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Olazipinium nicotinate

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Key indicators

Single-crystal X-ray study
T = 273 K
Mean σ(C–C) = 0.005 Å
R factor = 0.063
wR factor = 0.141
Data-to-parameter ratio = 13.4

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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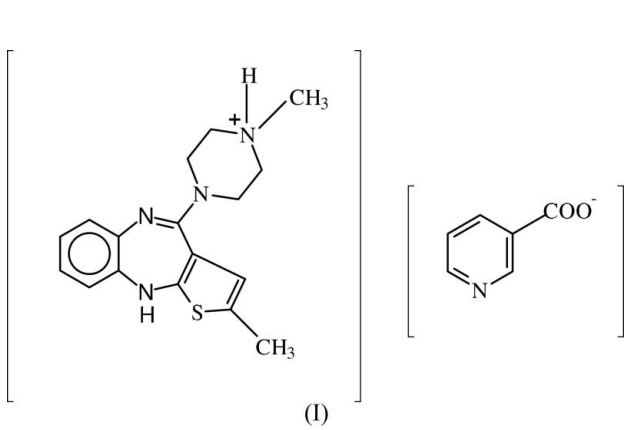
The crystal structure of the title compound, $C_{17}H_{21}N_4S^+\cdot C_6H_4NO_2^-$, [systematic name: 1-methyl-4-(2-methyl-10*H*-thieno[2,3-*b*][1,5]benzodiazepin-4-yl)hexahydropyrazin-1-ium nicotinate] is reported. The central seven-membered heterocycle is in a boat conformation, while the piperazine ring displays a chair conformation with its methyl group oriented equatorially. The coulombic interaction between olanzapinium and nicotinate ions is supplemented by intra- and intermolecular N—H···O hydrogen bonds, forming infinite chains along the *c* axis.

Comment

Olanzapine, the pharmaceutically active component of the title compound, a thienobenzodiazepine derivative, along with clozapine, quetiapine, risperidone and ziprasidone, belongs to the newer generation of atypical antipsychotic agents (Chakrabarti *et al.*, 1980; Callaghan *et al.*, 1999; Kennedy *et al.*, 2001; Tandon & Jibson, 2003). These atypical antipsychotic agents, in comparison with the older generation, show greater efficacy against both positive and negative symptoms of schizophrenia (a debilitating mental disorder) as well as associated cognitive deficits and are virtually devoid of extrapyramidal symptoms (Tandon, 2002). The therapeutic action of olanzapine against the symptoms of schizophrenia is thought to be due to its high affinity for dopaminergic D2 and serotonergic 5-HT2A receptor systems implicated in the pathogenesis of this disease (Bever & Perry, 1998). Recently, it was reported that increasing experience with atypical antipsychotics in real-world clinical settings demonstrated that the use of these drugs could be associated with adverse metabolic changes, including diabetes mellitus (Wilson *et al.*, 2003; Mir & Taylor, 2001) weight gain (Wirshing, 2001) and dyslipidemia (Osser *et al.*, 1999). Switching or combining agents may be sufficient in some cases, but in many instances additional drug treatment would be required. This includes oral antidiabetics, and agents to treat hyperlipidaemia and hypertension among others. Numerous pharmacokinetic and pharmacodynamic interactions with antipsychotics are possible. Nicotinic acid or niacin, the water-soluble B vitamin, which improves all lipoproteins when given in doses well above the vitamin requirement, is claimed to treat hyperlipidaemia in patients with schizophrenia (Hoffer, 1998; Baptista *et al.*, 2004). It is believed that the vitamin works by reducing the amount of oxidized adrenaline in the body, called adrenochome, which seems to be at least partially responsible for schizophrenia. Our particular interest lies in the crystalline complex of olanzapine with nicotinic acid, providing a means both for a structural study of this important drug and for examining the interactions between the components.



(I)

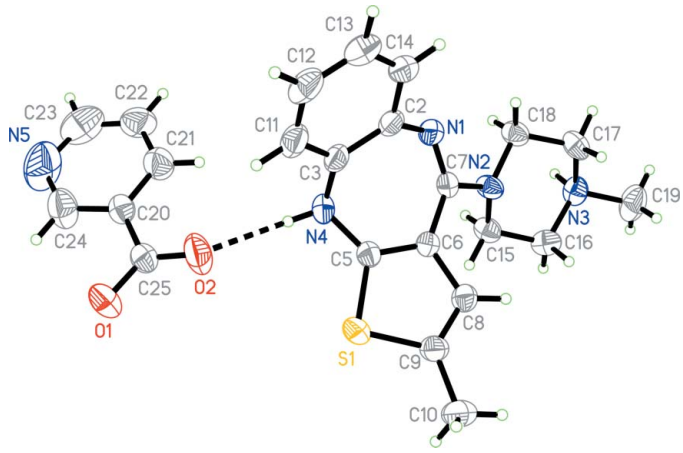


Figure 1
A view of (I), with the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii. The hydrogen bond is shown dashed.

The structure of the title compound, (I), reveals a proton-transfer complex as a well defined salt of a nicotinate anion and an olanzapinium cation (Fig. 1). The expected proton transfer from nicotinic acid to olanzapine occurs at atom N3 of the piperazine ring. Consequently, atom N3 shows quaternary character and bears a positive charge in a tetrahedral configuration with bond angles ranging from 110.9 (2) to 111.5 (2)°. The C7—N2 distance, 1.382 (3) Å, suggests partial double-bond character of this bond. The increased sp^2 character of the N atom has no effect on the conformation of the piperazine ring, which adopts the expected chair conformation [asymmetry parameter ΔC_2(N2—C18) = 0.008 (1); Nardelli, 1983]. Incidentally, the protonation at N3 has no effect on the orientation of the C19 methyl group (attached to N3), which is equatorial in (I) as well as in olanzapine free base (Wawrzycka *et al.*, 2004).

The central 1,5-diazepine ring adopts a boat conformation and may be described by three planes: a bow plane (C3/C4/N5), a central plane (C2/C3/C5/C6) and a stern plane (C2/N1/C7/C6). This enables the tricyclic thienobenzodiazepine ring skeleton to form an extended V-shaped conformation. Interestingly, a similar conformation can also be observed (Fig. 2) in the crystal structures of olanzapine free base, and the related antipsychotic agents clozapine (Petcher & Weber, 1974), loxapine and amoxapine (Cosulich & Lovell, 1977). Such a conformation may facilitate the drug-receptor binding interactions. The dihedral angle between the planes of the two aromatic rings (benzene and thiophene) flanking the diazepine ring is 119.9 (1)°. The corresponding angles have been reported as 127.2° for olanzapine free base, 115° for clozapine, 113.7° for loxapine and 119.5° for amoxapine. However, molecular modelling of olanzapine using *HYPERCHEM* predicts this angle as 135° (Lien *et al.*, 1996). The orientation of the piperazine ring with respect to the diazepine ring is defined by the torsion angle N1—C7—N2—C18 = 2.3 (4)°, while in the olazanpine free base it is −11.8°. The dihedral angles between the plane of the four C atoms in the piperazine ring and the planes of the benzene and thiophene rings are 32.3 (1) and 34.5 (1)°, respectively.

The structural features within the nicotinate ion are similar to those of nicotinic acid (Kutoglu & Scheringer, 1983). The deprotonated carboxylate group is essentially coplanar [O1—C25—C20—C21 = −179.2 (3)°] with the pyridine ring. The olazanpinium and nicotinate ions in (I) are linked by N—H···O hydrogen bonds between alternating cations and anions. This arrangement results in a chain of ions extending along the *c* axis. The piperazine ring is connected to a planar pyridine ring of the nicotinate anion by N—H···O hydrogen bonds (Table 2). The quarternary atom N3 acts as a donor to both the O atoms, O1 and O2, of the nicotinate anion, a consequence of a three-centred hydrogen bond (Jeffrey &

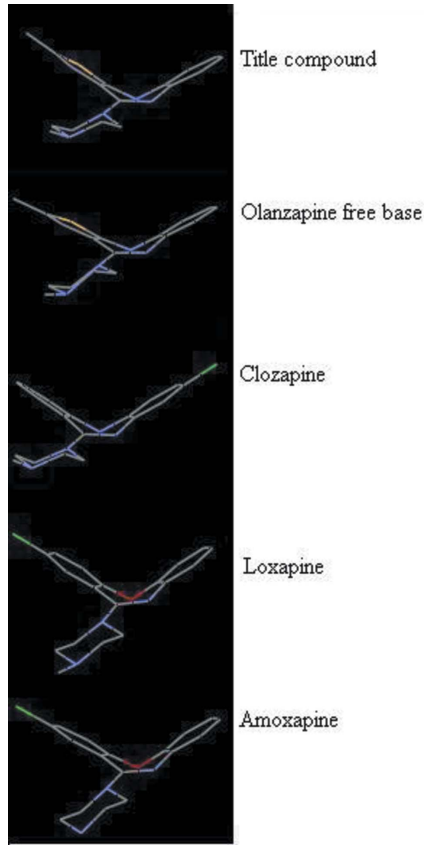


Figure 2
Conformational similarity observed in related antipsychotic drugs.

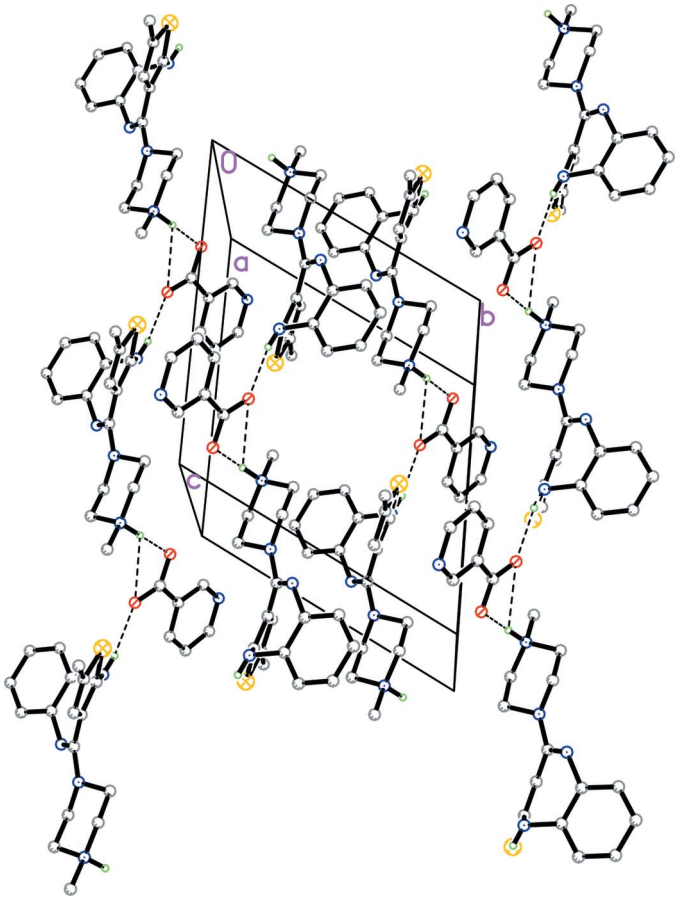


Figure 3
A view of the packing, showing the chains running along the *c* axis. Dashed lines indicate N—H···O hydrogen bonds. H atoms attached to C atoms have been omitted for clarity.

Saenger, 1991). The crystal packing is further stabilized by C—H···O and weak C—H···π(thiophene) interactions (Table 2).

Experimental

Olanzapine and nicotinic acid were mixed in the stoichiometic ratio 1:1 and dissolved in aqueous methanol solution (90%, 10 ml) to obtain crystals by slow evaporation.

Crystal data

$C_{17}H_{21}N_4S^+\cdot C_6H_4NO_2^-$
M_r = 435.54
Triclinic, $P\overline{1}$
a = 9.2565 (10) Å
b = 11.2224 (12) Å
c = 12.0629 (13) Å
α = 63.164 (2)°
β = 87.485 (2)°
γ = 83.735 (2)°
V = 1111.4 (2) Å^3
Z = 2
D_x = 1.301 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 1483 reflections
θ = 2.2–21.2°
μ = 0.18 mm^{-1}
T = 273 (2) K
Block, pale yellow
0.23 × 0.12 × 0.09 mm

Data collection

Bruker SMART APEX CCD area-detector diffractometer
ω scans
Absorption correction: none
8110 measured reflections
3894 independent reflections
2885 reflections with $I > 2\sigma(I)$
R_{int} = 0.034
θ_{max} = 25.0°
$h = -10 \rightarrow 10$
$k = -13 \rightarrow 13$
$l = -14 \rightarrow 13$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.063
$wR(F^2)$ = 0.141
S = 1.06
3894 reflections
290 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0569P)^2 + 0.338P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.32 e Å^{-3}
$\Delta\rho_{min}$ = −0.21 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

S1—C5	1.734 (3)	N4—C5	1.400 (3)
S1—C9	1.736 (3)	N4—C3	1.421 (4)
N1—C7	1.285 (3)	N5—C23	1.349 (5)
N1—C2	1.409 (3)	N5—C24	1.354 (5)
N3—C19	1.483 (4)	O1—C25	1.261 (3)
N3—C16	1.489 (4)	O2—C25	1.233 (3)
N3—C17	1.493 (4)		
C7—N1—C2	123.1 (2)	N1—C7—N2	118.4 (2)
C15—N2—C18	110.6 (2)	N1—C7—C6	126.0 (2)
C19—N3—C16	111.5 (2)	N2—C7—C6	115.4 (2)
C19—N3—C17	111.2 (2)	O2—C25—O1	124.5 (3)
C16—N3—C17	110.9 (2)	O2—C25—C20	118.7 (3)
C5—N4—C3	113.3 (2)	O1—C25—C20	116.8 (3)
C23—N5—C24	115.9 (3)		

Table 2
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N3—H3*N*···O1^{i}	1.00 (3)	1.63 (3)	2.628 (3)	175 (3)
N3—H3*N*···O2^{i}	1.00 (3)	2.57 (3)	3.219 (3)	122 (2)
N4—H4*N*···O2	0.81 (3)	2.12 (3)	2.922 (3)	170 (3)
C19—H19*A*···O2^{i}	0.96	2.54	3.173 (4)	124
C17—H17*B*···*Cg*1^{ii}	0.97	2.72	3.55	144

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

H atoms on N atoms were located in a difference density map and refined freely. All other H atoms were positioned geometrically and treated as riding atoms, with C—H distances in the range 0.93–0.97 Å and with U_{iso}(H) values of 1.5U_{eq}(C) for methyl H and 1.2U_{eq}(C) for other H atoms. The methyl groups were allowed to rotate but not to tip.

Data collection: *SMART* (Bruker, 2001); cell refinement: *SAINT* (Bruker, 2001); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *SHELXTL/PC* (Sheldrick, 1990); software used to prepare material for publication: *SHELXL97*.

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