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Buspirone free base

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Key indicators

Single-crystal X-ray study
T = 567 K
Mean σ(C–C) = 0.003 Å
R factor = 0.046
wR factor = 0.150
Data-to-parameter ratio = 17.0

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

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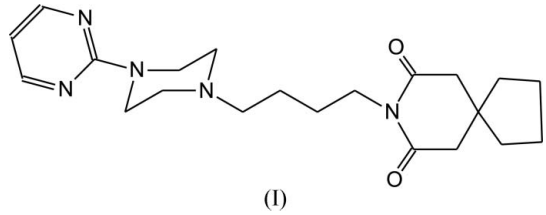
In the solid state, the title compound, 8-{4-[4-(pyrimidin-2-yl)-piperazin-1-yl]butyl}-8-azaspiro[4.5]decane-7,9-dione, $C_{21}H_{31}N_5O_2$, exists as an extended conformer with the piperazinyl and glutarimide units having chair and sofa conformations, respectively, while the butyl chain is *trans*,*trans*,*trans*.

Comment

Since early studies (Wu *et al.*, 1969, 1972; Wu & Rayburn, 1971, 1973) of the synthesis and biological activities of *N*-(4-aryl-1-piperazinyl-alkyl)-substituted cyclic imides, a dependance between the alkyl chain length, the type of aryl group or imide residue and the activity has been known. These compounds show psychotropic properties. The most effective compound from the series, 8-[4-(4-pyrimidin-2-ylpiperazin-1-yl)butyl]-8-azaspiro[4,5]decane-7,9-dione, (I), generic name buspirone, has been developed and, since 1986, has been used in the therapy of anxiety and depression (Bristol–Myers Squibb Co., 2000). It is one of the most effective psychosedative agents, having an anxioselective profile without negative side effects and no potential for addiction (*e.g.* Garattini *et al.*, 1982; Goa & Ward, 1986). The pharmacological action of (I) is explained as resulting from its high affinity for serotonin 5-HT_{1A} receptors, moderate affinity for dopamine D_2 receptors and low affinity for 5-HT_2 receptors (*e.g.* Taylor *et al.*, 1984; Eison & Temple, 1986; Ohlsen & Pilowsky, 2005). The marketed chemical form of (I) is the hydrochloride.



(I)

To date, physico-chemical studies of (I) and its salt include extensive spectroscopic analyses, namely NMR (Chilmonczyk *et al.*, 1996), IR, Raman (Cybulski *et al.*, 1997) and MS (Kerns *et al.*, 1997), and theoretical calculations. Although the crystal structures of the stable form of (I)·HCl (m.p. 476.7–478.7 K) and several analogues of (I) have been determined (Chilmonczyk *et al.*, 1995, 1997), crystals of the free base, (I), have not yet been studied.

The molecular conformer of (I) presented in this paper is an extendend one which results mainly from the *trans*,*trans*,*trans* conformation of the butyl spacer (Fig. 1 and Table 1). Theoretical calculations for the gas phase indicated that the fully

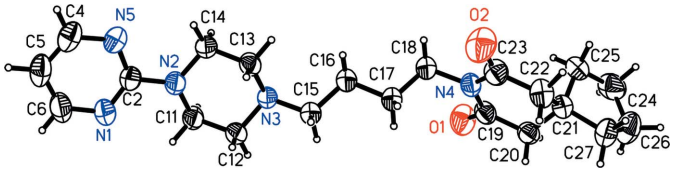


Figure 1
The molecular structure of (I), with the atom numbering scheme. Displacement ellipsoids of non-H atoms are drawn at the 50% probability level.

extended conformations of the free base and cation of (I) are those of minimum energy (Chilmonczyk *et al.*, 1995). These could suggest a rigid structure of *N*-(4-aryl-1-piperazinyl-alkyl)-substituted cyclic imides. However, structural studies of crystalline salts of another derivative, 3a,4,7,7a-tetrahydro-2-[4-(4-(quinolin-2-ylpiperazin-1-yl)butyl]-4,7-ethane-1*H*-isoindole-1,3(2*H*)-dione (Chilmonczyk *et al.*, 1997), indicated conformational flexibility even in the solid state.

The pyrimidine ring in (I) is an equatorial substituent of piperazine which has a chair conformation. The glutarimide fragment exists as an undistorted sofa conformer. Chemically equivalent bonds are of the same length, *e.g.* the C—N and C═O bonds (Table 1). This could be the result of only very weak intermolecular interactions in the crystal structure with (C—)H···O distances greater than 2.8 Å. The shortest contact is between the atoms N3 and C20($x, \frac{1}{2}-y, z-\frac{1}{2}$) [3.528 (3) Å; Fig. 2]. Molecules of (I) are parallel and arranged into columns running down the [101] direction (Fig. 2). This is a different packing from the cation···anion association in the crystal structure of (I)·HCl (Chilmonczyk *et al.*, 1995), where layers are formed and cations are inclined by 45° within the layer.

Experimental

Compound (I) was obtained according to the method published previously (Cybulski *et al.*, 1992, 1993). Recrystallization from an ethyl acetate solution gave crystals of melting point 378–380 K.

Crystal data

$C_{21}H_{31}N_5O_2$
M_r = 385.51
Monoclinic, $P2_1/c$
a = 10.548 (2) Å
b = 11.764 (2) Å
c = 16.998 (3) Å
β = 99.28 (3)°
V = 2081.6 (7) Å^3
Z = 4
D_x = 1.230 Mg m^{-3}
Cu $K\alpha$ radiation
μ = 0.65 mm^{-1}
T = 292 (2) K
Prism, colourless
0.35 × 0.28 × 0.19 mm

Data collection

Kuma KM-4 four-circle diffractometer
ω–2θ scans
Absorption correction: none
4454 measured reflections
4320 independent reflections
2791 reflections with $I > 2\sigma(I)$
R_{int} = 0.046
θ_{max} = 81.3°
3 standard reflections
every 100 reflections
intensity decay: 0.1%

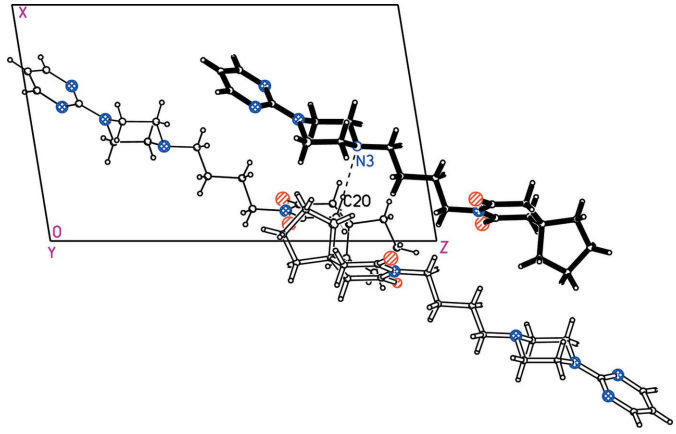


Figure 2
Part of the crystal structure of (I). The dashed line indicates a hydrogen bond.

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.046
$wR(F^2)$ = 0.150
S = 1.06
4320 reflections
254 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.08P)^2 + 0.26P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.20 e Å^{-3}
$\Delta\rho_{min}$ = −0.15 e Å^{-3}
Extinction correction: *SHELXL97*
Extinction coefficient: 0.0008 (2)

Table 1
Selected geometric parameters (Å, °).

C2—N2	1.356 (2)	C18—N4	1.472 (2)
N2—C11	1.456 (2)	N4—C23	1.397 (2)
N2—C14	1.457 (2)	N4—C19	1.397 (2)
C12—N3	1.457 (2)	C19—O1	1.207 (2)
N3—C13	1.460 (2)	C23—O2	1.212 (2)
N3—C15	1.462 (2)		
N3—C15—C16—C17	−173.9 (2)	C16—C17—C18—N4	177.7 (2)
C15—C16—C17—C18	172.3 (2)		

All H atoms were positioned geometrically and allowed to ride on their parent atoms, with C—H bond lengths of 0.97 Å for methylene and 0.93 Å for aryl H atoms. U_{iso}(H) values were set equal to 1.2U_{eq}(C).

Data collection: *KM-4 Software* (Kuma Diffraction, 1999); cell refinement: *KM-4 Software*; data reduction: *KM-4 Software*; 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* and *enCIFer* (Allen *et al.*, 2004).

References

Allen, F. H., Johnson, O., Shields, G. P., Smith, B. R. & Towler, M. (2004). *J. Appl. Cryst.* **37**, 335–338.
Bristol–Myers Squibb Co. (2000). *Instruction Sheet.* http://www.fda.gov.
Chilmonczyk, Z., Cybulski, J., Szelejewska-Wozniakowska, A. & Les, A. (1996). *J. Mol. Struct.* **385**, 195–207.
Chilmonczyk, Z., Les, A., Wozniakowska, A., Cybulski, J., Koziol, A. E. & Gdaniec, M. (1995). *J. Med. Chem.* **38**, 1701–1710.

Chilmonczyk, Z., Szelejewska-Wozniakowska, A., Cybulski, J., Cybulski, M., Koziol, A. E. & Gdaniec, M. (1997). *Arch. Pharm. Pharm. Med. Chem.* **330**, 146–160.
Cybulski, J., Chilmonczyk, Z., Glice, M., Cybulski, M., Bajdor, K. & Les, A. (1997). *J. Mol. Struct.* **404**, 221–234.
Cybulski, J., Chilmonczyk, Z., Szelejewski, W., Wojtasiewicz, K. & Wrobel, J. T. (1992). *Arch. Pharm. (Weinheim)*, **325**, 313–315.
Cybulski, J., Wojtasiewicz, K., Wrobel, J. T., Szelejewski, W. & Chilmonczyk, Z. (1993). Patent No. PL 161 295.
Eison, A. S. & Temple, D. L. Jr (1986). *Am. J. Med.* **80** (Suppl 3B), 1–9.
Garattini, S., Caccia, S. & Mennini, T. (1982). *J. Clin. Psychiatry*, **43**, 19–22.
Goa, K. & Ward, A. (1986). *Drugs*, **32**, 114–129.
Kerns, E. H., Rourick, R. A., Volk, K. J. & Lee, M. S. (1997). *J. Chromatogr. B*, **698**, 133–145.
Kuma Diffraction (1999). *KM-4 Software*. Kuma Diffraction, Wroclaw, Poland.
Ohlsen, R. I. & Pilowsky, L. S. (2005). *J. Psychopharmacol.* **19**, 408–413.
Sheldrick, G. M. (1990). *SHELXTL/PC*. User's Manual. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.
Sheldrick, G. M. (1997). *SHELXS97* and *SHELXL97*. University of Göttingen, Germany.
Taylor, D. P., Allen, L. E., Becker, J. A., Crane, M., Hyslop, D. K. & Riblet, L. A. (1984). *Drug. Dev. Res.* **4**, 95–108.
Wu, Y. H. & Rayburn, J. W. (1971). Patent No. DE 2 057 845.
Wu, Y.-H., Rayburn, J. W., Allen, L. E., Ferguson, H. C. & Kissel, J. W. (1972). *J. Med. Chem.* **15**, 477–479.
Wu, Y.-H., Smith, K. R., Rayburn, J. W. & Kissel, J. W. (1969). *J. Med. Chem.* **12**, 876–881.
Wu, Y. & Rayburn, J. (1973). Patent No. US 3 717 634.