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A Lamotrigine Analogue: 3,5-Diamino-6-(2-fluorophenyl)-1,2,4-triazine Methanol Solvate

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Abstract

The crystal of the title compound, C_9H_8-$FN_5.CH_3OH$, contains two conformers of the triazine molecule in the asymmetic unit, each with significantly distinct dihedral angles between their respective phenyl and triazine rings [50.8 (1) and 125.0 (1)°]. These two conformers exhibit significant differences in certain bond lengths and angles which may arise because of their different dihedral angles. An extensive hydrogen-bonding network maintains the crystal structure which also incorporates two solvent methanol molecules.

Comment

The title compound is an analogue of the anticonvulsant 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, known as lamotrigine (Janes, Lisgarten & Palmer, 1989), and was supplied by Wellcome Pharmaceuticals (UK). The structure determination was carried out as part of an ongoing investigation into structure–activity relationships of lamotrigine analogues.

(I)
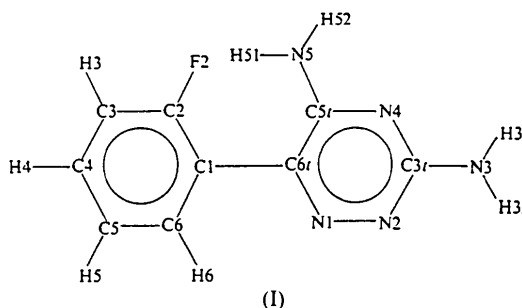
Two conformations of the 2-fluorophenyl analogue exist in the asymmetric unit (the atoms of the second conformer are distinguished with a prime). The F atoms are coplanar with their respective phenyl rings. Atom N5 lies 0.144 (1) Å from its triazine ring plane, while the remaining amino N atoms are coplanar. The dihedral angles between the phenyl and triazine ring moieties of the conformers are 50.8 (1) and 125.0 (1)°, respectively. There is a significant difference in length between the related bonds C1—C2 [1.376 (3) Å] and C1′—C2′ [1.398 (3) Å], and between C2—F2 [1.363 (3) Å] and C2′—F2′ [1.332 (3) Å], which may arise from the difference in the dihedral angles of the two conformers. In the first conformer there is a marked distortion about the common axis of the phenyl and triazine rings, denoted by the atoms C3t, C6t, C1 and C4. Atom C4 is displaced 0.172 (1) Å from the triazine ring plane while the non-bonding angle given by C3t···C6t···C4 is 176.3 (1)°. In contrast, the second conformer shows no significant distortion about the common axis of its rings. These various larger distortions in the first conformer compared with the second, together with those given in Table 2, may well arise from steric hindrance between the F atom, the triazine ring π electrons and the amino group on C5t.

There is an extensive hydrogen-bonding network within the crystal. The two conformers in the asymmetric unit are joined as a non-crystallographic dimer by hydrogen bonds between H52 and N4′, and H52′ and N4. An additional dimer union exists, from a c-glide plane, between the respective H31 and N2 atoms of the different conformers. The methanol O1A atom is linked to H51 and H32′, while H32 and H51′ are hydrogen bonded to O1B. In turn, the H1A

and H1B atoms of these methanol molecules hydrogen bond to N1 and N1′, respectively. Values for the geometries of these intermolecular hydrogen bonds are given in Table 3.
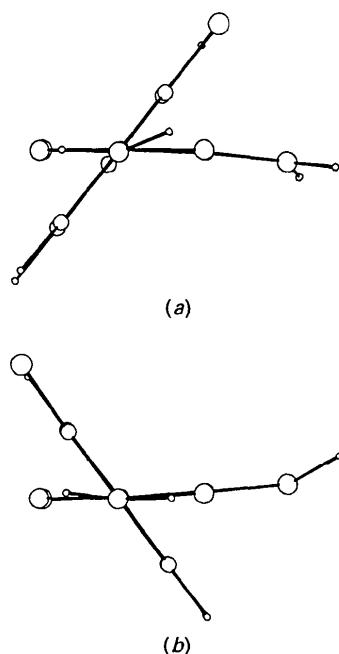

(a)

(b)

Fig. 1. View (*SNOOPI*; Karaulov, 1992) along the triazine ring atoms (a) C3t and C6t, and (b) C3$t′$ and C6$t′$ of the two conformers, illustrating the differences in the dihedral angles.
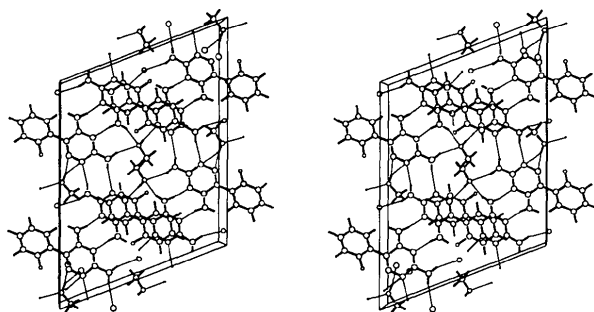

Fig. 2. Stereoview (*PLUTO*; Motherwell & Clegg, 1978) of the molecular packing along the b axis. Hydrogen bonds are shown as thin lines.

Experimental

The single crystal was grown by slow evaporation from methanol and was mounted in a capillary tube, with the mother liquor present to prevent drying and loss of crystallinity.

Crystal data

$C_9H_8FN_5.CH_4O$ Cu $K\alpha$ radiation
$M_r = 237.2$ $\lambda = 1.54178$ Å

Monoclinic Cell parameters from 25
$P2_1/c$ reflections
$a = 15.412$ (8) Å $\theta = 17-26°$
$b = 8.169$ (2) Å $\mu = 0.804$ mm^{-1}
$c = 19.487$ (4) Å $T = 293$ K
$\beta = 110.91$ (3)° Prismatic
$V = 2291.8$ (2) Å^3 $0.3 \times 0.3 \times 0.3$ mm
$Z = 8$ Pale yellow
$D_x = 1.37$ Mg m^{-3}

Data collection

Enraf–Nonius CAD-4 $R_{int} = 0.0185$
  diffractometer $\theta_{max} = 68°$
$\omega-2\theta$ scans $h = -18 \rightarrow 18$
Absorption correction: $k = -9 \rightarrow 9$
  none $l = 0 \rightarrow 23$
8770 measured reflections 3 standard reflections
4164 independent reflections frequency: 60 min
3095 observed reflections intensity decay: <10%
  $[I > 3\sigma(I)]$

Refinement

Refinement on F $(\Delta/\sigma)_{max} = 0.774$
$R = 0.0579$ $\Delta\rho_{max} = 0.32$ e Å^{-3}
$wR = 0.0733$ $\Delta\rho_{min} = -0.26$ e Å^{-3}
3095 reflections Extinction correction: none
365 parameters Atomic scattering fac-
$w = 1.0/[\sigma^2(F)$ tors from *SHELX76*
  $+ 0.023475(F)^2]$ (Sheldrick, 1976)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å^2)

$$U_{eq} = (1/3)\Sigma_i\Sigma_jU_{ij}a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
C1	0.4913 (1)	0.4602 (3)	0.2357 (1)	0.048 (1)
C2	0.4744 (2)	0.5255 (3)	0.1671 (1)	0.052 (1)
C3	0.3873 (2)	0.5406 (4)	0.1136 (2)	0.064 (1)
C4	0.3121 (2)	0.4856 (4)	0.1295 (2)	0.070 (1)
C5	0.3249 (2)	0.4189 (4)	0.1981 (2)	0.072 (2)
C6	0.4137 (2)	0.4074 (3)	0.2509 (2)	0.063 (1)
F2	0.5471 (1)	0.5819 (2)	0.1494 (1)	0.069 (1)
N1	0.5979 (1)	0.4970 (2)	0.3589 (1)	0.052 (1)
N2	0.6802 (1)	0.4815 (3)	0.4143 (1)	0.053 (1)
C3t	0.7496 (2)	0.4114 (3)	0.3983 (1)	0.049 (1)
N4	0.7434 (1)	0.3521 (2)	0.3325 (1)	0.048 (1)
C5t	0.6610 (1)	0.3634 (3)	0.2788 (1)	0.044 (1)
C6t	0.5858 (2)	0.4444 (3)	0.2922 (1)	0.045 (1)
N3	0.8306 (2)	0.3930 (3)	0.4536 (1)	0.059 (1)
N5	0.6505 (1)	0.2929 (3)	0.2150 (1)	0.049 (1)
C1′	1.0568 (2)	0.0207 (3)	0.2819 (1)	0.051 (1)
C2′	1.1302 (2)	0.1009 (3)	0.2699 (1)	0.063 (1)
C3′	1.2193 (2)	0.1002 (4)	0.3206 (2)	0.075 (1)
C4′	1.2381 (2)	0.0157 (4)	0.3857 (2)	0.071 (1)
C5′	1.1667 (2)	-0.0661 (4)	0.3993 (1)	0.067 (1)
C6′	1.0775 (2)	-0.0641 (3)	0.3480 (1)	0.059 (1)
F2′	1.1141 (1)	0.1862 (3)	0.2083 (1)	0.093 (1)
N1′	0.9473 (1)	-0.0191 (3)	0.1596 (1)	0.057 (1)
N2′	0.8621 (1)	-0.0173 (3)	0.1075 (1)	0.057 (1)
C3$t′$	0.7912 (2)	0.0311 (3)	0.1279 (1)	0.051 (1)
N4′	0.7990 (1)	0.0828 (2)	0.1951 (1)	0.049 (1)
C5$t′$	0.8839 (1)	0.0851 (3)	0.2457 (1)	0.045 (1)
C6$t′$	0.9611 (2)	0.0263 (3)	0.2271 (1)	0.048 (1)
N3′	0.7066 (2)	0.0291 (4)	0.0766 (1)	0.063 (2)
N5′	0.8945 (1)	0.1409 (3)	0.3123 (1)	0.054 (1)
O1A	0.5226 (1)	0.3397 (3)	0.5835 (1)	0.063 (1)
C1A	0.4777 (2)	0.2620 (4)	0.5161 (1)	0.072 (2)
O1B	0.0160 (1)	0.2752 (3)	0.4528 (1)	0.076 (1)
C1B	0.0742 (3)	0.2144 (6)	0.5197 (2)	0.102 (3)

C9H8FN5.CH4O

Table 2. *Selected geometric parameters* (Å, °)

C1—C2	1.376 (3)	C1'—C2'	1.398 (3)
C4—C5	1.391 (5)	C4'—C5'	1.391 (5)
C1—C6t	1.485 (3)	C1'—C6t'	1.481 (3)
N2—C3t	1.345 (3)	N2'—C3t'	1.349 (3)
C5t—C6t	1.436 (3)	C5t'—C6t'	1.445 (3)
C2—F2	1.363 (3)	C2'—F2'	1.332 (3)
C3—C4	1.379 (4)	C3'—C4'	1.381 (5)
C6—C1	1.399 (3)	C6'—C1'	1.394 (3)
N1—N2	1.347 (2)	N1'—N2'	1.344 (3)
N4—C5t	1.330 (3)	N4'—C5t'	1.329 (3)
C5t—N5	1.327 (3)	C5t'—N5'	1.329 (3)
C2—C3	1.380 (3)	C2'—C3'	1.376 (4)
C5—C6	1.391 (4)	C5'—C6'	1.383 (3)
C6t—N1	1.318 (3)	C6t'—N1'	1.307 (3)
C3t—N4	1.341 (3)	C3t'—N4'	1.340 (3)
C3t—N3	1.336 (3)	C3t'—N3'	1.331 (3)
C1A—O1A	1.398 (3)	C1B—O1B	1.383 (3)
C1—C2—C3	124.3 (2)	C1'—C2'—C3'	122.5 (2)
C4—C5—C6	120.1 (3)	C4'—C5'—C6'	120.4 (3)
C2—C1—C6t	123.3 (2)	C2'—C1'—C6t'	121.4 (2)
C6t—N1—N2	121.4 (2)	C6t'—N1'—N2'	121.5 (2)
C3t—N4—C5t	116.7 (2)	C3t'—N4'—C5t'	116.8 (2)
C5t—C6t—C1	123.2 (2)	C5t'—C6t'—C1'	121.7 (2)
N4—C5t—N5	118.0 (2)	N4'—C5t'—N5'	118.3 (2)
C3—C2—F2	116.4 (2)	C3'—C2'—F2'	117.8 (2)
C3—C4—C5	120.2 (2)	C3'—C4'—C5'	119.6 (3)
C6—C1—C2	116.5 (2)	C6'—C1'—C2'	117.1 (2)
C1—C6t—N1	117.3 (2)	C1'—C6t'—N1'	118.7 (2)
N2—C3t—N4	125.7 (2)	N2'—C3t'—N4'	125.6 (2)
C5t—C6t—N1	119.3 (2)	C5t'—C6t'—N1'	119.6 (2)
N4—C3t—N3	117.3 (2)	N4'—C3t'—N3'	117.4 (2)
C1—C2—F2	119.3 (2)	C1'—C2'—F2'	119.7 (2)
C2—C3—C4	118.0 (2)	C2'—C3'—C4'	119.4 (3)
C5—C6—C1	120.8 (2)	C5'—C6'—C1'	121.0 (3)
C6—C1—C6t	120.2 (2)	C6'—C1'—C6t'	121.5 (2)
N1—N2—C3t	117.0 (2)	N1'—N2'—C3t'	117.1 (2)
N4—C5t—C6t	119.7 (2)	N4'—C5t'—C6t'	119.3 (2)
N2—C3t—N3	116.9 (2)	N2'—C3t'—N3'	117.0 (2)
C6t—C5t—N5	122.2 (2)	C6t'—C5t'—N5'	122.3 (2)

Table 3. *Hydrogen-bonding geometry* (Å, °)

D—H···A	D—H	H···A	D···A	D—H···A
N5'—H52'···N4	1.07 (4)	1.98 (4)	3.035 (3)	168 (3)
N5—H52···N4'	0.89 (3)	2.12 (3)	2.995 (3)	168 (3)
N3'—H31'···N2^i	0.80 (4)	2.26 (4)	3.043 (3)	164 (4)
N3—H31···N2'^{ii}	0.89 (3)	2.17 (3)	3.037 (3)	168 (3)
N5—H51···O1A^i	0.87 (3)	2.02 (3)	2.832 (2)	155 (3)
N3'—H32'···O1A^i	0.90 (4)	2.21 (3)	3.079 (4)	1622 (3)
N3—H32···O1B^{iii}	0.91 (3)	2.16 (3)	3.020 (4)	157 (2)
N5'—H51'···O1B^{iii}	0.84 (2)	2.30 (3)	2.923 (2)	132 (3)
O1A—H1A···N1^{iv}	0.77 (6)	2.09 (6)	2.824 (3)	161 (5)
O1B—H1B···N1'^{v}	0.941 (2)	2.043 (2)	2.971 (3)	168.0 (1)

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

All H atoms of the phenyl ring were positioned from geometrical constraints, while the remaining H atoms were located on difference synthesis maps. One hydroxyl H atom (H1B) was fixed in position. All H atoms were refined isotropically.

Data collection: CAD-4 software. Programs used to solve structure: SHELX76 (Sheldrick, 1976). Programs used to prepare figures: SNOOPI (Karaulov, 1992), PLUTO (Motherwell & Clegg, 1988). Additional molecular geometry calculations: XANADU (Roberts & Sheldrick, 1975), PARST (Nardelli, 1983).

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: LI1096). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Thiooxalic Acid 2-Amide-1-hydrazide-2-hydrazone

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Abstract

The results of an X-ray analysis reveal that the title compound, $C_2H_7N_5S$, has zwitterionic character (2), instead of the initially assumed form of a neutral tautomer (1). The bonding in (2) can be described as a resonance of several dipolar limiting structures. Their particular contributions to the zwitterionic resonance hybrid were estimated through calculations using the HOSE model based on the observed bond lengths. The two predominant resonance contributors, together with four intramolecular hydrogen bonds, account for the almost perfect planarity of the molecules.