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Venlafaxine, an antidepressant drug

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Key indicators

Single-crystal X-ray study
T = 110 K
Mean σ(C–C) = 0.002 Å
R factor = 0.044
wR factor = 0.121
Data-to-parameter ratio = 18.5

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

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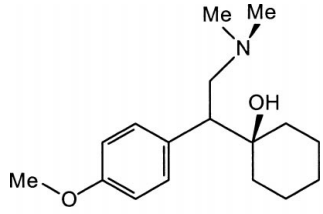
The title compound, racemic 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol, $C_{17}H_{27}NO_2$, was precisely characterized at *ca* 110 K, revealing an intramolecularly hydrogen-bonded structure with different conformational features than those observed earlier in its hydrochloride and hydrobromide derivatives.

Comment

Venlafaxine has shown an effective antidepressant activity in humans (Yardley *et al.*, 1990) and has been developed in recent years as a drug for oral administration in its hydrochloride form. Earlier crystallographic determinations of this compound relate to its hydrobromide (Yardley *et al.*, 1990) and hydrochloride (Vega *et al.*, 2000; Sivalakshmidevi *et al.*, 2002) derivatives. The corresponding structures were characterized by ion-pairing and hydrogen-bonding (N—H···halogen and O—H···halogen) interactions. The latter were facilitated by a diverging orientation of the ammonium and hydroxyl functions and resulted in the formation of hydrogen-bonded chains of the protonated venlafaxine molecules through the bromide/chloride anions.



(I)

The present report provides a precise structural determination of this pharmaceutically important compound in its parent form, (I) (Fig. 1), which now contains relatively strong proton-donor (OH) as well as proton-acceptor (tertiary-N) sites. Correspondingly, the molecular structure of (I) is characterized by an intramolecular O—H···N hydrogen bond (Table 1). This is associated with a converging orientation of the hydroxyl and amine functions, the corresponding N1—C3 and C5—O1 bonds being essentially coplanar and the N1—C3—C4—C5 and C3—C4—C5—O1 torsion angles being nearly *gauche*. These conformational features of (I) are compared with those of the hydrobromide [Yardley *et al.* (1990); Cambridge Structural Database (CSD, Version 5.25; Allen, 2002) refcode KIDGUZ] and two polymorphs of the hydrochloride [refcodes WOBMUV (Vega *et al.*, 2000) and WOBMUV01 (Sivalakshmidevi *et al.*, 2002)] derivatives in Table 2. In those compounds, which reveal similar conforma-

tional features, the corresponding N—C and C—O bonds are oriented in a nearly antiparallel fashion. The above observations confirm the conformational flexibility of the venlafaxine molecular framework, while preserving the chair conformation of the cyclohexane residue. The crystal packing of (I) is stablized by normal van der Waals interactions.

Experimental

The title compound was crystallized in its parent form by slow evaporation of a methanol solution.

Crystal data

$C_{17}H_{27}NO_2$
M_r = 277.40
Monoclinic, $P2_1/n$
a = 8.2670 (2) Å
b = 8.8246 (2) Å
c = 21.4946 (6) Å
β = 92.2130 (8)°
V = 1566.93 (7) Å^3
Z = 4
D_x = 1.176 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 3134 reflections
θ = 1.9–27.5°
μ = 0.08 mm^{-1}
T = 110 (2) K
Prism, colorless
0.35 × 0.20 × 0.20 mm

Data collection

Nonius KappaCCD diffractometer
φ scans
9690 measured reflections
3428 independent reflections
2600 reflections with $I > 2\sigma(I)$
R_{int} = 0.028
θ_{max} = 27.5°
$h = -10 \rightarrow 10$
$k = -10 \rightarrow 10$
$l = -28 \rightarrow 28$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.044
$wR(F^2)$ = 0.121
S = 1.03
3428 reflections
185 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0599P)^2 + 0.3518P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.22 e Å^{-3}
$\Delta\rho_{min}$ = −0.20 e Å^{-3}

Table 1
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
O1—HO1···N1	0.94	1.85	2.7272 (14)	154

Table 2
Comparison of corresponding torsion angles (°) in venlafaxine compounds.

	(I)[a]	KIDGUZ[b,c]	WOBMUV[b,d]	WOBMUV01[b,e]
N1—C3—C4—C5	61.75 (14)	144.1	144.8	137.6
N1—C3···C5—O1	0.86 (9)	166.9	167.9	160.8
C3—C4—C5—O1	59.35 (13)	45.7	46.2	47.2

Notes: (*a*) this work; (*b*) Cambridge Structural Database (Allen, 2002); (*c*) Yardley *et al.* (1990); (*d*) Vega *et al.* (2000); (*e*) Sivalakshmidevi *et al.* (2002).

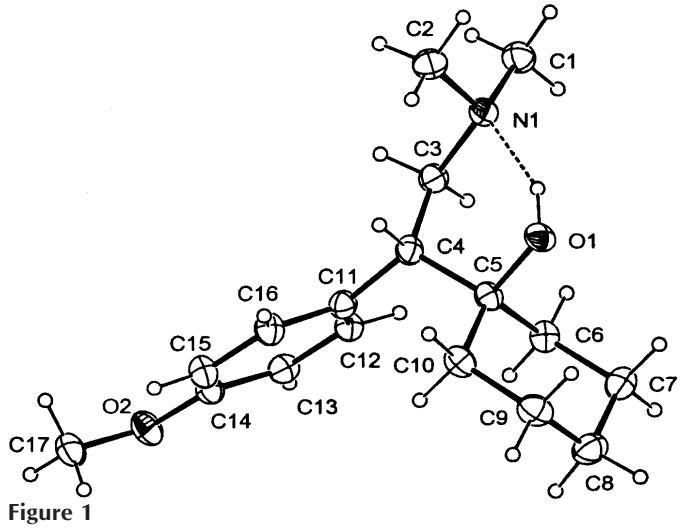


Figure 1
The molecular structure of venlafaxine, showing the atom-labeling scheme. The intramolecular O1—H···N1 hydrogen bond is indicated by a dotted line. Displacement ellipsoids are drawn at the 50% probability level.

H atoms bound to carbon were placed in idealized positions. They were refined using a riding model with fixed displacement parameters [U_{iso}(H) = 1.2U_{eq}(C) of the atom to which they are bonded]. The hydroxyl H atom was located in a difference Fourier map and its displacement parameter was refined as riding. The methyl groups were allowed to rotate but not to tip.

Data collection: *COLLECT* (Nonius, 1999); cell refinement: *DENZO* (Otwinowski & Minor, 1997); data reduction: *DENZO*; program(s) used to solve structure: *SIR*-92 (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*III (Burnett & Johnson, 1996); software used to prepare material for publication: *SHELXL*97.

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References

Allen, F. H. (2002). *Acta Cryst.* B**58**, 380–388.
Altomare, A., Cascarano, G., Giacovazzo, C., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1994). *J. Appl. Cryst.* **27**, 435.
Burnett, M. N. & Johnson, C. K. (1996). *ORTEP*III. Report ORNL-6895. Oak Ridge National Laboratory, Tennessee, USA.
Nonius (1999). *COLLECT*. Nonius BV, Delft, The Netherlands.
Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, *Macromolecular Crystallography*, Part A, edited by C. W. Carter Jr and R. M. Sweet, pp. 307–326. New York: Academic Press.
Sheldrick, G. M. (1997). *SHELXL*97. University of Göttingen, Germany.
Sivalakshmidevi, A., Vyas, K., Manender Rao, S. & Om Reddy, G. (2002). *Acta Cryst.* E**58**, o1072–o1074.
Vega, D., Fernandez, D. & Echeverria, G. (2000). *Acta Cryst.* C**56**, 1009–1010.
Yardley, J. P., Husbands, G. E. M., Stack, G., Butch, J., Bicksler, J., Moyer, J. A., Muth, E. A., Andree, T., Fletcher, H. III, James, M. N. G. & Sielecki, A. R. (1990). *J. Med. Chem.* **33**, 2899–2905.