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Two intermediates in the synthesis of decahydroisoquinolines with NMDA and AMPA receptor antagonist activity

J. Zukerman-Schpector,[a,b]* Mauricio Vega,[b] I. Caracelli,[b] Luiz C. Dias[c] and Anna M. A. P. Fernandes[c]

[a]Instituto de Química, Universidade de São Paulo, São Paulo, SP, Brazil, [b]Laboratório de Cristalografia, Estereodinâmica e Modelagem Molecular, Departamento Química, Universidade Federal de São Carlos, Caixa Postal 676, 13565-905 São Carlos, SP, Brazil, and [c]Instituto de Química, UNICAMP, Caixa Postal 6154, 13083-970 Campinas, SP, Brazil
Correspondence e-mail: julio@power.ufscar.br

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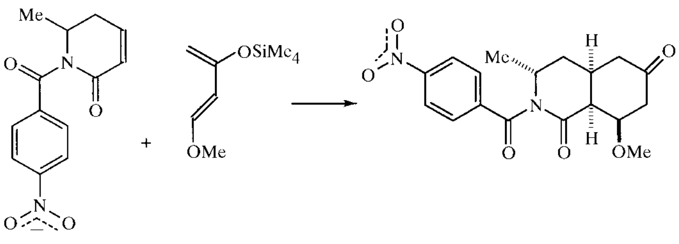
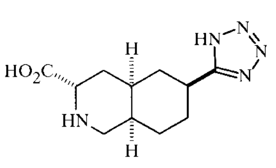
In 6-methyl-*N*-(4-nitrobenzoyl)-5,6-dihydropyridin-2(1*H*)-one, $C_{13}H_{12}N_2O_4$, (I), the piperidone ring is in a distorted half-chair conformation. In 8-methoxy-3-methyl-*N*-(4-nitrobenzoyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline-1,6-dione, $C_{18}H_{20}N_2O_6$, (II), the heterocyclic ring is in a slightly distorted half-boat conformation, while the other six-membered ring is in a distorted chair conformation. Compound (II) presents a strong intramolecular C—H···O hydrogen bond. In both (I) and (II), the molecules interact through C—H···O interactions.

Comment

Glutamate is the major excitatory neurotransmitter in the brain and can act on three major types of ligand-gated ion channels that are defined by the activity of the subtype-selective agonists NMDA (*N*-methyl-D-aspartate), kainate and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) (Ornstein *et al.*, 1994). In a search for new therapeutic agents which are potent and selective antagonists of glutamate, the excitatory amino acid antagonist activities of a series of decahydroisoquinoline-3-carboxylic acids were explored. It was found that compound (III) possesses both NMDA and AMPA receptor antagonist activity (Simmons *et al.*, 1998; O'Neill *et al.*, 1998).



(I) (IV) (II)



(III)

A new route to the synthesis of (III) was proposed, based on an intermolecular Diels–Alder cycloaddition reaction of a 6-substituted dihydropyridone with an appropriate diene. This key reaction would need a group at position 6 (to the nitrogen) in an axial position, so before the cycloaddition reaction was attempted, a crystal structure determination of (I) was undertaken. After confirmation that the methyl group (at position 6, labelled C5 in the figure) occupied an axial position, a thermally induced Diels–Alder reaction was performed using the highly reactive Danishefsky's diene, (IV). As the Diels–Alder reaction could lead to several different products and as the relative stereochemistry of this product is of great importance for subsequent reaction steps, the crystal structure of (II) was determined.

The molecular structure of (I) is shown in Fig. 1. As stated, the methyl group at C5 is in an axial position, as required for the continuation of the reaction path. The piperidone ring is in a half-chair conformation distorted towards a half-boat, as indicated by the Cremer & Pople (1975) puckering parameters shown in Table 3. The lone pair of the piperidone N atom is involved in conjugation with the carbonyl groups. This is indicated by the slight lengthening of the C═O double bond [1.214 (3) Å] and the concomitant shortening of the two N—Csp^2 single bonds [1.395 (3) and 1.399 (3) Å]. Accordingly, the state of hybridization of the N atom is sp^2, as shown by the sum (358.2°) of the angles around it and the small deviation [−0.050 (2) Å] of the atom from the N1/C2/C4/C13 plane.

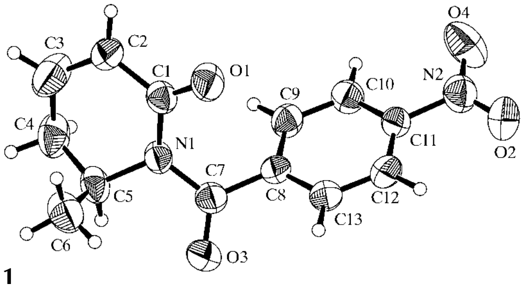


Figure 1
The molecular structure of (I) showing the atomic labelling and 50% probability displacement ellipsoids.

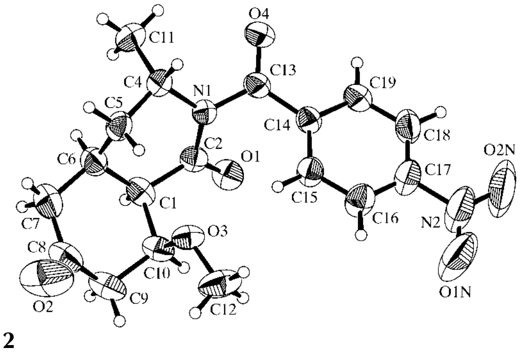


Figure 2
The molecular structure of (II) showing the atomic labelling and 50% probability displacement ellipsoids.

The molecular diagram of (II) is shown in Fig. 2, and shows that the two rings have a *cis* fused stereochemistry with an H1—C1—C6—H6 torsion angle of 41°. The heterocyclic ring is in a slightly distorted (towards a chair) half-boat conformation, whereas the other six-membered ring is in a distorted chair (towards a half-chair) conformation, as indicated by the Cremer & Pople (1975) puckering parameters given in Table 6. The existence of a C—H$\cdots\pi$ interaction between C12—H12*B* and the C14–C19 phenyl ring is noted. According to Ciunik *et al.* (1998), this kind of interaction should be characterized by three parameters. In the present structure, these are the H12*B*$\cdots$*Cg*$^{\rm i}$ (*Cg* is the centroid of the C14–C19 ring) distance of 2.69 Å, the C12—H12*B*$\cdots$*Cg*$^{\rm i}$ angle of 158° and the angle between the H$\cdots$*Cg* vector and the plane of the aromatic ring, which in this case is 88° [symmetry code: (i) $\frac{1}{2}+x, 1-y, z$]. These values are in the expected ranges of 2.7–3.4 Å, 140–160° and 80–100°, respectively, as described by Ciunik *et al.* (1998). This compound also exhibits three intramolecular hydrogen bonds (Table 5); in fact, C11—H11*A*$\cdots$O4 and C15—H15$\cdots$O3 are responsible for the particular arrangement of the phenyl ring. In order to study the influence of these hydrogen bonds on molecular conformation, a series of Potential Energy Surfaces (PES) calculations were performed [*MOPAC*7.01: Stewart (1990) and Csern (2000); *GAMESS*98: Schmidt *et al.* (1993)]. The geometry optimization calculations, using *AM*1 and 6–31G*, showed a change in the conformation involving the three C—H$\cdots$O interactions; the H15$\cdots$O3 distance changes from 2.49 to 2.58 Å, while the other two distances, H5*B*$\cdots$O3 and H11*C*$\cdots$O4, shorten to 2.47 and 2.49 Å, respectively. The PES obtained after rotation of the C4—N1—C13—C14 torsion angle showed that there were two minima, one corresponding to the global minimum (162.77°), which is close to the crystallographic conformation [144.0 (2)°], and the other at −77.32°. This last conformation is around 7 kcal higher (1 kcal = 4.184 kJ) than the other and results in the loss of the C15—H15$\cdots$O3 hydrogen bond. We can postulate that, in this case, the molecular conformation is driven more by the intramolecular interactions.

In both compounds, the molecules interact through a series of C—H$\cdots$O interactions, as shown in Tables 2 and 5. Whether all these interactions are true hydrogen bonds is difficult to assert because, as pointed out by Cotton *et al.* (1997), 'the field is getting muddier and muddier as the definition of a hydrogen bond is relaxed'. In any case, the Tables include those contacts with an H$\cdots$O distance less than the sum of the van der Waals radii (Pauling, 1960) plus 10% and a C—H$\cdots$O angle greater than 100°.

Table 1
Selected geometric parameters (Å, °) for (I).

N1—C7	1.395 (3)	N2—O2	1.210 (4)
N1—C1	1.399 (3)	N2—O4	1.226 (3)
N1—C5	1.481 (3)	N2—C11	1.482 (4)
C7—N1—C1	121.7 (2)	O2—N2—O4	123.6 (3)
C7—N1—C5	117.6 (2)	O2—N2—C11	118.5 (3)
C1—N1—C5	119.0 (2)	O4—N2—C11	118.0 (3)

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

D—H$\cdots$*A*	*D*—H	H$\cdots$*A*	*D*$\cdots$*A*	*D*—H$\cdots$*A*
C2—H2$\cdots$O2$^{\rm i}$	0.93	2.69	3.619 (4)	174
C3—H3$\cdots$O4$^{\rm ii}$	0.93	2.78	3.446 (5)	130
C12—H12$\cdots$O1$^{\rm iii}$	0.93	2.66	3.276 (3)	124
C6—H6*A*$\cdots$O4$^{\rm iii}$	0.96	2.82	3.710 (5)	154
C9—H9$\cdots$O3$^{\rm iv}$	0.93	2.55	3.451 (4)	163

Symmetry codes: (i) $2-x, \frac{1}{2}+y, \frac{3}{2}-z$; (ii) $\frac{3}{2}-x, 1-y, \frac{1}{2}+z$; (iii) $2-x, y-\frac{1}{2}, \frac{3}{2}-z$; (iv) $1-x, \frac{1}{2}+y, \frac{3}{2}-z$.

Table 3
Cremer & Pople (1975) puckering parameters (Å, °) for (I).

Ring	q_2	q_3	φ_2	θ_2	*Q*
N1—C1—C2—C3—C4—C5	0.27 (2)	−0.32 (2)	38 (5)	139 (3)	0.42 (2)

Experimental

Addition of methyl magnesium bromide to commercially available glutarimide, followed by treatment of the intermediate aminal with $NaBH_3CN/HCl$, afforded the corresponding lactam. The lactam was then N-protected using *n*-BuLi in tetrahydrofuran (THF) followed by addition of *p*-nitrobenzoyl chloride to afford the corresponding imide which, in turn, was deprotonated with LiHMDS in THF, followed by addition of phenylselenyl bromide. This last intermediate was converted into (I) using standard oxidation and elimination conditions. Heating of (I) with an excess of Danishefsky's diene (IV) at reflux in xylene in the presence of BHT, followed by treatment of the intermediate adduct with KF in THF, gave (II).

Compound (I)

Crystal data

$C_{13}H_{12}N_2O_4$
$M_r = 260.25$
Orthorhombic, $P2_12_12_1$
$a = 7.3677$ (9) Å
$b = 10.054$ (1) Å
$c = 16.834$ (2) Å
$V = 1247.0$ (2) Å^3
$Z = 4$
$D_x = 1.386$ Mg m^{-3}
Mo *K*α radiation
Cell parameters from 25 reflections
$\theta = 10.0$–18.4°
$\mu = 0.11$ mm^{-1}
$T = 293$ K
Irregular, colourless
0.20 × 0.10 × 0.05 mm

Data collection

Enraf–Nonius CAD-4–MACH3 diffractometer
$\omega/2\theta$ scans
2382 measured reflections
2098 independent reflections
995 reflections with $F^2 > 2\sigma F^2$
$R_{\rm int} = 0.018$
$\theta_{\rm max} = 30.0°$
$h = -1 \rightarrow 10$
$k = -14 \rightarrow 0$
$l = 0 \rightarrow 23$
3 standard reflections
frequency: 30 min
intensity decay: 1.1%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.037$
$wR(F^2) = 0.103$
$S = 0.98$
2098 reflections
173 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0692P)^2 + 0.0290P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\rm max} < 0.001$
$\Delta\rho_{\rm max} = 0.17$ e Å^{-3}
$\Delta\rho_{\rm min} = -0.18$ e Å^{-3}

Table 4
Selected geometric parameters (Å, °) for (II).

N1—C2	1.388 (3)	N2—O2N	1.180 (4)
N1—C13	1.414 (3)	N2—O1N	1.216 (4)
N1—C4	1.490 (3)	N2—C17	1.464 (4)
C2—N1—C13	120.7 (2)	O2N—N2—O1N	122.5 (3)
C2—N1—C4	122.3 (2)	O2N—N2—C17	119.2 (3)
C13—N1—C4	116.3 (2)	O1N—N2—C17	118.3 (3)

Table 5
Hydrogen-bonding geometry (Å, °) for (II).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C5—H5*B*···O3	0.97	2.49	3.124 (3)	123
C11—H11*C*···O4	0.96	2.52	3.078 (3)	118
C15—H15···O3	0.93	2.48	3.379 (3)	163
C4—H4···O4^{i}	0.98	2.68	3.576 (3)	152
C7—H7*B*···O1N^{ii}	0.97	2.58	3.354 (4)	136
C11—H11*B*···O2N^{ii}	0.96	2.69	3.393 (4)	130
C7—H7*A*···O2^{iii}	0.97	2.59	3.399 (4)	141
C9—H9*B*···O1^{iv}	0.97	2.51	3.473 (3)	171
C11—H11*A*···O1N^{v}	0.96	2.76	3.418 (5)	126
C12—H12*C*···O2^{vi}	0.96	2.67	3.407 (4)	134
C16—H16···O1^{vii}	0.93	2.43	3.337 (3)	166
C19—H19···O4^{viii}	0.93	2.73	3.382 (3)	128

Symmetry codes: (i) $-\frac{1}{2}-x, y, -z$; (ii) $x, y-1, z$; (iii) $x-\frac{1}{2}, -y, z$; (iv) $-\frac{1}{2}-x, \frac{1}{2}-y, \frac{1}{2}-z$; (v) $x-\frac{1}{2}, 1-y, z$; (vi) $\frac{1}{2}-x, \frac{1}{2}-y, \frac{1}{2}-z$; (vii) $\frac{1}{2}+x, 1-y, z$; (viii) $-1-x, 1-y, -z$.

Compound (II)

Crystal data

$C_{18}H_{20}N_2O_6$
$M_r = 360.36$
Monoclinic, $I2/a$
$a = 10.2455$ (9) Å
$b = 12.664$ (1) Å
$c = 27.446$ (3) Å
$\beta = 97.441$ (9)°
$V = 3531.1$ (6) Å^3
$Z = 8$
$D_x = 1.356$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
$\theta = 10.0$–17.2°
$\mu = 0.10$ mm^{-1}
$T = 293$ K
Irregular, colourless
0.25 × 0.20 × 0.15 mm

Data collection

Enraf–Nonius CAD-4–MACH3 diffractometer
$\omega/2\theta$ scans
7230 measured reflections
3574 independent reflections
1846 reflections with $F^2 > 2\sigma F^2$
$R_{\rm int} = 0.046$
$\theta_{\rm max} = 26.3°$
$h = -12 \rightarrow 0$
$k = -15 \rightarrow 15$
$l = -33 \rightarrow 34$
3 standard reflections
frequency: 30 min
intensity decay: 1.6%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.044$
$wR(F^2) = 0.113$
$S = 1.01$
3574 reflections
237 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0616P)^2 + 1.0264P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\rm max} < 0.001$
$\Delta\rho_{\rm max} = 0.20$ e Å^{-3}
$\Delta\rho_{\rm min} = -0.25$ e Å^{-3}

H atoms were located on stereochemical grounds, except those of the hydroxyl groups, and were refined riding on a carrier atom with an isotropic displacement parameter of 1.5 (for methyl H atoms) or 1.2 (for the other H atoms) times the value of the equivalent isotropic displacement parameter of the attached atom.

Table 6
Cremer & Pople (1975) puckering parameters (Å, °) for (II).

Ring	q_2	q_3	φ_2	θ_2	Q
C1—C6—C7—C8—C9—C10	0.11 (2)	0.47 (2)	−95 (11)	13 (3)	0.49 (2)
N1—C2—C1—C6—C5—C4	0.297 (3)	0.380 (3)	−122.4 (5)	38.2 (3)	0.482 (3)

For both compounds, data collection: *CAD*-4 *Software* (Enraf–Nonius, 1989); cell refinement: *CAD*-4 *Software*; data reduction: *XCAD*4 (Harms & Wocadlo, 1995). Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1985) for compound (I) and *SIR*92 (Altomare *et al.*, 1993) for compound (II). For both compounds, program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ZORTEP* (Zsolnai, 1995); software used to prepare material for publication: *PARST*95 (Nardelli, 1995), *PLATON* (Spek, 1998) and *WinGX* (Farrugia, 1999).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: DA1198). Services for accessing these data are described at the back of the journal.

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