$. Atom C14 forms a weak intermolecular C—H···O interaction with

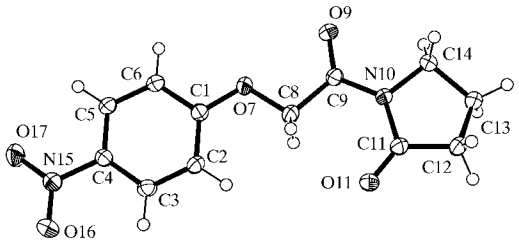


Figure 1
A view of the molecule of (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level. H atoms are represented by circles of arbitrary radii.

† Deceased.

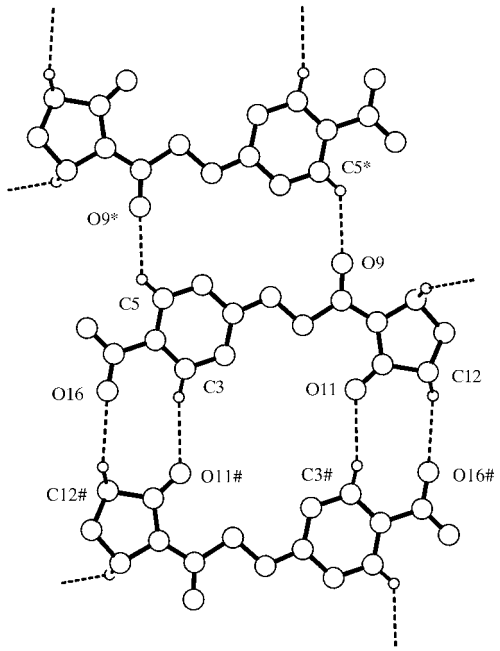


Figure 2
The connection of molecules of (I) into dimers. Atoms marked with an asterisk (*) or hash (#) are at the symmetry positions $(-x-1, -y+1, -z+1)$ and $(-x+1, -y, -z+1)$, respectively.

atom O17 of the nitro group 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 $C(12)$.

Experimental

A solution of (4-nitrophenoxy)acetyl chloride (1.0 g) in dichloromethane was stirred with pyrrolidinone. Dichloromethane was removed and crushed ice was added to the contents. The solid residue obtained was filtered off and crystallized from methanol, affording crystals of (I) (yield 0.78 g, 63.71%; m.p. 413–415 K).

Crystal data

$C_{12}H_{12}N_2O_5$
$M_r = 264.24$
Triclinic, $P\overline{1}$
$a = 5.2813$ (1) Å
$b = 8.7367$ (2) Å
$c = 12.9843$ (3) Å
$\alpha = 80.4656$ (14)°
$\beta = 81.4302$ (12)°
$\gamma = 83.8830$ (10)°
$V = 582.17$ (2) Å^3
$Z = 2$
$D_x = 1.507$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 3302 reflections
$\theta = 2.0$–$30.0°$
$\mu = 0.12$ mm^{-1}
$T = 160$ (2) K
Prism, colourless
0.25 × 0.25 × 0.17 mm

Data collection

Nonius KappaCCD diffractometer
φ and ω scans with κ offsets
16 366 measured reflections
3393 independent reflections
2701 reflections with $I > 2\sigma(I)$
$R_{int} = 0.033$
$\theta_{max} = 30.0°$
$h = 0 \rightarrow 7$
$k = -11 \rightarrow 12$
$l = -17 \rightarrow 18$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.043$
$wR(F^2) = 0.126$
$S = 1.06$
3393 reflections
172 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0735P)^2 + 0.0824P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.36$ e Å^{-3}
$\Delta\rho_{min} = -0.26$ e Å^{-3}

Table 1
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
C3—H3···O11^{i}	0.95	2.49	3.4235 (13)	166
C5—H5···O9^{ii}	0.95	2.40	3.0955 (13)	130
C12—H121···O16^{i}	0.99	2.51	3.2837 (14)	134
C14—H141···O17^{iii}	0.99	2.53	3.4406 (15)	153

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

All H atoms were placed in geometrically idealized positions (C—H = 0.95–0.99 Å) and were constrained to ride on their parent atoms with $U_{iso}(H)$ values equal to $1.2U_{eq}(C)$.

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: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (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).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1656). Services for accessing these data are described at the back of the journal.

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