Acta Crystallographica Section E
Structure Reports Online
ISSN 1600-5368

Polymorphic form II of 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno-[2,3-*b*][1,5]benzodiazepine

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Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.002 Å
R factor = 0.033
wR factor = 0.096
Data-to-parameter ratio = 12.4

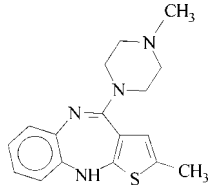
For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

Received 20 November 2003
Accepted 5 December 2003
Online 12 December 2003

The title compound, $C_{17}H_{20}N_4S$, generic name olanzapine, is an antipsychotic agent. The molecule consists of three fused rings (benzene, diazepine and thiophene) and an *N*-methylpiperazine substituent. The boat conformation of the central 1,5-diazepine ring defines the overall shape of the molecule. Two butterfly-like molecules form centrosymmetric dimers stabilized by C—H···π interactions between their cavities. The dimers are connected by intermolecular N—H···N, C—H···N and C—H···S hydrogen bonds.

Comment

Olanzapine, (I), along with clozapine, risperidone, quetiapine and ziprasidone, belongs to the newer generation, atypical antipsychotic agents (Chakrabarti *et al.*, 1980; Callaghan *et al.*, 1999; Kennedy *et al.*, 2001; Tandon, 2002; Tandon & Jibson, 2003). It has useful central nervous system activity and shows a wide range of therapeutic effects. Olanzapine is used for the treatment of schizophrenia, schizophreniform disorders, psychosis, mild anxiety states and functional bowel disorders (Bunnell *et al.*, 1998). The atypical antipsychotic agents, in comparison with the older ones, show better efficacy and reduced side effects, *e.g.* lesser dysphoria, less impaired cognition and lower risk of extrapyramidal movement disorders (Tandon, 2002).



(I)

Pharmaceutical formulations contain solid crystalline olanzapine; for this reason, well documented characteristics of its physicochemical properties are required (Bernstein, 2002; Clas, 2003). Thus far, five polymorphic forms of olanzapine have been characterized (Chakrabarti *et al.*, 1991, 1993; Bunnell *et al.*, 1996, 1998; Hamied *et al.*, 2002). Crystallization from an acetonitrile solution gives the metastable form I, while crystallization by cooling an anhydrous ethyl acetate solution gives stable form II (Chakrabarti *et al.*, 1991, 1993; Bunnell *et al.*, 1996, 1998).Both forms have been characterized by IR spectra and X-ray powder diffraction patterns. In our studies, we attempted to obtain single crystals of olanzapine using other anhydrous solvents. Crystals grown from toluene, propyl acetate, isopropyl acetate and butyl acetate appeared to be the same form of unsolvated olanzapine, crystallizing in

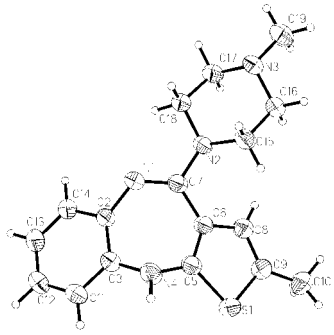


Figure 1
Perspective view of (I). Displacement ellipsoids are drawn at the 50% probability level.

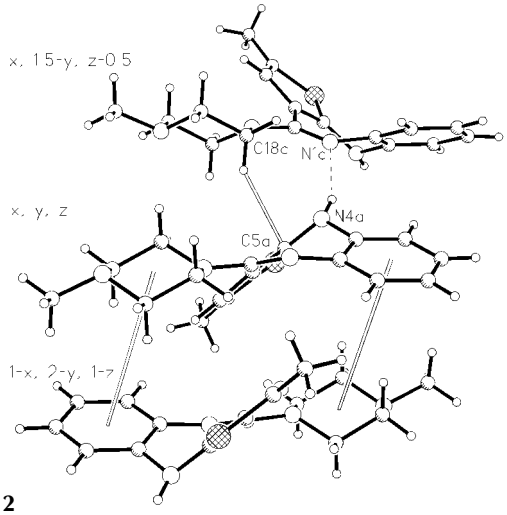


Figure 2
Intermolecular contacts. The N—H···N hydrogen bond is marked by a dashed line and fragments interacting through C—H···π contacts are linked by open lines.

the space group $P2_1/c$. Calculation of the powder diffraction pattern (Farrugia, 1999) for the structural model presented in this paper proved its identity with that published for form II (Bunnell *et al.*, 1996, 1998). A preliminary report of our work has been presented (Wawrzycka & Koziol, 1999).

The title molecule consists of three fused rings (benzene, diazepine and thiophene) and an *N*-methylpiperazine fragment (Fig. 1). The 1,5-diazepine ring, having a boat conformation, can be described by three planes: a bow (C3, N4 and C5), a central plane (C2, C3, C5 and C6) and a stern plane (C2, N1, C7 and C6). This conformation results in the butterfly-like shape of the molecule. The benzene and thiophene systems are each planar, the dihedral angle between them being 127.2 (1)°. The bond angles about the atom N2 (Table 1) indicate its flattened pyramidal configuration and the distance of 1.379 (2) Å suggests partial double bonding between atoms C7 and N2. This increased sp^2 character of the N atom has no effect on the conformation of the piperazine ring, which adopts a chair conformation with the C19 methyl group in the equatorial position.

In the crystal structure of (I), intermolecular N—H···N hydrogen bonds and C—H···N/S interactions are observed (Table 2). The N4—H4N···N1^{i} hydrogen bond (symmetry code as in Table 2) links two diazepine rings from neighbouring molecules and forms tapes along the *c* axis. These hydrogen bonds are accompanied by weak three-centre C—H···N contacts between the C18 methylene group and the N4 atom of diazepine (Fig. 2). Moreover, the distance between the C10 and S1 atoms indicates methylthiophene–methylthiophene interactions.

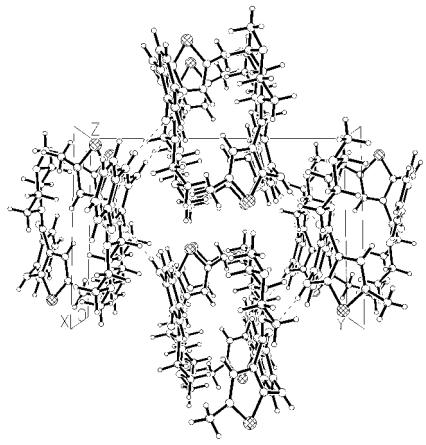


Figure 3
The packing of the molecules, viewed along the *a* axis.

The molecules of (I) form centrosymmetric dimers (Fig. 2, Table 2), in which three types of multiple C—H···π contacts are observed (Malone *et al.*, 1997): (i) between piperazine C18 and the thiophene C8—C9 fragment (with H···π distances less than 3.05 Å); (ii) between piperazine C17 and the thiophene C5—C6 fragment (with H···π distances in the range 3.05–3.40 Å); and (iii) between piperazine atoms C16, C17 and C19, and the phenyl ring (multiple interactions with H···π distances in the range 3.05–3.44 Å).

The association of molecular dimers (Fig. 3) creates columns along the *a* axis, and this structure is stabilized by a very short C—H···π contact between the methylene C18 and thiophene C5 atoms (Table 2).

Experimental

Prism-shaped yellow crystals were obtained by slow evaporation of a toluene solution at room temperature. The same product is obtained by crystallization from solutions in esters (butyl, propyl and isopropyl) of acetic acid.

Crystal data

$C_{17}H_{20}N_4S$
M_r = 312.43
Monoclinic, $P2_1/c$
a = 10.388 (3) Å
b = 14.839 (4) Å
c = 10.567 (3) Å
β = 100.64 (3)°
V = 1600.9 (8) Å^3
Z = 4
D_x = 1.296 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 30 reflections
θ = 6.4–24.4°
μ = 1.80 mm^{-1}
T = 293 (2) K
Prism, yellow
0.34 × 0.22 × 0.20 mm

Data collection

Kuma KM4 four-circle diffractometer
ω–2θ scans
Absorption correction: none
3564 measured reflections
3471 independent reflections
2896 reflections with $I > 2\sigma(I)$
R_{int} = 0.027
θ_{max} = 80.2°
$h = -8 \rightarrow 13$
$k = -18 \rightarrow 0$
$l = -13 \rightarrow 8$
3 standard reflections
every 100 reflections
intensity decay: 1.1%

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.054P)^2 + 0.2828P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.033$	$(\Delta/\sigma)_{max} = 0.001$
$wR(F^2) = 0.096$	$\Delta\rho_{max} = 0.22$ e Å^{-3}
$S = 1.04$	$\Delta\rho_{min} = -0.22$ e Å^{-3}
3471 reflections	Extinction correction: *SHELXL*
280 parameters	Extinction coefficient: 0.0102 (5)
All H-atom parameters refined	

Table 1
Selected geometric parameters (Å, °).

S1—C5	1.7321 (14)	N4—C5	1.3897 (18)
S1—C9	1.7403 (16)	C5—C6	1.3633 (17)
N1—C7	1.2945 (17)	C6—C8	1.4313 (19)
N1—C2	1.4148 (16)	C6—C7	1.4723 (17)
C2—C3	1.4089 (17)	C8—C9	1.3544 (19)
C3—N4	1.4132 (17)	C9—C10	1.496 (2)
C5—N4—C3	115.93 (11)	C7—N2—C15	120.51 (11)
C7—N2—C18	120.44 (11)	C18—N2—C15	111.56 (11)
C7—N1—C2—C3	43.1 (2)	N4—C5—C6—C7	4.2 (2)
N1—C2—C3—N4	−6.3 (2)	C2—N1—C7—C6	−4.9 (2)
C2—C3—N4—C5	−56.10 (17)	C5—C6—C7—N1	−35.4 (2)
C3—N4—C5—C6	56.60 (18)	C6—C7—N2—C15	−48.50 (17)

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

D—H···A	D—H	H···A	D···A	D—H···A
N4—H4N···N1^{i}	0.86 (2)	2.27 (2)	3.084 (2)	159 (2)
C18—H181···N4^{ii}	1.00 (2)	2.64 (2)	3.243 (2)	119 (2)
C18—H182···N4^{ii}	1.03 (2)	3.04 (2)	3.243 (2)	92 (2)
C10—H101···S1^{iii}	0.92 (3)	3.26 (4)	3.783 (2)	118 (2)
C16—H161···C13^{iv}	1.00 (2)	3.24 (2)	4.194 (2)	160 (2)
C16—H161···C14^{iv}	1.00 (2)	3.19 (2)	4.183 (2)	174 (2)
C17—H171···C3^{iv}	1.01 (2)	3.34 (2)	4.337 (2)	172 (2)
C17—H171···C5^{iv}	1.01 (2)	3.17 (2)	4.033 (2)	145 (2)
C17—H171···C6^{iv}	1.01 (2)	3.39 (2)	4.156 (2)	134 (2)
C18—H182···C8^{iv}	1.03 (2)	2.80 (2)	3.653 (2)	141 (2)
C18—H182···C9^{iv}	1.03 (2)	2.79 (2)	3.723 (2)	151 (2)
C18—H181···C5^{ii}	1.00 (2)	2.49 (2)	3.379 (2)	148 (2)
C19—H191···C11^{iv}	0.96 (3)	3.44 (3)	4.348 (2)	160 (2)
C19—H191···C12^{iv}	0.96 (3)	3.28 (3)	4.210 (2)	167 (2)

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

All H atoms were found in a difference electron-density map, and were refined isotropically (see Table 2 for distances).

Data collection: *KM*4 *Software* (Kuma Diffraction, 1991); cell refinement: *KM*4 *Software*; data reduction: *KM*4 *Software*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *SHELXTL/PC* (Sheldrick, 1990); software used to prepare material for publication: *SHELXL*97.

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