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

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The title compound, C12H12N2O5, 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 R21(12) 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, oxiracetam 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., 2003a,b,c, 2003).

The pyrrolidine ring in nootropics typically has a half-chair (C2, 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, , of 86.6 (1)° and a maximum torsion angle, , 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 pyrrolidinone 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 = 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.

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 R21(20) and R21(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 R21(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.
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).

Table 1

Hydrogen-bonding geometry (Å, °).

<table>
<thead>
<tr>
<th>D—H···A</th>
<th>D—H</th>
<th>H···A</th>
<th>D···A</th>
<th>D—H···A</th>
</tr>
</thead>
<tbody>
<tr>
<td>C3—H3···O11i</td>
<td>0.95</td>
<td>2.49</td>
<td>3.4255 (13)</td>
<td>166</td>
</tr>
<tr>
<td>C5—H5···O8ii</td>
<td>0.95</td>
<td>2.40</td>
<td>3.0855 (13)</td>
<td>130</td>
</tr>
<tr>
<td>C12—H12i···O16</td>
<td>0.99</td>
<td>2.51</td>
<td>3.2837 (14)</td>
<td>134</td>
</tr>
<tr>
<td>C14—H14i···O17iii</td>
<td>0.99</td>
<td>2.53</td>
<td>3.4405 (15)</td>
<td>153</td>
</tr>
</tbody>
</table>

Symmetry codes: (i) 1 − x, −y, −z; (ii) 1 − x, −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 Uiso(H) values equal to 1.2Ueq(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: SHELXS97 (Sheldrick, 1997); program(s) used to refine structure: SHELXL97 (Sheldrick, 1997); molecular graphics: ORTEP-3 for Windows (Farrugia, 1997); software used to prepare material for publication: PARST97 (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.

References