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Structure of 7-Chloro-5-(2-fluorophenyl)-1,3,4,5-tetrahydro-1,4-dimethyl-2*H*-1,4-benzodiazepin-2-one Monohydrate

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Abstract. $C_{17}H_{16}ClFN_2O.H_2O$, $M_r = 336.79$, monoclinic, $P2_1/c$, $a = 17.38(1)$, $b = 17.30(1)$, $c = 5.405(5)$ Å, $\beta = 94.20(5)°$, $U = 1621$ Å^3, $Z = 4$, $D_c = 1.380$ Mg m^{-3}, $F(000) = 704$, Mo $K\alpha$ radiation, $\lambda = 0.71069$ Å, μ(Mo $K\alpha$) = 0.21 mm^{-1}. $R = 5.0\%$ for 1904 observed counter amplitudes. E.s.d.'s average 0.004 Å for bond lengths and 0.3° for bond angles not involving H atoms. The fluorophenyl ring is inclined at an angle of 81.5° to the C(6)–(11) phenyl ring of the 1,4-benzodiazepine system.

Table 1. *Fractional atomic coordinates* (×10^4) *with e.s.d.'s in parentheses and equivalent isotropic temperature factors* U_{eq} (Å^2 × 10^3) *calculated from the anisotropic parameters by the method of Willis & Pryor* (1975)

	x	y	z	U_{eq}
Cl(7)	8440 (1)	3287 (1)	98 (2)	64
C(2)	5934 (2)	5452 (2)	6047 (6)	39
C(3)	6286 (2)	5909 (2)	4020 (6)	44
C(5)	7617 (2)	5607 (2)	5568 (6)	37
C(6)	7939 (2)	4460 (2)	2860 (6)	37
C(7)	7812 (2)	3711 (2)	2065 (6)	41
C(8)	7203 (2)	3285 (2)	2825 (6)	42
C(9)	6686 (2)	3629 (2)	4306 (6)	38
C(10)	6795 (2)	4396 (2)	5079 (6)	34
C(11)	7440 (2)	4812 (2)	4414 (5)	32
C(12)	5876 (2)	4264 (2)	8416 (7)	50
C(13)	7040 (2)	6811 (2)	6570 (8)	59
C(1')	8430 (2)	5882 (2)	5199 (6)	38
C(2')	9052 (2)	5643 (2)	6721 (7)	45
C(3')	9797 (2)	5885 (3)	6506 (8)	64
C(4')	9936 (2)	6392 (3)	4617 (9)	66
C(5')	9344 (3)	6637 (2)	3024 (8)	66
C(6')	8594 (2)	6397 (2)	3311 (7)	54
N(1)	6240 (1)	4741 (2)	6570 (5)	36
N(4)	7058 (2)	6202 (1)	4704 (5)	41
O(2)	5410 (1)	5711 (1)	7207 (5)	58
O(*W*)	4992 (2)	2744 (2)	1928 (6)	74
F(2')	8924 (1)	5129 (1)	8541 (4)	72
$H^1(3)$	6300	5624	2444	
$H^2(3)$	5951	6295	3666	
H(5)	7492	5464	7228	
H(6)	8372	4748	2400	
H(8)	7105	2791	2278	
H(9)	6251	3325	4761	
$H^1(12)$	5599	4550	9626	
$H^2(12)$	5452	4017	7620	
$H^3(12)$	6193	3848	8947	
$H^1(13)$	6875	6652	7973	
$H^2(13)$	6674	7214	5975	
$H^3(13)$	7449	7029	7085	
H(3')	10179	5750	7723	
H(4')	10464	6559	4456	
H(5')	9419	7039	1524	
H(6')	8192	6519	2315	
H^1(O*W*)	4847	3194	1967	
H^2(O*W*)	4986	2634	369	

Introduction. 5-Phenyl-1,4-benzodiazepines have found wide-spread clinical use as muscle-relaxant, anti-convulsant and anti-anxiety agents (Randall, Schallek, Sternbach & Ning, 1974). The present work reports the crystal structure of the title compound, a benzodiazepine of relatively low potency, as part of a study of structure–activity relationships for this class of compounds.

A crystal 0.1 × 0.2 × 0.3 mm was mounted along the direction of elongation which coincided with *c*. Cell dimensions and intensities were measured on a Stoe two-circle computer-controlled diffractometer with graphite-monochromated Mo $K\alpha$ radiation. The diffractometer was operated in the ω-scan mode with a step interval of 0.01°, a step time of 1 s and 30 s background counts at each end of the scan. For layers *hk*0–*hk*1 the scan range was 1.4° and for the higher layers *hk*2–*hk*6 $\Delta\omega$ was calculated from $[A + (B \sin\mu/\tan\theta')]°$, where μ is the equi-inclination angle, $2\theta'$ the azimuth angle, and A and B were assigned values of 1.0 and 0.5, respectively. Four zero-layer reflexions, remeasured after each layer of data collection, showed no significant variation of intensity.

Reflexions were scanned within the range $0.1 < \sin\theta/\lambda < 0.65$ Å^{-1} and of these 1904 were considered to be observed $[I > 2.5\sigma(I)]$.

The structure was solved by direct methods with *SHELX* (Sheldrick, 1976). An *E* map based on 608 reflexions revealed the positions of all non-hydrogen atoms. After refinement by least squares, H atoms and a molecule of water of crystallization were located from a difference synthesis. In the final cycles the heavier atoms were allowed to vibrate anisotropically. H atoms were included in the calculations in fixed positions and only their isotropic temperature factors were refined. Refinement was terminated when all calculated shifts were <0·1σ and R was 5·0% for the 1904 observed reflexions. The weighting scheme was $w = 1/[\sigma^2(F)]$ where $\sigma(F)$ is the standard deviation in the observed amplitudes derived from counting statistics. Final atomic coordinates are listed in Table 1,* and molecular dimensions in Table 2.

Computations were carried out on the Birmingham University ICL 1906A computer.

Discussion. The geometry of the molecule is shown in Fig. 1. The angle between the mean plane of phenyl ring C(6)–(11) and the 5-(2-fluorophenyl) ring is 81·5°, similar to the corresponding angles in the 5-(2-chlorophenyl)-1,4-benzodiazepines, clonazepam (Chananont, Hamor & Martin, 1979) and lorazepam (Bandoli & Clemente, 1976), where they are in the range 73–84° for four independent molecules (each of these crystal structures contains two independent molecules). In analogous compounds where the 5-phenyl ring is not substituted, the interplanar angle is some 15–20° smaller (Chananont, Hamor & Martin, 1980). A contributory cause of the large interplanar angle in the present structure may, however, be the steric effect of the adjacent 4-methyl group. The seven-membered ring is in a slightly distorted boat conformation, the bow and stern angles being 53·8 and 51·1°, respectively (Table 3).

Bond lengths and angles generally agree well with standard values. As in clonazepam, lorazepam and other analogous structures, the N(1)–C(2) single bond is shortened and the C(2)–O(2) carbonyl bond is slightly lengthened, indicating some electron delocalization. The disposition of bonds from N(1) is near-

Table 2. *Molecular dimensions*

(*a*) Bond lengths (Å)

N(1)–C(2)	1·362 (4)	C(10)–N(1)	1·432 (4)
C(2)–O(2)	1·228 (4)	C(10)–C(11)	1·401 (4)
C(2)–C(3)	1·516 (4)	C(12)–N(1)	1·473 (4)
C(3)–N(4)	1·457 (4)	C(13)–N(4)	1·460 (4)
N(4)–C(5)	1·469 (4)	C(1′)–C(5)	1·517 (4)
C(5)–C(11)	1·533 (4)	C(1′)–C(2′)	1·375 (5)
C(6)–C(11)	1·392 (4)	C(2′)–C(3′)	1·373 (5)
C(6)–C(7)	1·380 (4)	C(2′)–F(2′)	1·357 (4)
C(7)–Cl(7)	1·740 (3)	C(3′)–C(4′)	1·380 (6)
C(7)–C(8)	1·376 (4)	C(4′)–C(5′)	1·360 (6)
C(8)–C(9)	1·381 (4)	C(5′)–C(6′)	1·388 (5)
C(9)–C(10)	1·401 (4)	C(6′)–C(1′)	1·400 (5)
C(3)–H^1(3)	0·99	C(13)–H^1(13)	0·87
C(3)–H^2(3)	0·90	C(13)–H^2(13)	0·98
C(5)–H(5)	0·97	C(13)–H^3(13)	0·84
C(6)–H(6)	0·95	C(3′)–H(3′)	0·93
C(8)–H(8)	0·92	C(4′)–H(4′)	0·97
C(9)–H(9)	0·97	C(5′)–H(5′)	1·08
C(12)–H^1(12)	0·98	C(6′)–H(6′)	0·88
C(12)–H^2(12)	0·93	O(*W*)–H^1(O*W*)	0·82
C(12)–H^3(12)	0·94	O(*W*)–H^2(O*W*)	0·86

(*b*) Bond angles (°) (e.s.d.'s are 0·2–0·4°)

C(12)–N(1)–C(2)	117·8	C(8)–C(9)–C(10)	120·1
C(12)–N(1)–C(10)	119·2	C(9)–C(10)–C(11)	120·3
C(10)–N(1)–C(2)	121·9	C(9)–C(10)–N(1)	118·7
N(1)–C(2)–O(2)	121·1	C(11)–C(10)–N(1)	121·0
N(1)–C(2)–C(3)	116·7	C(10)–C(11)–C(6)	118·4
O(2)–C(2)–C(3)	122·2	C(10)–C(11)–C(5)	119·9
C(2)–C(3)–N(4)	114·3	C(6)–C(11)–C(5)	121·5
C(3)–N(4)–C(13)	111·2	C(5)–C(1′)–C(2′)	121·8
C(3)–N(4)–C(5)	114·3	C(5)–C(1′)–C(6′)	122·5
C(13)–N(4)–C(5)	109·4	C(6′)–C(1′)–C(2′)	115·7
N(4)–C(5)–C(1′)	109·8	C(1′)–C(2′)–C(3′)	124·3
N(4)–C(5)–C(11)	113·0	C(1′)–C(2′)–F(2′)	117·8
C(11)–C(5)–C(1′)	112·9	F(2′)–C(2′)–C(3′)	117·9
C(11)–C(6)–C(7)	120·4	C(2′)–C(3′)–C(4′)	118·3
C(6)–C(7)–Cl(7)	119·5	C(3′)–C(4′)–C(5′)	120·1
C(6)–C(7)–C(8)	121·3	C(4′)–C(5′)–C(6′)	120·6
Cl(7)–C(7)–C(8)	119·2	C(5′)–C(6′)–C(1′)	121·0
C(7)–C(8)–C(9)	119·4		

(*c*) Selected torsion angles (°) (e.s.d.'s are *ca* 0·5°)

C(10)–N(1)–C(2)–C(3)	−8·0
N(1)–C(2)–C(3)–N(4)	−71·3
C(2)–C(3)–N(4)–C(5)	55·4
C(3)–N(4)–C(5)–C(11)	29·2
N(4)–C(5)–C(11)–C(10)	−69·8
C(5)–C(11)–C(10)–N(1)	8·3
C(11)–C(10)–N(1)–C(2)	48·5
N(4)–C(5)–C(1′)–C(2′)	150·6
C(11)–C(5)–C(1′)–C(2′)	−82·3
C(9)–C(10)–N(1)–C(2)	−132·0
C(6)–C(11)–C(5)–N(4)	115·6
N(4)–C(3)–C(2)–O(2)	107·2
C(12)–N(1)–C(2)–C(3)	−176·1
C(12)–N(1)–C(2)–O(2)	5·4
C(12)–N(1)–C(10)–C(11)	−143·5
C(13)–N(4)–C(5)–C(1′)	−78·2
C(13)–N(4)–C(3)–C(2)	−69·2
C(13)–N(4)–C(5)–C(11)	154·7

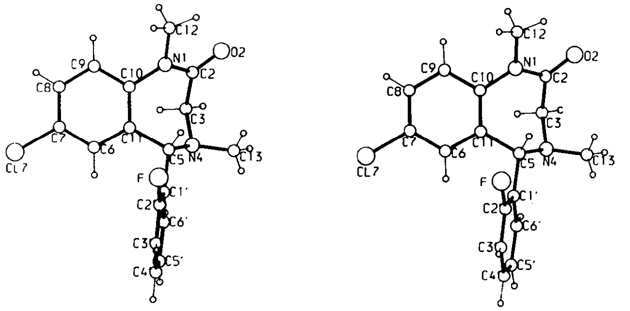

Fig. 1. Stereoscopic view of the molecule in a direction perpendicular to the mean plane through N(1), C(5)–(11).

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* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 35135 (14 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 3. *Mean-plane calculations*

(*a*) Deviations of atoms from planes (Å)

Distances marked with an asterisk refer to atoms defining the plane. E.s.d.'s are *ca* 0·004 Å.

Plane	I	II	III	IV	V
N(1)	−0·067		−0·063*		−0·018*
C(12)	0·660				
C(2)	−0·947		0·073*	0*	
O(2)	−1·057				
C(3)	−1·748		−0·647	0*	
N(4)	−0·970	0·707	−0·067*	0*	
C(13)	−0·552				
C(5)	0·203	0·020	0·057*		0·017*
C(6)	−0·002*				
C(7)	−0·018*				
C(8)	0·019*				
C(9)	0·000*				
C(10)	−0·019*		−0·976		0·037*
C(11)	0·020*	−1·372	−1·013		−0·035*
Cl(7)	−0·061				
C(1′)	0·587	0·003*			
C(2′)	1·887	−0·008*			
F(2′)	2·824	−0·046			
C(3′)	2·296	0·004*			
C(4′)	1·343	0·005*			
C(5′)	0·037	−0·010*			
C(6′)	−0·349	0·006*			

(*b*) Interplanar angles (°) (e.s.d.'s are *ca* 0·4°)

Plane I–plane II	81·5
Plane III–plane IV	53·8
Plane III–plane V	51·1

Table 4. *Hydrogen-bond geometry*

Distances (Å)	
$O(W)\cdots O(2^{I})$	2·811 (4)
$H^1(OW)\cdots O(2^{I})$	2·01
$O(W)\cdots O(W^{II})$	2·832 (6)
$H^2(OW)\cdots O(W^{II})$	1·97

Angles (°)	
$H^1(OW)–O(W)–H^2(OW)$	105
$H^1(OW)–O(W)\cdots O(2^{I})$	9
$H^2(OW)–O(W)\cdots O(W^{II})$	5

Symmetry code

(I) $1-x, 1-y, 1-z$ (II) $x, \frac{1}{2}-y, -\frac{1}{2}+z$

planar, the sum of the angles being 358·9°. The conformation about N(1)–C(2) approximates to that about a normal double bond as shown by the pertinent torsion angles [Table 2(*c*)]. The bonds at N(4) correspond in length to normal C–N single bonds and the disposition of the bonds is essentially pyramidal.

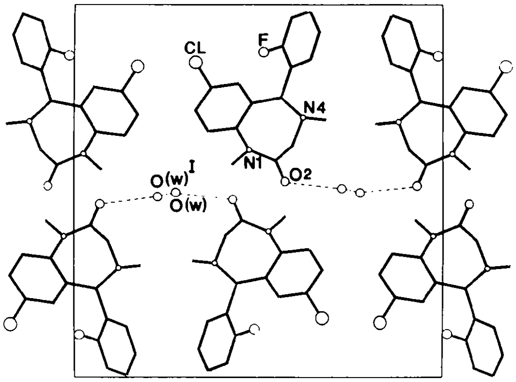

Fig. 2. The crystal structure projected along z^*. The x axis points up the page, the y axis to the right. Hydrogen bonds are indicated by broken lines.

The packing of the molecules is illustrated in Fig. 2. Molecules related by the *c*-glide plane are stacked parallel to the *z* axis, linked by hydrogen bonds *via* molecules of water of crystallization. Relevant distances and angles are in Table 4. All other intermolecular contacts correspond to normal van der Waals interactions.

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