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N-(2-Chloro-6-methylphenyl)-6-methyl-3-pyridinecarboxamide Hydrate: an Anticonvulsant Drug Exhibiting Solid-State Rotational Disorder

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Abstract

The phenyl ring, the pyridine ring and the carboxamide group are conformationally planar. The Cl atom and the methyl group on the phenyl ring are statistically disordered, by 180° rotation about the N(6)—C(6) linkage, with relative occupancies of 0.7061 (5) and 0.2939 (5) at the major and minor sites, respectively. Hydrogen bonds involving the nitrogen (donor) and the oxygen (acceptor) of the carboxamide moiety with the water oxygen, together with the hydrogen bond between the nitrogen (acceptor) of the pyridine moiety and the water oxygen structurally stabilize the pyridine and carboxamide groups.

Comment

6-Chloro-*N*-(2,6-dimethylphenyl)-3-pyridinecarboxamide is an anticonvulsant agent with a high therapeutic ratio and long half-life. Moreover, it has a lessened propensity to interact with drug metabolizing enzymes compared to other anticonvulsant amides (Robertson, 1990). It is effective against tonic-extensor seizures elicited by maximal electroshock and therefore has potential utility in treating grand-mal, cortical focal, temperoral lobe, focal and post-traumatic seizures. This compound, recrystallized from aqueous methanol, was supplied by Eli Lilly & Co. of Indianapolis, USA. The structure analysis reported here was undertaken as part of a study of convulsant and anticonvulsant drugs being carried out in this department.

The phenyl ring is planar. No significant deviations from the average bond length [1.385 (4) Å] or bond angle [120.0 (3)°] are observed for the phenyl ring. The pyridine ring is also planar, as is the carboxamide moiety. All bond distances are normal and in agreement with those quoted by Allen, Kennard, Watson, Brammer, Orpen & Taylor (1987). The angle between the normal to the least-squares plane through the atoms of the phenyl ring and the least-squares plane through the atoms of the pyrdine ring is 29.5 (9)°; for the phenyl ring plane and the plane through the carboxamide group atoms, the dihedral angle is 68.6 (9)°; and for the phenyl–pyridine ring planes 39.2 (8)°. The Cl atom and the methyl group on the phenyl ring are statistically disordered. Hydrogen bonds involving the

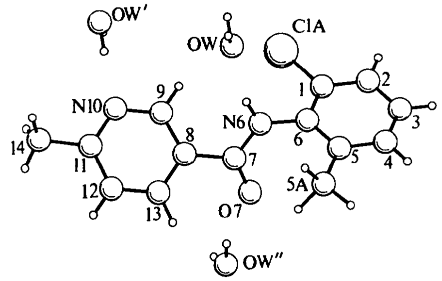

Fig. 1. View of the molecule showing the three hydrogen-bonded symmetry-related water molecules and the numbering scheme.

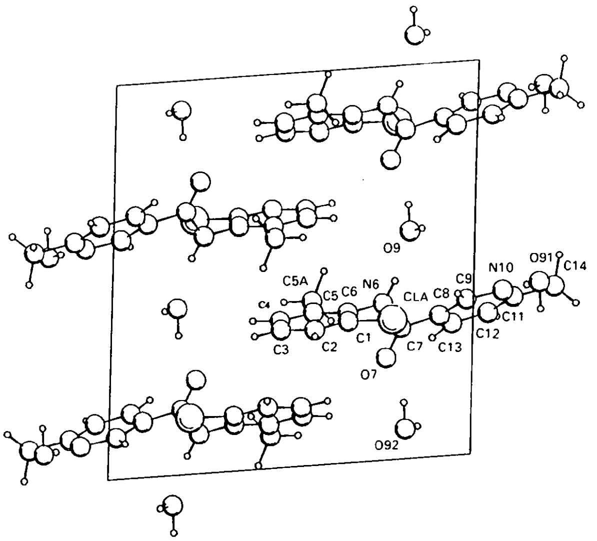

Fig. 2. Crystal packing along **b**.

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nitrogen (donor) and oxygen (acceptor) of the carboxamide group with the water oxygen, together with the hydrogen bond between the nitrogen (acceptor) of the pyridine moiety and the water oxygen, stabilize the pyridine and carboxamide groups.

Experimental

Crystal data

$C_{14}H_{13}ClN_2O.H_2O$
$M_r = 278.7$
Monoclinic
$P2_1/c$
$a = 12.647$ (6) Å
$b = 8.277$ (1) Å
$c = 13.551$ (6) Å
$\beta = 95.88$ (3)°
$V = 1411.0$ Å^3
$Z = 4$
$D_x = 1.22$ Mg m^{-3}

Cu $K\alpha$ radiation
$\lambda = 1.54178$ Å
Cell parameters from 25 reflections
$\theta = 20$-25°
$\mu = 21.61$ mm^{-1}
$T = 293$ K
Needles
0.25 × 0.20 × 0.05 mm
Clear
Crystal source: recrystallization from aqueous MeOH

Data collection

Enraf-Nonius CAD-4 diffractometer
ω-2θ scans
Absorption correction: none
5968 measured reflections
2772 independent reflections
1927 observed reflections $[I > 3\sigma(I)]$

$R_{\text{int}} = 0.0592$
$\theta_{\text{max}} = 70°$
$h = -14 \rightarrow 14$
$k = -9 \rightarrow 9$
$l = 0 \rightarrow 14$
3 standard reflections monitored every 100 reflections
intensity variation: <10%

Refinement

Refinement on F
Final $R = 0.0480$
$wR = 0.0501$
1927 reflections
216 parameters
$w = 21.4948/[\sigma^2(F) + 0.000202(F)^2]$

$(\Delta/\sigma)_{\text{max}} = 0.678$
$\Delta\rho_{\text{max}} = 0.199$ e Å^{-3}
$\Delta\rho_{\text{min}} = -0.225$ e Å^{-3}
Atomic scattering factors from *SHELX*76 (Sheldrick, 1976)

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

$U_{\text{eq}} = (U_1U_2U_3)^{1/3}$.

	x	y	z	U_{eq}
Cl*a*	0.7779 (1)	0.1823 (1)	0.6431 (1)	0.084
C(5*b*)	0.7617 (5)	0.1760 (5)	0.6608 (5)	0.090
C(1)	0.6564 (2)	0.0827 (3)	0.6396 (2)	0.056
C(2)	0.5633 (2)	0.1641 (3)	0.6554 (2)	0.073
C(3)	0.4686 (2)	0.0815 (3)	0.6495 (2)	0.079
C(4)	0.4661 (2)	−0.0808 (3)	0.6271 (2)	0.070
C(5)	0.5581 (2)	−0.1642 (3)	0.6117 (2)	0.053
C(5*a*)	0.5535 (3)	−0.3462 (4)	0.5816 (3)	0.050
Cl*b*	0.5584 (4)	−0.3605 (4)	0.5797 (4)	0.131
C(6)	0.6544 (2)	−0.0819 (2)	0.6188 (1)	0.046
N(6)	0.7509 (1)	−0.1605 (2)	0.6008 (1)	0.050
C(7)	0.8009 (2)	−0.2663 (3)	0.6650 (2)	0.050
O(7)	0.7629 (1)	−0.3145 (2)	0.7393 (1)	0.066
C(8)	0.9074 (2)	−0.3212 (2)	0.6417 (2)	0.049
C(9)	0.9804 (2)	−0.2169 (3)	0.6056 (2)	0.055
N(10)	1.0799 (1)	−0.2609 (2)	0.5903 (1)	0.058
C(11)	1.1097 (2)	−0.4147 (3)	0.6080 (2)	0.054
C(12)	1.0409 (2)	−0.5258 (3)	0.6439 (2)	0.062
C(13)	0.9410 (2)	−0.4764 (3)	0.6636 (2)	0.058
C(14)	1.2211 (2)	−0.4605 (3)	0.5894 (2)	0.075
O*W*	0.8191 (2)	−0.0440 (2)	0.4241 (1)	0.076
H(N6)	0.7816 (5)	−0.1358 (5)	0.5467 (5)	0.065
H(O1)	0.8112 (5)	−0.0678 (5)	0.3594 (5)	0.088
H(O2)	0.8485 (5)	0.0566 (5)	0.4191 (5)	0.053

Table 2. *Bond lengths* (Å), *bond angles* (°) *and hydrogen-bonding geometry* (Å, °)

C(1)—Cl*a*	1.741 (4)	H(O1)—O*W*	0.894 (8)
C(1)—C(5*b*)	1.541 (8)	C(2)—C(1)	1.391 (4)
C(6)—C(1)	1.391 (4)	C(3)—C(2)	1.375 (5)
C(4)—C(3)	1.376 (5)	C(5)—C(4)	1.387 (4)
C(5*a*)—C(5)	1.560 (6)	Clb—C(5)	1.681 (6)
C(6)—C(5)	1.391 (4)	N(6)—C(6)	1.426 (4)
C(7)—N(6)	1.345 (4)	O(7)—C(7)	1.226 (3)
C(8)—C(7)	1.486 (4)	C(9)—C(8)	1.389 (4)
C(13)—C(8)	1.376 (4)	N(10)—C(9)	1.346 (4)
C(11)—N(10)	1.342 (4)	C(12)—C(11)	1.388 (4)
C(14)—C(11)	1.504 (5)	C(13)—C(12)	1.381 (4)
H(N6)—N(6)	0.888 (8)	H(O2)—O*W*	0.917 (6)
C(2)—C(1)—Cl*a*	121.7 (3)	H(O2)—O*W*—H(O1)	97.6 (7)
C(2)—C(1)—C(5*b*)	117.2 (4)	C(6)—C(1)—Cl*a*	117.8 (3)
C(6)—C(1)—C(5*b*)	121.7 (4)	C(6)—C(1)—C(2)	120.5 (3)
C(3)—C(2)—C(1)	119.7 (3)	C(4)—C(3)—C(2)	119.9 (3)
C(5)—C(4)—C(3)	121.2 (3)	C(5*a*)—C(5)—C(4)	120.7 (3)
Cl*b*—C(5)—C(4)	123.0 (3)	C(6)—C(5)—C(5*a*)	120.0 (3)
C(6)—C(5)—C(4)	119.2 (3)	C(5)—C(6)—C(1)	119.4 (3)
C(6)—C(5)—Cl*b*	117.8 (3)	N(6)—C(6)—C(5)	121.6 (3)
N(6)—C(6)—C(1)	119.0 (3)	O(7)—C(7)—N(6)	123.1 (3)
C(7)—N(6)—C(6)	122.7 (3)	C(8)—C(7)—O(7)	121.2 (3)
C(8)—C(7)—N(6)	116.0 (3)	C(13)—C(8)—C(7)	120.4 (3)
C(9)—C(8)—C(7)	122.3 (3)	N(10)—C(9)—C(8)	123.4 (3)
C(13)—C(8)—C(9)	117.1 (3)	C(12)—C(11)—N(10)	121.1 (3)
C(11)—N(10)—C(9)	118.7 (3)	C(14)—C(11)—C(12)	121.5 (3)
C(14)—C(11)—N(10)	117.4 (3)	C(12)—C(13)—C(8)	120.2 (3)
C(13)—C(12)—C(11)	119.4 (3)	H(N6)—N(6$^{\text{i}}$)—C(7$^{\text{ii}}$)	117.9 (5)
H(N6)—N(6)—C(6)	119.3 (5)		

D—H···A	D—H	H···A	D···A	D—H···A
N(6)—H(N6)···O*W*	0.888 (8)	1.921 (12)	2.801 (8)	169.6 (8)
O*W*—H(O2)···O(7$^{\text{i}}$)	0.917 (6)	1.923 (12)	2.793 (8)	153.5 (8)
O*W*—H(O1)···N(10$^{\text{ii}}$)	0.894 (8)	1.886 (11)	2.842 (8)	179.7 (9)

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

The structure was solved by direct methods using the program *SHELXS*86 (Sheldrick, 1986). Refinement was by full-matrix least squares using *SHELX*76 (Sheldrick, 1976). Geometrical calculations were performed with *XANADU* (Roberts & Sheldrick, 1975) and molecular illustration was drawn with *SNOOPI* (Karaulov, 1992). Calculations were carried out on a VAX 11/750 computer and Amstrad PC2386/65.

Cl and C(5*a*) occupy similar sites related by 180° rotation about N(6)—C(6). Occupation factors for these atoms were refined, the sum being constrained to equal 1.000, the major and minor sites of both atoms being complementary (*i.e.* two occupation factors only were refined as such). H atoms on C(5) were fixed geometrically after final refinement. H atoms for N(6) and O*W* (water) were located on a ΔF map and refined in *xyz* and *U*. Other H atoms were fixed geometrically (riding mode), *U* being refined group-wise for CH_3 atoms.

Lists of structure factors, anisotropic thermal parameters and H-atom coordinates have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 71177 (9 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: LI1044]

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Structure of 5,7-Dinitro-2,1,3-benzoxadiazol-4-yl Phenyl Diketone

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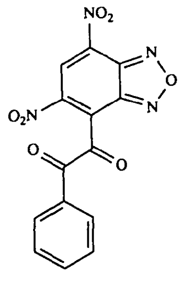
Abstract

In comparison to previous results, the bond lengths C(1)—C(2) and C(1)—C(6) (IUPAC numbering: C4—C3a, C4—C5) in the title compound are significantly shortened. The endocyclic angle C(3)—C(4)—C(5) (IUPAC numbering: C7a—C7—C6) is, in contrast to those in nitro-substituted benzene rings, smaller than 120°. A polymethinic structure of the dinitrobenzofurazan fragment is assumed. Stacking between the phenyl and furazan rings indicates weak π-electron interactions.

Comment

4,6-Dinitrobenzofurazan derivatives are of special significance because of their extraordinary electrophilic character. During the course of our studies of this type of compound, we have been interested in relationships between molecular structure and chemical reactivity; for example, 4-anilino-5,7-dinitrobenzofurazan was found to have a partial polymethinic structure and unusual chemical behaviour (Niclas, Göhrmann, Ramm & Schulz, 1990). In the present paper we report the crystal structure of 5,7-dinitrobenzofurazan-4-yl phenyl diketone (1) (5,7-dinitro-2,1,3-benzoxadiazol-4-yl phenyl diketone) which was prepared by nitric acid oxidation of 7-[aroyl(dimethylsulfonio)methyl]-4,6-dinitrobenzofurazanide (Niclas & Kind, 1993).



(1)

A drawing of the molecule with the atomic numbering scheme is shown in Fig. 1. The six-membered ring of the benzofurazan fragment contains two bonds which are significantly shorter [C(1)—C(6) 1.352 (2), C(4)—C(5) 1.340 (2) Å] than the others [1.423 (3)–1.429 (2) Å]. However, these bond lengths show small deviations in comparison to previous results (Mathew & Palenik, 1971; Niclas, Göhrmann, Ramm & Schulz, 1990). The C(1)—C(2) and C(1)—C(6) bonds are shortened significantly. The bond lengths correspond to the canonical form of the molecule with double bonds C(1)=C(6) and C(4)=C(5) and single bonds between the other C atoms. The C—NO_2 bond lengths [1.459 (3), 1.467 (2) Å] lie between those of *p*-dinitrobenzene [1.478 (2) Å; Di Rienzo, Domenicano & Riva di Sanseverino, 1980] and *p*-nitroaniline [1.434 Å; Colapietro, Domenicano, Manciante & Portalone, 1982], but closer to that of *p*-dinitrobenzene. The bond lengths of the furazan ring are in good agreement with previous findings (Mathew & Palenik, 1971; Niclas, Göhrmann, Ramm & Schulz, 1990).

Surprisingly, the angle C(3)—C(4)—C(5) is 119.5 (2)°. Comparable angles were measured in other benzofurazans and benzofuroxans (*cf.* Mathew & Palenik, 1971; Niclas, Göhrmann, Ramm & Schulz, 1990; Lowe-Ma, 1986). This is in contrast to nitro-substituted benzenes such as trinitrobenzene (Herbstein, Kapon & Reiner, 1986) and *m*-dinitrobenzene (Trotter & Williston, 1966). In these cases, the corresponding angles lie between 122.7 and 123.6°.

The average deviations of the atoms from the least-squares planes of the five and six-membered rings of the benzofurazan fragment are 0.001 (2) and 0.021 (2) Å, respectively. The five- and six-membered rings of the benzofurazan fragment are twisted by 4.3 (8)°. The two six-membered rings of the molecule enclose a dihedral angle of 67.7 (5)°. The nitro groups at C(4) and C(6) are inclined at 14.5 (5) and 15.4 (3)°, respectively, to the six-membered ring.